1 TITLE PAGE

SYNOPTIC CLINICAL STUDY REPORT:

full version FOR REGULATORY SUBMISSION

First in Human study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy of PPSGG (PN-1007) in anti-MAG neuropathy patients

Protocol Number:	PN-1007-001
EudraCT Number:	2020-000067-23
ClinicalTrials.gov Identifier:	NCT04568174
Test Product:	PPSGG (PN-1007)
Indication:	Anti-myelin-associated glycoprotein (MAG) neuropathy
Development Phase of Study:	Phase 1/2a
Sponsor:	Polyneuron Pharmaceuticals AG
Sponsor's Responsible Medical Officer:	Debra Barker, MD
Coordinating Investigator:	Emilien Delmont, MD APHM Hopital La Timone Adultes 264 Rue Saint Pierre F-13005 Marseille, France
Study initiation (FPFV):	04 NOV 2020
Study completion (LPLV):	26 JUN 2021
Early Study Termination:	24 SEP 2021
Date of final report:	03 FEB 202

FPFV = first patient's first visit; LPLV = last patient's last visit

This study was conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), including the archiving of essential documents.

Final version 1.0, 03 FEB 2022

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Name of finished product PPSGG (PN-1007)
Name of active ingredient PPSGG (Poly phenyl [disodium 3-O-sulf-beta-D-glyucopyranuronate)-(1-3)-beta-D-galactopyranoside

Title of study

First in Human study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy of PPSGG (PN-1007) in anti-MAG neuropathy patients

Study ID: PN-1007-001; EudraCT Number: 2020-000067-23; ClinicalTrials.gov Identifier: NCT04568174.

Principal/coordinating investigator name, number of study center(s) and countries

Emilien Delmont, MD, 2 study sites in France and Spain. Additional sites, which did not recruit patients, were also planned in the Netherlands, United Kingdom, and Switzerland

Publication (reference)

Not applicable.

Study period

First patient's first visit (FPFV): 04 NOV 2020

Last patient's last visit (LPLV): 15 DEC 2020

Reporting period

04 NOV 2020 to 26 JUN 2021

Phase of development of study

Phase 1/2a

Background and rationale for the study

Anti-myelin-associated glycoprotein (MAG) neuropathy is a demyelinating polyneuropathy associated with a monoclonal immunoglobulin M (IgM) gammopathy with anti-MAG activity (Latov 1981, Braun 1982, Steck 2006, Rison 2016). Patients with anti-MAG neuropathy suffer from sensorimotor deficits, sensory ataxia, paresthesia, muscle weakness, neuropathic pain, and tremor.

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Currently, there is no treatment for anti-MAG neuropathy approved by the European Medicines Agency (EMA) or by the United States (US) Food and Drug Administration (FDA). However, off-label treatments are used for treatment of anti-MAG neuropathy, including various immunomodulatory and immunosuppressive treatments used to manage anti-MAG neuropathy (Nobile-Orazio 1988). Nonetheless, these treatments are of limited efficacy and may be associated with side effects (Lunn 2017, Dalakas 2010).

Clinical improvement of neuropathic symptoms in patients with anti-MAG neuropathy correlates with reduced serum levels of anti-MAG IgM autoantibodies (Nobile-Orazio 1988, Pestronk 2003, Steck 2006, Benedetti 2008) and disease worsening is associated with increasing anti-MAG IgM levels during treatment follow-up (Benedetti 2008, Dalakas 2018).

PPSGG is intended to bind anti-MAG IgM autoantibodies, the underlying cause of anti-MAG neuropathy, in a highly selective manner, resulting in their neutralization and removal from the circulation.

This was the first clinical study of PPSGG in participants with anti-MAG neuropathy. Based on the preclinical toxicology studies in dogs and rats and following the EMA guidelines for First-in-Human Studies, the starting dose of PPSGG was defined to be 200 mg. The safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of PPSGG were to be evaluated in the eligible participants.

Objectives and endpoints

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of PPSGG after single and multiple intravenous (IV) administrations in patients with anti-MAG neuropathy	• Assessment of safety was to be based on vital signs, physical examination, electrocardiograms (ECGs), laboratory assessments, signs of infusion-related reactions (IRRs), including clinical signs and symptoms, changes in diastolic or systolic blood pressure, heart rate, oxygen saturation, and skin reactions or local reactions at the infusion site and collection of adverse events (AEs) assessed from consent signature until the end of the study visit. Presence of anti-drug antibodies (ADAs) was to be also investigated.

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Secondary	
• To evaluate the PK of PPSGG after single and multiple IV administrations	• Non-compartmental parameters related to PPSGG including but not limited to time to reach observed maximum concentration (t_{max}), observed maximum concentration (C_{max}), as well as trough (pre-dose) levels after multiple dose
• To investigate PD of PPSGG in reducing anti-MAG IgM levels	• Reduction of anti-MAG antibodies (anti-MAG IgM titers) • Paraprotein levels • Total IgM levels • Anti-human natural killer-1 (HNK-1) titers
• To investigate the preliminary efficacy of PPSGG in single ascending dose (SAD) and multiple ascending dose (MAD) phases	• Change in the Overall Neuropathy Limitations Scale (OLNS) score • Time to walk 10 meters • Rasch-built Overall Disability Scale (RODS) • Ataxia score
• To investigate the preliminary efficacy of PPSGG in MAD phase only	• Inflammatory neuropathy cause and treatment (INCAT) sensory sum score (ISS) • Grip strength.
Exploratory	
• To assess the effect of PPSGG on other biomarkers of mode of action in MAD phase only	• Neurofilament light chain (NfL) to measure the degree of axonal damage • B-cell activating factor (BAFF) • Indirect immunofluorescence on sciatic nerves • Motor Unit Number Index (MUNIX) in selected sites only.

Estimand

Estimand was not defined for this study.

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Methodology

This was a Phase 1/2a, First in Human (FiH), multicenter, single, and multiple ascending dose escalation trial of PPSGG.

SAD phase:

The single rising dose escalation phase was to enroll 6 patients in each of the 4 or 5 ascending dose cohorts. The first administration of PPSGG of any cohort was to be provided to a single patient (sentinel patient). The decision to continue dosing the remaining patients in a given cohort was to be based on all available safety data collected during the first 72 hours after treatment of the sentinel patient. The decision to escalate to the following dose (once a cohort was completed) was to be based on all available safety data, collected during a minimum of 72 hours after the start of the infusion for all patients, where no stopping rules were met and analyzed by an Independent Data Monitoring Committee (IDMC). The study drug was to be administered as a 60 min (120 min for optional 3200 mg dose) IV infusion.

MAD phase:

The multiple rising dose phase was to enroll 2 dose cohorts of at least 12 patients each (10 on active and 2 on placebo). Dose levels were to be determined based on the safety, tolerability, PK, and PK/PD outcome (anti-MAG IgM titers) from the SAD phase. The dosing of both cohorts in the MAD phase was not to exceed the exposures achieved in the SAD phase (C_{max} and area under the curve to the end of the dosing period [$AUC_{0\text{-}tau}$]), and was to commence at a dose at least one dose level lower than safely completed in the SAD. The dosing frequency was to be defined based on the PK/PD relationship established during the SAD phase (PPSGG half-life, anti-MAG IgM kinetic) and stimulation of it. The study drug was to be administered up to 11 times (as a 60 min [120 min for optional 3200 mg dose] IV infusion) over a 6-week period to explore the effect on anti-MAG antibody levels. For safety purposes, the first 2 patients in each cohort of the MAD phase were to be randomized to receive active or placebo treatment in a double-blind fashion. The decision to continue dosing in a given cohort was to be based on safety data of the first 2 patients collected for 2 weeks (minimum) after the start of the infusion. The decision to escalate to the following dose was to be based on safety data collected during the first 2 weeks after the start of infusion and analyzed by an IDMC.

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On 21 JAN 2021, the Sponsor decided to put the study on hold to further analyze the safety findings of the sentinel patient. On 24 SEP 2021, the Sponsor decided to discontinue the study due to safety findings in the sentinel patient and subsequent investigations that precluded further continuation of this clinical development program.

Number of patients

A total of 30 patients were planned to be enrolled with the aim of having at least 24 patients complete each phase. The number of patients planned per cohort in this SAD and MAD study was representative of other FiH studies and based on scientific advice from the EMA.

Only 1 patient was included in Cohort 1 (PPSGG 200 mg) of the SAD phase.

Diagnosis and main criteria for inclusion and exclusion

Male and female adults between 18 and 80 years, who had a confirmed diagnosis of monoclonal IgM associated with monoclonal gammopathy of undetermined significance (MGUS) with anti-MAG activity (titer of >10000 Bühlmann titer units [BTU]) and demyelinating neuropathy defined by electrophysiological criteria according to European Federation of Neurological Societies/Peripheral Nervous System paraproteinemic demyelinating neuropathy (EFNS/PNS PDN) guideline (EFNS 2010), had clear clinical signs of disability (at least ONLS ≥2 in lower extremities, at least ISS ≥2), and with adequate hepatic and renal function were eligible to participate in the study. Patients with total serum IgM levels >30 g, hematological malignancy or prior malignancy of any organ system (except basal cell carcinoma [BCC]), who had a previous immunosuppressive treatment with IV immunoglobulin (IVIG) or apheresis/plasmapheresis in the previous 3 months or cyclophosphamide or biological treatment in the previous 6 months before the start of their participation, or had any other neurological, neuromuscular, rheumatologic or orthopedic condition with significant impact on the capabilities of walk preventing evaluation of neurological scores were not eligible to participate in the study.

Test Product, dose, mode of administration, batch number(s)

PPSGG was the investigational medicinal product (IMP).

All doses that were to be administered were based on the assigned dosing cohort according to the dose table in Section 6.1 of the protocol (Appendix 5.1.1). PPSGG was administered intravenously over 60 min (120 min for 3200 mg dose). Batch number: P01997.

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Control product, dose, mode of administration, batch number(s)

Placebo was to be the control product in the MAD phase.

Placebo was to be IV administered over 60 min.

Duration of treatment

Single dose infusions were administered on Day 1 in the SAD phase.

Up to a maximum of 11 infusions over 6 weeks were to be administered on Days 1, 2, 3, 4, 5, 8, 14, 21, 28, 35 and 42 in the MAD phase.

Statistical methods

Continuous variables were to be summarized using descriptive statistics, ie, generally displaying number of patients in the respective analysis population, number of patients with data, number of patients with missing values, mean, standard deviation, minimum, lower quartile, median, upper quartile, and maximum. Categorical variables were to be summarized by using frequency counts and percentages.

Summary of results and conclusions

This study was terminated prematurely due to safety reasons and only 1 patient (sentinel patient) in Cohort 1 of the SAD phase was treated. Therefore, no statistical analysis was performed for this study. Study data collected during this study are presented below.

Subject disposition

2 patients were screened and 1 patient (sentinel patient) received 200 mg PPSGG. The sentinel patient completed the SAD phase of the study and agreed to provide a blood sample for additional laboratory tests on 26 JUN 2021.

Demography and baseline characteristics

Demography and baseline characteristics of the only treated patient in the study (sentinel patient) are provided in the safety results section below.

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Safety results

The study was stopped due to the safety signals detected in the sentinel patient. A narrative for this patient is provided below:

The sentinel patient was a 70-year old white female who was diagnosed with anti-MAG neuropathy and demyelinating neuropathy approximately 8 months before the study drug administration. Relevant medical and surgical history included hysterectomy, corneal transplant for Fuchs disease and intermittent insomnia. Prior and concomitant medications included gabapentin to treat neuropathic pain and zopiclone to treat intermittent insomnia. On Day 1, the patient was administered PPSGG as a single 60-minute IV infusion at a dose of 200 mg. Two minutes after the start of the infusion, the patient experienced a Grade 3 infusion related reaction which was considered serious for being a medically significant event and the dose of the study drug was stopped. The patient felt a bitter taste in the mouth, facial erythrosis, a warmth feeling throughout the body with a feeling of losing consciousness but did not experience hypotension, bronchospasm, loss of consciousness, desaturation, or digestive disorder. In addition, it was confirmed that there was an increase in heart rate and Grade 1 increase of systolic blood pressure (from 140 mmHg to154 mmHg) at the start of the infusion. Corrective measures to treat the infusion related reaction included elevation of lower limbs, oxygen therapy of 15 L/min as needed, and IV dexchlorpheniramine 5 mg. Routine laboratory analyses reported no changes in hematology and clinical chemistry compared to baseline. The event was considered related to the study drug and resolved the same day.

Further laboratory analyses revealed that, at one hour post PPSGG infusion, the patient had significant increases in complement activation product C5b9 (133.9 ng/mL to 827.8 ng/mL), in MIP-1 (34.3 pg/mL to 250.7 pg/mL), MCP-1 (301.7 pg/mL to 478.9 pg/mL), IL-8 (23.2 pg/mL to 239.2 pg/mL), and TNF-α (1.1 pg/mL to 18.7 pg/mL) (Appendix 5.1.3). The Sponsor concluded that the complement activation was likely a classical pathway subsequent to immune complex formation, thus resulting in this adverse event being assessed as serious, related to study drug, and unexpected.

Per protocol, in case of an infusion related reaction and as part of the PD sample, anti-MAG and anti-HNK-1 antibodies should be taken. Results revealed that anti-MAG antibodies and anti-HNK-1 antibodies (Appendix 5.1.4) remained during the day of the infusion within the same levels when compared to the baseline levels. However,

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thereafter, anti-HNK1 immunoglobulin G (IgG) antibodies (Appendix 5.1.4) increased after Visit 4 and remained high up to the last laboratory assessment (26 JUN 2021).

Pharmacokinetic results

The following qualitative results were obtained for the sentinel patient (Appendix 5.1.5):

- PPSGG detected in samples 30 minutes, 1 hour (both taken at the same time – one hour post infusion start) and 2 hours
- No PPSGG detected in samples 6 hours and 8 hours

Pharmacodynamic results

The following results were obtained for the sentinel patient (Appendix 5.1.4):

Study Visit/Day	Timepoint	Anti-MAG (BTU)	Anti-HNK1 (% Cal)	Anti-HNK1 IgG (% Cal)
Visit 2	-	42367	130	84.1160221
Visit 3/Day 1	30 min after infusion	40503	142	91.77954227
Visit 3/Day 1	1 h after infusion	43222	141	84.77347034
Visit 3/Day 1	2 h after infusion	40799	134	68.61878453
Visit 3/Day 1	8 h after infusion	42076	133	-
Visit 3/Day 2	-	39819	142	66.87845304
Visit 4/Day 4	-	42700	149	99.06586
Visit 5/Day 8	-	44971	133	111.2564
Visit 6/Day 14	-	-	-	174.8618785
Visit 7/Day 28	-	-	-	154.9723757
26 JUN 2021*	-	-	-	188.6299

*6-month follow-up outside the study plan

Efficacy results

Efficacy was not assessed.

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Discussion

This first-in-human, Phase 1/2a, multicenter study was intended to be conducted with the primary objective to assess the safety and tolerability of PPSGG after single and multiple IV administrations in patients suffering from anti-MAG neuropathy.

The single rising dose escalation phase planned to enroll 6 patients in each of 4 or 5 ascending dose cohorts. The first administration of PPSGG in any cohort was provided to a single patient (sentinel patient). The decision to continue dosing the remaining patients in a given cohort was to be based on all available safety data collected during the first 72 hours after treatment of the sentinel patient.

The administration of IV PPSGG at 200 mg dose (Cohort 1) showed that the sentinel patient experienced a serious and unexpected infusion related reaction which led to study drug withdrawal 2 minutes after the start of the infusion. Further investigations on the complement activation product C5b9 as well as MIP-1 and MCP-1, IL-8, TNF-α, and IgG revealed a significant activation of complement and subsequent cytokine induction which led the Sponsor to discontinue the study. In addition, the PPSGG clinical development program was discontinued due to the inability to identify a safe dose in animal studies.

Conclusions

- The safety findings (infusion related reaction) and subsequent investigations performed on the Cohort 1 (PPSGG 200 mg) sentinel patient precluded further continuation of the PPSGG clinical trial, and the PPSGG clinical development program was discontinued due to the inability to identify a safe dose in animal studies.

Date and version of this report

Regulatory Review Final version 1.0, 03 FEB 2022

4 REFERENCE LIST

Benedetti L, Briani C, Franciotta D, et al. Long-term effect of rituximab in anti-MAG polyneuropathy. Neurology 2008, 71(21): 1742-1744.

Braun PE, Frail DE, Latov N. Myelin-associated glycoprotein is the antigen for a monoclonal IgM in polyneuropathy. J. Neurochem. 1982; 39(5): 1261-1265.

Dalakas MC. Pathogenesis and Treatment of Anti-MAG Neuropathy. Curr. Treat. Options.Neurol. 2010, 12(2):71-83.

Dalakas MC. Advances in the diagnosis, immunopathogenesis and therapies of IgM Anti-MAG antibody-mediated neuropathies. Ther. Adv. Neurol. Disord. 2018, 11:1756285617746640.

Join Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of paraproteinemic demyelinating neuropathies. Report of a Joint Task Force of the European Federation of Neurological Societies and the Peripheral Nerve Society – first revision. J. Peripher. Nerv. Syst. JPNS 2010; 15(3):185-195

Latov N, Braun PE, Gross RB, et al. Plasma cell dyscrasia and peripheral neuropathy: identification of the myelin antigens that react with human paraproteins. Proc. Natl. Acad. Sci. U.S.A. 1981, 78(11): 7139-7142.

Lunn MP, Nobile-Orazio E. Immunotherapy for IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies. Cochrane Database Sys. Rev. 2016, 10:CD02827.

Nobile-Orazio E, Baldini L, Barbieri S, et al. Treatment of patients with neuropathy and anti-MAG IgM M-prorteins. Ann. Neurol. 1988, 24(1): 93-97.

Pestronk A, Florence J, Miller T, et al. Treatment of IgM antibody associated polyneuropathies using rituximab. J Neurol. Neurosurg. Psychiatry 2003, 74(4): 485-489.

Rison RA, Beydoun SR. Paraproteinemic neuropathy: a practical review. BMC Neurol. 2016, 16:13.

Steck AJ, Stalder AK, Renaud S. Anti-myelin associated glycoprotein neuropathy. Curr. Opin. Neurol. 2006, 19(5): 458-463.

5 APPENDICES

5.1 STUDY INFORMATION

5.1.1 Protocol and Protocol Amendments

PN1007-001 CSP v1.0 04 MAR 2020

PN1007-001 CSP Amendment v1.1 07 APR 2020

PN1007-001 CSP Amendment v1.2 16 APR 2020

PN1007-001 CSP v2.0 08 JUL 2020

CLINICAL STUDY PROTOCOL SYNOPSIS

Study title	First in Human study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy of PPSGG (PN-1007) in anti-MAG neuropathy patients.
Investigational Medicinal Product	PPSGG (PN-1007).
Study Number	PN-1007-001.
EudraCT number	2020-000067-23.
Study phase	Phase I/IIa
Version and Date of protocol	Version 1.0, 04 March 2020.
Sponsor	Polyneuron Pharmaceuticals AG Hochbergerstrasse 60C CH-4057 Basel, Switzerland.
Coordinating Investigator	Emilien Delmont, MD.

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Synopsis

Study Number and Title	First in Human study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy of PPSGG (PN-1007) in anti-MAG neuropathy patients.
Study Phase	Phase I/IIa
Study Duration	Overall planned study duration is Q2 2020 – Q2 2022. Up to 2 months and 8 visits per patient in the single ascending dose (SAD) phase and up to 6 months and 17 visits per patient in the multiple ascending dose (MAD) phase.
Indication	Anti-myelin-associated glycoprotein (MAG) neuropathy.
Rationale for the study	This is a Phase I/IIa, First in Human (FiH), multicenter, single and multiple ascending dose escalation trial of PPSGG, an antibody scavenger of pathogenic anti-MAG immunoglobulin M (IgM) autoantibodies for treatment of anti-MAG neuropathy. The aim of the study is to assess the safety and tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of PPSGG in a SAD and a MAD study in anti-MAG neuropathy patients. The safety and tolerability of PPSGG has been demonstrated in different animal species, for up to 11 single doses given over 15 min IV infusion. Currently, there is no treatment for anti-MAG neuropathy approved by the European Medicines Agency (EMA) or by the US Food and Drug Administration (FDA). However, off-label treatments are used for treatment of anti-MAG neuropathy, including various immunomodulatory and immunosuppressive treatments used to manage anti-MAG neuropathy. Nonetheless, these treatments are of limited efficacy and may induce side effects. Clinical improvement of neuropathic symptoms in patients with anti-MAG neuropathy correlates with reduced serum levels of anti-MAG IgM autoantibodies and disease worsening is associated with increasing anti-MAG IgM levels during treatment follow-up. Knowledge of the biological role of the MAG protein, the inhibitory activity of PPSGG on anti-MAG IgM antibodies, and the clinical correlation between anti-MAG IgM levels and clinical outcomes support the hypothesis that a reduction in anti-MAG IgM levels by PPSGG can be associated with clinical improvements for patients. During the SAD phase, PPSGG will be administered via intravenous (IV) infusion to patients with confirmed anti-MAG neuropathy. Based on the safety and PK/PD data of the SAD

phase, PPSGG will be administered up to 11 times during the MAD phase of this study for a maximum of 6 weeks.

Objectives

Primary objective

To assess the safety and tolerability after single and multiple intravenous administrations of PPSGG in patients suffering from anti-MAG neuropathy.

Secondary objectives

- To evaluate the PK of PPSGG after single and multiple intravenous administrations.
- To investigate PD of PPSGG in reducing anti-MAG IgM levels.
- To obtain preliminary efficacy data, neurological evaluations and clinical outcome using different clinical scores.

Study design

Phase Description

Phase I: FiH, open label, SAD escalation study in anti-MAG neuropathy patients to assess the safety, tolerability, PK and PD parameters of PPSGG.

After completion and evaluation of the SAD phase a MAD phase will follow.

Phase IIa: Randomized, dose escalation, double blind (patient and investigator blinded), placebo-controlled MAD in anti-MAG neuropathy patients to assess the safety, immunogenicity, tolerability, PK, PD and preliminary efficacy parameters of PPSGG.

- Single Ascending Dose (SAD)

The single rising dose escalation phase will enroll 6 patients in each of the 4 or 5 ascending dose cohorts. The first administration of PPSGG of any cohort will be provided to a single patient (sentinel patient). The decision to complete a given cohort will be based on safety data up to 72 hours after treatment of the sentinel patient. The decision to escalate to the following dose (once completed a cohort) will be based on safety data, collected during the first 72 hours after the start of the infusion, where no stopping rules are met and analyzed by an Independent Data Monitoring Committee (IDMC). The study drug will be administered as a 60 min IV infusion.

In the SAD phase each patient will have the following 8 visits: Screening, Baseline, Treatment (4 visits), end of study (EOS) and Follow-up.

- Multiple Ascending Dose (MAD)

The multiple rising dose phase will enroll 2 dose cohorts of at least 12 patients each (10 on active and 2 on placebo). Dose levels will be determined based on the safety, tolerability, PK and PK/PD outcome (anti-MAG IgM titers) from the SAD phase. The dosing frequency will be defined based on the PK/PD relationship established during the SAD phase (PPSGG half-life, anti-MAG IgM kinetic) and simulation of it. The study drug will be administered for up to 11 times (as a 60 min IV infusion) for six weeks to explore the effect on anti-MAG antibody levels. For safety purposes the first 2 patients in each cohort of the MAD phase will be randomized to receive active or placebo treatment in a double-blind fashion. The decision to complete a given cohort will be based on safety data of the first 2 patients collected during 2 weeks after the start of the infusion. The decision to escalate to the following dose will be based on safety data collected during the first 2 weeks after the start of infusion and analyzed by an IDMC.

In the MAD phase each patient will have up to 17 visits: Screening, Baseline, Treatment (up to 14 visits), EOS and Follow-up.

The MAD phase will be adapted for dosing regimen in accordance with PK, PD, safety and tolerability data collected during the SAD phase. Dosing regimen includes the dose level administered, the frequency of dosing and the duration of dosing, i.e. the number of doses administered. The maximum starting dose in the MAD phase will be one of the tested doses in the SAD phase. Based on the safety toxicology studies performed in animals the maximum number of dosing is 11 infusions for 6 weeks. The goal is to define a potential dose and regime to reliably and safely reduce anti-MAG IgM antibody levels by at least 50%.

The following assessments will be performed in each of the two phases (SAD and MAD):

- Safety and tolerability (adverse events [AEs], vital signs, laboratory data, electrocardiograms [ECGs], and local tolerability assessment).
- Blood sampling for anti-drug antibodies (ADA) development (immunogenicity).
- Blood sampling for PPSGG pharmacokinetics.
- Blood sampling for pharmacodynamic (anti-MAG antibodies levels and titers, paraprotein level, anti-human natural killer- 1 [anti-HNK1] antibodies and total IgM) markers.
- Clinical assessments based on overall neuropathy limitations scale [ONLS] score, time to walk 10 meters, and

	Rasch-built overall disability scale [RODS] and Ataxia scores. The SAD and MAD phases will be split in two parts: (1) an active treatment part of one infusion in SAD and multiple administrations in the MAD and (2) and an observation period of 1 month in SAD and 3 months in the MAD phase, respectively. After this, patients whose antibody levels have not returned to baseline will enter in the follow-up phase, the duration of which will depend on the evolution of the anti-MAG IgM antibody levels.
Number of patients	Approximately 48 patients will participate. Six patients per cohort (4 or more cohorts) in Phase I (SAD) and 12 patients (10 active and 2 placebo) per cohort (total 2 cohorts) in Phase IIa (MAD) respectively. In order to have enough evaluable patients, up to 2 additional patients per cohort will be recruited.
Sites	Approximately 8 sites from 5 European countries are planned to participate.
Inclusion criteria	• Written informed consent. • Age between 18 and 80 years, male and female. • Patient with a confirmed diagnosis of monoclonal IgM associated with monoclonal gammopathy of undetermined significance (MGUS) with anti-MAG activity (titer of > 10'000 Bühlmann Titer units [BTU]) and demyelinating neuropathy defined by electrophysiological criteria according to European Federation of Neurological Societies/Peripheral Nervous System paraproteinemic demyelinating neuropathy (EFNS/PNS PDN) guideline, 2010. • Clear clinical signs of disability: with at least ONLS ≥ 2 in lower extremities. • Inflammatory Neuropathy Cause and Treatment sensory sum score (INCAT) ≥ 2. • Patients must have adequate hepatic function as evidenced by total bilirubin < 1.5 mg/dL, and alkaline phosphatase and aspartate transaminase/alanine aminotransferase < 2X the upper limit of normal (ULN). • Absence of cause of neuropathy independent from anti- MAG activity: e.g. diabetes, hypothyroidism, past or current dependence on alcohol, past or current treatment with neurotoxic drug. • Patients must have adequate renal function as evidenced by serum creatinine <2 mg/dL or calculated creatinine clearance of ≥30 mL/min within 28 days before the first

investigational medicinal product (IMP) administration using the Modification of Diet in Renal Disease (MDRD) formula.

- Capability to meet the requirements of the study.

Exclusion criteria

- Patients with total serum IgM levels >30 g.
- Hematological malignancy (e.g. known multiple myeloma or confirmed Waldenström's macroglobulinemia based on bone marrow analysis).
- Patients with any history of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
- Previous immunosuppressive treatment with intravenous immunoglobulin (IVIG) for less than 3 months, and cyclophosphamide and biologicals (e.g. rituximab): less than 6 months prior to enrolment.
- Other neurological, neuromuscular, rheumatologic or orthopedic condition with significant impact on the capabilities of walk preventing evaluation of neurological scores.
- Anti-MAG neuropathy patients with persistent clinically significant laboratory abnormalities not related to the anti-MAG neuropathy, as significant renal dysfunction, hepatic dysfunction, cardiac disease or other significant neurological disorder.
- Anti-MAG neuropathy patients with a modified Rankin Scale (mRS) score > 4.
- Participation in another interventional clinical trial.
- Any other significant finding that would increase, according to the Investigator, the risk of having an adverse outcome from participating in the study.
- Any other medical condition, including mental illness or substance abuse deemed by the investigator(s) to likely interfere with the patient's ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results.
- Patients who have undergone major surgery ≤ 2 weeks prior to starting study drug or who have not recovered from the side-effects of surgery.
- A history of clinically significant ECG abnormalities, or any of the following ECG abnormalities at screening:
    - PR > 200 msec.

- QRS complex > 120 msec.
- QTcF > 450 msec (males).
- QTcF > 460 msec (females).
- History of familial long QT syndrome or known family history of Torsades de Pointes.
- Use of agents known to prolong the QT interval unless they can be permanently discontinued for the duration of the study.

- Sexually active males must use a condom during intercourse after the start of the IMP administration and for at least 3 days after stopping study medication and should not father a child in this period after completion of the study medication (SAD and MAD phases). A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. In addition, male participants should not donate sperm for the time period specified above.
- Use of other investigational drugs at the time of enrolment, or within 5 half-lives of enrolment, or within 30 days, whichever is longer; or longer if required by local regulations.
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 1 week after discontinuation of the investigational drug. Highly effective contraception methods include:
  - Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
  - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking the investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
  - Male sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
  - Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or

placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure <1%), for example hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking the investigational drug. If local regulations deviate from the contraception methods listed above and require more extensive measures to prevent pregnancy, local regulations apply and will be described in the informed consent form (ICF).

Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking the investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment then she considered not of childbearing potential.

Investigational Medicinal Product IMP	**Formulation**	Liquid formulation 10 mg/mL for IV administration.
	Name	Test product: PPSGG: Poly phenyl (disodium 3-O-sulfo-beta-D-glucopyranuronate)-(1-3)-beta-D-galactopyranoside. Reference product: Placebo (phosphate buffered saline (PBS)).
	Route	IV infusion over 60 minutes.
	Dose	SAD phase: Single IV administration of 200, 400, 800 mg and 1600 mg per patient in 4 cohorts. A higher dose (3200 mg) may be administered. MAD phase: Multiple intravenous doses for 6 weeks (up to 11 administrations) of PPSGG over 2 dose levels (dose level and frequency determined from SAD results).

Safety endpoints

The following parameters will be monitored throughout the study or as specified:

- Frequency, duration, severity and outcome of AEs, treatment emergent AEs (TEAEs), and Serious AEs (SAEs) from time of informed consent signature to the EOS visit including follow-up as required.

- Any concomitant medications and relevant non-drug therapies.
- Signs and symptoms of infusion-related reactions on infusion days continuously during the infusion of the study drug until 1 hour after the end of infusion, and at 8 and 24 hours after the start of administration.
- Physical examination from screening, baseline, on infusion days (before dosing with the IMP), Day 4 and 8 during SAD and EOS visit and during MAD once a month and at the EOS visit.
- Vital signs with the 12-lead ECG at screening, on infusion days predose, during the infusion of the IMP at 60 min and then at 2 hours and 8 hours after start of infusion and EOS visit.
- 1-lead ECG on infusion days continuously during the infusion of the IMP until 2 hours after start of infusion.
- Safety hematology, clinical chemistry and urinalysis at screening, baseline, on days at the site on Day 8, 28 and EOS visits during the SAD and on and on Day 8, 28, 42, 98 and EOS during the MAD.

Pharmacokinetic endpoint	**Timing of sampling**	PPSGG's PK will be determined in serum during baseline (Day -1), on infusion Day 1 (at 5 min, 30 min, 60 min, 2h, 6h, and 8h after start of administration), and on Day 2, 4, 8 and 14 of the SAD phase. In the MAD phase just before first infusion on infusion Day 1 (at 5 min, 30 min, 60 min, at 2h, 6h, and 8h after start of administration) then trough levels before each infusion and at 5 min, 30 min, 60 min, 2h, 6h, and 8h after start of administration) on each infusion day (Day 1 to 5, Day 8, 14, 21, 28, 35 and 42) and on Day 53, 70, 98 and EOS. The time points for PK sampling will be defined based on the PK data collected during SAD phase.
	Method	Enzyme-Linked Immunosorbent Assay (ELISA)/chromatography
Pharmacodynamic endpoints	**Timing of sampling**	PPSGG's PD biomarkers will be determined in serum during screening, baseline (Day -1), and on Days 2, 4, 8 and 14 and until anti-MAG titers reach pre-treatment levels or end of the study

		during the SAD phase and during MAD on the days of infusion.
	Methods	ELISA, capillary electrophoresis, chemistry immunoassay.

Efficacy endpoints

Clinical efficacy assessments will be performed at screening, and Day 14, and EOS during SAD and during MAD then every 8 weeks.

Clinical efficacy outcome for the SAD and MAD phases

- ONLS score.
- Time to walk 10 meters.
- RODS.
- Ataxia score.

Endpoints for the MAD phase only

All the above and then additionally every 8 weeks from Day 14 the following ones:

- INCAT sensibility score and modified INCAT.
- Motor Unit Number Index (MUNIX).
- Grip Strength.

Exploratory endpoints

Endpoints for the MAD phase only

- Neurofilament light chain (NfL) to measure the degree of axonal damage.
- B-cell activating factor (BAFF).
- Indirect immunofluorescence on sciatic nerves.
- Classical pathway of the complement.

Independent Data Monitoring Committee

An IDMC will review the safety data and will provide its recommendations to Polyneuron to escalate to the next higher dose cohort (Dose Escalation) in both SAD and MAD phases and to continue within a given cohort after the sentinel patient dosing (Dose continuation, MAD phase only).

Analyses populations

The two study phases SAD and MAD described in this protocol form an exploratory investigation without any formal statistical hypotheses. All results will be interpreted descriptively only from the following analyses sets:

Safety population (SP): All patients who receive at least one dose of study medication. The SP will be the primary analysis set for the safety and tolerability analyses.

Intent-to-treat (ITT) population: all patients who were enrolled. The ITT population will be used as analysis set to confirm the efficacy.

Per-protocol (PP) population: all patients, who meet the inclusion/exclusion criteria, received full-course of the study drug as per randomization during the MAD and have completed the main relevant visits (at least 1 visit, 1 week, and 1 month during the SAD phase after dosing is needed to assess biomarker and scores. During the MAD phase, at least 1 visit 1 month after the last dosing, for safety and efficacy assessments and who satisfactorily completed a PD blood sampling period without any major protocol violations which would render the data unreliable. The PP population will constitute the primary analysis set for the PD and PK, and efficacy analyses.

Pharmacokinetic (PK) population: all patients who satisfactorily completed a PK blood sampling period without any major protocol violations which would render the data unreliable.

Pharmacodynamic (PD) population: all patients who satisfactorily completed a PD blood sampling period without any major protocol violations which would render the data unreliable.

Statistical Method

Sample size

This is a FiH study of PPSGG which its primary objective is to assess its safety and tolerability. The total number of at least 24 evaluable planned patients per phase (SAD and MAD) to be included in this study is thought to be sufficient for an early assessment of the safety and tolerability of PPSGG. No previous PK nor PD data for single or multiple doses of PPSGG in patients are available.

Patients who withdraw for reasons other than safety can be substituted in agreement with Polyneuron.

Statistical analysis

Physical examination, ECG and vital signs (blood pressure assessments, pulse rate, body temperature), signs of infusion-related reactions, laboratory assessments and AEs, TEAEs and SAEs will be analyzed. Signs of infusion-related reactions include clinical signs and symptoms, changes in diastolic or systolic blood pressure, heart rate, and skin reactions or local reactions at the infusion site. TEAEs will be summarized in frequency tables according to Preferred Term (PT) and System Organ Class (SOC). TEAEs will also be summarized according to their severity and causality regarding the IMP. When a TEAE occurs more than once in the same patient, maximal severity and strongest causality will be counted. All SAEs and TEAEs leading to premature withdrawal from the study will be listed. Laboratory variables will be examined using mean changes from baseline. Laboratory values will also be categorized according to the updated Common Terminology Criteria for Adverse Events (CTCAE) toxicity grade version and tabulated by their highest

on-study toxicity grade. Shift tables will present numbers and percentages of patients with high / normal / low (or normal/abnormal) laboratory results at baseline and last measurement available. Non-TEAEs will be listed only. Use of concomitant medications will be summarized.

Descriptive statistics will be provided for the PK parameters and scatter plots may be used to investigate PK/PD or efficacy relationships. Statistical general linear model procedures and regression analysis will be applied for the analysis of the PK and PD parameters when applicable.

Descriptive statistics will also be used for the PD assessments.

Efficacy analysis

The efficacy analysis will be performed separately for the SAD and MAD phase. In the SAD phase changes in the following parameters will be assessed on Day 14, 28 and at EOS visit:

- Clinical scores.
- PK/PD.
- Evolution of anti-MAG antibodies (time to reach the lowest level after starting IMP treatment and time to achieve baseline values).

The MAD phase, in addition to all the above, will also include clinical and score assessments every 8 weeks until the EOS visit.

Statistical methods

Descriptive statistics (n, mean, standard deviation [SD], median and ranges for continuous variables, frequencies and percentages for categorical variables) will be provided by treatment group and/or visit, if applicable. All data will be listed by patient, treatment group and, where applicable, visit. Data from all placebo treated patients in MAD will be pooled for comparison with active cohorts. Further technical details will be described in the Statistical Analysis Plan (SAP).

CLINICAL STUDY PROTOCOL

Study title	First in Human study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy of PPSGG (PN-1007) in anti-MAG neuropathy patients.
Investigational Medicinal Product	PPSGG (PN-1007).
Study Number	PN-1007-001.
EudraCT number	2020-000067-23.
Study phase	Phase I/IIa.
Version and Date of protocol	Version 1.1 (including Amendment 1), 07 April 2020.
Sponsor	Polyneuron Pharmaceuticals AG Hochbergerstrasse 60C CH-4057 Basel, Switzerland.
Coordinating Investigator	Emilien Delmont, MD.

This document is the sole property of Polyneuron Pharmaceuticals AG and all information contained herein has to be considered and treated as strictly confidential. This document shall be used only for the purpose of the disclosure herein provided. No disclosure or publication shall be made without the prior written consent of Polyneuron Pharmaceuticals AG.

SPONSOR SIGNATURE PAGE

Protocol Title: First in Human study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy of PPSGG (PN-1007) in anti-MAG neuropathy patients.

Protocol Number: PN-1007-001.

Sponsor: Polyneuron Pharmaceuticals AG.

I approve the contents of this clinical protocol for Study No. PN-1007-001 version 1.1 (including Amendment 1), dated 07 April 2020 and agree to meet all obligations of Polyneuron Pharmaceuticals as detailed in all applicable regulations and guidelines. In addition, I will inform the Coordinating Investigator and all other investigators of all relevant information that becomes available during the conduct of this study.

Sponsor Signatory:

Debra Barker, MD
CMO, Polyneuron Pharmaceuticals AG
Hochbergerstrasse 60C
CH-4057 Basel, Switzerland.

Debra S Barker
Signature

7 - 4 - 20
Date

Coordinating Investigator:

Emilien Delmont, MD
APHM Hopital La Timone Adultes
264 Rue Saint Pierre,
F- 13005 Marseille, France.

Signature

Date
07/04/2020

PROTOCOL INVESTIGATOR AGREEMENT

As Investigator of this study, I agree:

- To conduct the study in compliance with this protocol, and with mutually agreed future protocol amendments, protocol administrative changes, other study conduct procedures and study conduct documents provided by Polyneuron Pharmaceuticals AG.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study (my Staff) are adequately informed about the investigational medicinal product and other study-related duties and functions as described in the protocol and have the necessary skill and competencies to manage them.
- To co-operate with the representative of Polyneuron Pharmaceutical AG's appointed Contract Research Organization (CRO) in the monitoring of the study and resolution of queries about the data.
- That I have been informed that the agency and Ethics Committee may require the sponsor to obtain and supply, as necessary, details about the Investigator's ownership interest in the sponsor or the investigational product, and more generally about the financial ties with the sponsor. Polyneuron Pharmaceuticals AG will use and disclose the information solely for the purpose of complying with regulatory requirements.
- To provide Polyneuron Pharmaceuticals AG or CRO with a current Curriculum Vitae and other documents required by the Ethics or authorities for this study.

Study title	First in Human Study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy of PPSGG in anti-MAG neuropathy patients.
EudraCT number	2020-000067-23.
Versions and Date of protocol	Version 1.1 (including Amendment 1), 07 April 2020.
Protocol code number	PN-1007-001.
Name and address of Investigator	

_____	_____
Signature	**Date**

Amendment 1 (07 April 2020)

Amendment rationale

The purpose of this substantial amendment is to address questions raised by ANSM. The changes are summarized below.

Changes to the protocol

The following changes have been implemented throughout the protocol:

1. Recent apheresis/plasmapheresis has been added as exclusion criterion in Section 4.3.
2. Additional pregnancy tests on a monthly basis (on Days 28, 56 and 98) in the MAD phase have been added. The Assessment schedule in Section 8.1. has been updated accordingly.
3. The limit for creatinine clearance at inclusion has been raised to 60 mL/min. The inclusion criterion in the protocol in Section 4.3. has been adapted accordingly.
4. The wording of the starting dose of MAD phase has been adapted. The dosing of both cohorts in the MAD phase will not exceed the exposures achieved in the SAD phase (Cmax and AUC0-tau), and will commence at a dose at least one dose level lower than safely completed in the SAD.
5. In Section 7.6 the study stopping rules have been adapted based on the feedback by Health Authorities.
6. A back-up system in support of IVRS in case of the necessity for the investigator to unblind study treatment during MAD part of the study in has been implemented and is described in Section 6.8.
7. The plan for rapid communication of serious adverse events and suspected unexpected serious adverse reactions (SUSARs) between the sponsor, the investigators of all sites and the patients has been described in Section 9.1.7.
8. A section “Reference safety information (RSI) has been added and is reflected in Section 9.1.8.
9. The synopsis is updated to reflect the above changes as appropriate.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes herein affect the Informed Consent/Assent.

Synopsis

Study Number and Title	First in Human study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy of PPSGG (PN-1007) in anti-MAG neuropathy patients.
Study Phase	Phase I/IIa.
Study Duration	Overall planned study duration is Q2 2020 – Q2 2022. Up to 2 months and 8 visits per patient in the single ascending dose (SAD) phase and up to 6 months and 17 visits per patient in the multiple ascending dose (MAD) phase.
Indication	Anti-myelin-associated glycoprotein (MAG) neuropathy.
Rationale for the study	This is a Phase I/IIa, First in Human (FiH), multicenter, single and multiple ascending dose escalation trial of PPSGG, an antibody scavenger of pathogenic anti-MAG immunoglobulin M (IgM) autoantibodies for treatment of anti-MAG neuropathy. The aim of the study is to assess the safety and tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of PPSGG in a SAD and a MAD study in anti-MAG neuropathy patients. The safety and tolerability of PPSGG has been demonstrated in different animal species, for up to 11 single doses given over 15 min IV infusion. Currently, there is no treatment for anti-MAG neuropathy approved by the European Medicines Agency (EMA) or by the US Food and Drug Administration (FDA). However, off-label treatments are used for treatment of anti-MAG neuropathy, including various immunomodulatory and immunosuppressive treatments used to manage anti-MAG neuropathy. Nonetheless, these treatments are of limited efficacy and may induce side effects. Clinical improvement of neuropathic symptoms in patients with anti-MAG neuropathy correlates with reduced serum levels of anti-MAG IgM autoantibodies and disease worsening is associated with increasing anti-MAG IgM levels during treatment follow-up. Knowledge of the biological role of the MAG protein, the inhibitory activity of PPSGG on anti-MAG IgM antibodies, and the clinical correlation between anti-MAG IgM levels and clinical outcomes support the hypothesis that a reduction in anti-MAG IgM levels by PPSGG can be associated with clinical improvements for patients. During the SAD phase, PPSGG will be administered via intravenous (IV) infusion to patients with confirmed anti-MAG neuropathy. Based on the safety and PK/PD data of the SAD phase, PPSGG will be administered up to 11 times during the MAD phase of this study for a maximum of 6 weeks.

Objectives	**Primary objective** To assess the safety and tolerability after single and multiple intravenous administrations of PPSGG in patients suffering from anti-MAG neuropathy. **Secondary objectives** • To evaluate the PK of PPSGG after single and multiple intravenous administrations. • To investigate PD of PPSGG in reducing anti-MAG IgM levels. • To obtain preliminary efficacy data, neurological evaluations and clinical outcome using different clinical scores.
Study design	
Phase Description	Phase I: FiH, open label, SAD escalation study in anti-MAG neuropathy patients to assess the safety, tolerability, PK and PD parameters of PPSGG. After completion and evaluation of the SAD phase a MAD phase will follow. Phase IIa: Randomized, dose escalation, double blind (patient and investigator blinded), placebo-controlled MAD in anti-MAG neuropathy patients to assess the safety, immunogenicity, tolerability, PK, PD and preliminary efficacy parameters of PPSGG. • Single Ascending Dose (SAD) The single rising dose escalation phase will enroll 6 patients in each of the 4 or 5 ascending dose cohorts. The first administration of PPSGG of any cohort will be provided to a single patient (sentinel patient). The decision to complete a given cohort will be based on safety data up to 72 hours after treatment of the sentinel patient. The decision to escalate to the following dose (once completed a cohort) will be based on safety data, collected during the first 72 hours after the start of the infusion, where no stopping rules are met and analyzed by an Independent Data Monitoring Committee (IDMC). The study drug will be administered as a 60 min (120 min for optional 3200 mg dose) IV infusion. In the SAD phase each patient will have the following 8 visits: Screening, Baseline, Treatment (4 visits), end of study (EOS) and Follow-up. • Multiple Ascending Dose (MAD) The multiple rising dose phase will enroll 2 dose cohorts of at least 12 patients each (10 on active and 2 on placebo). Dose levels will be determined based on the safety, tolerability, PK and PK/PD outcome (anti-MAG IgM titers) from the SAD phase.

The dosing of both cohorts in the MAD phase will not exceed the exposures achieved in the SAD phase (Cmax and AUC0-tau), and will commence at a dose at least one dose level lower than safely completed in the SAD. The dosing frequency will be defined based on the PK/PD relationship established during the SAD phase (PPSGG half-life, anti-MAG IgM kinetic) and simulation of it. The study drug will be administered for up to 11 times (as a 60 min (120 min for optional 3200 mg dose) IV infusion) for six weeks to explore the effect on anti-MAG antibody levels. For safety purposes the first 2 patients in each cohort of the MAD phase will be randomized to receive active or placebo treatment in a double-blind fashion. The decision to complete a given cohort will be based on safety data of the first 2 patients collected during 2 weeks after the start of the infusion. The decision to escalate to the following dose will be based on safety data collected during the first 2 weeks after the start of infusion and analyzed by an IDMC.

In the MAD phase each patient will have up to 17 visits: Screening, Baseline, Treatment (up to 14 visits), EOS and Follow-up.

The MAD phase will be adapted for dosing regimen in accordance with PK, PD, safety and tolerability data collected during the SAD phase. The dosing of both cohorts in the MAD phase will not exceed the exposures achieved in the SAD phase (Cmax and AUC0-tau), and will commence at a dose at least one dose level lower than safely completed in the SAD. Dosing regimen includes the dose level administered, the frequency of dosing and the duration of dosing, i.e. the number of doses administered. Based on the safety toxicology studies performed in animals the maximum number of doses is 11 infusions in 6 weeks. The goal is to define a potential dose and regime to reliably and safely reduce anti-MAG IgM antibody levels by at least 50%.

The following assessments will be performed in each of the two phases (SAD and MAD):

- Safety and tolerability (adverse events [AEs], vital signs, laboratory data, electrocardiograms [ECGs], and local tolerability assessment).
- Blood sampling for anti-drug antibodies (ADA) development (immunogenicity).
- Blood sampling for PPSGG pharmacokinetics.
- Blood sampling for pharmacodynamic (anti-MAG antibodies levels and titers, paraprotein level, anti-human natural killer- 1 [anti-HNK1] antibodies and total IgM) markers.
- Clinical assessments based on overall neuropathy limitations scale [ONLS] score, time to walk 10 meters, and

	Rasch-built overall disability scale [RODS] and Ataxia scores. The SAD and MAD phases will be split in two parts: (1) an active treatment part of one infusion in SAD and multiple administrations in the MAD and (2) and an observation period of 1 month in SAD and 3 months in the MAD phase, respectively. After this, patients whose antibody levels have not returned to baseline will enter in the follow-up phase, the duration of which will depend on the evolution of the anti-MAG IgM antibody levels.
Number of patients	Approximately 48 patients will participate. Six patients per cohort (4 or more cohorts) in Phase I (SAD) and 12 patients (10 active and 2 placebo) per cohort (total 2 cohorts) in Phase IIa (MAD) respectively. In order to have enough evaluable patients, up to 2 additional patients per cohort will be recruited.
Sites	Approximately 8 sites from 5 European countries are planned to participate.
Inclusion criteria	• Written informed consent. • Age between 18 and 80 years, male and female. • Patient with a confirmed diagnosis of monoclonal IgM associated with monoclonal gammopathy of undetermined significance (MGUS) with anti-MAG activity (titer of > 10’000 Bühlmann Titer units [BTU]) and demyelinating neuropathy defined by electrophysiological criteria according to European Federation of Neurological Societies/Peripheral Nervous System paraproteinemic demyelinating neuropathy (EFNS/PNS PDN) guideline, 2010. • Clear clinical signs of disability: with at least ONLS ≥ 2 in lower extremities. • Inflammatory Neuropathy Cause and Treatment sensory sum score (INCAT) ≥ 2. • Patients must have adequate hepatic function as evidenced by total bilirubin < 1.5 mg/dL, and alkaline phosphatase and aspartate transaminase/alanine aminotransferase < 2X the upper limit of normal (ULN). • Absence of cause of neuropathy independent from anti- MAG activity: e.g. diabetes, hypothyroidism, past or current dependence on alcohol, past or current treatment with neurotoxic drugs. • Patients must have adequate renal function as evidenced by serum creatinine <2 mg/dL or calculated creatinine clearance of ≥60 mL/min within 28 days before the first investigational medicinal product (IMP) administration using the Modification of Diet in Renal Disease (MDRD) formula.

- Capability to meet the requirements of the study.

Exclusion criteria

- Patients with total serum IgM levels >30 g.
- Hematological malignancy (e.g. known multiple myeloma or confirmed Waldenström's macroglobulinemia based on bone marrow analysis).
- Patients with any history of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
- Previous immunosuppressive treatment with intravenous immunoglobulin (IVIG) or apheresis/plasmapheresis in the preceeding 3 months, and cyclophosphamide and biologicals (e.g. rituximab): in the preceeding 6 months prior to enrolment.
- Other neurological, neuromuscular, rheumatologic or orthopedic conditions with significant impact on the capability of walking preventing evaluation of neurological scores.
- Anti-MAG neuropathy patients with persistent clinically significant laboratory abnormalities not related to the anti-MAG neuropathy, such as significant renal dysfunction, hepatic dysfunction, cardiac disease or other significant neurological disorder.
- Anti-MAG neuropathy patients with a modified Rankin Scale (mRS) score > 4.
- Participation in another interventional clinical trial.
- Any other significant finding that would increase, according to the Investigator, the risk of having an adverse outcome from participating in the study.
- Any other medical condition, including mental illness or substance abuse deemed by the investigator(s) to likely interfere with the patient's ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results.
- Patients who have undergone major surgery ≤ 2 weeks prior to starting study drug or who have not recovered from the side-effects of surgery.
- A history of clinically significant ECG abnormalities, or any of the following ECG abnormalities at screening:
    - PR > 200 msec.
    - QRS complex > 120 msec.
    - QTcF > 450 msec (males).

- QTcF > 460 msec (females).
- History of familial long QT syndrome or known family history of Torsades de Pointes.
- Use of agents known to prolong the QT interval unless they can be permanently discontinued for the duration of the study.

- Sexually active males must use a condom during intercourse after the start of the IMP administration and for at least 3 days after stopping study medication and should not father a child in this period after completion of the study medication (SAD and MAD phases). A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. In addition, male participants should not donate sperm for the time period specified above.
- Use of other investigational drugs at the time of enrolment, or within 5 half-lives of enrolment, or within 30 days, whichever is longer; or longer if required by local regulations.
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 1 week after discontinuation of the investigational drug. Highly effective contraception methods include:
  - Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
  - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking the investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
  - Male sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
  - Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure <1%), for example

hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking the investigational drug. If local regulations deviate from the contraception methods listed above and require more extensive measures to prevent pregnancy, local regulations apply and will be described in the informed consent form (ICF).

Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking the investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment then she considered not of childbearing potential.

Investigational Medicinal Product IMP

Formulation Liquid formulation 10 mg/mL for IV administration.

Name Test product: PPSGG: Poly phenyl (disodium 3-O-sulfo-beta-D-glucopyranuronate)-(1-3)-beta-D-galactopyranoside.

Reference product: Placebo (phosphate buffered saline (PBS)).

Route IV infusion over 60 minutes (the potential dose of 3200 mg will require a 120 minutes infusion).

Dose SAD phase: Single IV administration of 200, 400, 800 mg and 1600 mg per patient in 4 cohorts. A higher dose (3200 mg) may be administered.

MAD phase: Multiple intravenous doses for 6 weeks (up to 11 administrations) of PPSGG over 2 dose levels (dose level and frequency determined from SAD results).The dosing of both cohorts in the MAD phase will not exceed the exposures achieved in the SAD phase (Cmax and AUC0-tau), and will commence at a dose at least one dose level lower than safely completed in the SAD.

Safety endpoints

The following parameters will be monitored throughout the study or as specified:

- Frequency, duration, severity and outcome of AEs, treatment emergent AEs (TEAEs), and Serious AEs (SAEs) from time

of informed consent signature to the EOS visit including follow-up as required.

- Any concomitant medications and relevant non-drug therapies.
- Signs and symptoms of infusion-related reactions on infusion days continuously during the infusion of the study drug until 1 hour after the end of infusion, and at 8 and 24 hours after the start of administration.
- Physical examination from screening, baseline, on infusion days (before dosing with the IMP), Day 4 and 8 during SAD and EOS visit and during MAD once a month and at the EOS visit.
- Vital signs with the 12-lead ECG at screening, on infusion days predose, during the infusion of the IMP at 60 min (120 min for optional 3200 mg dose) and then at 2 hours and 8 hours after start of infusion and EOS visit.
- 1-lead ECG on infusion days continuously during the infusion of the IMP until 2 hours after start of infusion.
- Safety hematology, clinical chemistry and urinalysis at screening, baseline, on days at the site on Day 8, 28 and EOS visits during the SAD and on and on Day 8, 28, 42, 98 and EOS during the MAD.

Pharmacokinetic endpoint	**Timing of sampling**	PPSGG's PK will be determined in serum during baseline (Day -1), on infusion Day 1 (at 5 min, 30 min, 60 min, 2h, 6h, and 8h after start of administration), and on Day 2, 4, 8 and 14 of the SAD phase. The sampling for the potential 3200 mg dose would be at 30 min, 60 min, 2h, 3h, 6h, 8h and 10h after start of administration on the infusion day. In the MAD phase just before first infusion on infusion Day 1 (at 5 min, 30 min, 60 min, at 2h, 6h, and 8h after start of administration) then trough levels before each infusion and at 5 min, 30 min, 60 min, 2h, 6h, and 8h after start of administration) on each infusion day (Day 1 to 5, Day 8, 14, 21, 28, 35 and 42) and on Day 53, 70, 98 and EOS. The time points for PK sampling for the MAD phase will be confirmed based on the PK data collected during SAD phase.
	Method	Enzyme-Linked Immunosorbent Assay (ELISA)/chromatography

Pharmacodynamic endpoints	**Timing of sampling**	PPSGG's PD biomarkers will be determined in serum during screening, baseline (Day -1), and on Days 2, 4, 8 and 14 and until anti-MAG titers reach pre-treatment levels or end of the study during the SAD phase and during MAD on the days of infusion.
	Methods	ELISA, capillary electrophoresis, chemistry immunoassay.

Efficacy endpoints

Clinical efficacy assessments will be performed at screening, and Day 14, and EOS during SAD and during MAD then every 8 weeks.

Clinical efficacy outcome for the SAD and MAD phases

- ONLS score.
- Time to walk 10 meters.
- RODS.
- Ataxia score.

Endpoints for the MAD phase only

All the above and then additionally every 8 weeks from Day 14 the following ones:

- INCAT sensibility score and modified INCAT.
- Motor Unit Number Index (MUNIX).
- Grip Strength.

Exploratory endpoints

Endpoints for the MAD phase only

- Neurofilament light chain (NfL) to measure the degree of axonal damage.
- B-cell activating factor (BAFF).
- Indirect immunofluorescence on sciatic nerves.
- Classical pathway of the complement.

Independent Data Monitoring Committee

An IDMC will review the safety data and will provide its recommendations to Polyneuron to escalate to the next higher dose cohort (Dose Escalation) in both SAD and MAD phases and to continue within a given cohort after the sentinel patient dosing (Dose continuation, MAD phase only).

Analyses populations

The two study phases SAD and MAD described in this protocol form an exploratory investigation without any formal statistical hypotheses. All results will be interpreted descriptively only from the following analyses sets:

Safety population (SP): All patients who receive at least one dose of study medication. The SP will be the primary analysis set for the safety and tolerability analyses.

Intent-to-treat (ITT) population: all patients who were enrolled. The ITT population will be used as analysis set to confirm the efficacy.

Per-protocol (PP) population: all patients, who meet the inclusion/exclusion criteria, received full-course of the study drug as per randomization during the MAD and have completed the main relevant visits (at least 1 visit, 1 week, and 1 month during the SAD phase after dosing is needed to assess biomarker and scores. During the MAD phase, at least 1 visit 1 month after the last dosing, for safety and efficacy assessments and who satisfactorily completed a PD blood sampling period without any major protocol violations which would render the data unreliable. The PP population will constitute the primary analysis set for the PD and PK, and efficacy analyses.

Pharmacokinetic (PK) population: all patients who satisfactorily completed a PK blood sampling period without any major protocol violations which would render the data unreliable.

Pharmacodynamic (PD) population: all patients who satisfactorily completed a PD blood sampling period without any major protocol violations which would render the data unreliable.

Statistical Method

Sample size

This is a FiH study of PPSGG which its primary objective is to assess its safety and tolerability. The total number of at least 24 evaluable planned patients per phase (SAD and MAD) to be included in this study is thought to be sufficient for an early assessment of the safety and tolerability of PPSGG. No previous PK nor PD data for single or multiple doses of PPSGG in patients are available.

Patients who withdraw for reasons other than safety can be substituted in agreement with Polyneuron.

Statistical analysis

Physical examination, ECG and vital signs (blood pressure assessments, pulse rate, body temperature), signs of infusion-related reactions, laboratory assessments and AEs, TEAEs and SAEs will be analyzed. Signs of infusion-related reactions include clinical signs and symptoms, changes in diastolic or systolic blood pressure, heart rate, and skin reactions or local reactions at the infusion site. TEAEs will be summarized in frequency tables according to Preferred Term (PT) and System Organ Class (SOC). TEAEs will also be summarized according to their severity and causality regarding the IMP. When a TEAE occurs more than once in the same patient, maximal severity and strongest causality will be counted. All SAEs and TEAEs leading to premature withdrawal from the study will be listed. Laboratory variables will be examined using mean changes from baseline. Laboratory values will also be categorized according to the

updated Common Terminology Criteria for Adverse Events (CTCAE) toxicity grade version and tabulated by their highest on-study toxicity grade. Shift tables will present numbers and percentages of patients with high / normal / low (or normal/abnormal) laboratory results at baseline and last measurement available. Non-TEAEs will be listed only. Use of concomitant medications will be summarized.

Descriptive statistics will be provided for the PK parameters and scatter plots may be used to investigate PK/PD or efficacy relationships. Statistical general linear model procedures and regression analysis will be applied for the analysis of the PK and PD parameters when applicable.

Descriptive statistics will also be used for the PD assessments.

Efficacy analysis

The efficacy analysis will be performed separately for the SAD and MAD phase. In the SAD phase changes in the following parameters will be assessed on Day 14, 28 and at EOS visit:

- Clinical scores.
- PK/PD.
- Evolution of anti-MAG antibodies (time to reach the lowest level after starting IMP treatment and time to achieve baseline values).

The MAD phase, in addition to all the above, will also include clinical and score assessments every 8 weeks until the EOS visit.

Statistical methods

Descriptive statistics (n, mean, standard deviation [SD], median and ranges for continuous variables, frequencies and percentages for categorical variables) will be provided by treatment group and/or visit, if applicable. All data will be listed by patient, treatment group and, where applicable, visit. Data from all placebo treated patients in MAD will be pooled for comparison with active cohorts. Further technical details will be described in the Statistical Analysis Plan (SAP).

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List of abbreviations

ADA	Anti-drug antibody
ADL	Activities of Daily Living
ADM	Abductor digiti minimi
AE	Adverse event
ALT	Alanine aminotransferase
Anti-HNK1	Anti-human natural killer-1
APB	Abductor pollicis brevis
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC0-t	The area under the concentration-time curve from time zero to time ‘t’
AUCinf	The AUC from time zero to infinity
BTU	Bühlmann Titer Units
BUN	Blood urea nitrogen
BW	Body weight
CHMP	Committee for Medicinal Products for Human Use
CL	The total body clearance of drug from the serum
C_{max}	The maximum (peak) observed serum, blood, serum, or other body fluid drug concentration after single dose administration
CMAP	Compound muscle action potential
CNS	Central nervous system
CoA	Certificate of Analysis
CRO	Contract research organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DRF	Dose Range Finding
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form

EDC	Electronic data collection
EFNS/PNS PDN	European Federation of Neurological Societies/Peripheral Nervous system Paraproteinemic Demyelinating Neuropathy
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EENT	Eye, ears, nose and throat
EOS	End-of-study
EudraCT	European union drug regulating authorities Clinical Trials
FDA	Food and Drug Administration
FiH	First-in-Human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HgA1c	Hemoglobin A1c
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDL	High density lipoprotein
HED	Human equivalent dose
HIPPA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HNK-1	Human natural killer-1
IB	Investigators' Brochure
ICF	Informed consent form
ICH	International Council on Harmonization
ICMUC	Ideal case motor unit count
IDMC	Independent Data Monitoring Committee
IgE	Immunoglobulin E
IgM	Immunoglobulin M
IL	Interleukin

IMP	Investigational Medicinal Product
INCAT	Inflammatory Neuropathy Cause and Treatment Sensory Scale
INR	International normalized ratio
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRR	Infusion-related reaction
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous
IVIG	Intravenous immunoglobulin
IVRS	Interactive Voice Response System
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LLOQ	Lower limit of quantification
MABEL	Minimum anticipated biological effect level
MAD	Multiple Ascending Dose
MAG	Myelin-associated glycoprotein
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MFD	Maximum feasible dose
MGUS	Monoclonal gammopathy of undetermined significance
mRS	modified Rankin Scale
MRSD	Maximum recommended starting dose
MPS	Mononuclear Phagocyte System
MUNIX	Motor Unit Number Index
N	number
NfL	Neurofilament light chain
NOAEL	No Observed Adverse Effect Level
ONLS	Overall Neuropathy Limitations Scale
PBMC	Peripheral blood mononuclear cells

PBS	Phosphate buffered saline
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per protocol
PPSGG (PN-1007)	Poly (phenyl disodium 3-O-sulfo-ß-D-glucopyranuronate-(1→3)-ß-D-galactopyranoside)
PT	Preferred Term
PTE	Therapeutic plasma exchange
RBC	Red blood cell count
RODS	Rasch-built Overall Disability Scale
SAF	Safety population
SAD	Single Ascending Dose
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SC	Study Completion
SD	Standard deviation
SF-36	36-Item Short Form Survey
SGOT	Serum glutamic oxaloacetic transaminase (= AST)
SGPT	Serum glutamic pyruvic transaminase (= ALT)
SIP	Surface interference pattern
SM	Sphingomyelin
SOC	System Organ Class
SOP	Standard Operating Procedure
SP	Safety population
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Serum half-life
$T_{1/2}$	The elimination half-life associated with the terminal slope of a semi logarithmic concentration-time curve
TA	Tibilis anterior
TEAE	Treatment-emergent adverse event(s)
Tmax	The time to reach maximum (peak) serum, blood, serum, or other body fluid drug concentration after single dose administration

TNF	Tumor necrosis factor
TPE	Therapeutic Plasma Exchange
Vd	Volume of distribution
Vss	The apparent volume of distribution at steady state
WBC	White blood cell count
γ-GT	γ-Glutamyltransferase

1 Introduction

1.1 Background

Anti-myelin-associated glycoprotein (MAG) neuropathy is a demyelinating polyneuropathy associated with a monoclonal immunoglobulin M (IgM) gammopathy with anti-MAG activity. Patients with anti-MAG neuropathy suffer from sensorimotor deficits, sensory ataxia, paresthesias, muscle weakness, neuropathic pain, and tremor. Anti-MAG neuropathy is an autoimmune disease strongly associated with monoclonal IgM autoantibodies (anti-MAG IgM) with reactivity against MAG [1],[2],[3],[4]. Anti-MAG IgM deposits are found in the basal lamina of myelin-forming Schwann cells and paranodal loops, leading to the typical widening of myelin lamellae, demyelination, and eventually axonal damage. During the last few years, much progress has been made in understanding the pathophysiological mechanism of the disease [5],[6]. The prevalence of this rare disease is about 1 in 100,000 [7]. Anti-MAG neuropathy is an age-related disease and typically, the disease onset occurs after the age of 50 years. The disease is 2.7 times more frequent in men than in women [8].

Currently there is no treatment for anti-MAG neuropathy approved by the European Medicines Agency (EMA) or the US Food and Drug Administration (FDA). However, off-label treatments are used for treatment of anti-MAG neuropathy, which are discussed below. The primary objective of the treatment is to reduce the pathogenic anti-MAG autoantibody titers [9]. Therefore, various immunomodulatory and immunosuppressive treatments have been used to manage anti-MAG neuropathy. Nonetheless, these treatments are of limited efficacy and have potential side effects [10],[11].

Clinical improvement of neuropathic symptoms in patients with anti-MAG neuropathy correlates with reduced serum levels of anti-MAG IgM [9],[12],[3],[13] and disease worsening is associated with increasing anti-MAG IgM levels during treatment follow-up [13,14]. The therapeutic goal is a reduction in anti- MAG IgM (paraprotein) levels in the Bühlman test by at least 50% from baseline level [15].

1.2 Current Treatment Options for anti-MAG neuropathy

The pathogenic role of the monoclonal anti-MAG IgM paraprotein in anti-MAG neuropathy, based on clinical studies that show correlations between disease outcomes and anti-MAG IgM levels, is widely accepted [14],[16]. In addition, myelin damage of peripheral nerves is observed in experimental animals after the passive transfer of anti-MAG antibodies from patient sera [17]. Therefore, a novel antigen-specific therapeutic approach that allows the highly selective and efficient removal of the disease-causing antibodies without adverse immunosuppression, would bring a significant benefit in the treatment of this debilitating neuropathy. The most relevant data for the present study are summarized in the sections below. For detailed information, please refer to the Investigator's Brochure [18].

1.3 PPSGG (PN-1007)

The active substance is poly (phenyl disodium 3-O-sulfo-ß-D-glucopyranuronate)-(1→3)-ß-D-galactopyranoside and will be referred to as poly(phenyl sulfoglucuronate galactoside) (PPSGG) throughout the document. PPSGG is a glycopolymer consisting of two structural units coupled to a poly-L-lysine backbone, glycan and thioglycerol units.

PPSGG is a fully synthetic molecule obtained from (disodium 3-O-sulfo-ß-D-glucopyranuronate)-(1→3)-β-D-galactopyranoside that binds to a chloroacetylated poly-L-lysine hydrobromide backbone through a tyramine-based thiol-linker. Multiple copies of the active part of the molecule, phenyl (disodium 3-O-sulfo-ß-D-glucopyranuronate)-(1→3)-ß-D-galactopyranoside, are coupled to the chloroacetylated poly-L-lysine; the remaining

chloroacetylated poly-L-lysine polymers are coupled with thioglycerol, which promotes the solubility of the overall molecule. 25-45% of the poly-L-lysine backbone is coupled to glycan units, and 55-75% are coupled to thioglycerol units.

PPSGG is formulated as a liquid ready to use drug product for intravenous (IV) infusion.

PPSGG is intended to bind anti-MAG IgM autoantibodies, the underlying cause of anti-MAG neuropathy, in a highly selective manner, resulting in their neutralization and removal from the circulation. While the anti-MAG IgM autoantibodies do not cross the blood-brain barrier, they can cross the blood-nerve barrier to enter the peripheral nervous system. In contrast, based on tissue distribution studies and the physico-chemical properties of the glycopolymer [19, 20], PPSGG does not cross the blood-nerve barrier; therefore, binding of PPSGG to the anti-MAG IgM antibodies occurs in the blood. This allows specific targeting of anti-MAG IgM in the circulation and circumvents unspecific immunosuppression associated with current treatment strategies.

1.4 Nonclinical data

It has been demonstrated that PPSGG prevented the binding of patients' anti-MAG IgM autoantibodies to MAG at low nanomolar concentrations in a competitive enzyme-linked immunosorbent assay (ELISA) and selectively bound to anti-MAG IgM. PPSGG efficiently reduced the anti-MAG IgM antibody titers in an immunological mouse model for anti-MAG neuropathy at a dose range of 2- 10 mg/kg [19] and was able to efficiently inhibit the binding of patients' anti-MAG IgM to sciatic nerve myelin of non-human primates ex vivo within the same concentration range. In vitro experiments and in a dose titration study in mice, showed that the binding stoichiometry of PPSGG:anti-human natural killer-1 (anti-HNK-1) IgM is 1:1 to 1:2. Based on an estimated average patient population with 1-10 g/L of monoclonal anti-MAG IgM, doses of 120-1200 mg should remove most circulating autoantibodies [10, 21]. Moreover, no signs of large immune complex formation (in vitro) or immune complex related toxicity (in vivo) were observed.

PPSGG has a short half-life at pharmacological doses (approximately 20 to 30 min in 2 rodent and 1 non-rodents' species) with a low volume of distribution in rats and dogs, distributing only within the vascular system and is cleared through the mononuclear phagocyte system (MPS). PPSGG, once cleared by phagocytes, is most likely broken down in the liver to different natural components which may be recycled or eliminated: for instance, the poly-L-lysine backbone to shorter poly-L-lysine chains and then recycled in protein synthesis; the glycomimetic part is cleaved into monosaccharides and may enter the catabolic pathway or is excreted; and the thioglycerol part is expected to be eliminated by renal excretion or, similar to glycerol, by hepatic metabolism. In humans, clearance (CL), metabolism and distribution are expected to be similar to that observed in animal models since these pathways are highly conserved among mammalian species.

Exploratory non-GLP and repeat-dose GLP toxicology and safety studies did not identify a target organ of toxicity which is not unexpected given the low volume of distribution, rapid clearance and low systemic dosing from weekly administrations. Dose escalation was limited by infusion-related findings in the rat and dog (tremors, decreased activity, flushing). Clinically PPSGG was well tolerated in dogs with up to 200 mg/kg/dose (no-observed-adverse-effect level (NOAEL)) with intravenous (IV) infusion over 15 min administered intermittently over six weeks in GLP repeat dose toxicology studies. In rats, initial DRF studies demonstrated 400 mg/kg/dose infused over 15 min was not tolerated, with clinical signs consistent with a mast cell degranulation (of unknown mechanism). Repeat dose GLP toxicology studies with up to 150 mg/kg/dose with 15 min IV infusion administered intermittently over 6 weeks was

well tolerated without adverse findings (NOAEL). A subsequent exploratory non-GLP study examining the dose versus infusion rate relationship found that the clinical tolerability in rats was highly dependent on the time/length of infusion, with Cmax of PPSGG driving the observed clinical findings. In this study, no increase in histamine or tryptase levels were evident 1 h after infusion, and there was no binding of IgE to PPSGG. PPSGG does not affect neurological behaviour (Modified Irwin) or respiratory function in rats and has no clinically relevant effect on human cardiac channels up to the physiological limits of solubility for the molecule. PPSGG did not induce an innate immune response (cytokine release) in human peripheral blood mononuclear cells (PBMC) or induce the formation of anti-drug antibodies over repeat administration in rats.

Based on these results, the NOAEL was considered to be 200 mg/kg/dose for dogs and 150 mg/kg for rats, respectively.

The potential of PPSGG to interact with co-administered medication has not been assessed. No formal drug interaction studies have been conducted with PPSGG in humans.

No reproductive or developmental toxicity studies using PPSGG have been conducted to date.

1.5 Clinical data

1.5.1 Human safety and tolerability data

This is the first in human (FiH) study, therefore no clinical data are available yet.

1.6 Study rationale

This is a FiH Phase I/IIa multicenter, single ascending dose (SAD) and multiple ascending dose (MAD) study, to assess the safety and preliminary efficacy of PPSGG, an antibody scavenger of pathogenic anti-MAG IgM autoantibodies, for treatment of anti-MAG neuropathy. The safety and tolerability of PPSGG has been demonstrated in different animal species, for 6 weeks with 11 single doses via slow IV infusion over 15 min in rats and dogs during the non- clinical toxicology studies.

The design has been chosen as a classical Dose Escalation design as required in this type of trial with the starting dose calculated following the recommendations from the EMA Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products (September 2007) and FDA Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (July 2005) [22, 23].

The unique therapeutic approach of PPSGG is intended to bind to anti-MAG IgM autoantibodies in a highly selective manner, resulting in their neutralization and removal from the circulation. While the anti-MAG IgM autoantibodies do not pass the blood-brain barrier, they can pass the blood-nerve barrier to enter the peripheral nervous system. In contrast, based on tissue distribution study data and established physico-chemical properties of the glycopolymer [19, 20], PPSGG does not pass the blood-nerve barrier; therefore, binding of PPSGG to the anti-MAG IgM antibodies occurs in the blood. This allows specific targeting of anti-MAG IgM in the circulation, the underlying cause of the disease. This concept has been verified in vitro and in vivo. Currently, there is no treatment for anti-MAG neuropathy approved by the EMA or FDA. However, some medicinal products are used off-label for management of anti-MAG neuropathy; these products employ either an immunomodulatory or immunosuppressive approach to reduce the pathogenic anti- MAG autoantibody are summarized below.

- Immunomodulatory approaches include intravenous immunoglobulins (IVIG), therapeutic plasma exchange (TPE) and apheresis, and treatment with interferon alpha. However, none of the immunomodulatory treatments consistently demonstrated satisfactory short- and long-term efficacy in clinical studies.

- Immunosuppressive approaches include rituximab, corticosteroids and chemotherapeutic drugs, such as cladribine, fludarabine, cyclophosphamide and chlorambucil. These treatments cause a general immune suppression by lymphocyte depletion, which includes a reduction of disease-causing anti-MAG autoantibodies. However, immunosuppressive treatments have failed to demonstrate efficacy consistently in clinical trials and are associated with severe side effects, including anemia, neutropenia, thrombocytopenia, gastrointestinal distress, and opportunistic infections.

Since these alternative off-label treatment approaches are unspecific, their efficacy for treatment of anti-MAG neuropathy has not been convincingly demonstrated, and some of these treatments are associated with severe side effects. The unmet medical need remains and requires new approaches of treatment for the anti-MAG neuropathy.

1.7 Rationale for study design

Data from toxicological studies with PPSGG have shown a benign safety profile. The design of the SAD phase of this study (open label, single ascending dose) efficiently addresses the primary objective to assess the safety and tolerability of PPSGG and will also provide information on its pharmacokinetics (PK), and pharmacodynamics (PD); while very little can be expected in terms of efficacy (short term reduction of levels of anti-MAG antibodies, only, may be expected) with minimal clinical impact on the disease. Since these autoantibodies are only present in patients with anti-MAG neuropathy, but not in healthy humans, information obtained from a study in healthy subjects would be limited in respect to PK, PD, and any potential target related toxicities.

In the MAD phase, the study drug is compared in a double-blind design with placebo. Placebo is chosen to enable a proper efficacy assessment as well as safety evaluation of PPSGG in patients with anti-MAG neuropathy

Clinical endpoints including assessments of signs and symptoms on neurological scales will be included as secondary endpoints in the MAD cohorts. Given the potential for bias in such evaluations the placebo control is necessary to enable an unbiased evaluation of any potential early signs of efficacy in these cohorts.

An Independent Data Monitoring Committee (IDMC) will provide recommendations about stopping, modifying or continuing the study; the decision to continue and/or to escalate the dose of PPSGG will be based on the review of safety and tolerability results. Given the short half-life of PPSGG shown in preclinical studies and assuming a short half-life in humans, a 72-hour safety review in the SAD phase and a 2-week safety data review in the MAD phase for Dose Escalation are considered adequate.

1.8 Rationale for dose/regimen, route of administration and duration of treatment

The maximum recommended starting dose (MRSD) of the FiH trial of PPSGG was calculated following both the “FDA Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers” (July 2005) and the “EMA Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products” (September 2007) [22, 23]. Taking both guidelines into

account the NOAEL of PPSGG was determined in non-clinical toxicological studies. Based on the findings of these studies the surrogate NOAEL of PPSGG was established at 200 mg/kg in dogs and 150 mg/kg in rats. In a next step the human equivalent dose (HED) was calculated applying the allometric scaling factor of 1.8 for dogs and 6.2 for rats as outlined in Table 1. The planned starting dose is a flat dose of 200 mg, which corresponds to approximately 2.8 mg/kg body weight (BW) for a patient of 70 kg. Flat dosing is most appropriate for treatment as the target and route of elimination are largely independent of body weight. Hence the surrogate NOAEL determined in non-clinical safety studies translates to a maximum recommended starting dose of maximum 111.1 mg/kg BW, which leads to a safety factor of 39.7 without considering the safety factor of 10.

Table 1 Staring dose of PPSGG based on the NOAEL from non-clinical safety studies

Species tested	Determined surrogate NOAEL	Allometric scaling factor	Calculated HED human equivalent dose applying a safety factor of 10	Planned starting dose	Safety Factor
Dog	200 mg/kg	1.8	200 mg/kg / 1.8 / 10 = 11.11 mg/kg BW	2.8 mg/kg	39.7
Rat	150 mg/kg	6.2	150 mg/kg / 6.2 / 10 = 2.42 mg/kg BW	2.8 mg/kg	8.6

BW = Body weight; HED = Human equivalent dose; NOAEL + No-observed-adverse-effect-level

The planned PPSGG dose range and regimen of the proposed study covers the efficacious dose range demonstrated in the pre-clinical efficacy studies and offers a large safety margin according to the in vivo toxicology studies conducted in rat and dogs.

Despite the limitation regarding calculating the minimum anticipated biological effect level (MABEL) it is still possible to consider other PD effects when defining the clinical starting dose in humans (e.g. dose response curves of the in vivo efficacy model experiments).

To corroborate that the dose range of 2-10 mg/kg in the in vitro and in vivo PD studies would be sufficient to deplete circulating anti-MAG autoantibodies in anti-MAG neuropathy patients, a dose titration study, using passive immunization with a monoclonal anti-HNK1 IgM was performed. The IV injection of 5 µg PPSGG was sufficient to bind 89.43% (±1.33 standard deviation [SD]) of the 60 µg anti-MAG IgM and 10 µg PPSGG was sufficient to bind 93.28% (±0.50 SD) of the 120 µg anti-HNK1 IgM. Based on these findings, a dose of 80 mg PPSGG would be sufficient to bind and remove 1 g of anti-MAG IgM, whereas 40 mg of PPSGG, would be sufficient to bind and remove most of 1 g anti-MAG IgM autoantibodies in humans. Of note, since no antibody-signal was detected at later time points after the administration, the anti-HNK1 IgM antibodies have been eliminated and not only bound by the glycopolymer. In general, the paraprotein (anti-MAG IgM) levels in anti-MAG patients are in the range of 1–10 g/L, whereas in healthy subjects the total paraprotein level is between 2- 6 g/L [10, 21]. Based on the a range of 1-10 g/L of monoclonal anti-MAG IgM (3-30 g total paraprotein), 240 mg to 2400 mg of PPSGG are expected to be sufficient to completely remove the circulating anti-MAG IgM antibodies and doses of 120-1200 mg should remove most of the paraprotein load. Finally, based on an estimated population average of 4 g/L paraprotein, a dose of 1000 mg PPSGG is expected to lead to a complete response for the majority of anti- MAG neuropathy patients.

Beginning from the proposed starting dose for PPSGG, all subsequent doses that will be used during Dose Escalation will be calculated by applying an escalation factor of 2. The dose of 1600 mg per patient has been selected to achieve at least 2-fold the predicted exposure needed for efficacy based on relative reductions in titers of anti-MAG autoantibodies and would be anticipated to reduce by 50% the relative titers of patients with very high pre-dose anti-MAG levels. An additional cohort of 3200 mg per patient may be included if the relative reductions in anti-MAG antibody titers do not reach the target of 50% relative reduction. Based on this consideration the dose groups of the FiH study of PPSGG are defined as outlined in Table 2.

Table 2 Foreseen Dose Escalation groups in the single ascending dose phase

Cohort 1	Cohort 2	Cohort 3	Cohort 4	Optional Cohort 5
200 mg	400 mg	800 mg	1600 mg	3200 mg

SAD: The design of the SAD phase of this study allows evaluation of the safety of the low dose of PPSGG (200 mg) before proceeding to the administration of higher doses. During each cohort of the SAD phase after treatment of the first patient (sentinel patient), Polyneuron and investigator will review the safety data from 72 hours after the starting dose before completing the given cohort. Dosing can only commence for the next cohort (Dose Escalation) after satisfactory review of the safety data from the proceeding cohort by the IDMC.

MAD: During each cohort of the MAD phase after treatment of the first 2 patients, the IDMC will review the safety data after 2 weeks of the starting dose before the rest of the given cohort will be dosed (cohort completion). Dosing can only commence for the next cohort (Dose Escalation) after satisfactory review of the safety data from the proceeding cohort by the IDMC.

1.9 Rationale for choice of comparator

As there is no approved therapy for anti-MAG neuropathy, and PPSGG is the first in class compound, patients will be randomized to receive either PPSGG or placebo in the MAD phase to reduce bias in safety and efficacy assessments

2 Objectives and endpoints

2.1 Primary objective(s)

Primary objective(s)	Endpoints related to primary objective(s)
To assess the safety and tolerability of PPSGG after single and multiple IV administrations in patients with anti- MAG neuropathy.	Assessment of safety based on vital signs, physical examination, electrocardiograms (ECGs), laboratory assessments, Signs of infusion-related reactions (IRRs), including clinical signs and symptoms, changes in diastolic or systolic blood pressure, heart rate, oxygen saturation, and skin reactions or local reactions at the infusion site and collection of adverse events (AEs) assessed from consent signature until the end of the study visit. Presence of Anti-drug antibodies will also be investigated.

2.2 Secondary objective(s)

Secondary objective(s)	Endpoints related to secondary objective(s)
To evaluate the PK of PPSGG after single and multiple IV administrations	Non-compartmental parameters related to PPSGG, including but not limited to T_{max}, C_{max}, as well as trough (pre-dose) levels after multiple dose
To investigate PD of PPSGG in reducing anti-MAG IgM levels	• Reduction of anti-MAG antibodies and time to reduction. • Time to anti-MAG IgM rebound (to pre-treatment Bühlmann Titer Units [BTU] levels). • Paraprotein levels (g/L). • Total IgM levels (g/L). • Anti-HNK1 IgM titers.
To investigate the preliminary efficacy of PPSGG	• Reduction of anti-MAG antibodies by ≥50% and time to reduction. • Change in the Overall Neuropathy Limitations scale (ONLS) score. • Time to walk 10 meters. • Rasch-built Overall Disability Scale (RODS). • Ataxia score. • INCAT sensory sum score. • Motor Unit Number Index (MUNIX). • Grip Strength.

2.3 Exploratory objective(s)

Exploratory objective(s)	Endpoints related to exploratory objective(s)
To assess the effect of PPSGG on other biomarkers of mode of action in serum	• Neurofilament light chain (NfL) to measure the degree of axonal damage. • B-cell activating factor (BAFF). • Indirect immunofluorescence on sciatic nerves. • Classical pathway of the complement.

3 Investigational plan

3.1 Study design

This protocol describes the planned conduct of a SAD phase and a MAD phase to be performed with PPSGG. These two phases will be conducted sequentially.

In each phase (SAD and MAD) the cohorts will be executed in a sequential order after the review of the safety data by an IDMC.

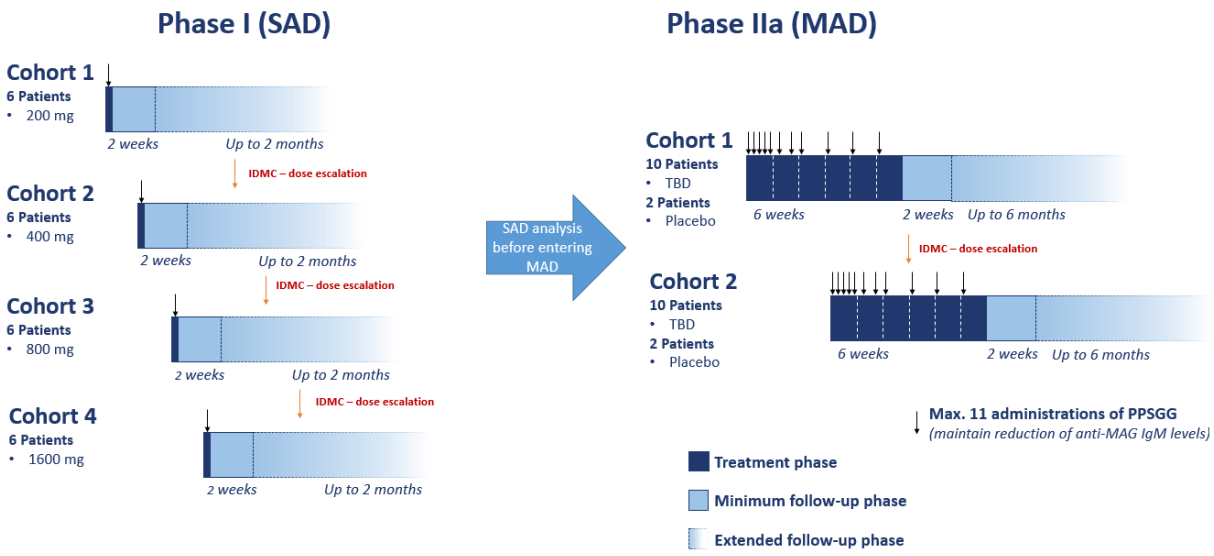
In the SAD phase each patient will have the following 8 visits: Screening, Baseline, Treatment (4 visits), end of study (EOS) and Follow-up.

In the MAD phase each patient will have up to 17 visits: Screening, Baseline, Treatment (up to 14 visits), EOS and Follow-up.

The MAD phase will be adapted for dosing regimen in accordance with PK, PD, safety and tolerability data collected during the SAD phase. The dosing of both cohorts in the MAD phase will not exceed the exposures achieved in the SAD phase (Cmax and AUC0-tau), and will commence at a dose at least one dose level lower than safely completed in the SAD. Dosing regimen includes the dose level administered, the frequency of dosing and the duration of dosing, i.e. the number of doses administered. Based on the safety toxicology studies performed in animals the maximum number of dosing is 11 infusions for 6 weeks. The goal is to define a potential dose and regime to reliably and safely reduce anti-MAG IgM antibody levels by at least 50%.

Patients to be screened must have a confirmed diagnosis of monoclonal IgM associated with monoclonal gammopathy of undetermined significance (MGUS) with anti-MAG activity (titer of > 10'000 BTU) and demyelinating neuropathy defined by electrophysiological criteria according to European Federation of Neurological Societies/Peripheral Nervous System Paraproteinemic Demyelinating Neuropathy (EFNS/PNS PDN) guideline, 2010. [24]

Patients fulfilling the inclusion and exclusion criteria will be sequentially assigned to a cohort starting with the lowest dose in the SAD phase. In the MAD phase the patient will be randomly assigned to active or placebo treatment in a given dose cohort. Please refer to the scheme below:



3.2 Design of the single ascending dose phase (Phase I)

The first phase, SAD, is a FiH, open label, single dose escalation study in anti-MAG neuropathy patients to establish safety, tolerability, PK, and PD parameters of PPSGG. The study will enroll 6 patients per cohort (4 or 5 cohorts), up to a maximal dose of 3200 mg. The first dose of any cohort will be provided to a single patient first (sentinel patient). The decision to complete a given dose cohort of the sentinel patient will be based on the safety data, collected during the first 72 hours after the start of the infusion and reviewed by Polyneuron and the investigator The study will be halted after the completion of each cohort (6 patients), for the evaluation of all safety- relevant data from these 6 patients, collected within the first 72 hours from the start of the investigational medicinal product (IMP) and additional data as available (with particular focus on events occurring immediately after the start of treatment) by an IDMC. The decision

to escalate to the following dose will be based on the safety data from these 6 patients provided no study stopping rules are met and the recommendations from the IDMC.

The study drug will be administered as a single 60 min (120 min for optional 3200 mg dose) IV infusion on Day 1 in the morning (between 7 AM and 10 AM). Patients will be hospitalized from the day before (Day -1), unless they live in the vicinity of the hospital and could be there early in the morning, until 24 hours after the start of the infusion.

The SAD phase will involve the following assessments after all inclusion and exclusion criteria have been checked during the screening and baseline visits (see Section 8.2 Schedule of Assessments):

- Vital signs.
- Blood and urine sampling for clinical safety laboratory.
- Blood sampling for PK.
- Blood sampling for PD markers anti-MAG IgM and time to anti-MAG IgM rebound (pre-treatment BTU) by at least 50%, paraprotein levels (g/L), total IgM levels (g/L), and anti- HNK1 IgM titers.
- Blood sampling for anti-drug antibodies (ADA) responses (immunogenicity).
- 12-lead ECG.
- Physical examination.
- Optional blood sampling for biobanking.

The study duration per patient is up to 2 months. Each patient will have the following 8 visits: Screening, Baseline, Treatment (4 visits), EOS and Follow-up.

3.3 Single ascending dose/Multiple ascending dose transition

Following the completion of the SAD phase which includes assessments of safety and tolerability, anti-MAG antibodies PK, PD responses and ADA responses, an evaluation of all these data will be performed by Polyneuron in collaboration with a modeler and the IDMC to decide doses and schedules of PPSGG in the MAD phase. The goal is to define a potential dose and regime to reliably and safely reduce anti-MAG IgM antibody levels by at least 50%.

3.4 Design of the multiple ascending dose phase (Phase IIa)

Thirty patients will be enrolled in the MAD phase, to allow for a drop-out rate of 20% to have 24 patients to complete this phase of the study.

The MAD phase that consists of two sequential and ascending cohorts will establish the safety and tolerability, immunogenicity, PK parameters, and PD effects after repeated escalated doses.

Many of the same patients involved in the SAD phase will enter the MAD phase. If “new” patients need to be recruited, they will need to undergo the complete screening procedure (see Section 8.3 Study performance).

The Dose Escalation will follow the same rules as for the SAD phase. The first 2 patients per cohort will be randomized to receive PPSGG or placebo in a double-blind fashion. At the end of each cohort a Dose Escalation assessment will be performed by the IDMC based on the safety data collected after 2 weeks of the start of the PPSGG administration.

The MAD phase will be adapted for dosing regimen in accordance with PK, PD, safety and tolerability data collected during the SAD phase. The dosing of both cohorts in the MAD phase will not exceed the exposures achieved in the SAD phase (Cmax and AUC0-tau), and will commence at a dose at least one dose level lower than safely completed in the SAD. Dosing regimen includes the dose level administered, the frequency of dosing and the duration of

dosing, i.e. the number of doses administered. Based on the safety toxicology studies performed in animals the maximum number of dosing is 11 infusions for 6 weeks. The goal is to define a potential dose and regime to reliably and safely reduce anti-MAG IgM antibody levels by at least 50%.

In the first week, all patients may receive a maximum of 1 dose per day for 5 consecutive days until the desired reduction of anti-MAG IgM antibody titers is achieved. For the following 5 weeks we aim to maintain the antibody levels below the 50% of baseline. The exact dosing regimen for the MAD phase will be adjusted based on PK data from the SAD phase.

The MAD phase will last for maximum 11 infusions for 6 weeks, with a 3-month observation phase, which can be extended until the anti-MAG IgM titers reach pre-treatment levels (up to 6 months after end of treatment). The MAD phase will involve the following assessments:

For safety (time points indicated in the Schedule of Assessments):

- Vital signs.
- Blood and urine sampling for clinical safety laboratory.
- Blood sampling for PK.
- Blood sampling for ADA responses (immunogenicity).
- ECG.
- Physical examination.

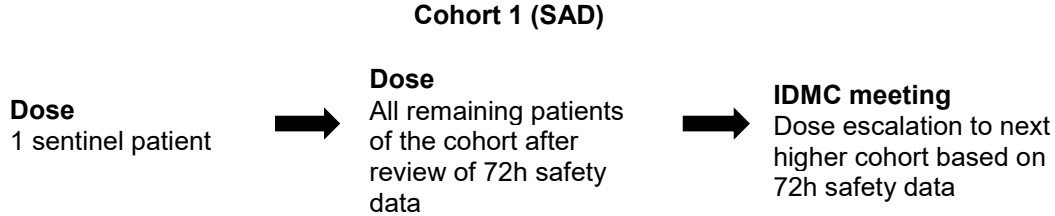
For efficacy (time points indicated in the Schedule of Assessment):

- Blood sampling for PD markers anti-MAG IgM and time to anti-MAG IgM rebound (pre-treatment BTU), paraprotein levels (g/L), total IgM levels g/L), and anti-HNK-1 IgM titers.
- Scores for clinical efficacy assessment.
- Blood sampling for assessment of exploratory biomarkers will be collected.

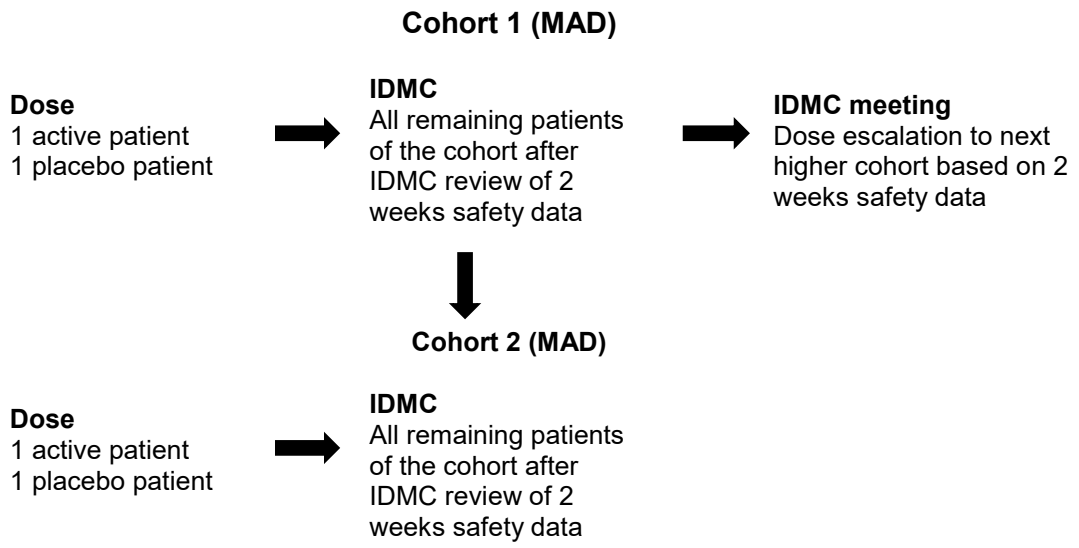
The study duration per patient is 6 months. Each patient will have up to 17 visits: Screening, Baseline, Treatment (up to 14 visits covering 11 infusions for 6 weeks), EOS and Follow-up.

3.5 Cohort completion and Dose Escalation

As this is the first time of administration of PPSGG in humans, the design of this study is similar to a Phase I FiH study in which 3 or more different increasing single doses (cohort 1, cohort 2, cohort 3, cohort 4 and optional cohort 5) in the SAD phase will be tested. Six patients per cohort will be dosed via an IV infusion over 60 minutes (120 min for optional 3200 mg dose) with PPSGG.



During the MAD phase 2 different multiple ascending doses will be administered in a double- blinded manner. Each cohort in the MAD phase also includes 2 patients that will receive placebo. Each dose of PPSGG or placebo will be administered via an IV infusion over 60 minutes (120 min for optional 3200 mg). After treatment of the first 2 patients in every cohort and after treatment of all patients in that cohort, a safety analysis will be performed. The dosing cohorts and safety assessments are schematically represented below.



In the SAD phase the first patient (sentinel patient) of a given cohort will be dosed. In the MAD phase the first 2 patients in each cohort will be randomized as follows: 1 patient will be treated with PPSGG and 1 patient with placebo. The following safety data, obtained from the sentinel patient(s) during the first 72 hours post study drug administration in the SAD phase and 2 weeks post drug administration in the MAD phase, will be checked by Polyneuron and will consist of:

- AEs.
- Baseline characteristics.
- Vital signs, including core temperature, blood pressure and heart rate.
- Laboratory data including hematology, clinical chemistry and urinalysis.
- ECG.

This review will be based on data entered in the electronic case report form (eCRF).

The remaining patients of the cohort will be dosed if no safety concerns are observed after reviewing the safety data of the sentinel patient in the SAD phase and the first 2 patients in the MAD phase, as listed above. The treating investigator might be involved in the review of the data for clarification in case of medical questions.

The decision to escalate to the following dose (once completed a cohort) will be based on the safety data, as listed above collected during the first 72 hours after the start of the infusion in the SAD phase and after 2 weeks for the MAD phase, where no stopping rules are met and analyzed by an IDMC.

If the SAD phase is stopped at one dose level due to clinically relevant toxicity, the maximum dose appropriate for the MAD phase will be defined in that case as the dose level below the dose inducing the relevant toxicity.

- No transition to the next dose cohort during the SAD and/or MAD phases can occur before the review of all safety data of the previous cohort by the IDMC
- Usage of the next higher dose level in the study will be suspended if any of the following occurs:

- 6 or more patients in a dose cohort meet one of the individual stopping criteria (see Section 7.5 Study Stopping rules).
- 4 or more patients in a dose cohort experience a treatment related (i.e. moderate and/or severe) AEs.
- 1 or more patients in a dose cohort experience a treatment related serious adverse event (SAE)

In the Dose Escalation Assessments, the Polyneuron staff and the IDMC will review unblinded data also during the MAD phase.

3.6 Risks and benefits

This study is the first administration of PPSGG in humans; therefore, no prior human safety and tolerability data are available. As with any drug, it is possible that adverse reactions are caused by PPSGG. There may be unknown or unforeseeable risks. However, the risk to patients in this study will be minimized by adherence to the inclusion/exclusion criteria, close clinical monitoring in an hospital setting, strict adherence to standard practice including training of staff and provision of manuals for study procedures, infusion procedure, stopping rules for an individual patient (see Section 7.5 Study Stopping rules), as well as a safety review after the first part of the study and monitoring by an IDMC (see Section 10.2 Independent Data Monitoring Committee).

Evaluation of the safety of PPSGG in dogs and rats demonstrated a favorable toxicity profile (see IB). In a 6-week repeat-dose study in rats and dogs of doses from 20 mg/kg up to 200 mg/kg IV of 11 infusions over 6 weeks followed by a 2-week recovery, there were no clinical signs, no effects on organ weight or macroscopic observations, and no safety pharmacology findings; clinical chemistry and hematology results were remarkable. Neither microscopic findings were reported.

Based on the experimental animal studies that were carried out, investigation of the safety and tolerability of PPSGG showed no special dangers for humans. Therefore, based on the safety profile of PPSGG the risks in participating in the trial are considered acceptable. However, they include the usual risks of participating in clinical trials, which are related to possible allergic reactions, infusion related adverse event, blood drawing via venepuncture. Patients' safety will be observed during all study phases. Before the drug administration, participants will be informed about the potential and/or observed adverse effects, if any, that occurred in the previous cohort.

Medical progress is based on research which ultimately must rest in part on experimentation involving humans. Eligible patients may consider participation in this clinical trial because they want to contribute to the advancement of medical knowledge. Still, considerations related to the well-being of the individual patients enrolled into this clinical study must take precedence over the interests of science and society. Based on the available information and the design of the study, Polyneuron and the Principal investigator consider the trial to be ethically acceptable. The duration of hospitalization and the medical surveillance are considered adequate to ensure safety of the patients

There may be unknown risks of PPSGG which may be serious.

3.6.1 Blood sample volumes

Approximately 150 mL of blood is planned to be collected during the whole SAD phase and approximately 250 mL during the whole MAD phase, from each patient as part of the study. Additional samples may be required for safety monitoring.

The timing of blood sample collections is outlined in the Schedule of Assessments (see Section 8.2 Schedule of Assessments).

3.6.2 Risk mitigation strategy

There are preclinical findings of undetermined clinical relevance that will be mitigated by careful clinical monitoring. Thus, vital signs and ECG will be monitored before and after the first dose during the SAD phase and before and after the doses during the MAD phase and at other visits throughout the study.

Patients will return to the study site on a regular basis. During these visits, safety, tolerability, efficacy, and PK/PD data will be collected. Standard safety assessments will include vital signs, ECGs, clinical laboratory evaluations (hematology, blood chemistry and urinalysis), and AEs as outlined in the Schedule of Assessments (see Section 8.2 Schedule of Assessments). In addition to the standard clinical laboratory assessments, patients will be regularly monitored for signs and symptoms, inflammation, and hematologic and hepatic function. Patients will be informed to report any symptoms to the clinical staff to assure proper assessment and so that care can be administered in a timely manner.

In addition, the clinical opinion of the Investigator will be used to protect individual patient safety during the trial.

Finally, key safety data will be reviewed by Polyneuron in an open manner on an ongoing basis. An IDMC will regularly review safety data to assess whether the benefit/risk of each treatment arm remains acceptable.

3.6.3 Management of Infusion Related Reactions (IRR):

In case of occurrence of an IRR, the following measures are to be taken:

- PPSGG infusion should be interrupted and vital signs monitored until the IRR resolves to the Common Terminology Criteria for Adverse Events (CTCAE) Grade ≤1 and then the infusion can be restarted at a slower rate
- Treatment with antihistamines and methylprednisolone can be initiated, or other treatments can be given as necessary in line with the patient's condition and local standard of care.
- The patient can be pre-treated with antihistamines prior to the next PPSGG infusion during the MAD phase in cases with mild reactions. In case of a moderate, severe or serious reaction the patients will be withdrawn.
- If the IRR continues, the PPSGG infusion rate can be slowed down to 3 hours and if not resolved, Polyneuron shall be contacted and patient from the trial will stop.
- When anaphylaxis is suspected and/or confirmed, treatment with epinephrine must be initiated immediately. In case of severe reactions during the infusion of PPSGG the treatment should be stopped immediately and discontinued permanently.

AEs of IRRs and hypersensitivity must be captured on the patient's source data and on the AE page of the eCRF, along with their signs and symptoms. If dosing is interrupted, discontinued or the patient is withdrawn from the study as a result of an infusion site reaction, this must be recorded in the patient's source data and the eCRF. In the event of IRRs, blood samples taken at the end of infusion will be analyzed for complement, histamine, and cytokines to elucidate the mechanism.

4 Study Population

4.1 Anti-MAG neuropathy patients

PPSGG is targeting anti-MAG IgM autoantibodies, which are the underlying cause of anti-MAG neuropathy. Since these autoantibodies are only present in patients with anti-MAG neuropathy, but not in healthy humans, information obtained from a study in healthy patients would be limited in respect to PK, PD, and any potential target related toxicities.

Moreover, since PPSGG acts as a mimetic of the antigen, the potential for immunogenicity is an important safety concern in healthy volunteers. Potential ADAs resulting from exposure of healthy individuals to PPSGG may bind to the human natural killer-1 (HNK-1) epitope in the PNS and trigger the development of the anti-MAG neuropathy. Of note, no immunogenicity was detected in the non-clinical development so far (see Section 1.1 Background) [19]. However, it is acknowledged that it is not possible to fully predict immunogenicity in humans based on non-clinical studies. Therefore, we consider a FiH study directly in a small number of patients the most appropriate approach to minimize the potential risk for immunogenicity, as also confirmed by the EMA during a scientific advice meeting.

The following inclusion and exclusion criteria are chosen to select the appropriate study population regarding homogeneity in order to meet the requirements for reliable evaluation of the data collected.

Eligible patients will be included in the study after having given voluntary written informed consent before the first screening examination procedure takes place.

A confirmed diagnosis of anti-MAG neuropathy should be available. Sites will provide documentation of disease confirmation (i.e. previously performed tests) to the medical monitor for review. A formal process for eligibility review for any patients recommended by the investigator is done by the medical monitor based on the data entered during the screening visit.

4.2 Inclusion criteria

Anti-MAG neuropathy patients eligible for inclusion in this study must fulfill **all** of the following criteria:

- Written informed consent.
- Age between 18 and 80 years, male and female.
- Patient with a confirmed diagnosis of monoclonal IgM associated with MGUS with anti-MAG activity (titer of > 10’000 BTU) and demyelinating neuropathy defined by electrophysiological criteria according to EFNS/PNS PDN guideline, 2010.
- Clear clinical signs of disability: with at least ONLS ≥ 2 in lower extremities.
- Inflammatory Neuropathy Cause and Treatment (INCAT) sensory sum score ≥2.
- Patients must have adequate hepatic function as evidenced by total bilirubin <1.5 mg/dL, alkaline phosphatase and aspartate transaminase/alanine aminotransferase < 2X the upper limit of normal (ULN).
- Absence of cause of neuropathy independent from anti- MAG activity: e.g. diabetes, hypothyroidism, past or current dependence on alcohol, past or current treatment with neurotoxic drugs.

- Patients must have adequate renal function as evidenced by serum creatinine <2mg/dL or calculated creatinine clearance of ≥60 mL/min within 28 days before first IMP administration using Modification of Diet in Renal Disease (MDRD) formula.
- Capability to meet the requirements of the study.

4.3 Exclusion criteria

Anti-MAG neuropathy patients fulfilling any of the following criteria are not eligible for inclusion in this study:

- Patients with total serum IgM levels >30 g.
- Hematological malignancy (e.g. known multiple myeloma or confirmed Waldenström's macroglobulinemia based on bone marrow analysis).
- Patients with any history of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
- Previous immunosuppressive treatment with IVIG or apheresis/plasmapheresis in the preceeding 3 months, and cyclophosphamide and biologicals (e.g. rituximab): in the preceeding 6 months prior to enrolment.
- Other neurological, neuromuscular, rheumatologic or orthopedic conditions with significant impact on the capability of walking preventing evaluation of neurological scores.
- Anti-MAG neuropathy patients with persistent clinically significant laboratory abnormalities not related to the anti-MAG neuropathy, such as significant renal dysfunction, hepatic dysfunction, cardiac disease or other significant neurological disorder.
- Anti-MAG neuropathy patients with a modified Rankin Scale (mRS) score > 4.
- Participation in another Interventional clinical trial.
- Any other significant finding that would increase, according to the investigator, the risk of having an adverse outcome from participating in the study.
- Any other medical condition, including mental illness or substance abuse deemed by the investigator(s) to likely interfere with the patient's ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results.
- Patients who have undergone major surgery ≤ 2 weeks prior to starting study drug or who have not recovered from the side-effects of surgery.
- A history of clinically significant ECG abnormalities, or any of the following ECG abnormalities at screening:
    - PR > 200 msec.
    - QRS complex > 120 msec.
    - QTcF > 450 msec (males).
    - QTcF > 460 msec (females).
    - History of familial long QT syndrome or known family history of Torsades de Pointes.

- Use of agents known to prolong the QT interval unless they can be permanently discontinued for the duration of the study.

- Sexually active males must use a condom during intercourse after the start of IMP administration and for at least 3 days after stopping study medication and should not father a child in this period after completion of the study medication (SAD and MAD phases). A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. In addition, male participants should not donate sperm for the time period specified above.
- Use of other investigational drugs at the time of enrolment, or within 5 half-lives of enrolment, or within 30 days, whichever is longer; or longer if required by local regulations.
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 1 week after stopping of investigational drug. Highly effective contraception methods include:
    - Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking the investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
    - Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure <1%), for example hormone vaginal ring or transdermal hormone contraception.

  In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug. If local regulations deviate from the contraception methods listed above and require more extensive measures to prevent pregnancy, local regulations apply and will be described in the informed consent form (ICF).

  Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking the investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment then she considered not of childbearing potential.

4.4 Patients participating in SAD and MAD phases

Patients that have participated in the SAD phase may enter the MAD phase but not all the screening and tests procedures performed in the SAD phase during screening need to be repeated. Just “newly” recruited patients need to go through the complete screening assessment as described in Section 8.3 Patient screening.

5 Restrictions for Study Patients

For the duration of the study, the patients should be informed and reminded of the restrictions outlined in this section.

5.1 Fasting

After an 8-hour fasting overnight, patients will have a light breakfast in the morning at least an hour before the IMP administration.

5.2 Contraception requirements

Women of childbearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, they should agree that in order to participate in the study they must adhere to the highly effective contraception requirements outlined in the Section 4.3 Exclusion criteria.

If there is any question that a patient will not reliably comply, the patient should not be entered or continue in the study.

6 Treatment

6.1 Study treatment

PPSGG and placebo is manufactured for Polyneuron by BAG Healthcare GmbH, Amtsgerichtsstraße 1 - 5, 35423 Lich, Germany. QP release is carried out by BAG Healthcare GmbH, which holds appropriate cGMP authorization.

Polyneuron will provide the site with investigational products manufactured and tested according to applicable good manufacturing practice (GMP) requirements for clinical trial supplies together with a certificate of analysis (CoA) and a confirmation that the investigational products are released for human use in clinical trials.

Polyneuron will ensure that the drugs, PPSGG and placebo, to be applied during the MAD phase, are identical in their appearance (colorless solution). Thus, neither the patient nor the investigators will be aware of whether the drug administered is the test or the reference drug.

Handling Requirements:

The designated person (e.g. pharmacist) at the study site will be responsible for ensuring that the study drugs are stored in compliance with GMP in a locked refrigerator (+2ºC to +8ºC) prior to administration with limited access and in accordance with the instructions on the study medication labels.

Patients will receive 1 infusion (SAD phase) or up to maximum 11 infusions (MAD phase) for 6 weeks during the study. Drug administrations will take place in the morning. The respective treatments will consist of the following:

Table 3 Dose regimen during SAD phase

Cohort No	IMP Single dose	Dose Level (mg) per patient	Dose volume (mL)	Dose concentration (mg/mL)

1	PPSGG	200	20	10
2	PPSGG	400	40	10
3	PPSGG	800	80	10
4	PPSGG	1600	160	10

An additional cohort of 3200 mg per patient may be included if the relative reductions in anti- MAG antibody titers have not reached the target of 50% relative reduction, no stopping rule for safety has been met and the end of cohort review by the IDMC from the previous patients considers proceeding to the final cohort justified by the previous safety and tolerability profile.

The specific Dose regimen during the MAD phase will be based on the data (PK / PD) derived from the SAD phase.

PPSGG will be provided to the sites in sufficient quantity. The IMP is supplied as liquid solution in 50 mL vials containing 10 mg/mL as solution for infusion. IMPs will be stored at the site in a refrigerator/refrigeration unit at 5±3°C (2-8°C). The IMP must not be allowed to freeze. The solution should be visually inspected prior to use. Only clear solutions without particles should be used. A single administration of PPSGG in the SAD phase and up to 11 infusions of PPSGG or placebo in the MAD phase will be given by intravenously over 60 minutes (120 min for 3200 mg dose) to the patient.

Detailed information on IMP handling will be provided in an IMP manual that is based on information provided in Polyneuron's pharmaceutical instruction. Immediately prior to administration, the assigned personnel dispense the study drug according to the cohort and dose of the patient. The dispensing of medication for administration will follow the randomization list.

The study medication will be prepared based on Table 4. The pump syringes will be filled with the study medication and the IV line filled up completely before the start of the infusion. Treatment with study drug will be administered intravenously into the arm contralateral to the arm used for blood collection. Infusions of the sterile solutions will be given through an infusion set and an IV catheter with the rate controlled by the infusion pump. At the end of the infusion, the IV catheter will be flushed with a saline solution.

Table 4 Study medication

Dose	Original concentration in mg/mL	Original Volume in mL	Infusion Speed in 60 min in mL/min
200	10	20	0,333
400	10	40	0,667
800	10	80	1,333
1600	10	160	2.667

6.1.1 Identity of Investigational treatment PPSGG

The drug product, PPSGG solution for infusion is a sterile, clear, and colorless solution filled in a sterile Type I glass vial. Concentration is expressed in terms of the amount of PPSGG free and pure acid per mL.

The solution contains PPSGG sodium as the active ingredient and a standard phosphate buffered saline (PBS) solution for pH 7.4, as inactive ingredient.

Component	Function	Quantity per Unit (40 mL)
		10 mg/mL
PPSGG sodium	Drug substance	400 mg
PBS solution	Solvent	40 mL, q.s.

Batch number	P01997
Route	IV
Retest date	Shelf life controlled by Interactive Voice Response System (IVRS)

6.1.2 Identity of Placebo

Strength	10 mg/mL
Route	intravenous
Batch number	P01963
Retest date	Shelf life controlled by IVRS

Placebo is a standard PBS solution, pH 7.4, composed of disodium hydrogen phosphate dodecahydrate, potassium dihydrogen phosphate, sodium chloride, and water for injection. An adjustment of the pH is not necessary. It is the same composition as used for the inactive ingredient for the PPSGG solution.

Component	Quality Reference	Molecular Weight	Concentration (mg/mL)
$Na_2HPO_4 \bullet 2H_2O^*$	Ph.Eur./USP	177.99	1.43
KH_2PO_4	Ph.Eur./USP	136.08	0.20
KCl	Ph.Eur./USP	74.55	0.20
NaCl	Ph.Eur./NF	58.44	8.00
Water for injection (WFI)	Ph.Eur./USP/In-House	-	1 mL (q.s)

Ph. Eur/USP = Pharmacopoeia Europaea/United States Pharmacopeia; Ph. Eur/NF = Pharmacopoeia Europaea/National Formulary

6.2 Labelling

The study drug will be provided by Polyneuron with appropriate labelling. Polyneuron will supply sufficient trial medication. The medication will be identified by project and protocol number, vial number, expiry date, storage requirements and contents. Polyneuron will provide a CoA.

The study products will be labelled in accordance with the Good Clinical Practice (GCP) ordinance and local regulatory requirements.

The labels on the vial and secondary packaging (box) of the IMP will contain the following information

- Polyneuron's study code.
- Polyneuron's name, address and phone number.
- European Union Drug Regulating Authorities Clinical Trials (EudraCT) number.
- Product name, strength and dosage form.
- Application form.
- Content by weight, volume, number of units.
- Route of administration.
- Directions for use.
- Batch number.
- Expiry date.
- Storage instructions.
- The term "For clinical trial use only".

Each manufacturing/packaging process will be performed and documented in conformity with GMP.

6.3 Treatment assignment

At the end of the SAD phase, a randomization will be done for the MAD phase. In total there will be two randomization lists created in this study, one per cohort of the MAD phase. During the SAD phase, all patients will receive PPSGG.

During the MAD phase only, patients will be randomized to receive either PPSGG or placebo. Blinded treatment with PPSGG and placebo is used to reduce potential bias during data collection and evaluation of clinical efficacy endpoints during the MAD phase.

The randomization during the MAD phase will be done via IVRS. The randomization schedule will link sequential numbers to treatment assignment allocated to treatment with PPSGG and placebo. The randomization number will be used to link the patient to a treatment arm and specify a unique medication number for the first package of investigational treatment to be dispensed to the patient.

Patients allocated to one of the groups within a cohort will receive a randomization number.

Each patient must be given only the study treatment assigned to their randomization number by the IVRS. The investigator must document the randomization number on the patient's eCRF.

These randomization numbers are linked to the different cohorts, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Polyneuron using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

6.4 Treatment blinding

SAD is an open label phase. MAD is a double-blind phase (patient and investigator blinded). Patients and investigators will remain blinded to study treatment throughout the MAD phase, except where indicated below.

The identity of treatments will be concealed by the use of study drugs that are all identical in packaging, labelling, schedule of administration, appearance, and odor.

Site staff: All site staff (including study investigator and study nurse) will be blinded to study treatment throughout the MAD phase.

Unblinding a single patient at a site for safety reasons (necessary for patient management) during the MAD phase, will occur via the process defined in place at the site (see Section 6.8 Emergency breaking of assigned treatment code).

Polyneuron staff: Polyneuron clinical staff is required to assist in the management and re-supply of the IMP. These individuals are not provided with randomization lists directly during the MAD phase.

During the MAD phase the sample analysts handling PK samples will receive a copy of the randomization schedule, to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team in a way that does not unblind individuals who are meant to be blinded.

Personnel involved in the analysis and the IDMC: An independent data analysis team of will be employed to produce the analysis results and to communicate with the IDMC at the time of safety review for the dose continuation and escalation meetings.

Polyneuron staff responsible for decision making at the clinical program development level will receive the aggregated unblinded results at the treatment group level at the time of the analysis at the end of the SAD phase. The team will not have access to the individual patient treatment codes during the MAD phase.

6.4.1 Unblinding plan for the MAD phase

See Table 5 for an overview of the blinding/unblinding plan.

Table 5 Unblinding plan for the study applicable for the MAD phase only

Role	Randomization list generated	Treatment allocation & dosing	Safety event	IDMC Safety review	Interim Analysis at end of treatment in MAD
Patients	B	B	UI	B	B
Site staff	B	B	UI	B	B
IVRS of Clinipace	UI	UI	UI	UI	UI
IDMC	B	B	UI	UI	UI
Independent analysis team	B	B	UI	UI	UI
Polyneuron team	B	B	B	B	UG

B=Blinded; UG = Unblinded at the group level; UI = Unblinded at the individual level; SAD = Single Ascending Dose; IDMC = Independent Data Monitoring Committee; MAD = Multiple Ascending dose

6.5 Treating the patient

PPSGG will be administered to the patient intravenously over a 60-minute (120 min for optional 3200 mg dose) infusion.

Polyneuron's qualified medical personnel will be readily available to advise on trial related medical questions or problems.

6.6 Patient identification

Each patient for whom an ICF is obtained will be assigned a unique 6-digit patient number xxx - yyy (country and site - patient number) strictly in chronological order of enrolment within each study site. Patients who withdraw from the study will keep their screening respective patient number even if the withdrawal occurs before randomization. The screening number corresponds to the patient number and will be documented on the eCRF and used to identify the patient throughout the study.

6.7 Permitted dose adjustments and interruptions of study treatment

Dose adjustments of study drug treatment are not permitted.

6.8 Emergency breaking of assigned treatment code

During the MAD phase, emergency code breaks must only be undertaken when it is required to safely treat the patient. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IVRS. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the study monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IVRS at any time in case of emergency. The investigator will need to provide:

- Protocol number.
- Study drug name (if available).
- Patient number.

In addition, the investigator must provide to the patient with oral and written information on how to contact his/her backup in cases of emergency when he/she is unavailable to ensure that un- blinding can be performed at any time.

An assessment will be done by the appropriate site personnel and Polyneuron after an emergency unblinding to assess whether or not study treatment should be discontinued for a given patient.

If an investigator wishes to unblind the treatment allocation information for a patient, they would first be encouraged to discuss this decision with the Sponsor's Medical Monitor. In the event the investigator wishes to proceed with unblinding the patient, they should attempt to complete this task using the IVRS.
In the case where the investigator cannot obtain the unblinded treatment allocation from the IWRS for any reason, they will be provided with sealed envelopes containing the treatment allocation information for each patient. Should these be required, the investigator can select the appropriate envelope for the patient to be unblinded and open accordingly to obtain this information. In both cases the reason for unblinding must be documented and the Sponsor informed.

The CRO will generate this set of sealed envelopes, which will be provided to all participating sites before the study treatment has started The envelopes will be used in the case of emergency when the patient needs to be unblinded and this cannot be achieved through the IVRS.

6.9 Treatment exposure and compliance

PK parameters (measures of treatment exposure) will be determined in all patients treated with PPSGG and placebo during the MAD phase, as detailed in Section 8.6 Pharmacokinetics.

The investigator must promote compliance by properly infusing the patient according to dose cohort.

All study treatment dispensed must be recorded on the Drug Accountability Log.

6.10 Recommended treatment of adverse events

At present, there is insufficient information to provide specific recommendations regarding treatment of AEs. There is no treatment that can reverse the activity of PPSGG. PPSGG has a relatively short half-life potential. AEs should therefore be treated symptomatically at the discretion of the investigator. Medication used to treat AEs must be recorded on the concomitant medications/significant non-drug therapies page of the eCRF. For treatment of IRR refer to Section 3.6.3 Management of Infusion Related Reactions (IRR).

6.11 Concomitant therapy

The investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study.

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the appropriate page of the eCRF.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication (see Section 6.12 Prohibited concomitant treatment). If in doubt, the investigator should contact Polyneuron before enrolling a patient or, if the patient is already enrolled, to determine if the patient should continue participation in the study.

6.12 Prohibited concomitant treatment

Any prescribed medication, over-the-counter drugs and significant non-drug therapies (plasmapheresis) known to have a possible impact in the clinical status of anti-MAG neuropathy are prohibited.

7 Study completion and discontinuation

7.1 Study completion and post-study treatment

All efforts will be done to facilitate the patients to complete the study in its entirety and thereafter no further study treatment will be made available to them.

An EOS visit, for each patient, is scheduled at the end of each corresponding phase (SAD and MAD phases).

Study Completion (SC) is defined as when the last patient completes their EOS visit at the end of the MAD phase, or at the end of SAD, if the patient decides not to continue with the MAD, and any repeated assessments associated with this visit have been followed-up appropriately by the investigator, or in the event of an early study termination decision, the date of that decision.

7.2 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study treatment is stopped earlier than the protocol planned duration.

Study treatment must be discontinued under the following circumstances:

- Patient decision - patients may choose to discontinue study treatment for any reason at any time.
- The investigator believes that continuation would negatively impact the safety of the patient or the risk/benefit ratio of trial participation.
- Any protocol deviation that results in a significant risk to the patient's safety.
- Pregnancy (see Section 9.4 Pregnancy reporting).
- Use of prohibited treatment as described in Section 6.12.
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the patient's overall status, prevents the patient from continuing participation in the study

If discontinuation of study treatment occurs, investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the patient's eCRF.

7.3 Withdrawal of informed consent

A patient can decide to withdraw from the study participation at any time, for any reason, specified or unspecified, and without penalty or loss of benefits to which the patient is otherwise entitled. In this case, the patient must immediately contact the investigator and state that it is his/her desire to withdraw from the study. The patient should be informed of the possibility to withdraw consent without giving any reason and to require that all previously retained identifiable samples will be destroyed to prevent future analyses, according to national provisions. The consent should include a statement that the consequence of the patient's withdrawal of consent will be that no new information will be collected from the patient and added to existing data or a database.

Patients who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 7.3 Withdrawal of informed consent). Where possible, they should return for EOS visit within 14 days after last study medication administration. If they fail to return for EOS visit for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the patient/pre-designated contact as specified in Section 7.4 Lost to follow-up. This contact should preferably be done according to the study visit schedule.

Withdrawal of consent from the study is defined as when a patient:

- Does not want to participate in the study anymore,
- Does not want to participate in any further visits or assessments,

- Does not want any further study related contacts or,
- Does not allow analysis of already obtained biologic material.

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the patient's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued, and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing. In the event of a patient deciding to stop participation in the study, he/she is requested to take part in the final medical examination including the required blood withdrawal (for the laboratory tests). This final examination is for the patient's safety. It is only by this examination that any impairment to the patient's health which may require treatment and could be related to the patient's participation in the study can be detected. If the patient is withdrawn for safety reasons, the investigator will make thorough efforts to document the final AE/SAE outcome.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

Patients can also be withdrawn from study at the description of the investigator for safety, compliance, behavioral or administrative reasons.

As the aim of this study is to generate information on the safety and tolerability, preliminary efficacy, and PD properties of the substance under investigation as well as PK data, patients who are withdrawn from the study for reasons other than safety issues may be replaced at the discretion of Polyneuron and the Investigator.

7.4 Lost to follow-up

For patients whose status is unclear because they fail to return for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents the steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. At least 3 attempts should be documented. A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the site for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.

Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

7.5 Study Stopping rules

During and after the administration of PPSGG, the patient will be closely monitored, in particular for signs and symptoms of IRRs, including skin reactions (urticaria, erythema, facial edema, facial rash, pruritus, eruptions), hypotension or hypertension, drop in oxygen saturation, respiratory problems (laryngospasm, laryngeal edema, bronchospasm, dyspnea), pain (joint pain, back pain, abdominal pain, chest pain) or other manifestations of hypersensitivity (fever, chills, rigors, diaphoresis, nausea, vomiting, neurological changes). One-lead ECG will be monitored continuously during the infusion, and 12-lead ECG pre-dose and at the end of infusion and at 2h and 8h after start of infusion. In the absence of symptoms, or in case of mild (asymptomatic with only incidental findings) or moderate (symptomatic without intervention required), the infusion should be stopped until the AE resolves to grade 1 and may be restarted with a lower infusion rate and treatment with antihistamines or methyl prednisolone may be initiated. If not resolved, Polyneuron shall be contacted and the patient withdrawn from the trial.

The IDMC will perform reviews of safety data throughout the study.

Enrolment in the study will be placed on hold and no further dosing will occur pending a full safety review if:

- One fatal or life-threatening SAE occurs, that is considered by the Investigator as potentially or possibly related to PPSGG and later confirmed the patient received IMP.
- Polyneuron, investigators and/or the IDMC considers that the number and/or severity of AEs, abnormal safety monitoring tests or abnormal laboratory findings justify putting the study on hold. Examples are:
    - One severe systemic infusion-related reaction occurs and does not resolve within 24 hours.
    - Three or more similar severe AEs occur as defined by the CTCAE v5.0, which are judged related to PPSGG.
    - Two SAEs which are judged related to PPSGG.

The IDMC can recommend (i) for the study to continue without amendment, (ii) to continue the study with modifications to the protocol (iii) to stop the study.

The study may continue after the safety review, if the IDMC and Polyneuron agree it is safe to proceed.

7.6 Individual stopping rules

Infusion related adverse events
If a patient experiences an infusion related adverse event that judged to be related or possibly related to the study drug, and is graded as severe or SAE, no further doses of study drug will be administered to the patient concerned.
If a patient experiences an infusion related adverse event that judged to be related to the study drug, and is graded as mild or moderate, the patient may receive a further dose of study drug following discussion with the investigator and sponsor, dependent on the nature of the AEs reported. For example, an asymptomatic localised erythematous rash would be less concerning that mild bronchospasm. If patients are to receive a further dose (i.e. re-challenged), an oral or IV antihistamine and oral acetaminophen will be administered approximately 30-60 minutes prior to the start of the infusion.

Non-Infusion related adverse events
If a patient experiences an adverse event following administration of study drug (i.e. post-treatment) that judged to be related to the study drug, and is graded as severe or SAE, no further doses of study drug will be administered.
If a patient experiences an adverse event that judged to be related to the study drug, and is graded as mild or moderate, the patient may receive a further dose of study drug following discussion with the investigator and sponsor, dependent on the nature of the AEs reported. The number of subjects reporting similar AEs and reports of the same or similar AE/s in an individual patient, will form part of the assessment to determine if patients should be re-challenged.

7.7 Early study termination by the sponsor

The study may be terminated by Polyneuron at any time for any reason. This may include reasons related to the benefit/risk assessment of participating in the study, practical reasons (including slow enrolment), or for regulatory, medical, scientific or ethical reasons. Should this be necessary, patients must be seen as soon as possible and treated as a prematurely discontinued patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the institutional review boards/independent ethics committees (IRBs/IECs) of the early termination of the trial.

8 Procedures and assessments

8.1 Repeat and additional assessments

Should it become necessary to repeat an assessment (e.g. ECG, laboratory tests, vital signs, etc.), the results of the repeated evaluation should be entered on the appropriate section of the eCRF, including date and hour of the repeated assessment. A statement should be included in the comments section explaining why the repeated or additional evaluation was performed.

8.2 Schedule of Assessments

Patients should be seen for all visits/assessments as outlined in the schedule of assessments or as close to the designated day/time as possible.

Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the AEs and concomitant medications recorded on the eCRF.

Table 6 Schedule of Assessments for the SAD phase

Period	Screening	Baseline	Treatment											EOS	FU[5]
Visit numbers	**1**	**2**	**3**								**4**	**5**	**6**	**7**	**8**
Study Day	**-14 to -1**	**-1**	**1**							**2**	**4**	**8±1**	**14±2**	**28±2**	**42±2**
Time			**Predose**	**5min**	**30min**	**60min**	**2h**	**6h**	**8h**						
Informed consent	X														
Biobank consent (optional)	X														
Inclusion/Exclusion criteria	X	X													
Medical history/current med condition	X														
Eligibility assessment	X														
Demography	X														
Physical Examination	X	X									X	X		X	
Serum creatinine	X														
HbA1c test	X														
Pregnancy test	X	X												X	
Vital signs (BP, PR, body temp)	X		X			X	X		X	X				X	
12-lead ECG	X	X	X			X	X		X	X				X	
1-lead ECG					X										
Hematology	X	X										X		X	
Clinical chemistry[1]	X	X										X		X	
Urinalysis	X	X										X		X	
Study Drug administration					X										
PK blood collection		X		X	X	X	X	X	X	X	X	X	X		
PD blood collection[2, 6]	X	X		X	X	X	X	X	X	X	X	X	X	X	X
ADA blood collection[3]		X											X	X	X
Biobank sampling (optional)		X													
Scores[4]	X												X	X	X
Exploratory biomarkers[7]		X								X				X	
Hospitalization						X									

Period	Screening	Baseline	Treatment											EOS	FU[5]
Visit numbers	1	2	3								4	5	6	7	8
Study Day	-14 to -1	-1	1							2	4	8±1	14±2	28±2	42±2
Time			Predose	5min	30min	60min	2h	6h	8h						
Concomitant medication	X														
Infusion related AE assessment				X	X	X	X	X	X	X					
Adverse events	X														X
Serious adverse events	X														X
Study completion information														X	

EOS = End of study; FU = Follow up; BP = Blood pressure; PR = Pulse rate; PK = Pharmacokinetics; PD = Pharmacodynamics; ADA = anti-drug antibodies; AE = Adverse event; ECG = electrocardiogram
1 Including liver safety monitoring (ALT, AST, ALP, TBL, PT/INR, GGT level assessment)
2 Including Bühlmann test and HNK-1 antibodies
3 will be combined with PD blood collection
4 Includes ONLS, RODS, INCAT sensory sum score, mRS, time to 10 m walking test, ataxia score. MUNIX and grip strength
5 The follow up (FU) period will depend on the anti-MAG antibody levels and will be extended until the levels reach baseline
6 In case of a reaction during infusion, the PD samples will be used to analyze tryptase, histamine, classical complement pathway, and cytokines
7 including assessment of neurofilament light chain and BAFF, indirect immunofluorescence assay, classical pathway complement cascade
8 For the optional 3200 mg dose cohort the time for PK sampling will be the following: predose, 30 min, 60 min, 2h, 3h, 6h, 8h and 10h.

Table 7 **Schedule of Assessments for the MAD phase during each infusion day**

Visit name	Treatment						
Study Day	Infusion Day						
Time	Predose	5 min	30 min	60 min	2h	6h	8h
Vital signs (BP, PR, body temp)	X			X	X		X
12-lead ECG	X			X	X		X
1-lead ECG	X						
Urinalysis	X						
PK blood collection	X	X	X	X	X	X	X
PD blood collection	X	X	X	X	X	X	X
Study Drug administration		X					
Infusion related AE assessment		X	X	X	X	X	X
Adverse events	X						
Serious adverse events	X						

Table 8 Schedule of Assessment (MAD)

Visit name	Screening	Baseline	Treatment														EOS	FU[6]
Study Day	**-14 to -1**	**-1**	**1**	**2**	**3**	**4**	**5**	**8±1**	**14±2**	**21±3**	**28±3**	**35±3**	**42±3**	**56±3**	**70±4**	**98±4**	**150±8**	**180±8**
*Informed consent	X																	
*Biobank consent (optional)	X																	
Inclusion/Exclusion criteria	X	X																
*Medical history/current med condition	X																	
Eligibility assessment	X																	
*Demography	X																	
Physical Examination	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum creatinine	X																	
HbA1c test	X																	
Pregnancy test	X	X									X			X		X	X	
Vital signs (BP, PR, body temp)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology	X	X						X			X		X			X	X	
Clinical chemisrty[1]	X	X						X			X		X			X	X	
Urinalysis	X	X	X													X	X	
Study Drug administration[5]			X	X	X	X	X	X	X	X	X	X	X					
PK blood collection[7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PD blood collection[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Visit name	**Screening**	**Baseline**	**Treatment**														**EOS**	**FU[6]**
Study Day	**-14 to -1**	**-1**	**1**	**2**	**3**	**4**	**5**	**8±1**	**14±2**	**21±3**	**28±3**	**35±3**	**42±3**	**56±3**	**70±4**	**98±4**	**150±8**	**180±8**
ADA blood collection[3]		X							X	X	X	X				X	X	X
Biobank sampling (optional)		X													X		X	
Scores[4]	X								X				X			X	X	X
Exploratory biomarkers[8]		X					X		X				X				X	
Concomitant medication	X																	
Infusion related AE assessment			X	X	X	X	X	X	X	X	X	X	X					
Adverse events	X																	X
Serious adverse events	X																	X
Study completion information																	X	

EOS = End of study; FU = Follow up; BP = Blood pressure; PR = Pulse rate; PK = Pharmacokinetics; PD = Pharmacodynamics; ADA = anti-drug antibodies; AE = Adverse event; ECG = electrocardiogram

1 Including liver safety monitoring (ALT, AST, ALP, TBL, PT/INR, GGT level assessment)
2 Including Bühlmann test and HNK-1 antibodies
3 will be combined with PD blood collection
4 Includes ONLS, RODS, INCAT sensory sum score, mRS, time to 10 m walking test, ataxia score. MUNIX and grip strength
5 Study Days and dosing schedule to be confirmed based on data from SAD phase
6 The follow up (FU) period will depend on the anti-MAG antibody levels and will be extended until the levels reach baseline
7 In case of a reaction during infusion, the PD samples will be used to analyze tryptase, histamine, classical complement pathway, and cytokines
8 including assessment of neurofilament light chain and BAFF, indirect immunofluorescence assay, classical pathway complement cascade

*Just newly recruited patients need to follow this assessment

8.3 Patient screening (Day -14 to -1, Visit no 1)

It is allowed to re-screen a patient if s/he fails the initial screening; however, each case must be discussed and agreed with Polyneuron on a case-by-case basis.

In each of the two study phases described in this protocol, all patients will undergo a screening examination to evaluate their health status and to check for inclusion and exclusion criteria. This examination will be conducted not more than 14 days prior to the planned first drug administration. Only patients meeting the inclusion and exclusion criteria will be admitted to the study.

During the screening examination, the patients are identified by a 6-digit patient number.

In addition, before inclusion into the study all patients screening data will be entered into the database to be assessed by the medical monitor.

This screening examination will consist of the following:

- Medical history, including collection of demographic data.
- Complete physical examination: respiratory rate, review of systems (eyes, ears, nose and throat [EENT], cardiac, peripheral vascular, pulmonary, musculoskeletal, neurologic, abdominal, lymphatic, dermatologic).
- Vital signs (blood pressure, pulse rate, and body temperature).
- Assessment of compliance with inclusion/exclusion criteria.
- ECG (12-lead).
- Evaluation of laboratory results.
- Blood sampling for pharmacodynamic markers.
- Blood for PD, including Bühlmann test, HNK-1 antibodies
- Laboratory tests, to include hematology, biochemistry, coagulation, serology, urinalysis, and exclusion tests (see Section 8.5 Safety for details).
- scores (ONLS, RODS, INCAT and mRS, ataxia), time to 10 meters walking test, MUNIX and grip strength
- concomitant medication

Patients entering the MAD, who completed the SAD phase need not to perform all assessments as new recruited patients, according to the list in the Schedule of Assessment. The following assessments could only be left out for patients entering the MAD phase after completion of the SAD phase:

- Informed consent
- Biobank consent (optional)
- Medical history/current med condition
- Demography

8.3.1 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data will be collected on all patients during screening. Relevant medical history/current medical conditions data will also be collected until signature of informed consent.

Patient demographics will include, following and adapted local regulations: age, sex, race, ethnicity. Other baseline disease characteristics will include relevant medical history, current medical conditions, results of laboratory screens, transplant history, donor characteristics (e.g., age, sex, race, type) and any other relevant information.

Investigators have the discretion to record abnormal test findings on the medical history eCRF, if in their judgment, the test abnormality occurred prior to the informed consent signature.

8.3.2 Eligibility review

An eligibility review will be performed based on the data entered during the screening by the medical monitor to assess the eligibility of the potential patient. The site will be informed about the decision in due time.

8.3.3 Study performance

The patients willing to participate in the study will only be included when all screening examination procedures have demonstrated that all inclusion criteria and none of the exclusion criteria apply. The patients will be assigned a patient number within the study. For detailed information about the procedure of assigning patient numbers please refer to Section 6.3. Treatment assignment.

8.3.4 Baseline (Day -1, Visit no 2)

During the Baseline visit, defined as one day before the start of the infusion, the following assessments will be performed:

- Confirmation of inclusion and exclusion criteria.
- Physical examination.
- Pregnancy test in women of childbearing potential.
- 12-lead ECG.
- Blood collection for hematology and clinical chemistry.
- Blood collection for PPSGG PK.
- Blood collection for PD, including Bühlmann test, HNK-1 antibodies
- Blood collection for ADA
- Exploratory biomarkers: assessment of neurofilament light chain and BAFF, indirect immunofluorescence assay and classical pathway complement cascade.
- Urine collection for urinalysis.
- Blood for biobanking (optional).

8.3.5 Treatment period (starting on Day 1, from Visit no 3)

The treatment period consists of 4 visits in the SAD and of up to 11 visits in the MAD phase. After screening and baseline assessment enrolment the treatment period will be performed. The interval between screening and the start of the IMP administration must not exceed 14 days. Patients meeting all inclusion and none of the exclusion criteria will be enrolled.

Patients will then receive one single administration of the IMP through IV infusion, on Day 1 in the SAD phase and for 6 weeks in the MAD phase with a maximum of 11 infusions. The patient will be closely observed during and after the administration of the IMP. Appropriate medical treatment will be kept available in case of an IRR during or following the administration of the IMP. The following procedures and assessments will be performed during and after the treatment: Please refer to the Schedule of Assessment

- Monitor vital signs during the infusion up to 8 hours after start of infusion.
- Monitor 1-lead ECG continuously during the infusion and for a total of 8 hours.

- 12-lead ECG at predose, during the infusion of the IMP at 60 min and then at 2 hours and 8 hours after start of infusion.
- Blood collection for PPSGG PK during baseline (Day -1), on infusion Day 1 (at 5 min, 30 min, 60 min, 2h, 6h, and 8h after start of administration), and on Day 2, 4, 8 and 14 of the SAD phase. In the MAD phase just before first infusion on infusion Day 1 (at 5 min, 30 min, 60 min, at 2h, 6h, and 8h after start of administration) then trough levels before each infusion and on each infusion day (Day 1 to 5, Day 8, 14, 21, 28, 35 and 42) and on Day 53, 70, 98 and EOS.
- Blood collection for PD, including Bühlmann test, HNK-1 antibodies on Day on infusion Day 1 (at 5 min, 30 min, 60 min, 2h, 6h, and 8h after start of administration), and on Day 2, 4, 8 and 14 of the SAD phase. In the MAD phase just before first infusion on infusion Day 1 and on Day 5, 14, 42 and EOS.
- Exploratory biomarkers: assessment of neurofilament light chain and BAFF, indirect immunofluorescence assay, and classical pathway complement cascade.
- Blood collection for hematology and clinical chemistry on Day 8, 28 and EOS visits during the SAD and on Day 8, 28, 42, 98 and EOS during the MAD.
- scores (ONLS, RODS, INCAT and mRS, ataxia), time to 10 meters walking test, MUNIX and grip strength at Day 14 and EOS (Visit no 6) during SAD phase, on Day 14, 98 and EOS for the MAD phase.
- Pregnancy test on Day 28, 56 and 96
- AEs (including infusion related AEs) and SAEs.
- Check for signs of infusion-related reactions, including clinical signs and symptoms, changes in diastolic or systolic blood pressure, heart rate, oxygen saturation, and skin reactions or local reactions at the infusion site during the infusion.

All the assessments are to be performed at the clinical site, except for the safety laboratory, PD biomarkers (blood) and the PPSGG pharmacokinetic (blood).

8.3.6 End-Of-Study (EOS) and optional Follow-up period

The length of the follow-up period will depend on the anti-MAG antibody levels and will last from Day 28 until EOS (Day 42) for the SAD phase. In exceptional cases, when the anti-MAG antibody levels did not reach the baseline level, the patient will be asked to come for an additional visit to check for these levels. In the MAD phase the schedule of assessments will be defined based on the outcome data of the SAD phase. The following assessments will be done on Days 28 and 42 for SAD, according to the schedule specified in Section 8.2 Schedule of Assessments.

The following assessments will be performed in each patient/phase at the EOS visit:

- Physical examination.
- Pregnancy test in all women of child-bearing potential.
- Vital signs.
- 12-lead ECG.
- Blood collection for hematology, clinical chemistry and urine collection for urinalysis.

- Blood collection for PD
- Blood collection for ADA
- scores (ONLS, RODS, INCAT and mRS, ataxia), time to 10 meters walking test, MUNIX and grip strength
- Exploratory biomarkers: assessment of neurofilament light chain and BAFF, indirect immunofluorescence assay, and classical pathway complement cascade
- Collection of AEs and SAEs.

The following assessments will be performed during the follow-up visit:

- Blood collection for PD and ADA.
- scores (ONLS, RODS, INCAT and mRS, ataxia), time to 10 meters walking test, MUNIX and grip strength.
- AE/SAE reporting

All assessments are to be performed at the hospital. The analysis of the PD biomarkers (blood) and the PPSGG PK (blood) will be done at the dedicated laboratories.

The EOS assessments are required on Day 28 for the SAD phase or whenever a patient discontinues or is discontinued from the study prematurely (see section 7.2); they should be performed on the last available study day.

8.4 Safety

Hematology, clinical chemistry will be performed at the local laboratory. Urine dipstick will be performed locally. Values considered clinically significant and/or IMP-related will be noted in the comments of the eCRF with reference to the date, study day and time (using the 24-hour clock), if applicable. The Investigator will record his/her medical opinion on the clinical significance of each laboratory value outside of the reference range both on the laboratory report and the eCRF. This decision will be based upon the nature and degree of the observed abnormality. The Investigator may choose to repeat any abnormal result, but only once, in order to rule out a laboratory error.

Clinically relevant deviations of laboratory test results from the normal range that occur during the course of the study or at a post-study examination will be reported. Repeated assessments are mandatory until their normalization or until the time course and reason of the underlying process are clearly determined. In case of doubt, Polyneuron's medical monitor must be contacted

Safety assessments are specified in the Section 8.2 Schedule of Assessments detailing when each assessment is to be performed.

8.4.1 Vital signs

This assessment of vital signs will include heart rate, systolic and diastolic blood pressure and core body temperature. The core temperature can be assessed orally, tympanically, or rectally. If patient is in hypothermia (< 35ºC), the temperature will be measured rectally, or via pulmonary artery thermistor catheters or bladder thermistor catheters.

8.4.2 1- lead Electrocardiogram

The 1-lead ECG will be assessed for occurrence of or change to abnormal ECG patterns (change in 1-lead ECG "yes/no", clinically relevant ""yes/no"; only monitoring; recording and

printout is not requested unless clinical significant abnormalities) and documented on the eCRF.

8.4.3 12- lead Electrocardiogram (ECG)

The 12-lead ECG recordings (I, II, III, aVR, aVL, aVF, V1-V6) will be recorded as follows: normal or abnormal (with specification of finding reported in the eCRF), ventricular rate and RR (msec), PR (msec), QRS (msec), QT (msec) and QTc (with Bazett's and Fridericia's QT corrections) intervals.

The tracings will be printed out, clinically assessed, dated and signed prior to submission to the Sponsor. Scanned tracings will be uploaded in the eCRF. The patient's identification number, the date and time of the tracing must appear on the printout of the tracing.

8.4.4 Hematology

Hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differentials and platelet count will be measured. Coagulation tests including prothrombin time (PT) also reported as INR and activated partial thromboplastin time (aPTT).

8.4.5 Clinical Chemistry

Albumin, alkaline phosphatase, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, gamma-glutamyl-transferase, lactate dehydrogenase, bicarbonate, calcium, magnesium, phosphorus, chloride, sodium, potassium, creatinine, creatine kinase, direct bilirubin, indirect bilirubin, total bilirubin, total cholesterol (including low density lipoprotein (LDL) and high density lipoprotein (HD) fractions), triglycerides, total protein, blood urea nitrogen (BUN) or urea, uric acid, amylase, lipase, and glucose will be measured in the local laboratory.

8.4.6 Urinalysis

Routine analysis at the hospital with a dipstick will be performed including glucose, protein, bilirubin, urobilinogen and nitrite.

8.4.7 Pregnancy and assessments of fertility

In any woman of childbearing potential, i.e. not > 1 year postmenopausal or surgically sterilized, a urine dipstick pregnancy test will be performed at screening, Day 28, 56, 98 and end-of-study visits. If the dipstick test indicates a positive result, a human chorionic gonadotropin (hCG) laboratory blood test will be performed to confirm pregnancy.

A woman of childbearing potential cannot be included in the study if any of the following occurs:

- The urine dipstick pregnancy test indicates a positive result and the pregnancy has been not yet been ruled out by the following hCG blood test.
- No urine dipstick pregnancy test has been performed at screening.
- The urine dipstick pregnancy test indicates a negative result, but a pregnancy is suspected by the Investigator based on clinical elements and cannot be ruled out by further investigation.

If a positive urine dipstick pregnancy test occurs at end-of-study, or if a pregnancy is suspected at any time during the study, a hCG blood test will be performed to confirm the pregnancy.

Refer to Section 9.4 Pregnancy reporting for details on pregnancy reporting.

8.4.8 Physical Examination

A complete physical examination should include the examination of general appearance, skin, neck (including thyroid), EENT, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological systems.

If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed (this information for all physical examinations must be included in the source documentation at the study site but it will not be recorded on the eCRF).

Significant findings that are present prior to informed consent are included in the CRF capturing Medical History. Significant findings observed after informed consent signature which meet the definition of an AE must be appropriately recorded on the appropriate CRF capturing AEs.

8.5 Pharmacokinetics

PK samples will be collected at the time points defined the Section 8.2 Schedule of Assessments.

PK samples will be obtained and evaluated in all patients at all dose levels.

PPSGG in serum will be determined by an ELISA/chromatography method. Concentrations below the lower limit of quantification (LLOQ) will be reported as “zero” and missing data will be labelled as such in the Bioanalytical Data Report.

Serum samples remaining after completion of the determination of PPSGG may be used for exploratory purposes to further characterize the PK or PK/PD of PPSGG. These analyses may include assessment of for example protein binding, or other bioanalytical purposes (e.g. cross check between different sites, stability assessment).

The following PK parameters of PPSGG will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.3 or later):

$AUC_{0\text{-}t}$, AUC_{inf}, C_{max}, CL, T_{max}, $T_{1/2}$ and V_{ss} and other PK parameters will be measured as appropriate. To denote parameters determined at steady state “ss” will be used.

8.6 Pharmacodynamics

Pharmacodynamic samples will be collected at the time points defined in the Section 8.2 Schedule of Assessments.

PD samples will be obtained and evaluated in all patients at all dose levels, including the placebo group.

PD assessments will include, but not be limited to: reduction of anti-MAG IgM antibody levels by at least 50% and time to anti-MAG IgM rebound (pre-treatment BTU), paraprotein levels (g/L), total IgM levels (g/L), and anti-HNK1) IgM titers.

PD evaluations will be performed primarily in the PD analysis set of patients, who completed the study according to the protocol (i.e., without serious deviations, such as more than 3 missing samples per profile). The PD population is specified in Section Study populations 11.1.

8.7 Efficacy assessments

Clinical efficacy assessments will be performed at screening, and Day 14, and EOS during SAD and during MAD then every 8 weeks. Efficacy assessments will include physical exam and the following scores:

Clinical efficacy outcome for the SAD and MAD phases

- ONLS score.
- Time to walk 10 meters.
- RODS.
- Ataxia score.

Endpoints for the MAD phase only

All the above and then additionally every 8 weeks from Day 14 the following ones:

- INCAT sensibility score and modified INCAT.
- Motor Unit Number Index (MUNIX).
- Grip Strength.

Endpoints for the MAD phase only

- Neurofilament light chain (NfL) to measure the degree of axonal damage.
- B-cell activating factor (BAFF).
- Indirect immunofluorescence on sciatic nerves.
- Classical pathway of the complement.

8.8 Other assessments

The study includes an optional biobank research component which requires a separate informed consent signature if the patient agrees to participate. As permitted by local governing regulations and by IRB/EC, it is required as part of this protocol that the Investigator presents these options to the patient.

The aim is to collect additional blood for a biobank to obtain serum and cells. This should help to better characterize the disease, its pathology and the antibody producing cells in anti-MAG neuropathy patients.

8.9 Use of residual biological samples

Any residual samples remaining after the protocol-defined analysis has been performed may be used for additional exploratory analysis. This may include, but is not limited to, using residual samples for protein binding, metabolite profiling, biomarkers of transporters or metabolic enzyme activity or other bioanalytical purposes (e.g., cross check between different sites and/or stability assessment). Given the exploratory nature of the work, the analytical method used for those assessments will not be validated. As such, the results from this exploratory analysis will not be included in the clinical study report.

9 Adverse Events and Serious Adverse Events

9.1 Definitions

9.1.1 Adverse Events

An **AE** is defined as any untoward medical occurrence in a clinical study patient to whom an IMP has been administered and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of an IMP, whether or not considered related to the IMP.

Events Meeting the AE definition

- Other safety assessments (e.g., physical examination, vital signs measurements), including those that worsen from baseline, considered clinically significant in the

medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events Not Meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient’s condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

9.1.2 Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death.

b. Is life-threatening.

   The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization:

   - In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications (except hospitalization due to planned study procedure) that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event

is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity:

- The term disability means a substantial disruption of a person’s ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

9.1.3 Abnormal Laboratory Parameters

Abnormal laboratory findings (e.g., clinical chemistry, hematology, urinalysis) or other abnormal assessments (e.g., vital signs) will be judged by the investigator as “clinically significant/relevant” or “not clinically significant/relevant” based on the investigator’s medical and scientific expertise.

Clinically significant abnormal findings or other clinically significant abnormal assessments that are detected during the clinical study or that were present at baseline and significantly worsen during the study will be recorded as an AE. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with a medical condition already documented as medical history or AE will not be recorded separately, unless judged by the investigator as more severe than expected for the patient’s condition.

If during treatment with the IMP abnormal laboratory findings occur which were not present before the treatment started and which were judged by the investigator as “clinically relevant” and recorded as AE in the eCRF, further clinical or laboratory tests must be carried out by the investigator until the values return to the normal range or until a plausible explanation is given by the investigator (e.g., disease) of the change of the laboratory values.

9.1.4 Overdose, Abuse, Misuse, Medication Errors and other Uses Outside what is foreseen in this Protocol

There are situations that may present a risk to the patients or conduct of the study even if no immediate AE is noted. Such events (i.e., drug overdose, drug abuse, drug misuse, medication

errors, and other uses outside what is foreseen in the protocol) should be reported in the same format and within the same timelines as a SAE even if they may not result in an adverse outcome.

Overdose: Administration of a quantity of an IMP given per administration or cumulatively that is above the maximum recommended dose according to the protocol dosing instructions or authorized product information. Clinical judgment should always be applied.

Abuse: Persistent or sporadic, intentional excessive use of an IMP that is accompanied by harmful physical or psychological effects.

Misuse: Situations where the IMP is intentionally and inappropriately used not in accordance with the protocol dosing instructions or authorized product information.

Medication error: Unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

9.1.5 Recording and Follow-Up of Adverse Events and/or Serious Adverse Events

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information on the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Polyneuron/Clinipace Pharmacovigilance in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by Polyneuron/Clinipace Pharmacovigilance. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to Polyneuron/Clinipace Pharmacovigilance.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will assess intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- **Mild:** An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- **Moderate:** An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe:** An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the causal relationship between study treatment and each occurrence of each AE/SAE according to the available data as:

  - **Related:** There is a reasonable causal relationship, which means that there are facts, evidence, and/or arguments to suggest a causal relationship. The AE could medically (pharmacologically/clinically) be attributed to the IMP in this study.
  - **Not related:** There is no reasonable causal relationship, which means that there is no evidence to suggest a causal relationship. The AE could not medically (pharmacologically/clinically) be attributed to the IMP in this study.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the IB in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to Polyneuron/Clinipace Drug Safety. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Polyneuron/Clinipace Drug Safety.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Events and Serious Adverse Events

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Polyneuron/Clinipace Pharmacovigilance to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a patient dies during participation in the study, the investigator will provide Polyneuron/Clinipace Pharmacovigilance with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to Polyneuron/Clinipace Pharmacovigilance within 24 hours of receipt of the information.

9.1.6 Reporting of Serious Adverse Events

Serious Adverse Events Reporting to Polyneuron/Clinipace Drug Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Polyneuron/Clinipace Drug Safety will be the electronic data collection (EDC) tool.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken

off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor by telephone.

SAE Reporting to Sponsor/Clinipace Pharmacovigilance via Paper eCRF only if EDC system is unavailable

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Sponsor/Clinipace Pharmacovigilance within 24 hours. Fax number: +49 6196 7709-112.
- In rare circumstances, and in the absence of facsimile equipment, notification by email is acceptable. Reports should be emailed to: Safety@clinipace.com

9.1.7 Rapid communication plan of serious adverse events and suspected unexpected serious adverse reactions (SUSARs) between the sponsor, the investigators of all sites and the patients

If an event is reported as 'serious' in the eCRF database, an automatic SAE notification e-mail will inform the CRO's Pharmacovigilance team and the Sponsor. In the event a SUSAR is confirmed, this will be reported in all countries where the trial is approved, according to local requirements. SUSARs associated with the IMP undergo expedited reporting to Regulatory Authorities, ECs/ Autonomous Communities (for Spain) and investigators according to the following timelines:

SUSARs: within 15 calendar days
Fatal or life threatening SUSAR: within 7 calendar days
SAE: Annual report

If the CRO's Pharmacovigilance team is notified of very severe, unanticipated, suspected adverse reactions during the study (e.g., anaphylactic reaction to IMP, Stevens Johnson syndrome, acute organ failure), the report will be rapidly escalated to the Pharmacovigilance management team and the Sponsor Medical Monitor for immediate action.

9.1.8 Reference safety information (RSI)

No SARs are considered expected by the sponsor for the purpose of expedited reporting of SUSARs and identification of SUSARs.

9.2 Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information

All SAEs and AEs will be collected from the signing of the ICF until the end of the study including Follow-up.

All SAEs will be recorded and reported to Polyneuron or designee immediately and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to Polyneuron within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Polyneuron/Clinipace Pharmacovigilance.

9.3 Documentation and Reporting of Adverse Events

The occurrence of AEs will be assessed by non-directive questioning of the patient at each visit. Further, AEs reported by the patient during or between visits or detected through observation, physical examination, laboratory test or other assessments will be documented. AEs that were ongoing at the end of the previous visit should be queried for resolution or change in severity or seriousness until resolution or until Follow-up, whichever comes first.

The patients will be instructed that they must report any AE, patientive complaints or objective changes in their well-being to the investigator or the clinic personnel, regardless of the perceived relationship between event and IMP.

All AEs must be documented in the patient's eCRF. If in one patient the same AEs occur on several occasions, then the AE in question must be documented and assessed as new each time.

For any AE, the following data must be recorded on the eCRF:

- **Description of the AE** in medical terms (preferably: diagnosis), not as reported by the patient.

  Note: Every attempt should be made to describe the AE in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent a typical or extreme manifestation of the diagnosis, in which case they should be reported as separate AE.

- **Date of onset** (start date and time) and **date of recovery** (stop date and time).

- **Intensity of the AE** as assessed by the investigator according to the following definitions
    - **Mild**: The AE is easily tolerated and does not interfere with routine activities/ normal functioning of the patient.
    - **Moderate**: The AE causes discomfort and affects the patient's normal activities, i.e., interferes with routine activities, but are not hazardous, uncomfortable or embarrassing to the patient.
    - **Severe**: The AE causes considerable interference with the patient's usual activities, e.g., inability to work.

- **Causal relationship** between the occurrence of an AE and the administration of the IMP as assessed by the investigator according to the available data as:
    - **Related**: There is a reasonable causal relationship, which means that there is evidence to suggest a causal relationship. The AE could medically (pharmacologically/clinically) be attributed to the IMP in this study.
    - **Not related**: There is no reasonable causal relationship, which means that there is no evidence to suggest a causal relationship. The AE could not medically (pharmacologically/clinically) be attributed to the IMP in this study.

- **Actions taken on the IMP**
    - e.g., corrective treatment.

- **Outcome**
    - **Recovered/ resolved**: The AE had stopped completely, and the stop date is recorded.

- **Recovered/ resolved with sequelae**: No further changes are expected due to the AE and residual symptoms are assumed to persist.
- **Not recovered/ not resolved**: The AE is ongoing; the event is followed up.
- **Fatal**: The patient died as a consequence of the AE; date of death is recorded as stop date of the AE.
- **Unknown**: Unknown to the investigator (e.g., patient lost to follow-up).

- **Seriousness** according to the definition given in Section 9.1.2 Definition of Serious Adverse Events.

9.3.1 Notification of Serious Adverse Events

Prompt notification by the investigator to the Polyneuron/Clinipace Pharmacovigilance of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study treatment under clinical investigation are met.

The Polyneuron/Clinipace Pharmacovigilance has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Polyneuron/Pharmacovigilance will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Any SAE will be reported immediately (i.e., within 24 hours after receipt) by the investigator to the Drug Safety of Polyneuron/Pharmacovigilance (for details, see Section 9.1.6 Reporting of Serious Adverse Events). The initial SAE report must be as complete as possible. The report should include at least the following information:

- **Patient identification** (e.g., assigned patient number, year of birth).
- **Identifiable reporting source** (e.g., site number, name of investigator, telephone number, fax and/ or e-mail address).
- **Identification of the clinical study** (e.g., study code) or IMP.
- **SAE term** (preferably: diagnosis; if possible, also including description and course of the SAE).
- **Seriousness criterion** according to the definition given in Section 9.1.2 Definition of Serious Adverse Events.
- **Causal relationship** between the occurrence of an AE and the administration of the IMP as assessed by the investigator according to the available data. If based on follow-up information the investigator changes his/her initial causality assessment, this should be submitted to sponsor/CRO Drug Safety immediately (i.e., within 24 hours after receipt).
- **Signature of the investigator**

If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying the Polyneuron/Clinipace Pharmacovigilance of the event and completing the SAE report form. Information not available at the time of the initial report (e.g., an end date for the AE or laboratory values received after the report) will be documented on a follow-up SAE report form and reported immediately (i.e., within 24 hours after receipt) to Polyneuron/Clinipace Pharmacovigilance.

Additional information not covered by the SAE report form, including copies of hospital reports, autopsy reports or other relevant documents, will be requested, if necessary, by either the

clinical monitor or the Polyneuron/Clinipace Pharmacovigilance for a detailed description and a final evaluation of the case. All personal identifiers (e.g., name, detailed birth of date, address) must be pseudonymized prior to submission by blinding personal data and using the assigned identification code of the study patient.

The investigator should institute any supplementary investigations of SAE based on their clinical judgment of the likely causative factors. This may include seeking further opinion from a specialist in the field of the AE.

If the SAE information is incomplete or inconsistent and directly affects the sponsor's reporting obligation to health authorities, the Polyneuron/Clinipace Pharmacovigilance may directly contact the investigator for clarification.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary. The sponsor will be responsible for notification of the competent authorities, Ethics Committees (ECs) and investigators in the event of SUSAR and any other important safety issues requiring expedited reporting.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Polyneuron/Clinipace Pharmacovigilance will review and then file it along with the IB, and will notify the IRB/IEC, if appropriate according to local requirements.

9.4 Pregnancy reporting

No embryo-fetal development studies have been performed. Therefore, this study excludes enrolment of women of child-bearing potential unless they are using highly effective methods of contraception, thus pregnancy is not an expected outcome for any female study patient. However, in the case that a pregnancy in a female study patient should occur, please follow the below reporting guidelines.

To ensure patient safety, each pregnancy occurring after signing the informed consent must be **reported to Polyneuron within 24 hours** of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Polyneuron. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on an SAE form.

The study drug must be discontinued, though the patient may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The patient may continue all other protocol assessments.

9.5 Early phase safety monitoring

The Investigator will monitor AEs in an ongoing manner and inform Polyneuron of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing Polyneuron and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Polyneuron and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, Polyneuron will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

10 Quality assurance and quality control

All patient data relating to the study will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IEC review, and regulatory agency inspections and provide direct access to source data documents.

This study will be monitored regularly by Clinipace according to ICH-GCP and their monitoring SOPs. Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

Clinipace is responsible for the data management of this study including data quality checking.

Polyneuron assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

Monitoring will be done by personal visits from a representative of Clinipace. Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patient are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, International Council on Harmonization (ICH) GCP, and all applicable regulatory requirements.

Patient confidentiality must be maintained in accordance with local requirements. The monitoring standards also require full verification for the presence of ICF, adherence to the inclusion/exclusion criteria, documentation of SAEs, and recording of the main efficacy and safety endpoints.

In addition to the monitoring visits, frequent communications (letter, telephone, and fax) by the clinical monitor will ensure that the investigation is conducted according to the clinical protocol and regulatory requirements.

The results of monitoring visits will be documented in monitoring reports. Issues arising will be escalated and dealt with in a timely manner. The escalation process is defined in the respective SOPs of Clinipace.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion. If source documents are not durable as long as needed (e.g. printouts on thermo labile paper), they must be preserved as certified copy. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1 Data collection

Data capture and management will be conducted using the Clinipace clinical management and EDC/eCRF system. The processes and responsibilities of data collection, management and quality assurance will be specified in the Data Management Plan.

All applicable study data collected on each patient will be entered by approved site personnel into the eCRF. Instructions for the completion and submission of eCRFs will be provided to the sites in a separate document.

Authorized personnel will verify all data entered into eCRFs for completeness and accuracy with reference to the source documents and records and will issue data queries to correct missing data or discrepancies found against the source within the EDC system. Data validation will consist of automated and manual edit checks that are created directly in the EDC system. Edit checks will be executed on all data points defined and documented by the study team and data management will be able to issue manual queries as needed to the eCRF. Study metrics will be reported from the EDC system. Only authorized site personnel will be able to enter/modify/correct data in the eCRF.

10.2 Independent Data Monitoring Committee

An IDMC will review the safety data and anti-MAG antibodies results and will provide its recommendations to Polyneuron.

The membership of the IDMC and the responsibilities of the IDMC and Polyneuron will be defined in a separate document entitled the “Independent Data Monitoring Committee Charter”. The IDMC Charter will include information about data flow, purpose and timing of IDMC meetings, guidance in the decision-making process, communication strategy, procedures for ensuring confidentiality, and procedures to address conflicts of interest.

11 Data analysis

The analysis will be conducted on all patients at the time the study ends. Any data analysis carried out independently by the investigator should be submitted to Polyneuron at least 30 days before submission for publication or presentation to enable review for Intellectual Property matters. Descriptive statistics (number (N), mean, SD, median and ranges for continuous variables, frequencies and percentages for categorical variables) will be provided by treatment group and/or by visit, if applicable. All data will be listed by patient, treatment group and, where applicable, by visit. Full details of the analyses will be provided in the Statistical Analysis Plan (SAP).

11.1 Analysis sets (study populations)

The statistical analysis will be based on separate analysis populations, defined as follows:

The two study phases SAD and MAD described in this protocol form an exploratory investigation without any formal statistical hypotheses. All results will be interpreted descriptively only from the following analyses sets:

Safety population (SP): All patients who receive at least one dose of study medication. The SP will be the primary analysis set for the safety and tolerability analyses.

Intent-to-treat (ITT) population: all patients who were enrolled. The ITT population will be used as analysis set to confirm efficacy.

Per-protocol (PP) population: all patients, who meet the inclusion/exclusion criteria, received full-course of the study drug as per enrolment and have completed the main relevant visits (at least one visit one week and one month during SAD after study drug dosing is needed to

assess biomarker and scores. During MAD at least one visit one month after the last dosing), for safety and efficacy assessment and who satisfactorily completed a pharmacodynamic blood sampling period without any major protocol violations which would render the data unreliable. The PP population will be used as analysis set to confirm the efficacy analyses and will constitute the primary analysis set for the PD and PK analyses. At least one visit one week and one month during SAD after dosing is needed to assess biomarker and scores. During MAD at least one visit one month after the last dosing.

Pharmacokinetic (PK) population: all patients who are included in the Safety population and who satisfactorily completed a pharmacokinetic blood sampling period without any major protocol violations which would render the data unreliable.

Pharmacodynamic (PD) population: all patients who are included in the PP and who satisfactorily completed a pharmacodynamic blood sampling period without any major protocol violations which would render the data unreliable.

11.2 Statistical hypothesis

The two study phases SAD and MAD described in this protocol form an exploratory investigation without any formal statistical hypotheses. All results will be interpreted descriptively only.

11.3 Protocol Deviation

Important deviations from the protocol, such as deviations from inclusion and exclusion criteria, relevant deviations in sampling times or from the planned time schedule of safety assessments will be reported in the clinical study report.

If an unexpected important deviation from the study protocol occurs, the investigator will consult Polyneuron to make a decision on how this deviation can be handled.

11.4 Patient demographics and other baseline characteristics

All data for background and demographic variables will be listed by dose group and patient. Summary statistics will be provided by dose group.

Relevant medical history, current medical conditions and other relevant information will be listed by treatment group and patient.

11.5 Treatments

Data for study drug administration and concomitant therapies will be summarized by dose group.

Total duration of time on study drug (Exposure) and reasons for discontinuation of study drug will be summarized by treatment group.

11.6 Analysis of safety

Safety endpoints will be summarized by treatment:

- Frequency, duration, severity and outcome of TEAEs.
- Changes in physical examination.
- Changes in clinical signs and scores.
- Signs of IRRs.
- Vital signs and ECGs.

- Hematology, clinical chemistry and urinalysis.

TEAEs are all AEs that that first appear during or after treatment with the IMP including those that worsened relative to the pre-treatment state.

Signs of IRRs include clinical signs and symptoms, changes in diastolic or systolic blood pressure, heart rate, oxygen saturation, and skin reactions or local reactions at the infusion site, which are monitored during and shortly after the administration of the IMP.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 22.0 or higher and summarized in frequency tables according to Preferred Term (PT) and System Organ Class (SOC). AEs will also be summarized according to their severity and causality. When an AE occurs more than once in the same patient, maximal severity and strongest causality will be counted. All SAEs and AEs leading to premature withdrawal from the study will be listed. Laboratory variables will be examined using mean changes from baseline. Laboratory values will also be categorized according to CTCAE toxicity grade and tabulated by their highest on-study toxicity grade. Shift tables will present numbers and percentages of patients with high / normal / low (or normal / abnormal) laboratory results at baseline and the last measurement available. Use of concomitant medications and of rescue antibiotics will be summarized.

Vital signs

All vital signs data will be listed by treatment, patient, and time point and abnormalities will be flagged. Summary statistics will be provided by treatment and time.

To assess the effect of PPSGG on blood pressure after dosing with PPSGG, blood pressure and heart rate on each infusion day (see Schedule of Assessments) expressed as change from baseline will be summarized. This represents the blood pressure at the approximate time of C_{max} after first dose and at steady state. The relationship between changes in blood pressure and heart rate and the C_{max} concentrations will also be investigated graphically.

ECG

All ECG data will be listed by treatment, patient, and time point and abnormalities will be flagged. Summary statistics will be provided by treatment and time and the number of patients with values above key threshold values will be displayed.

Clinical laboratory evaluations

All laboratory data will be listed by treatment, patient and time point and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and time point.

Adverse events

All information obtained on AEs will be displayed by treatment and patient.

The number and percentage of patients with AEs will be tabulated by SOC and PT with a breakdown by treatment. A patient with multiple AEs events within a SOC is only counted once towards the total of this SOC.

Summaries of SAEs will be provided in a similar manner.

Further displays of AEs may be produced in order to appropriately describe the outcomes seen in this trial.

11.6.1 Sample Handling procedures

All the safety analysis will be performed in local laboratory.

Sample handling is described separately in a Laboratory Manual.

Each sample will be labelled to indicate not less than: Polyneuron, study number, patient number, and sampling time.

All sample handling procedures, including the time of each sample collection, the time of placement into frozen storage (at the end of the sample workup), and the date of transfer or shipment of the samples to the responsible analyst will be documented in detail. Any missing blood draws must be reported in the eCRF. The exact time (using the 24-hour clock) of sample collection and possible problems occurring during the sampling will be entered in the respective sections of the eCRF.

All samples will be stored for a period of 6 months after submission of the final report to Polyneuron. If no separate contract for further storage has been agreed by Polyneuron, the samples will then be destroyed or shipped to Polyneuron. Both, return and destruction of samples requires Polyneurons approval.

Each sample will be labelled to indicate the study number, patient number, period number (MAD phase only), and sampling time.

All sample handling procedures, including the time of each sample collection, the time of placement into frozen storage (at the end of the sample workup), and the date of transfer or shipment of the samples to the responsible analyst will be documented in detail.

After sampling, blood and urine samples will be worked up and analyzed in a central laboratory, all results will be judged by a physician individually and commented as follows:

- Values within the reference ranges will not be commented. A '*' representing the value will be plotted within the brackets representing the reference range.
- For values slightly outside the reference ranges without clinical relevance a '*' representing the value will be plotted outside the brackets representing the reference range.
- For values outside the reference ranges with major deviation and/or possible pathological relevance a '*' representing the value will be plotted outside the brackets representing the reference range. In addition, the respective parameter will be shaded.

For all findings with major deviation and/or possible pathological relevance, follow-up examinations will be carried out until the deviation returns to normal or the absence of pathological relevance can be confirmed. If a deviation considered clinically relevant has not returned to a normal or not clinically relevant value when it is checked during the screening laboratory tests, the patient will not be included in the study.

The investigator has to decide whether a laboratory abnormality represents an adverse event

11.7 Analysis of Pharmacodynamics

Secondary variables supporting the secondary objective to assess the effect of PPSGG on reduction of anti-MAG IgM levels, change reduction of anti-MAG IgM antibody levels and time to anti-MAG IgM rebound (pre-treatment BTU), paraprotein levels (g/L), total IgM levels (g/L), and anti-HNK-1 IgM titers will be analyzed. Descriptive summary statistics will be provided by dose and dosing frequency. Appropriate transformations will be detailed in the SAP. Estimates of the differences between each does of PPSGG and placebo will be calculated.

11.8 Analysis of Pharmacokinetics

PPSGG concentration data will be listed by dose, patient and time point (described in Section 8.6). Descriptive summary statistics will be provided by treatment and time, including the frequency (n, %) of samples collected. Sample concentrations below the LLOQ will be reported and used in PK calculation as zero.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. An exception to this is T_{max}. Since T_{max} is generally evaluated by a nonparametric method, median values and ranges will be given for this parameter. A geometric mean will not be reported if the dataset includes zero values.

The relationship between doses of PPSGG and the PK parameters AUC and C_{max} will be explored and used to calculate PPSGG half-life (T1/2, volume of distribution (Vd) and CL rate. Descriptive summary statics will also be provided for $T_{1/2}$, Vd and CL.

Graphical methods will be employed to show mean and individual concentration-time profiles and dose-exposure proportionality.

11.9 Analysis of exploratory variables (if applicable)

Statistical analysis for exploratory variables will be described in more detail in the Statistical Analysis Plan.

11.9.1 Exploratory endpoints

- NfL to measure the degree of axonal damage.
- BAFF.
- Indirect immunofluorescence on sciatic nerves.
- Classical pathway of the complement.

All biomarker data will be listed by treatment, patient, and time. Summary statistics will be provided by doses and time. Change from baseline until EOS will be summarized.

Graphical measures will be used to explore relationships between PPSGG treatment and biomarkers.

11.10 Sample size calculation

The sample size per cohort in this SAD and MAD study is representative of other FiH studies and based on feedback from EMA for a scientific advice.

It is anticipated that the specified number of patients should complete the study in accordance with this protocol. An insufficient number of evaluable cases might impair the aim of the study.

To allow for a drop-out rate of up to 20% in MAD phase, 30 patients will be enrolled with the aim of having at least 24 patients complete each phase.

11.11 Interim analyses

No formal interim analysis is planned for this study. Safety data will be gathered and reviewed by the IDMC on continuous basis. The data will be frozen after the SAD phase to define the schedule and doses for the MAD phase based on the SAD data as described previously.

12 Regulatory and Ethical considerations

12.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with

applicable local regulations (including European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki.

12.2 Responsibilities of the investigator and Institutional Review Board/Independent Ethics Committee

Before the start of the study Polyneuron or authorized applicant will apply for approval for the performance of the study at the Competent Authority. The sites will apply for approval for the performance of the study at the respective EC. All documents required by the EC and by the Competent Authority will be submitted.

Any notification / submission has to be dated and to contain sufficient information to identify the respective protocol.

The study will only be started after receipt of the written approval of the respective EC and Competent Authority.

The Principal Investigator and Clinipace are responsible for maintaining the approval documents in the study documentation files.

The Principal Investigator or Clinipace will report promptly to the EC new information that may adversely affect the safety of the patients or the conduct of the trial.

Polyneuron (or authorized applicant), should submit a written report about the safety of the patients as well as a list of occurred suspected serious adverse drug reactions caused by the investigational medicinal product of the clinical study to the EC and the Competent Authority annually, or more frequently if requested by the EC or the Competent Authority.

A declaration of the end of trial should be forwarded by Polyneuron (or authorized applicant), to the Competent Authority and to the EC within 90 days after the study has been completed or in the event of premature termination of the study within 15 days.

Polyneuron (or authorized applicant) should provide a summary of the clinical study report to the EC and Competent Authority within 1 year after completion of the study

The reporting to the EC and the Competent Authority is clearly defined in the Quality Agreement and responsibility list for clinical study.

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation) informed consent.

12.3 Informed consent procedure

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Clinipace will provide to investigators a proposed ICF that complies with the ICH E6 GCP guideline and regulatory requirements and is considered appropriate for this study. The procedures set out in the main consent form concerning the storage, maintenance of privacy, and release of the data or specimens for the main study will also be adhered to for any future research. Any changes to the proposed consent form suggested by the investigator must be agreed to by Polyneuron before submission to the IRB/IEC.

The investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.
Patients must be informed that their participation is voluntary. Patients will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations,

ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative

Information about potential side effects in humans about the investigational drug can be found in the IB. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and then must be discussed with the patient.

Ensure patients are informed of the contraception requirements outlined in the Section (Exclusion criteria) and in Section (Contraception requirements).

A separate consent for an optional Biobanking component will be obtained. The Investigator presents this option to the patient, as permitted by local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in this biobank collection will in no way affect the patient's ability to participate in the main research study.

A copy of the approved version of all consent forms must be provided to the Polyneuron monitor after IRB/IEC approval.

12.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

12.5 Quality Control and Quality Assurance

Audits of investigator sites, vendors, and Polyneuron systems are performed or overseen by Polyneuron Pharma Auditing and Compliance Quality Assurance (or contract research organization [CRO] working on behalf of Polyneuron), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk-based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Polyneuron processes.

13 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study patients. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances is an

investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Polyneuron and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

13.1 Protocol Amendments

Neither the investigator nor the sponsor will alter this clinical study protocol without obtaining the written agreement of the other party. Once the study has started, amendment should be made only in exceptional cases. The changes then become part of the clinical study protocol.

Substantial amendment, i.e., changes in the clinical study protocol which may have a significant impact on the safety of the patients, or on the scientific value of the study, or on the conduct or management of the study, may not be implemented without a favorable opinion of the ECs/IRBs unless the changes consist of urgent safety measures to protect study patients. In such a case, approval must be obtained as soon as possible after implementation.

Amendments which are minor and/or refer to changes regarding logistical and administrative aspects of the study (i.e., change in telephone numbers) are always sent to the ECs for information.

14 References

1. Latov N, Braun PE, Gross RB et al. Plasma cell dyscrasia and peripheral neuropathy: identification of the myelin antigens that react with human paraproteins. Proc. Natl. Acad. Sci. U. S. A. 1981; 78(11):7139–7142.

2. Braun PE, Frail DE, Latov N. Myelin-associated glycoprotein is the antigen for a monoclonal IgM in polyneuropathy. J. Neurochem. 1982; 39(5):1261–1265.

3. Steck AJ, Stalder AK, Renaud S. Anti-myelin-associated glycoprotein neuropathy. Curr. Opin. Neurol. 2006; 19(5):458–463.

4. Rison RA, Beydoun SR. Paraproteinemic neuropathy: a practical review. BMC Neurol. 2016; 16:13.

5. Ritz MF, Erne B, Ferracin F et al. Anti-MAG IgM penetration into myelinated fibers correlates with the extent of myelin widening. Muscle Nerve 1999; 22(8):1030–1037.

6. Dalakas MC. Pathogenesis of immune-mediated neuropathies. Biochim. Biophys. Acta 2015; 1852(4):658–666.

7. Talamo G, Mir MA, Pandey MK et al. IgM MGUS associated with anti-MAG neuropathy: a single institution experience. Ann. Hematol. 2015; 94(6):1011–1016.

8. Vallat J-M, Magy L, Ciron J et al. Therapeutic options and management of polyneuropathy associated with anti-MAG antibodies. Expert Rev. Neurother. 2016; 16(9):1111–1119.

9. Nobile-Orazio E, Baldini L, Barbieri S et al. Treatment of patients with neuropathy and anti-MAG IgM M-proteins. Ann. Neurol. 1988; 24(1):93–97.

10. Lunn MP, Nobile-Orazio E. Immunotherapy for IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies. Cochrane Database Syst. Rev. 2016; 10:CD002827.

11. Dalakas MC. Advances in the diagnosis, immunopathogenesis and therapies of IgM-anti-MAG antibody-mediated neuropathies. Ther. Adv. Neurol. Disord. 2018; 11:1756285617746640.

12. Pestronk A, Florence J, Miller T et al. Treatment of IgM antibody associated polyneuropathies using rituximab. J. Neurol. Neurosurg. Psychiatry 2003; 74(4):485–489.

13. Benedetti L, Briani C, Franciotta D et al. Long-term effect of rituximab in anti-mag polyneuropathy. Neurology 2008; 71(21):1742–1744.

14. Dalakas MC. Pathogenesis and Treatment of Anti-MAG Neuropathy. Curr. Treat. Options Neurol. 2010; 12(2):71–83.

15. Latov N. Diagnosis and treatment of chronic acquired demyelinating polyneuropathies. Nat. Rev. Neurol. 2014; 10(8):435–446.

16. Quarles RH, Weiss MD. Autoantibodies associated with peripheral neuropathy. Muscle Nerve 1999; 22(7):800–822.

17. Tatum AH. Experimental paraprotein neuropathy, demyelination by passive transfer of human IgM anti-myelin-associated glycoprotein. Ann. Neurol. 1993; 33(5):502–506.

18. Polyneuron; PN-1007 (PPSGG) IB, version 1 January 2020., .

19. Herrendorff R, Hänggi P, Pfister H et al. Selective in vivo removal of pathogenic anti-MAG autoantibodies, an antigen-specific treatment option for anti-MAG neuropathy. Proc. Natl. Acad. Sci. U. S. A. 2017; 114(18):E3689–E3698.

20. Katopodis AG, Warner RG, Duthaler RO et al. Removal of anti-Galalpha1,3Gal xenoantibodies with an injectable polymer. J. Clin. Invest. 2002; 110(12):1869–1877.

21. Cook L, Macdonald DHC. Management of paraproteinaemia. Postgrad. Med. J. 2007; 83(978):217–223.

22. Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. [http://www.fda.gov/regulatory-information/search-fda-guidance-documents/estimating-maximum-safe-starting-dose-initial-clinical-trials-therapeutics-adult-healthy-volunteers].

23. Strategies to identify and mitigate risks for first-in-human early clinical trials with investigational medicinal products. [https://www.ema.europa.eu/en/strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational-medicinal].

24. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of paraproteinemic demyelinating neuropathies. Report of a Joint Task Force of the European Federation of Neurological Societies and the Peripheral Nerve Society--first revision. J. Peripher. Nerv. Syst. JPNS 2010; 15(3):185–195.

15 Appendices

15.1 Common Terminology Criteria for Adverse Events v5.0 (CTCAE)

Publish Date: November 27, 2017

Introduction

The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

SOC

System Organ Class (SOC), the highest level of the MedDRA1 hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v5.0 term is a MedDRA LLT (Lowest Level Term).

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1

Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2

Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental Activities of Daily Living (ADL)*.

Grade 3

Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

Grade 4

Life-threatening consequences; urgent intervention indicated. Grade 5 Death related to AE. A Semi-colon indicates ‘or’ within the description of the grade. A single dash (-) indicates a Grade is not available. Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Definitions

A brief Definition is provided to clarify the meaning of each AE term. A single dash (-) indicates a Definition is not available.

Navigational Notes

A Navigational Note is used to assist the reporter in choosing a correct AE. It may list other AEs that should be considered in addition to or in place of the AE in question. A single dash (-) indicates a Navigational Note has not been defined for the AE term.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

15.2 Overall Neuropathy Limitations Scale (ONLS)

Name:
Date:

Overall Neuropathy Limitations Scale (ONLS)

Instructions: The examiner should question **and** observe the patient in order to determine the answers to the following questions. Note should be made of any other disorder other than peripheral neuropathy which limits function at the foot of the page.

ARM SCALE

Does the patient have any symptoms in their hands or arms, eg tingling, numbness or weakness? **Yes** ☐ **No** ☐
(if "no", please go to "legs" section)

Is the patient affected in their ability to:	Not affected	Affected but not prevented	Prevented
Wash and brush their hair	☐	☐	☐
Turn a key in a lock	☐	☐	☐
Use a knife and fork together (or spoon, if knife and fork not used)	☐	☐	☐
Do or undo buttons or zips	☐	☐	☐
Dress the upper part of their body excluding buttons or zips	☐	☐	☐

If all these functions are prevented can the patient make purposeful movements with their hands or arms? Yes ☐ No ☐ Not applicable ☐

Arm Grade
0–Normal
1–Minor symptoms in one or both arms but not affecting any of the functions listed **SCORE=____**
2–Disability in one or both arms affecting but not preventing any of the functions listed
3–Disability in one or both arms preventing at least one but not all functions listed
4–Disability in both arms preventing all functions listed but purposeful movement still possible
5–Disability in both arms preventing all purposeful movements

LEG SCALE

	Yes	No	Not applicable
Does the patient have difficulty running or climbing stairs?	☐	☐	☐
Does the patient have difficulty with walking?	☐	☐	☐
Does their gait look abnormal?	☐	☐	☐
How do they mobilise for about 10 metres (ie 33 feet)?			
Without aid	☐	☐	☐
With one stick or crutch or holding to someone's arm	☐	☐	☐
With two sticks or crutches or one stick or crutch holding onto someone's arm or frame	☐	☐	☐
With a wheelchair	☐	☐	☐
If they use a wheelchair, can they stand and walk 1 metre with the help of one person?	☐	☐	☐
If they cannot walk as above are they able to make some purposeful movements of their legs, eg reposition legs in bed?	☐	☐	☐
Does the patient use **ankle foot orthoses/braces?** (please circle)	☐	☐ **If yes:** (please circle) **right/left**	

Leg grade
0–Walking/climbing stairs/running not affected
1–Walking/climbing stairs/running is affected, but gait does not look abnormal **SCORE=____**
2–Walks independently but gait looks abnormal
3–Requires unilateral support to walk 10 metres (stick, single crutch, one arm)
4–Requires bilateral support to walk 10 metres (sticks, crutches, crutch and arm,frame)
5–Requires wheelchair to travel 10 metres but able to stand and walk 1 metre with the help of one person
6–Restricted to wheelchair, unable to stand and walk 1 metre with the help of one person, but able to make some purposeful leg movements
7–Restricted to wheelchair or bed most of the day, unable to make any purposeful movements of the legs

Overall Neuropathy Limitation Scale–arm scale (range 0 to 5)+leg scale (range 0 to 7);
(range: 0 (no disability) to 12 (maximum disability)) **TOTAL SCORE=____**
Is there any disorder, other than peripheral neuropathy, which affects the above functions **Yes** ☐ **No** ☐
If **yes** please describe:

15.3 Inflammatory Neuropathy Cause and Treatment (INCAT) Sensory Sum Score (ISS)

The ISS ranges from 0 (normal sensation) to 20 (most severe sensory deficit) and is composed of the summation of the following sensation qualities:

- Pinprick arm grade (range 0-4).
- Vibration arm grade (range 0-4).
- Pinprick leg grade (range 0-4).
- Vibration leg grade (range 0-4).
- Two-point discrimination grade (range 0-4).

Pinprick is tested with the sharp end of an esthesiometer, patients indicate normal or abnormal. Paresthesia, dysesthesia or hyperesthesia are to be scored as abnormal. Normal reference point: face.

Vibration sense is tested using the graduated Rydel-Seiffer tuning fork, measures obtained are compared with the reported normative threshold values.

Pinprick and vibration sense examination take place distal to proximal and only the highest extension of dysfunction of the most affected arm and leg are recorded separately for both qualities.

Pinprick sensation (sites of examination and corresponding grades)		**Vibration sensation (sites of examination and corresponding grades)**		**Two-point discrimination (sites of examination and corresponding grades)**
Arms	Legs	Arms	Legs	Index finger [K]
Normal sense 0, at index finger A	Normal sense 0, at hallux F	Normal sense 0, at index finger A	Normal sense 0, at hallux F	Normal sense 0, <4 mm
Abnormal sense	Abnormal sense	Abnormal sense	Abnormal sense	Abnormal sense
1, at index finger [B]	1, at hallux [G]	1, at index finger [B]	1, at hallux [G]	1, 5-9 mm
2, at wrist [C]	2, at ankle [H]	2, at wrist [C]	2, at ankle [H]	2, 10-14 mm
3, at elbow [D]	3, at knee [I]	3, at elbow [D]	3, at knee [I]	3, 15-19 mm
4, at shoulder [E]	4, at groin [J]	4, at shoulder [E]	4, at groin [J]	4, > 20 mm

A,B: index finger (dorsum distal interphalangeal joint); C: ulnar styloid process; D: medial humerus epicondyle; E: acromioclavicular joint; F,G: hallux (dorsum inter-phalangeal joint); H: medial malleolus; I: patella; J: anterior superior iliac spine; K: index finger (ventral side: distal phalanx).

15.4 Rasch-built Overall Disability Scale (RODS) Scale

INSTRUCTIONS: This is a questionnaire about the relationship between daily activities and your health. Your answers give information about how your polyneuropathy affects your daily and social activities and to what degree you are able to perform your usual activities.

Answer each question by marking the correct box ("x"). If you are not sure about your ability to perform a task, you are still requested to mark an answer that comes as close as possible to your judged ability to complete such a task. All questions should be completed. You can only choose one answer to each question. If you situation fluctuates, your answer should be based on how you *usually* perform the task.

If you need assistance or you are using special devices to perform the activity, you are requested to mark "possible, but with some difficulty ". In case you never perform the activity due to your polyneuropathy mark "not possible".

Are you able to	Mark the best option with "x"		
Task	Not possible to perform [0]	Possible, but with some difficulty [1]	Possible, without any difficulty [2]
1. read a newspaper/book?	☐	☐	☐
2. eat?	☐	☐	☐
3. brush your teeth?	☐	☐	☐
4. wash upper body?	☐	☐	☐
5. sit on a toilet?	☐	☐	☐
6. make a sandwich?	☐	☐	☐
7. dress upper body?	☐	☐	☐
8. wash lower body?	☐	☐	☐
9. move a chair?	☐	☐	☐
10. turn a key in a lock?	☐	☐	☐
11. go to the general practitioner?	☐	☐	☐
12. take a shower?	☐	☐	☐
13. do the dishes?	☐	☐	☐

14. do the shopping?	☐	☐	☐
15. catch an object (e.g., ball)?	☐	☐	☐
16. bend and pick up an object?	☐	☐	☐
17. walk one flight of stairs?	☐	☐	☐
18. travel by public transportation?	☐	☐	☐
19. walk and avoid obstacles?	☐	☐	☐
20. walk outdoor < 1 km?	☐	☐	☐
21. carry and put down a heavy object?	☐	☐	☐
22. dance?	☐	☐	☐
23. stand for hours?	☐	☐	☐
24. run?	☐	☐	☐

15.5 Hand Grip Strength Test

With the Martin Vigorimeter, the patient squeezes a rubber ball that is connected to a manometer with rubber tubing.

The patient's grip strength is expressed in kilopascal (kPa), with a range of 0–160 kPa.

The same dynamometer will be used for a patient throughout the study. When performing the test, patients will stand, holding the dynamometer in dominant hand, with their arm parallel to the body without squeezing the arm against the body. This assessment will be performed in triplicate on same day at each time point.

15.6 The Modified Rankin Scale (mRS)

The scale runs from 0-6, running from perfect health without symptoms to death.

0 - No symptoms.

1 - No significant disability. Able to carry out all usual activities, despite some symptoms.

2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.

3 - Moderate disability. Requires some help, but able to walk unassisted.

4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.

5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent.

6 - Dead.

15.7 Motor Unit Number Index (MUNIX)

MUNIX will be performed on the tibialis anterior (TA), abductor digiti mini (ADM) and abductor pollicis brevis (APB) muscles as previously reported (Delmont et al. 2016).

Supramaximal distal stimulations of the corresponding nerves will be performed to achieve maximal CMAP amplitude with minimum rise time and sharp negative take-off. The recordings will be assessed on a 300ms window with filter setting of 3Hz-3000Hz. Ten isometric contractions will be recorded as surface interference pattern (SIP) ranging from 10 to 100% of contraction. The degree of the force increment will be estimated by the resistance given by the examiner and by the amplitude and the fullness of the SIP. SIP epochs will be accepted if SIP area >20mV/ms, ideal case motor unit count (ICMUC) <100 and SIP area/CMAP area >1. A MUNIX sumscore will be calculated by adding the results of the ADM, APB and TA muscles.

APB: Place hand upon flat surface, palm up. Place recording electrode on thenar eminence just lateral to mid-point of first metacarpal, aligned with first metacarpal. Place reference electrode distally at the thumb. Grounding electrode is placed on the dorsum of the hand. Place stimulator at wrist between flexor carpi radialis and palmaris longus tendons. Avoid partial abduction of the thumb and pronation of the forearm. Counter resistance: place your hand over the patient's hand, with your thumb giving resistance to the patient's thumb.

ADM: Place hand upon flat surface, palm up. Place recording electrode on ADM at midpoint fifth metacarpal. Place reference electrode distally at the little finger. Grounding electrode is placed on the dorsum of the hand. Place stimulator at wrist adjacent to flexor carpi ulnaris tendon. In some subjects, maximal compound muscle action potential (CMAP) is achieved with more proximal placement of the recording electrode. Be aware of initial baseline shift due to electrode movement on the skin while increasing force levels. Counter resistance: stabilize with your fingers/thumb. Do not allow abduction of digit V.

TA: Lower leg is positioned naturally with sole of the foot on the floor, knee flexed approximately 90 degrees. Place recording electrode lateral to tibial crest, one-third of distance between ankle and knee (closer to knee). Place reference electrode over the patellar tendon. Grounding electrode should be places above at the level of the fibular head. Place stimulator one to two fingerbreadths inferior to fibular head. Counter resistance: use your hand to give resistance with the foot positioned at 90 degrees. Avoid pronation/supination of the foot.

15.8 Ataxia Score

- normal posture with closed eyes (0).
- slight postural alteration with closed eyes (1).
- severe postural alteration with closed eyes (2).
- inability to stand with closed eyes (3).

15.9 Timed 10-Meter Walk Test Instructions

Description:

Individual walks without assistance 10 meters (32.8 feet) and the time is measured.

Set-up

- Measure and mark a 10-meter indoor walkway, along a flat, quiet corridor with a non-carpeted surface.
- Place chairs at the start and finish of the walkway.

Site instructions:

- Patients should be evaluated for lower limb injury immediately prior the test.
- A 10-minute rest period should always be given prior to the start of the test.
- Start timing when the toes of the leading foot crosses the 0-meter mark.
- Stop timing when the toes of the leading foot crosses thee 10-meter mark
- Ambulatory aids such as cones and walkers are permitted.
- No support may be given by an assistant unless the patient needs help to rise from a fall or to sit down.
- Subjects may not touch the walls.
- Due to possibility of subject falls, the course should be within easy access of appropriate medical assistance.
- Test results should be recorded on the 10 Meter Walk Test Worksheet.

Patient instructions

- Patients should wear comfortable clothing and appropriate shoes for walking. Since patients will be tested at multiple time points, they should make an effort to wear the same type of shoes each time.
- The tester will say ”Ready, Set, Go”. When the tester says go, begin walking at your normal comfortable pace.

CLINICAL STUDY PROTOCOL

Study title	First in Human study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy of PPSGG (PN-1007) in anti-MAG neuropathy patients.
Investigational Medicinal Product	PPSGG (PN-1007).
Study Number	PN-1007-001.
EudraCT number	2020-000067-23.
Study phase	Phase I/IIa.
Version and Date of protocol	Version 1.2 (including Amendment 1.1), 16 April 2020.
Sponsor	Polyneuron Pharmaceuticals AG Hochbergerstrasse 60C CH-4057 Basel, Switzerland.
Coordinating Investigator	Emilien Delmont, MD.

This document is the sole property of Polyneuron Pharmaceuticals AG and all information contained herein has to be considered and treated as strictly confidential. This document shall be used only for the purpose of the disclosure herein provided. No disclosure or publication shall be made without the prior written consent of Polyneuron Pharmaceuticals AG.

SPONSOR SIGNATURE PAGE

Protocol Title: First in Human study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy of PPSGG (PN-1007) in anti-MAG neuropathy patients.

Protocol Number: PN-1007-001.

Sponsor: Polyneuron Pharmaceuticals AG.

I approve the contents of this clinical protocol for Study No. PN-1007-001 version 1.2 (including Amendment 1.1), dated 16 April 2020 and agree to meet all obligations of Polyneuron Pharmaceuticals as detailed in all applicable regulations and guidelines. In addition, I will inform the Coordinating Investigator and all other investigators of all relevant information that becomes available during the conduct of this study.

Sponsor Signatory:

Debra Barker, MD
CMO, Polyneuron Pharmaceuticals AG
Hochbergerstrasse 60C
CH-4057 Basel, Switzerland.

Signature

16.4.20

Date

Coordinating Investigator:

Emilien Delmont, MD
APHM Hopital La Timone Adultes
264 Rue Saint Pierre,
F- 13005 Marseille, France.

Signature

Date

16/04/2020

PROTOCOL INVESTIGATOR AGREEMENT

As Investigator of this study, I agree:

- To conduct the study in compliance with this protocol, and with mutually agreed future protocol amendments, protocol administrative changes, other study conduct procedures and study conduct documents provided by Polyneuron Pharmaceuticals AG.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study (my Staff) are adequately informed about the investigational medicinal product and other study-related duties and functions as described in the protocol and have the necessary skill and competencies to manage them.
- To co-operate with the representative of Polyneuron Pharmaceutical AG's appointed Contract Research Organization (CRO) in the monitoring of the study and resolution of queries about the data.
- That I have been informed that the agency and Ethics Committee may require the sponsor to obtain and supply, as necessary, details about the Investigator's ownership interest in the sponsor or the investigational product, and more generally about the financial ties with the sponsor. Polyneuron Pharmaceuticals AG will use and disclose the information solely for the purpose of complying with regulatory requirements.
- To provide Polyneuron Pharmaceuticals AG or CRO with a current Curriculum Vitae and other documents required by the Ethics or authorities for this study.

Study title	First in Human Study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy of PPSGG in anti-MAG neuropathy patients.
EudraCT number	2020-000067-23.
Versions and Date of protocol	Version 1.2 (including Amendment 1.1), 16 April 2020.
Protocol code number	PN-1007-001.
Name and address of Investigator	

_____	_____
Signature	**Date**

Amendment 1.1 (16 April 2020)

Amendment rationale

The purpose of this substantial amendment is to address questions raised by MHRA. The changes are summarized below.

Changes to the protocol

The following changes have been implemented throughout the protocol:

1. Recent apheresis/plasmapheresis has been added as exclusion criterion in Section 4.3.
2. The limit for creatinine clearance at inclusion has been raised to 60 mL/min. The inclusion criterion in the protocol in Section 4.3. has been adapted accordingly.
3. Additional pregnancy tests on a monthly basis (on Days 28, 56 and 98) in the MAD phase have been added. The Assessment schedule in Section 8.1. has been updated accordingly.
4. The exclusion criterion (Section 4.4) has been updated to specify that progesterone containing hormonal tablets must be associated with inhibition of ovulation in order to qualify as highly effective.
5. The durations of contraceptive use between males and females have been aligned to one week.
6. In Section 7.6 the study stopping rules have been adapted based on the feedback by MHRA.
7. The plan for rapid communication of serious adverse events and suspected unexpected serious adverse reactions (SUSARs) between the sponsor, the investigators of all sites and the patients has been described in Section 9.1.7.
8. Section 1.8 has been updated to provide some clarification on the justification of the doses.
9. The synopsis is updated to reflect the above changes as appropriate.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes herein affect the Informed Consent/Assent.

Synopsis

Study Number and Title	First in Human study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy of PPSGG (PN-1007) in anti-MAG neuropathy patients.
Study Phase	Phase I/IIa.
Study Duration	Overall planned study duration is Q2 2020 – Q2 2022. Up to 2 months and 8 visits per patient in the single ascending dose (SAD) phase and up to 6 months and 17 visits per patient in the multiple ascending dose (MAD) phase.
Indication	Anti-myelin-associated glycoprotein (MAG) neuropathy.
Rationale for the study	This is a Phase I/IIa, First in Human (FiH), multicenter, single and multiple ascending dose escalation trial of PPSGG, an antibody scavenger of pathogenic anti-MAG immunoglobulin M (IgM) autoantibodies for treatment of anti-MAG neuropathy. The aim of the study is to assess the safety and tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of PPSGG in a SAD and a MAD study in anti-MAG neuropathy patients. The safety and tolerability of PPSGG has been demonstrated in different animal species, for up to 11 single doses given over 15 min IV infusion. Currently, there is no treatment for anti-MAG neuropathy approved by the European Medicines Agency (EMA) or by the US Food and Drug Administration (FDA). However, off-label treatments are used for treatment of anti-MAG neuropathy, including various immunomodulatory and immunosuppressive treatments used to manage anti-MAG neuropathy. Nonetheless, these treatments are of limited efficacy and may induce side effects. Clinical improvement of neuropathic symptoms in patients with anti-MAG neuropathy correlates with reduced serum levels of anti-MAG IgM autoantibodies and disease worsening is associated with increasing anti-MAG IgM levels during treatment follow-up. Knowledge of the biological role of the MAG protein, the inhibitory activity of PPSGG on anti-MAG IgM antibodies, and the clinical correlation between anti-MAG IgM levels and clinical outcomes support the hypothesis that a reduction in anti-MAG IgM levels by PPSGG can be associated with clinical improvements for patients. During the SAD phase, PPSGG will be administered via intravenous (IV) infusion to patients with confirmed anti-MAG neuropathy. Based on the safety and PK/PD data of the SAD phase, PPSGG will be administered up to 11 times during the MAD phase of this study for a maximum of 6 weeks.

Objectives

Primary objective

To assess the safety and tolerability after single and multiple intravenous administrations of PPSGG in patients suffering from anti-MAG neuropathy.

Secondary objectives

- To evaluate the PK of PPSGG after single and multiple intravenous administrations.
- To investigate PD of PPSGG in reducing anti-MAG IgM levels.
- To obtain preliminary efficacy data, neurological evaluations and clinical outcome using different clinical scores.

Study design

Phase Description

Phase I: FiH, open label, SAD escalation study in anti-MAG neuropathy patients to assess the safety, tolerability, PK and PD parameters of PPSGG.

After completion and evaluation of the SAD phase a MAD phase will follow.

Phase IIa: Randomized, dose escalation, double blind (patient and investigator blinded), placebo-controlled MAD in anti-MAG neuropathy patients to assess the safety, immunogenicity, tolerability, PK, PD and preliminary efficacy parameters of PPSGG.

- Single Ascending Dose (SAD)

The single rising dose escalation phase will enroll 6 patients in each of the 4 or 5 ascending dose cohorts. The first administration of PPSGG of any cohort will be provided to a single patient (sentinel patient). The decision to complete a given cohort will be based on safety data up to 72 hours after treatment of the sentinel patient. The decision to escalate to the following dose (once completed a cohort) will be based on safety data, collected during the first 72 hours after the start of the infusion, where no stopping rules are met and analyzed by an Independent Data Monitoring Committee (IDMC). The study drug will be administered as a 60 min IV infusion.

In the SAD phase each patient will have the following 8 visits: Screening, Baseline, Treatment (4 visits), end of study (EOS) and Follow-up.

- Multiple Ascending Dose (MAD)

The multiple rising dose phase will enroll 2 dose cohorts of at least 12 patients each (10 on active and 2 on placebo). Dose levels will be determined based on the safety, tolerability, PK and PK/PD outcome (anti-MAG IgM titers) from the SAD phase. The dosing frequency will be defined based on the PK/PD

relationship established during the SAD phase (PPSGG half-life, anti-MAG IgM kinetic) and simulation of it. The study drug will be administered for up to 11 times (as a 60 min IV infusion) for six weeks to explore the effect on anti-MAG antibody levels. For safety purposes the first 2 patients in each cohort of the MAD phase will be randomized to receive active or placebo treatment in a double-blind fashion. The decision to complete a given cohort will be based on safety data of the first 2 patients collected during 2 weeks after the start of the infusion. The decision to escalate to the following dose will be based on safety data collected during the first 2 weeks after the start of infusion and analyzed by an IDMC.

In the MAD phase each patient will have up to 17 visits: Screening, Baseline, Treatment (up to 14 visits), EOS and Follow-up.

The MAD phase will be adapted for dosing regimen in accordance with PK, PD, safety and tolerability data collected during the SAD phase. Dosing regimen includes the dose level administered, the frequency of dosing and the duration of dosing, i.e. the number of doses administered. The maximum starting dose in the MAD phase will be one of the tested doses in the SAD phase. Based on the safety toxicology studies performed in animals the maximum number of doses is 11 infusions in 6 weeks. The goal is to define a potential dose and regime to reliably and safely reduce anti-MAG IgM antibody levels by at least 50%.

The following assessments will be performed in each of the two phases (SAD and MAD):

- Safety and tolerability (adverse events [AEs], vital signs, laboratory data, electrocardiograms [ECGs], and local tolerability assessment).
- Blood sampling for anti-drug antibodies (ADA) development (immunogenicity).
- Blood sampling for PPSGG pharmacokinetics.
- Blood sampling for pharmacodynamic (anti-MAG antibodies levels and titers, paraprotein level, anti-human natural killer- 1 [anti-HNK1] antibodies and total IgM) markers.
- Clinical assessments based on overall neuropathy limitations scale [ONLS] score, time to walk 10 meters, and Rasch-built overall disability scale [RODS] and Ataxia scores.

The SAD and MAD phases will be split in two parts: (1) an active treatment part of one infusion in SAD and multiple administrations in the MAD and (2) and an observation period of 1 month in SAD and 3 months in the MAD phase, respectively. After this, patients whose antibody levels have not

	returned to baseline will enter in the follow-up phase, the duration of which will depend on the evolution of the anti-MAG IgM antibody levels.
Number of patients	Approximately 48 patients will participate. Six patients per cohort (4 or more cohorts) in Phase I (SAD) and 12 patients (10 active and 2 placebo) per cohort (total 2 cohorts) in Phase IIa (MAD) respectively. In order to have enough evaluable patients, up to 2 additional patients per cohort will be recruited.
Sites	Approximately 8 sites from 5 European countries are planned to participate.
Inclusion criteria	• Written informed consent. • Age between 18 and 80 years, male and female. • Patient with a confirmed diagnosis of monoclonal IgM associated with monoclonal gammopathy of undetermined significance (MGUS) with anti-MAG activity (titer of > 10'000 Bühlmann Titer units [BTU]) and demyelinating neuropathy defined by electrophysiological criteria according to European Federation of Neurological Societies/Peripheral Nervous System paraproteinemic demyelinating neuropathy (EFNS/PNS PDN) guideline, 2010. • Clear clinical signs of disability: with at least ONLS ≥ 2 in lower extremities. • Inflammatory Neuropathy Cause and Treatment sensory sum score (INCAT) ≥ 2. • Patients must have adequate hepatic function as evidenced by total bilirubin < 1.5 mg/dL, and alkaline phosphatase and aspartate transaminase/alanine aminotransferase < 2X the upper limit of normal (ULN). • Absence of cause of neuropathy independent from anti- MAG activity: e.g. diabetes, hypothyroidism, past or current dependence on alcohol, past or current treatment with neurotoxic drugs. • Patients must have adequate renal function as evidenced by serum creatinine <2 mg/dL or calculated creatinine clearance of ≥60 mL/min within 28 days before the first investigational medicinal product (IMP) administration using the Modification of Diet in Renal Disease (MDRD) formula. • Capability to meet the requirements of the study.

Exclusion criteria

- Patients with total serum IgM levels >30 g.
- Hematological malignancy (e.g. known multiple myeloma or confirmed Waldenström's macroglobulinemia based on bone marrow analysis).
- Patients with any history of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
- Previous immunosuppressive treatment with intravenous immunoglobulin (IVIG) or apheresis/plasmapheresis in the preceeding 3 months, and cyclophosphamide and biologicals (e.g. rituximab): in the preceeding 6 months prior to enrolment.
- Other neurological, neuromuscular, rheumatologic or orthopedic conditions with significant impact on the capability of walking preventing evaluation of neurological scores.
- Anti-MAG neuropathy patients with persistent clinically significant laboratory abnormalities not related to the anti-MAG neuropathy, such as significant renal dysfunction, hepatic dysfunction, cardiac disease or other significant neurological disorder.
- Anti-MAG neuropathy patients with a modified Rankin Scale (mRS) score > 4.
- Participation in another interventional clinical trial.
- Any other significant finding that would increase, according to the Investigator, the risk of having an adverse outcome from participating in the study.
- Any other medical condition, including mental illness or substance abuse deemed by the investigator(s) to likely interfere with the patient's ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results.
- Patients who have undergone major surgery ≤ 2 weeks prior to starting study drug or who have not recovered from the side-effects of surgery.
- A history of clinically significant ECG abnormalities, or any of the following ECG abnormalities at screening:
    - PR > 200 msec.
    - QRS complex > 120 msec.
    - QTcF > 450 msec (males).
    - QTcF > 460 msec (females).

- History of familial long QT syndrome or known family history of Torsades de Pointes.
- Use of agents known to prolong the QT interval unless they can be permanently discontinued for the duration of the study.

- Sexually active males must use a condom during intercourse after the start of the IMP administration and for at least one week after stopping study medication and should not father a child in this period after completion of the study medication (SAD and MAD phases). A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. In addition, male participants should not donate sperm for the time period specified above.
- Use of other investigational drugs at the time of enrolment, or within 5 half-lives of enrolment, or within 30 days, whichever is longer; or longer if required by local regulations.
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 1 week after discontinuation of the investigational drug. Highly effective contraception methods include:
  - Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
  - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking the investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
  - Male sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
  - Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure <1%), for example hormone vaginal ring or transdermal hormone contraception. Progesterone containing hormonal

tablets must be associated with inhibition of ovulation in order to qualify as highly effective.

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking the investigational drug. If local regulations deviate from the contraception methods listed above and require more extensive measures to prevent pregnancy, local regulations apply and will be described in the informed consent form (ICF).

Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking the investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment then she considered not of childbearing potential.

Investigational Medicinal Product IMP

Formulation Liquid formulation 10 mg/mL for IV administration.

Name Test product: PPSGG: Poly phenyl (disodium 3-O-sulfo-beta-D-glucopyranuronate)-(1-3)-beta-D-galactopyranoside.

Reference product: Placebo (phosphate buffered saline (PBS)).

Route IV infusion over 60 minutes.

Dose SAD phase: Single IV administration of 200, 400, 800 mg and 1600 mg per patient in 4 cohorts. A higher dose (3200 mg) may be administered.

MAD phase: Multiple intravenous doses for 6 weeks (up to 11 administrations) of PPSGG over 2 dose levels (dose level and frequency determined from SAD results).

Safety endpoints

The following parameters will be monitored throughout the study or as specified:

- Frequency, duration, severity and outcome of AEs, treatment emergent AEs (TEAEs), and Serious AEs (SAEs) from time of informed consent signature to the EOS visit including follow-up as required.
- Any concomitant medications and relevant non-drug therapies.
- Signs and symptoms of infusion-related reactions on infusion days continuously during the infusion of the study drug until

1 hour after the end of infusion, and at 8 and 24 hours after the start of administration.

- Physical examination from screening, baseline, on infusion days (before dosing with the IMP), Day 4 and 8 during SAD and EOS visit and during MAD once a month and at the EOS visit.
- Vital signs with the 12-lead ECG at screening, on infusion days predose, during the infusion of the IMP at 60 min and then at 2 hours and 8 hours after start of infusion and EOS visit.
- 1-lead ECG on infusion days continuously during the infusion of the IMP until 2 hours after start of infusion.
- Safety hematology, clinical chemistry and urinalysis at screening, baseline, on days at the site on Day 8, 28 and EOS visits during the SAD and on and on Day 8, 28, 42, 98 and EOS during the MAD.

Pharmacokinetic endpoint	**Timing of sampling**	PPSGG's PK will be determined in serum during baseline (Day -1), on infusion Day 1 (at 5 min, 30 min, 60 min, 2h, 6h, and 8h after start of administration), and on Day 2, 4, 8 and 14 of the SAD phase. In the MAD phase just before first infusion on infusion Day 1 (at 5 min, 30 min, 60 min, at 2h, 6h, and 8h after start of administration) then trough levels before each infusion and at 5 min, 30 min, 60 min, 2h, 6h, and 8h after start of administration) on each infusion day (Day 1 to 5, Day 8, 14, 21, 28, 35 and 42) and on Day 53, 70, 98 and EOS. The time points for PK sampling will be defined based on the PK data collected during SAD phase.
	Method	Enzyme-Linked Immunosorbent Assay (ELISA)/chromatography
Pharmacodynamic endpoints	**Timing of sampling**	PPSGG's PD biomarkers will be determined in serum during screening, baseline (Day -1), and on Days 2, 4, 8 and 14 and until anti-MAG titers reach pre-treatment levels or end of the study during the SAD phase and during MAD on the days of infusion.
	Methods	ELISA, capillary electrophoresis, chemistry immunoassay.

Efficacy endpoints

Clinical efficacy assessments will be performed at screening, and Day 14, and EOS during SAD and during MAD then every 8 weeks.

Clinical efficacy outcome for the SAD and MAD phases

- ONLS score.
- Time to walk 10 meters.
- RODS.
- Ataxia score.

Endpoints for the MAD phase only

All the above and then additionally every 8 weeks from Day 14 the following ones:

- INCAT sensibility score and modified INCAT.
- Motor Unit Number Index (MUNIX).
- Grip Strength.

Exploratory endpoints

Endpoints for the MAD phase only

- Neurofilament light chain (NfL) to measure the degree of axonal damage.
- B-cell activating factor (BAFF).
- Indirect immunofluorescence on sciatic nerves.
- Classical pathway of the complement.

Independent Data Monitoring Committee

An IDMC will review the safety data and will provide its recommendations to Polyneuron to escalate to the next higher dose cohort (Dose Escalation) in both SAD and MAD phases and to continue within a given cohort after the sentinel patient dosing (Dose continuation, MAD phase only).

Analyses populations

The two study phases SAD and MAD described in this protocol form an exploratory investigation without any formal statistical hypotheses. All results will be interpreted descriptively only from the following analyses sets:

Safety population (SP): All patients who receive at least one dose of study medication. The SP will be the primary analysis set for the safety and tolerability analyses.

Intent-to-treat (ITT) population: all patients who were enrolled. The ITT population will be used as analysis set to confirm the efficacy.

Per-protocol (PP) population: all patients, who meet the inclusion/exclusion criteria, received full-course of the study drug as per randomization during the MAD and have completed the main relevant visits (at least 1 visit, 1 week, and 1 month during the SAD phase after dosing is needed to assess biomarker and scores. During the MAD phase, at least 1 visit 1 month after the

last dosing, for safety and efficacy assessments and who satisfactorily completed a PD blood sampling period without any major protocol violations which would render the data unreliable. The PP population will constitute the primary analysis set for the PD and PK, and efficacy analyses.

Pharmacokinetic (PK) population: all patients who satisfactorily completed a PK blood sampling period without any major protocol violations which would render the data unreliable.

Pharmacodynamic (PD) population: all patients who satisfactorily completed a PD blood sampling period without any major protocol violations which would render the data unreliable.

Statistical Method

Sample size

This is a FiH study of PPSGG which its primary objective is to assess its safety and tolerability. The total number of at least 24 evaluable planned patients per phase (SAD and MAD) to be included in this study is thought to be sufficient for an early assessment of the safety and tolerability of PPSGG. No previous PK nor PD data for single or multiple doses of PPSGG in patients are available.

Patients who withdraw for reasons other than safety can be substituted in agreement with Polyneuron.

Statistical analysis

Physical examination, ECG and vital signs (blood pressure assessments, pulse rate, body temperature), signs of infusion-related reactions, laboratory assessments and AEs, TEAEs and SAEs will be analyzed. Signs of infusion-related reactions include clinical signs and symptoms, changes in diastolic or systolic blood pressure, heart rate, and skin reactions or local reactions at the infusion site. TEAEs will be summarized in frequency tables according to Preferred Term (PT) and System Organ Class (SOC). TEAEs will also be summarized according to their severity and causality regarding the IMP. When a TEAE occurs more than once in the same patient, maximal severity and strongest causality will be counted. All SAEs and TEAEs leading to premature withdrawal from the study will be listed. Laboratory variables will be examined using mean changes from baseline. Laboratory values will also be categorized according to the updated Common Terminology Criteria for Adverse Events (CTCAE) toxicity grade version and tabulated by their highest on-study toxicity grade. Shift tables will present numbers and percentages of patients with high / normal / low (or normal/abnormal) laboratory results at baseline and last measurement available. Non-TEAEs will be listed only. Use of concomitant medications will be summarized.

Descriptive statistics will be provided for the PK parameters and scatter plots may be used to investigate PK/PD or efficacy

relationships. Statistical general linear model procedures and regression analysis will be applied for the analysis of the PK and PD parameters when applicable.

Descriptive statistics will also be used for the PD assessments.

Efficacy analysis

The efficacy analysis will be performed separately for the SAD and MAD phase. In the SAD phase changes in the following parameters will be assessed on Day 14, 28 and at EOS visit:

- Clinical scores.
- PK/PD.
- Evolution of anti-MAG antibodies (time to reach the lowest level after starting IMP treatment and time to achieve baseline values).

The MAD phase, in addition to all the above, will also include clinical and score assessments every 8 weeks until the EOS visit.

Statistical methods

Descriptive statistics (n, mean, standard deviation [SD], median and ranges for continuous variables, frequencies and percentages for categorical variables) will be provided by treatment group and/or visit, if applicable. All data will be listed by patient, treatment group and, where applicable, visit. Data from all placebo treated patients in MAD will be pooled for comparison with active cohorts. Further technical details will be described in the Statistical Analysis Plan (SAP).

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List of abbreviations

ADA	Anti-drug antibody
ADL	Activities of Daily Living
ADM	Abductor digiti minimi
AE	Adverse event
ALT	Alanine aminotransferase
Anti-HNK1	Anti-human natural killer-1
APB	Abductor pollicis brevis
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC0-t	The area under the concentration-time curve from time zero to time ‘t’
AUCinf	The AUC from time zero to infinity
BTU	Bühlmann Titer Units
BUN	Blood urea nitrogen
BW	Body weight
CHMP	Committee for Medicinal Products for Human Use
CL	The total body clearance of drug from the serum
C_{max}	The maximum (peak) observed serum, blood, serum, or other body fluid drug concentration after single dose administration
CMAP	Compound muscle action potential
CNS	Central nervous system
CoA	Certificate of Analysis
CRO	Contract research organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DRF	Dose Range Finding
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form

EDC	Electronic data collection
EFNS/PNS PDN	European Federation of Neurological Societies/Peripheral Nervous system Paraproteinemic Demyelinating Neuropathy
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EENT	Eye, ears, nose and throat
EOS	End-of-study
EudraCT	European union drug regulating authorities Clinical Trials
FDA	Food and Drug Administration
FiH	First-in-Human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HgA1c	Hemoglobin A1c
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDL	High density lipoprotein
HED	Human equivalent dose
HIPPA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HNK-1	Human natural killer-1
IB	Investigators' Brochure
ICF	Informed consent form
ICH	International Council on Harmonization
ICMUC	Ideal case motor unit count
IDMC	Independent Data Monitoring Committee
IgE	Immunoglobulin E
IgM	Immunoglobulin M
IL	Interleukin

IMP	Investigational Medicinal Product
INCAT	Inflammatory Neuropathy Cause and Treatment Sensory Scale
INR	International normalized ratio
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRR	Infusion-related reaction
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous
IVIG	Intravenous immunoglobulin
IVRS	Interactive Voice Response System
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LLOQ	Lower limit of quantification
MABEL	Minimum anticipated biological effect level
MAD	Multiple Ascending Dose
MAG	Myelin-associated glycoprotein
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MFD	Maximum feasible dose
MGUS	Monoclonal gammopathy of undetermined significance
mRS	modified Rankin Scale
MRSD	Maximum recommended starting dose
MPS	Mononuclear Phagocyte System
MUNIX	Motor Unit Number Index
N	number
NfL	Neurofilament light chain
NOAEL	No Observed Adverse Effect Level
ONLS	Overall Neuropathy Limitations Scale
PBMC	Peripheral blood mononuclear cells

PBS	Phosphate buffered saline
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per protocol
PPSGG (PN-1007)	Poly (phenyl disodium 3-O-sulfo-ß-D-glucopyranuronate-(1→3)-ß-D-galactopyranoside)
PT	Preferred Term
PTE	Therapeutic plasma exchange
RBC	Red blood cell count
RODS	Rasch-built Overall Disability Scale
SAF	Safety population
SAD	Single Ascending Dose
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SC	Study Completion
SD	Standard deviation
SF-36	36-Item Short Form Survey
SGOT	Serum glutamic oxaloacetic transaminase (= AST)
SGPT	Serum glutamic pyruvic transaminase (= ALT)
SIP	Surface interference pattern
SM	Sphingomyelin
SOC	System Organ Class
SOP	Standard Operating Procedure
SP	Safety population
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Serum half-life
$T_{1/2}$	The elimination half-life associated with the terminal slope of a semi logarithmic concentration-time curve
TA	Tibilis anterior
TEAE	Treatment-emergent adverse event(s)
Tmax	The time to reach maximum (peak) serum, blood, serum, or other body fluid drug concentration after single dose administration

TNF	Tumor necrosis factor
TPE	Therapeutic Plasma Exchange
Vd	Volume of distribution
Vss	The apparent volume of distribution at steady state
WBC	White blood cell count
γ-GT	γ-Glutamyltransferase

1 Introduction

1.1 Background

Anti-myelin-associated glycoprotein (MAG) neuropathy is a demyelinating polyneuropathy associated with a monoclonal immunoglobulin M (IgM) gammopathy with anti-MAG activity. Patients with anti-MAG neuropathy suffer from sensorimotor deficits, sensory ataxia, paresthesias, muscle weakness, neuropathic pain, and tremor. Anti-MAG neuropathy is an autoimmune disease strongly associated with monoclonal IgM autoantibodies (anti-MAG IgM) with reactivity against MAG [1],[2],[3],[4]. Anti-MAG IgM antibodies have been demonstrated to be causally related to the neuropathy in a number of animal models. IgM and complement are deposited on the myelin sheath, splitting the myelin lamellae causing demyelination, and eventually axonal damage. During the last few years, much progress has been made in understanding the pathophysiological mechanism of the disease [5],[6] and adoptive transfer of patient sera into susceptible host animals has been demonstrated to cause sensory ataxia and reproduce the human pathology [11], [17]. The prevalence of this rare disease is about 1 in 100,000 [7]. Anti-MAG neuropathy is an age-related disease and typically, the disease onset occurs after the age of 50 years. The disease is 2.7 times more frequent in men than in women [8].

Currently there is no treatment for anti-MAG neuropathy approved by the European Medicines Agency (EMA) or the US Food and Drug Administration (FDA). However, off-label treatments are used for treatment of anti-MAG neuropathy, which are discussed below. The primary objective of the treatment is to reduce the pathogenic anti-MAG autoantibody titers [9]. Therefore, various immunomodulatory and immunosuppressive treatments have been used to manage anti-MAG neuropathy. Nonetheless, these treatments are of limited efficacy and have potential side effects [10],[11].

Clinical improvement of neuropathic symptoms in patients with anti-MAG neuropathy correlates with reduced serum levels of anti-MAG IgM [9],[12],[3],[13] and disease worsening is associated with increasing anti-MAG IgM levels during treatment follow-up [13,14]. The therapeutic goal is a reduction in anti- MAG IgM (paraprotein) levels in the Bühlman test by at least 50% from baseline level [15].

1.2 Current Treatment Options for anti-MAG neuropathy

The pathogenic role of the monoclonal anti-MAG IgM antibody in anti-MAG neuropathy, based on clinical studies that show correlations between disease outcomes and anti-MAG IgM levels, is widely accepted [14],[16], and therapeutic approaches are therefore generally directed at reduction of antibody levels.

No therapies have yet been approved for this serious disease due to the lack of evidence from well- controlled clinical trials. Anecdotally, rituximab has been the most successful but shows some benefit in only 30-50% of patients with a variable impact on anti-MAG antibody levels and occasionally causes a paradoxical worsening. Clinical improvement is typically associated with at least a 50% decrease in IgM [15]. The target antigen of rituximab, CD20 is a lineage restricted molecule and is expressed on B cells throughout B-Cell differentiation prior to terminal differentiation of B cells to plasma cells. Primary failure of rituximab in a proportion of patients as above may be associated with the presence of CD 20 negative plasma cells in the spleen and tissues [18] but in these patients, removal of the pathogenic autoantibodies could be expected to provide a therapeutic benefit.

A number of chemotherapeutic and targeted agents used in Waldenstroms and other haematological malignancies have been tried [11], therapeutic benefit has been limited and

the associated toxicities of these agents are substantial. Patients with an underlying malignancy are excluded from the proposed clinical trial thus the intended patient population is one with neurological symptoms but a normal life expectancy.

Severe adverse events with rituximab, Ibrutinib and other agents used in haematological malignancies are noted to be more frequent in patients over 65 years of age. Given that 65 is the median age of onset of anti-MAG neuropathy the patient population in the proposed study would be one with increased risk.

Therefore, given that responses to agents used to treat malignancies are limited and associated with substantial myelotoxicity and increased mortality in this patient group [19] there remains an unmet medical need for a more effective and less toxic treatment for these patients. Targeted removal of the pathogenic antibodies rather than broad immunosuppression remains an approach to address this unmet need in this orphan disease. This antigen specific approach could offer both initial symptomatic relief and disease modification if treatment can maintain antibody levels below pathogenic levels.

1.3 PPSGG (PN-1007)

The active substance is poly (phenyl disodium 3-O-sulfo-ß-D-glucopyranuronate)-(1→3)-ß-D-galactopyranoside and will be referred to as poly(phenyl sulfoglucuronate galactoside) (PPSGG) throughout the document. PPSGG is a glycopolymer consisting of two structural units coupled to a poly-L-lysine backbone, glycan and thioglycerol units.

PPSGG is a fully synthetic molecule obtained from (disodium 3-O-sulfo-ß-D-glucopyranuronate)-(1→3)-β-D-galactopyranoside that binds to a chloroacetylated poly-L-lysine hydrobromide backbone through a tyramine-based thiol-linker. Multiple copies of the active part of the molecule, phenyl (disodium 3-O-sulfo-ß-D-glucopyranuronate)-(1→3)-ß-D-galactopyranoside, are coupled to the chloroacetylated poly-L-lysine; the remaining chloroacetylated poly-L-lysine polymers are coupled with thioglycerol, which promotes the solubility of the overall molecule. 25-45% of the poly-L-lysine backbone is coupled to glycan units, and 55-75% are coupled to thioglycerol units [20].

PPSGG is formulated as a liquid ready to use drug product for intravenous (IV) infusion.

PPSGG is intended to bind anti-MAG IgM autoantibodies, the underlying cause of anti-MAG neuropathy, in a highly selective manner, resulting in their neutralization and removal from the circulation. While the anti-MAG IgM autoantibodies do not cross the blood-brain barrier, they can cross the blood-nerve barrier to enter the peripheral nervous system. In contrast, based on tissue distribution studies and the physico-chemical properties of the glycopolymer [21, 22], PPSGG does not cross the blood-nerve barrier; therefore, binding of PPSGG to the anti-MAG IgM antibodies occurs in the blood. This allows specific targeting of anti-MAG IgM in the circulation and circumvents unspecific immunosuppression associated with current treatment strategies.

1.4 Nonclinical data

It has been demonstrated that PPSGG prevented the binding of patients' anti-MAG IgM autoantibodies to MAG at low nanomolar concentrations in a competitive enzyme-linked immunosorbent assay (ELISA) and selectively bound to anti-MAG IgM. PPSGG efficiently reduced the anti-MAG IgM antibody titers in an immunological mouse model for anti-MAG neuropathy at a dose range of 2- 10 mg/kg [19] and was able to efficiently inhibit the binding of patients' anti-MAG IgM to sciatic nerve myelin of non-human primates ex vivo within the

same concentration range. In vitro experiments and in a dose titration study in mice, showed that the binding stoichiometry of PPSGG:anti-human natural killer-1 (anti-HNK-1) IgM is 1:1 to 1:2. Based on an estimated average patient population with 1-10 g/L of monoclonal anti-MAG IgM, doses of 120-1200 mg should remove most circulating autoantibodies [10, 23]. Moreover, no signs of large immune complex formation (in vitro) or immune complex related toxicity (in vivo) were observed.

PPSGG has a short half-life at pharmacological doses (approximately 20 to 30 min in 2 rodent and 1 non-rodents' species) with a low volume of distribution in rats and dogs, distributing only within the vascular system and is cleared through the mononuclear phagocyte system (MPS). PPSGG, once cleared by phagocytes, is most likely broken down in the liver to different natural components which may be recycled or eliminated: for instance, the poly-L-lysine backbone to shorter poly-L-lysine chains and then recycled in protein synthesis; the glycomimetic part is cleaved into monosaccharides and may enter the catabolic pathway or is excreted; and the thioglycerol part is expected to be eliminated by renal excretion or, similar to glycerol, by hepatic metabolism. In humans, clearance (CL), metabolism and distribution are expected to be similar to that observed in animal models since these pathways are highly conserved among mammalian species.

Exploratory non-GLP and repeat-dose GLP toxicology and safety studies did not identify a target organ of toxicity which is not unexpected given the low volume of distribution, rapid clearance and low systemic dosing from weekly administrations. Dose escalation was limited by infusion-related findings in the rat and dog (tremors, decreased activity, flushing). Clinically PPSGG was well tolerated in dogs with up to 200 mg/kg/dose (no-observed-adverse-effect level (NOAEL)) with intravenous (IV) infusion over 15 min administered intermittently over six weeks in GLP repeat dose toxicology studies. In rats, initial DRF studies demonstrated 400 mg/kg/dose infused over 15 min was not tolerated, with clinical signs consistent with a mast cell degranulation (of unknown mechanism). Repeat dose GLP toxicology studies with up to 150 mg/kg/dose with 15 min IV infusion administered intermittently over 6 weeks was well tolerated without adverse findings (NOAEL). A subsequent exploratory non-GLP study examining the dose versus infusion rate relationship found that the clinical tolerability in rats was highly dependent on the time/length of infusion, with Cmax of PPSGG driving the observed clinical findings. In this study, no increase in histamine or tryptase levels were evident 1 h after infusion, and there was no binding of IgE to PPSGG. PPSGG does not affect neurological behaviour (Modified Irwin) or respiratory function in rats and has no clinically relevant effect on human cardiac channels up to the physiological limits of solubility for the molecule. PPSGG did not induce an innate immune response (cytokine release) in human peripheral blood mononuclear cells (PBMC) or induce the formation of anti-drug antibodies over repeat administration in rats.

Based on these results, the NOAEL was considered to be 200 mg/kg/dose for dogs and 150 mg/kg for rats, respectively.

The potential of PPSGG to interact with co-administered medication has not been assessed. No formal drug interaction studies have been conducted with PPSGG in humans.

No reproductive or developmental toxicity studies using PPSGG have been conducted to date.

1.5 Clinical data

1.5.1 Human safety and tolerability data

This is the first in human (FiH) study, therefore no clinical data are available yet.

1.6 Study rationale

This is a FiH Phase I/IIa multicenter, single ascending dose (SAD) and multiple ascending dose (MAD) study, to assess the safety and preliminary efficacy of PPSGG, an antibody scavenger of pathogenic anti-MAG IgM autoantibodies, for treatment of anti-MAG neuropathy. The safety and tolerability of PPSGG has been demonstrated in different animal species, for 6 weeks with 11 single doses via slow IV infusion over 15 min in rats and dogs during the non- clinical toxicology studies.

The design has been chosen as a classical Dose Escalation design as required in this type of trial with the starting dose calculated following the recommendations from the EMA Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products (September 2007) and FDA Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (July 2005) [24, 25].

The unique therapeutic approach of PPSGG is intended to bind to anti-MAG IgM autoantibodies in a highly selective manner, resulting in their neutralization and removal from the circulation. While the anti-MAG IgM autoantibodies do not pass the blood-brain barrier, they can pass the blood-nerve barrier to enter the peripheral nervous system. In contrast, based on tissue distribution study data and established physico-chemical properties of the glycopolymer [19, 20], PPSGG does not pass the blood-nerve barrier; therefore, binding of PPSGG to the anti-MAG IgM antibodies occurs in the blood. This allows specific targeting of anti-MAG IgM in the circulation, the underlying cause of the disease. This concept has been verified in vitro and in vivo. Currently, there is no treatment for anti-MAG neuropathy approved by the EMA or FDA. However, some medicinal products are used off-label for management of anti-MAG neuropathy; these products employ either an immunomodulatory or immunosuppressive approach to reduce the pathogenic anti- MAG autoantibody are summarized below.

- Immunomodulatory approaches include intravenous immunoglobulins (IVIG), therapeutic plasma exchange (TPE) and apheresis, and treatment with interferon alpha. However, none of the immunomodulatory treatments consistently demonstrated satisfactory short- and long-term efficacy in clinical studies.

- Immunosuppressive approaches include rituximab, corticosteroids and chemotherapeutic drugs, such as cladribine, fludarabine, cyclophosphamide and chlorambucil. These treatments cause a general immune suppression by lymphocyte depletion, which includes a reduction of disease-causing anti-MAG autoantibodies. However, immunosuppressive treatments have failed to demonstrate efficacy consistently in clinical trials and are associated with severe side effects, including anemia, neutropenia, thrombocytopenia, gastrointestinal distress, and opportunistic infections.

Since these alternative off-label treatment approaches are unspecific, their efficacy for treatment of anti-MAG neuropathy has not been convincingly demonstrated, and some of these treatments are associated with severe side effects. The unmet medical need remains and requires new approaches of treatment for the anti-MAG neuropathy.

1.7 Rationale for study design

Data from toxicological studies with PPSGG have shown a benign safety profile. The design of the SAD phase of this study (open label, single ascending dose) efficiently addresses the primary objective to assess the safety and tolerability of PPSGG and will also provide

information on its pharmacokinetics (PK), and pharmacodynamics (PD); while very little can be expected in terms of efficacy (short term reduction of levels of anti-MAG antibodies, only, may be expected) with minimal clinical impact on the disease. Since these autoantibodies are only present in patients with anti-MAG neuropathy, but not in healthy humans, information obtained from a study in healthy subjects would be limited in respect to PK, PD, and any potential target related toxicities.

In the MAD phase, the study drug is compared in a double-blind design with placebo. Placebo is chosen to enable a proper efficacy assessment as well as safety evaluation of PPSGG in patients with anti-MAG neuropathy

Clinical endpoints including assessments of signs and symptoms on neurological scales will be included as secondary endpoints in the MAD cohorts. Given the potential for bias in such evaluations the placebo control is necessary to enable an unbiased evaluation of any potential early signs of efficacy in these cohorts.

An Independent Data Monitoring Committee (IDMC) will provide recommendations about stopping, modifying or continuing the study; the decision to continue and/or to escalate the dose of PPSGG will be based on the review of safety and tolerability results. Given the short half-life of PPSGG shown in preclinical studies and assuming a short half-life in humans, a 72-hour safety review in the SAD phase and a 2-week safety data review in the MAD phase for Dose Escalation are considered adequate.

1.8 Rationale for dose/regimen, route of administration and duration of treatment

The maximum recommended starting dose (MRSD) of the FiH trial of PPSGG was calculated following both the “FDA Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers” (July 2005) and the “EMA Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products” (September 2007) [22, 23]. Taking both guidelines into account the NOAEL of PPSGG was determined in non-clinical toxicological studies. Based on the findings of these studies the surrogate NOAEL of PPSGG was established at 200 mg/kg in dogs and 150 mg/kg in rats. In a next step the human equivalent dose (HED) was calculated applying the allometric scaling factor of 1.8 for dogs and 6.2 for rats as outlined in Table 1. The planned starting dose is a flat dose of 200 mg, which corresponds to approximately 2.8 mg/kg body weight (BW) for a patient of 70 kg. Flat dosing is most appropriate for treatment as the target and route of elimination are largely independent of body weight. Hence the surrogate NOAEL determined in non-clinical safety studies translates to a maximum recommended starting dose of maximum 111.1 mg/kg BW, which leads to a safety factor of 39.7 without considering the safety factor of 10.

Table 1 Starting dose of PPSGG based on the NOAEL from non-clinical safety studies

Species tested	Determined surrogate NOAEL	Allometric scaling factor	Calculated HED human equivalent dose applying a safety factor of 10	Planned starting dose	Safety Factor
Dog	200 mg/kg	1.8	200 mg/kg / 1.8 / 10 = 11.11 mg/kg BW	2.8 mg/kg	39.7
Rat	150 mg/kg	6.2	150 mg/kg / 6.2 / 10 = 2.42 mg/kg BW	2.8 mg/kg	8.6

BW = Body weight; HED = Human equivalent dose; NOAEL + No-observed-adverse-effect-level

The planned PPSGG dose range and regimen of the proposed study covers the efficacious dose range demonstrated in the pre-clinical efficacy studies and offers a large safety margin according to the in vivo toxicology studies conducted in rat and dogs.

In order to predict the human exposure (Cmax and AUC) at the proposed doses in this clinical trial protocol, PK and TK data from the preclinical studies have been used to develop a PK/PD model. Based on this model, the predicted exposures and resultant margins of safety are shown in Table 2.

Table 2 PK/PD model based on PK / TK data for predicted exposures

Parameter	Dose (mg)	Species for prediction	Human prediction (70 kg)		Predicted fold difference[1]	
			Estimated β	Theoretical β	Estimated β	Theoretical β
AUC_{0-inf} (mg*h/mL)	200	Rat	0.04	0.13	NA[2]	NA[2]
		Dog		0.06	923	615
	1600	Rat	0.33	1.01	NA[2]	NA[2]
		Dog		0.47	112	79
	3200	Rat	1.85	6.71	NA[2]	NA[2]
		Dog		3.05	20	12
C_{max} (mg/mL)	200	Rat	0.05	0.04	70	88
		Dog		0.05	71	71
	1600	Rat	0.40	0.33	8.8	11
		Dog		0.37	8.9	9.6
	3200	Rat	0.55	0.96	6.4	3.6
		Dog		0.71	6.5	5.0

[1] Relative to observed mean at day 1 at highest dose in GLP TOX study:
Rat GLP Tox 150 mg/kg : C_{max} = 3.50 mg/mL, AUC_{0-inf} = Not reported
Dog GLP Tox 200 mg/kg : C_{max} = 3.55 mg/mL, AUC_{0-inf} = 36.90 mg*h/mL
[2] AUC_{0-inf} not reported at 150 mg/kg in rat GLP tox study

At the proposed dose of 200 mg total, the estimated safety margins are ≥70 for Cmax and ≥600 for AUC whilst at the highest optional dose proposed (3200mg), the estimated safety margin is ≥3.6 for Cmax and ≥12 for AUC.
While animals were treated with a 15 min IV infusion, the minimum infusion duration in this study is 1hr. As a result of the slower infusion rate, it is expected the predicted Cmax values are higher than those that will be observed in patients, thus adding to the safety margin for this parameter.

During the SAD part of the study, PK and PD data will be reviewed on an ongoing basis and the predicted exposure for a subsequence dosing cohort will be calculated, based on all available data from previous cohort/s.

Despite the limitation regarding calculating the minimum anticipated biological effect level (MABEL) it is still possible to consider other PD effects when defining the clinical starting dose in humans (e.g. dose response curves of the in vivo efficacy model experiments).

To corroborate that the dose range of 2-10 mg/kg in the in vitro and in vivo pharmacodynamics studies would be sufficient to deplete circulating anti-MAG autoantibodies in anti-MAG neuropathy patients, a dose titration study, using passive immunization with a monoclonal anti-HNK-1 IgM was performed. The IV injection of 5 µg PPSGG was sufficient to bind 89.43% (±1.33 SD) of the 60 µg anti-MAG IgM and 10 µg PPSGG was sufficient to bind 93.28% (±0.50 SD) of the 120 µg anti-HNK-1 IgM. Based on these findings, a dose of 80 mg PPSGG would be sufficient to bind and remove 1 g of anti-MAG IgM autoantibodies in humans. Of note, since no antibody-signal was detected at later time points after administration the anti-HNK-1 IgM antibodies have been eliminated and not only bound by the glycopolymer. The pentameric IgM has a molecular weight of 900-1000 kDa and is therefore approximately five times heavier than PPSGG with a calculated average weight of 194 kD. In general, the paraprotein (anti-MAG IgM) levels in anti-MAG neuropathy patients are in the range of 1–10 g/L or in some patients even higher [10, 23]. Clinical improvement in anti-MAG neuropathy patients has been correlated to occur with a minimum of 50% and sustainable relative depletion of anti-MAG autoantibodies [10, 24].

Based on a range of 1-10 g/L of monoclonal anti-MAG IgM, 240 mg to 2400 mg of PPSGG should remove the circulating anti-MAG IgM antibodies in the majority of the patients. Based on an estimated average patient with 4 g/L anti-MAG IgM in a plasma volume of 3 L, the estimated dose of PPSGG is 960 mg.

Beginning from the proposed starting dose for PPSGG, all subsequent doses that will be used during Dose Escalation will be calculated by applying an escalation factor of 2. The dose of 1600 mg per patient has been selected to achieve at least 2-fold the predicted exposure needed for efficacy based on relative reductions in titers of anti-MAG autoantibodies and would be anticipated to reduce by 50% the relative titers of patients with very high pre-dose anti-MAG levels. An additional cohort of 3200 mg per patient may be included if the relative reductions in anti-MAG antibody titers do not reach the target of 50% relative reduction. Based on this consideration the dose groups of the FiH study of PPSGG are defined as outlined in Table 3.

Table 3 Foreseen Dose Escalation groups in the single ascending dose phase

Cohort 1	Cohort 2	Cohort 3	Cohort 4	Optional Cohort 5
200 mg	400 mg	800 mg	1600 mg	3200 mg

SAD: The design of the SAD phase of this study allows evaluation of the safety of the low dose of PPSGG (200 mg) before proceeding to the administration of higher doses. During each cohort of the SAD phase after treatment of the first patient (sentinel patient), Polyneuron and investigator will review the safety data from 72 hours after the starting dose before completing the given cohort. Dosing can only commence for the next cohort (Dose Escalation) after satisfactory review of the safety data from the proceeding cohort by the IDMC.

MAD: During each cohort of the MAD phase after treatment of the first 2 patients, the IDMC will review the safety data after 2 weeks of the starting dose before the rest of the given cohort will be dosed (cohort completion). Dosing can only commence for the next cohort (Dose Escalation) after satisfactory review of the safety data from the proceeding cohort by the IDMC.

1.9 Rationale for choice of comparator

As there is no approved therapy for anti-MAG neuropathy, and PPSGG is the first in class compound, patients will be randomized to receive either PPSGG or placebo in the MAD phase to reduce bias in safety and efficacy assessments.

2 Objectives and endpoints

2.1 Primary objective(s)

Primary objective(s)	Endpoints related to primary objective(s)
To assess the safety and tolerability of PPSGG after single and multiple IV administrations in patients with anti- MAG neuropathy.	Assessment of safety based on vital signs, physical examination, electrocardiograms (ECGs), laboratory assessments, Signs of infusion-related reactions (IRRs), including clinical signs and symptoms, changes in diastolic or systolic blood pressure, heart rate, oxygen saturation, and skin reactions or local reactions at the infusion site and collection of adverse events (AEs) assessed from consent signature until the end of the study visit. Presence of Anti-drug antibodies will also be investigated.

2.2 Secondary objective(s)

Secondary objective(s)	Endpoints related to secondary objective(s)
To evaluate the PK of PPSGG after single and multiple IV administrations	Non-compartmental parameters related to PPSGG, including but not limited to T_{max}, C_{max}, as well as trough (pre-dose) levels after multiple dose
To investigate PD of PPSGG in reducing anti-MAG IgM levels	• Reduction of anti-MAG antibodies and time to reduction. • Time to anti-MAG IgM rebound (to pre-treatment Bühlmann Titer Units [BTU] levels). • Paraprotein levels (g/L). • Total IgM levels (g/L). • Anti-HNK1 IgM titers.
To investigate the preliminary efficacy of PPSGG	• Reduction of anti-MAG antibodies by ≥50% and time to reduction. • Change in the Overall Neuropathy Limitations scale (ONLS) score. • Time to walk 10 meters. • Rasch-built Overall Disability Scale (RODS). • Ataxia score. • INCAT sensory sum score. • Motor Unit Number Index (MUNIX). • Grip Strength.

2.3 Exploratory objective(s)

Exploratory objective(s)	Endpoints related to exploratory objective(s)
To assess the effect of PPSGG on other biomarkers of mode of action in serum	• Neurofilament light chain (NfL) to measure the degree of axonal damage. • B-cell activating factor (BAFF). • Indirect immunofluorescence on sciatic nerves. • Classical pathway of the complement.

3 Investigational plan

3.1 Study design

This protocol describes the planned conduct of a SAD phase and a MAD phase to be performed with PPSGG. These two phases will be conducted sequentially.

In each phase (SAD and MAD) the cohorts will be executed in a sequential order after the review of the safety data by an IDMC.

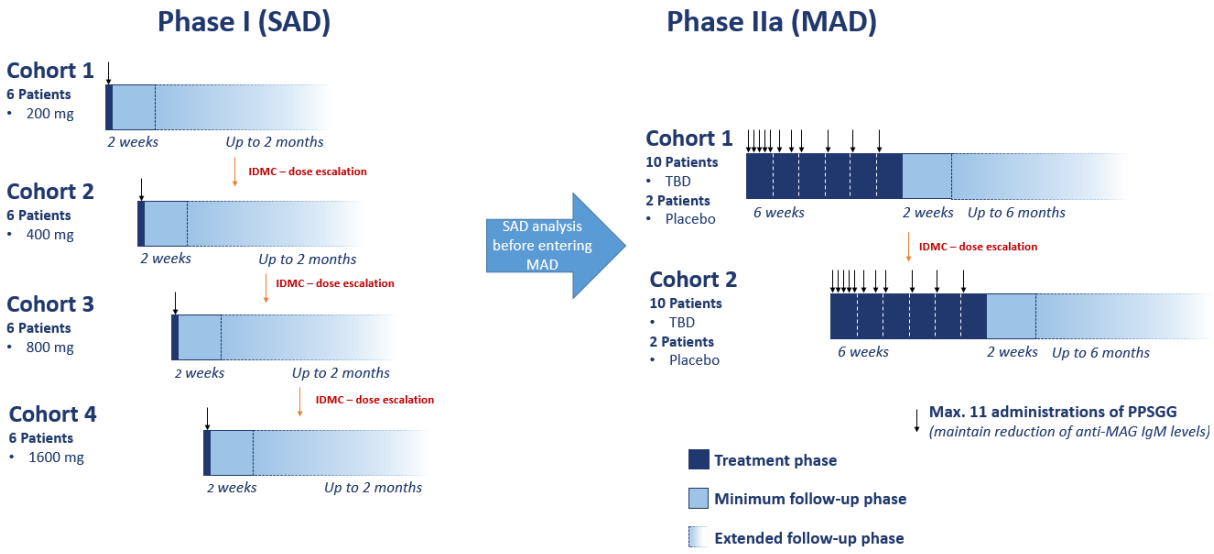
In the SAD phase each patient will have the following 8 visits: Screening, Baseline, Treatment (4 visits), end of study (EOS) and Follow-up.

In the MAD phase each patient will have up to 17 visits: Screening, Baseline, Treatment (up to 14 visits), EOS and Follow-up.

The MAD phase will be adapted for dosing regimen in accordance with PK, PD, safety and tolerability data collected during the SAD phase. Dosing regimen includes the dose level administered, the frequency of dosing and the duration of dosing, i.e. the number of doses administered. The maximum starting dose in the MAD phase will be one of the tested doses in the SAD phase. Based on the safety toxicology studies performed in animals the maximum number of dosing is 11 infusions for 6 weeks. The goal is to define a potential dose and regime to reliably and safely reduce anti-MAG IgM antibody levels by at least 50%.

Patients to be screened must have a confirmed diagnosis of monoclonal IgM associated with monoclonal gammopathy of undetermined significance (MGUS) with anti-MAG activity (titer of > 10’000 BTU) and demyelinating neuropathy defined by electrophysiological criteria according to European Federation of Neurological Societies/Peripheral Nervous System Paraproteinemic Demyelinating Neuropathy (EFNS/PNS PDN) guideline, 2010. [26]

Patients fulfilling the inclusion and exclusion criteria will be sequentially assigned to a cohort starting with the lowest dose in the SAD phase. In the MAD phase the patient will be randomly assigned to active or placebo treatment in a given dose cohort. Please refer to the scheme below:



3.2 Design of the single ascending dose phase (Phase I)

The first phase, SAD, is a FiH, open label, single dose escalation study in anti-MAG neuropathy patients to establish safety, tolerability, PK, and PD parameters of PPSGG. The study will enroll 6 patients per cohort (4 or 5 cohorts), up to a maximal dose of 3200 mg. The first dose of any cohort will be provided to a single patient first (sentinel patient). The decision to complete a given dose cohort of the sentinel patient will be based on the safety data, collected during the first 72 hours after the start of the infusion and reviewed by Polyneuron and the investigator The study will be halted after the completion of each cohort (6 patients), for the evaluation of all safety- relevant data from these 6 patients, collected within the first 72 hours from the start of the investigational medicinal product (IMP) and additional data as available (with particular focus on events occurring immediately after the start of treatment) by an IDMC. The decision to escalate to the following dose will be based on the safety data from these 6 patients provided no study stopping rules are met and the recommendations from the IDMC.

The study drug will be administered as a single 60 min IV infusion on Day 1 in the morning (between 7 AM and 10 AM). Patients will be hospitalized from the day before (Day -1), unless they live in the vicinity of the hospital and could be there early in the morning, until 24 hours after the start of the infusion.

The SAD phase will involve the following assessments after all inclusion and exclusion criteria have been checked during the screening and baseline visits (see Section 8.2 Schedule of Assessments):

- Vital signs.
- Blood and urine sampling for clinical safety laboratory.
- Blood sampling for PK.
- Blood sampling for PD markers anti-MAG IgM and time to anti-MAG IgM rebound (pre-treatment BTU) by at least 50%, paraprotein levels (g/L), total IgM levels (g/L), and anti- HNK1 IgM titers.
- Blood sampling for anti-drug antibodies (ADA) responses (immunogenicity).
- 12-lead ECG.
- Physical examination.
- Optional blood sampling for biobanking.

The study duration per patient is up to 2 months. Each patient will have the following 8 visits: Screening, Baseline, Treatment (4 visits), EOS and Follow-up.

3.3 Single ascending dose/Multiple ascending dose transition

Following the completion of the SAD phase which includes assessments of safety and tolerability, anti-MAG antibodies PK, PD responses and ADA responses, an evaluation of all these data will be performed by Polyneuron in collaboration with a modeler and the IDMC to decide doses and schedules of PPSGG in the MAD phase. The goal is to define a potential dose and regime to reliably and safely reduce anti-MAG IgM antibody levels by at least 50%.

3.4 Design of the multiple ascending dose phase (Phase IIa)

Thirty patients will be enrolled in the MAD phase, to allow for a drop-out rate of 20% to have 24 patients to complete this phase of the study.

The MAD phase that consists of two sequential and ascending cohorts will establish the safety and tolerability, immunogenicity, PK parameters, and PD effects after repeated escalated doses.

Many of the same patients involved in the SAD phase will enter the MAD phase. If “new” patients need to be recruited, they will need to undergo the complete screening procedure (see Section 8.3 Study performance).

The Dose Escalation will follow the same rules as for the SAD phase. The first 2 patients per cohort will be randomized to receive PPSGG or placebo in a double-blind fashion. At the end of each cohort a Dose Escalation assessment will be performed by the IDMC based on the safety data collected after 2 weeks of the start of the PPSGG administration.

The MAD phase will be adapted for dosing regimen in accordance with PK, PD, safety and tolerability data collected during the SAD phase. Dosing regimen includes the dose level administered, the frequency of dosing and the duration of dosing, i.e. the number of doses administered. The maximum starting dose in the MAD phase will be one of the tested doses in the SAD phase. Based on the safety toxicology studies performed in animals the maximum number of dosing is 11 infusions for 6 weeks. The goal is to define a potential dose and regime to reliably and safely reduce anti-MAG IgM antibody levels by at least 50%.

In the first week, all patients may receive a maximum of 1 dose per day for 5 consecutive days until the desired reduction of anti-MAG IgM antibody titers is achieved. For the following 5 weeks we aim to maintain the antibody levels below the 50% of baseline. The exact dosing regimen for the MAD phase will be adjusted based on PK data from the SAD phase.

The MAD phase will last for maximum 11 infusions for 6 weeks, with a 3-month observation phase, which can be extended until the anti-MAG IgM titers reach pre-treatment levels (up to 6 months after end of treatment). The MAD phase will involve the following assessments:

For safety (time points indicated in the Schedule of Assessments):

- Vital signs.
- Blood and urine sampling for clinical safety laboratory.
- Blood sampling for PK.
- Blood sampling for ADA responses (immunogenicity).
- ECG.
- Physical examination.

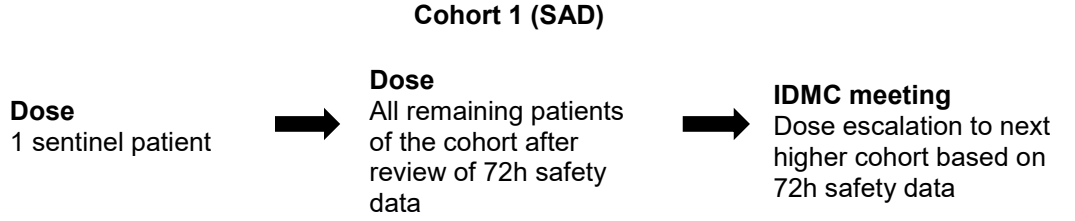
For efficacy (time points indicated in the Schedule of Assessment):

- Blood sampling for PD markers anti-MAG IgM and time to anti-MAG IgM rebound (pre-treatment BTU), paraprotein levels (g/L), total IgM levels g/L), and anti-HNK-1 IgM titers.
- Scores for clinical efficacy assessment.
- Blood sampling for assessment of exploratory biomarkers will be collected.

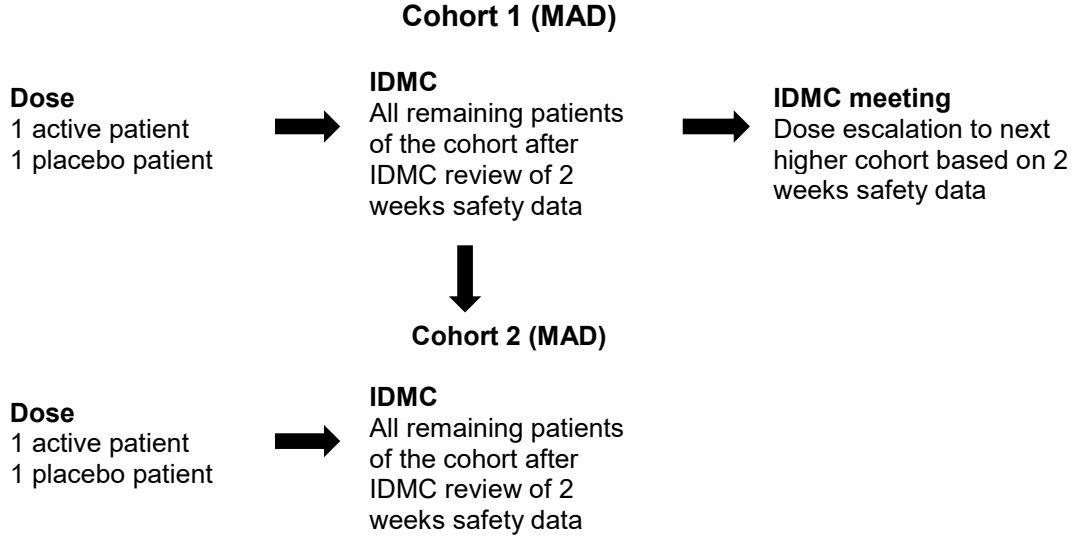
The study duration per patient is 6 months. Each patient will have up to 17 visits: Screening, Baseline, Treatment (up to 14 visits covering 11 infusions for 6 weeks), EOS and Follow-up.

3.5 Cohort completion and Dose Escalation

As this is the first time of administration of PPSGG in humans, the design of this study is similar to a Phase I FiH study in which 3 or more different increasing single doses (cohort 1, cohort 2, cohort 3, cohort 4 and optional cohort 5) in the SAD phase will be tested. Six patients per cohort will be dosed via an IV infusion over 60 minutes with PPSGG.



During the MAD phase 2 different multiple ascending doses will be administered in a double- blinded manner. Each cohort in the MAD phase also includes 2 patients that will receive placebo. Each dose of PPSGG or placebo will be administered via an IV infusion over 60 minutes. After treatment of the first 2 patients in every cohort and after treatment of all patients in that cohort, a safety analysis will be performed. The dosing cohorts and safety assessments are schematically represented below.



In the SAD phase the first patient (sentinel patient) of a given cohort will be dosed. In the MAD phase the first 2 patients in each cohort will be randomized as follows: 1 patient will be treated with PPSGG and 1 patient with placebo. The following safety data, obtained from the sentinel

patient(s) during the first 72 hours post study drug administration in the SAD phase and 2 weeks post drug administration in the MAD phase, will be checked by Polyneuron and will consist of:

- AEs.
- Baseline characteristics.
- Vital signs, including core temperature, blood pressure and heart rate.
- Laboratory data including hematology, clinical chemistry and urinalysis.
- ECG.

This review will be based on data entered in the electronic case report form (eCRF).

The remaining patients of the cohort will be dosed if no safety concerns are observed after reviewing the safety data of the sentinel patient in the SAD phase and the first 2 patients in the MAD phase, as listed above. The treating investigator might be involved in the review of the data for clarification in case of medical questions.

The decision to escalate to the following dose (once completed a cohort) will be based on the safety data, as listed above collected during the first 72 hours after the start of the infusion in the SAD phase and after 2 weeks for the MAD phase, where no stopping rules are met and analyzed by an IDMC.

If the SAD phase is stopped at one dose level due to clinically relevant toxicity, the maximum dose appropriate for the MAD phase will be defined in that case as the dose level below the dose inducing the relevant toxicity.

- No transition to the next dose cohort during the SAD and/or MAD phases can occur before the review of all safety data of the previous cohort by the IDMC
- Usage of the next higher dose level in the study will be suspended if any of the following occurs:
    - 6 or more patients in a dose cohort meet one of the individual stopping criteria (see Section 7.5 Study Stopping rules).
    - 4 or more patients in a dose cohort experience a treatment related (i.e. moderate and/or severe) AEs.
    - 1 or more patients in a dose cohort experience a treatment related serious adverse event (SAE)

In the Dose Escalation Assessments, the Polyneuron staff and the IDMC will review unblinded data also during the MAD phase.

3.6 Risks and benefits

This study is the first administration of PPSGG in humans; therefore, no prior human safety and tolerability data are available. As with any drug, it is possible that adverse reactions are caused by PPSGG. There may be unknown or unforeseeable risks. However, the risk to patients in this study will be minimized by adherence to the inclusion/exclusion criteria, close clinical monitoring in an hospital setting, strict adherence to standard practice including training of staff and provision of manuals for study procedures, infusion procedure, stopping rules for an individual patient (see Section 7.5 Study Stopping rules), as well as a safety review after the first part of the study and monitoring by an IDMC (see Section 10.2 Independent Data Monitoring Committee).

Evaluation of the safety of PPSGG in dogs and rats demonstrated a favorable toxicity profile (see IB). In a 6-week repeat-dose study in rats and dogs of doses from 20 mg/kg up to

200 mg/kg IV of 11 infusions over 6 weeks followed by a 2-week recovery, there were no clinical signs, no effects on organ weight or macroscopic observations, and no safety pharmacology findings; clinical chemistry and hematology results were remarkable. Neither microscopic findings were reported.

Based on the experimental animal studies that were carried out, investigation of the safety and tolerability of PPSGG showed no special dangers for humans. Therefore, based on the safety profile of PPSGG the risks in participating in the trial are considered acceptable. However, they include the usual risks of participating in clinical trials, which are related to possible allergic reactions, infusion related adverse event, blood drawing via venepuncture. Patients' safety will be observed during all study phases. Before the drug administration, participants will be informed about the potential and/or observed adverse effects, if any, that occurred in the previous cohort.

Medical progress is based on research which ultimately must rest in part on experimentation involving humans. Eligible patients may consider participation in this clinical trial because they want to contribute to the advancement of medical knowledge. Still, considerations related to the well-being of the individual patients enrolled into this clinical study must take precedence over the interests of science and society. Based on the available information and the design of the study, Polyneuron and the Principal investigator consider the trial to be ethically acceptable. The duration of hospitalization and the medical surveillance are considered adequate to ensure safety of the patients

There may be unknown risks of PPSGG which may be serious.

3.6.1 Blood sample volumes

Approximately 150 mL of blood is planned to be collected during the whole SAD phase and approximately 250 mL during the whole MAD phase, from each patient as part of the study. Additional samples may be required for safety monitoring.

The timing of blood sample collections is outlined in the Schedule of Assessments (see Section 8.2 Schedule of Assessments).

3.6.2 Risk mitigation strategy

There are preclinical findings of undetermined clinical relevance that will be mitigated by careful clinical monitoring. Thus, vital signs and ECG will be monitored before and after the first dose during the SAD phase and before and after the doses during the MAD phase and at other visits throughout the study.

Patients will return to the study site on a regular basis. During these visits, safety, tolerability, efficacy, and PK/PD data will be collected. Standard safety assessments will include vital signs, ECGs, clinical laboratory evaluations (hematology, blood chemistry and urinalysis), and AEs as outlined in the Schedule of Assessments (see Section 8.2 Schedule of Assessments). In addition to the standard clinical laboratory assessments, patients will be regularly monitored for signs and symptoms, inflammation, and hematologic and hepatic function. Patients will be informed to report any symptoms to the clinical staff to assure proper assessment and so that care can be administered in a timely manner.

In addition, the clinical opinion of the Investigator will be used to protect individual patient safety during the trial.

Finally, key safety data will be reviewed by Polyneuron in an open manner on an ongoing basis. An IDMC will regularly review safety data to assess whether the benefit/risk of each treatment arm remains acceptable.

3.6.3 Management of Infusion Related Reactions (IRR):

In case of occurrence of an IRR, the following measures are to be taken:

- PPSGG infusion should be interrupted and vital signs monitored until the IRR resolves to the Common Terminology Criteria for Adverse Events (CTCAE) Grade ≤1 and then the infusion can be restarted at a slower rate
- Treatment with antihistamines and methylprednisolone can be initiated, or other treatments can be given as necessary in line with the patient's condition and local standard of care.
- The patient can be pre-treated with antihistamines prior to the next PPSGG infusion during the MAD phase in cases with mild reactions. In case of a moderate, severe or serious reaction the patients will be withdrawn.
- If the IRR continues, the PPSGG infusion rate can be slowed down to 3 hours and if not resolved, Polyneuron shall be contacted and patient from the trial will stop.
- When anaphylaxis is suspected and/or confirmed, treatment with epinephrine must be initiated immediately. In case of severe reactions during the infusion of PPSGG the treatment should be stopped immediately and discontinued permanently.

AEs of IRRs and hypersensitivity must be captured on the patient's source data and on the AE page of the eCRF, along with their signs and symptoms. If dosing is interrupted, discontinued or the patient is withdrawn from the study as a result of an infusion site reaction, this must be recorded in the patient's source data and the eCRF. In the event of IRRs, blood samples taken at the end of infusion will be analyzed for complement, histamine, and cytokines to elucidate the mechanism.

4 Study Population

4.1 Anti-MAG neuropathy patients

PPSGG is targeting anti-MAG IgM autoantibodies, which are the underlying cause of anti-MAG neuropathy. Since these autoantibodies are only present in patients with anti-MAG neuropathy, but not in healthy humans, information obtained from a study in healthy patients would be limited in respect to PK, PD, and any potential target related toxicities.

Moreover, since PPSGG acts as a mimetic of the antigen, the potential for immunogenicity is an important safety concern in healthy volunteers. Potential ADAs resulting from exposure of healthy individuals to PPSGG may bind to the human natural killer-1 (HNK-1) epitope in the PNS and trigger the development of the anti-MAG neuropathy. Of note, no immunogenicity was detected in the non-clinical development so far (see Section 1.1 Background) [19]. However, it is acknowledged that it is not possible to fully predict immunogenicity in humans based on non-clinical studies. Therefore, we consider a FiH study directly in a small number of patients the most appropriate approach to minimize the potential risk for immunogenicity, as also confirmed by the EMA during a scientific advice meeting.

The following inclusion and exclusion criteria are chosen to select the appropriate study population regarding homogeneity in order to meet the requirements for reliable evaluation of the data collected.

Eligible patients will be included in the study after having given voluntary written informed consent before the first screening examination procedure takes place.

A confirmed diagnosis of anti-MAG neuropathy should be available. Sites will provide documentation of disease confirmation (i.e. previously performed tests) to the medical monitor

for review. A formal process for eligibility review for any patients recommended by the investigator is done by the medical monitor based on the data entered during the screening visit.

4.2 Inclusion criteria

Anti-MAG neuropathy patients eligible for inclusion in this study must fulfill **all** of the following criteria:

- Written informed consent.
- Age between 18 and 80 years, male and female.
- Patient with a confirmed diagnosis of monoclonal IgM associated with MGUS with anti-MAG activity (titer of > 10'000 BTU) and demyelinating neuropathy defined by electrophysiological criteria according to EFNS/PNS PDN guideline, 2010.
- Clear clinical signs of disability: with at least ONLS ≥ 2 in lower extremities.
- Inflammatory Neuropathy Cause and Treatment (INCAT) sensory sum score ≥2.
- Patients must have adequate hepatic function as evidenced by total bilirubin <1.5 mg/dL, alkaline phosphatase and aspartate transaminase/alanine aminotransferase < 2X the upper limit of normal (ULN).
- Absence of cause of neuropathy independent from anti- MAG activity: e.g. diabetes, hypothyroidism, past or current dependence on alcohol, past or current treatment with neurotoxic drugs.
- Patients must have adequate renal function as evidenced by serum creatinine <2mg/dL or calculated creatinine clearance of ≥60 mL/min within 28 days before first IMP administration using Modification of Diet in Renal Disease (MDRD) formula.
- Capability to meet the requirements of the study.

4.3 Exclusion criteria

Anti-MAG neuropathy patients fulfilling any of the following criteria are <u>not</u> eligible for inclusion in this study:

- Patients with total serum IgM levels >30 g.
- Hematological malignancy (e.g. known multiple myeloma or confirmed Waldenström's macroglobulinemia based on bone marrow analysis).
- Patients with any history of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
- Previous immunosuppressive treatment with IVIG or apheresis/plasmapheresis in the preceeding 3 months, and cyclophosphamide and biologicals (e.g. rituximab): in the preceeding 6 months prior to enrolment.
- Other neurological, neuromuscular, rheumatologic or orthopedic conditions with significant impact on the capability of walking preventing evaluation of neurological scores.
- Anti-MAG neuropathy patients with persistent clinically significant laboratory abnormalities not related to the anti-MAG neuropathy, such as significant renal

dysfunction, hepatic dysfunction, cardiac disease or other significant neurological disorder.

- Anti-MAG neuropathy patients with a modified Rankin Scale (mRS) score > 4.
- Participation in another Interventional clinical trial.
- Any other significant finding that would increase, according to the investigator, the risk of having an adverse outcome from participating in the study.
- Any other medical condition, including mental illness or substance abuse deemed by the investigator(s) to likely interfere with the patient's ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results.
- Patients who have undergone major surgery ≤ 2 weeks prior to starting study drug or who have not recovered from the side-effects of surgery.
- A history of clinically significant ECG abnormalities, or any of the following ECG abnormalities at screening:
    - PR > 200 msec.
    - QRS complex > 120 msec.
    - QTcF > 450 msec (males).
    - QTcF > 460 msec (females).
    - History of familial long QT syndrome or known family history of Torsades de Pointes.
    - Use of agents known to prolong the QT interval unless they can be permanently discontinued for the duration of the study.
- Sexually active males must use a condom during intercourse after the start of IMP administration and for at least one week after stopping study medication and should not father a child in this period after completion of the study medication (SAD and MAD phases). A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. In addition, male participants should not donate sperm for the time period specified above.
- Use of other investigational drugs at the time of enrolment, or within 5 half-lives of enrolment, or within 30 days, whichever is longer; or longer if required by local regulations.
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 1 week after stopping of investigational drug. Highly effective contraception methods include:
    - Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking the investigational drug. In case of oophorectomy alone, only when the

reproductive status of the woman has been confirmed by follow up hormone level assessment.

- Male sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
- Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure <1%), for example hormone vaginal ring or transdermal hormone contraception. Progesterone containing hormonal tablets must be associated with inhibition of ovulation in order to qualify as highly effective.

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug. If local regulations deviate from the contraception methods listed above and require more extensive measures to prevent pregnancy, local regulations apply and will be described in the informed consent form (ICF).

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking the investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment then she considered not of childbearing potential.

4.4 Patients participating in SAD and MAD phases

Patients that have participated in the SAD phase may enter the MAD phase but not all the screening and tests procedures performed in the SAD phase during screening need to be repeated. Just “newly” recruited patients need to go through the complete screening assessment as described in Section 8.3 Patient screening.

5 Restrictions for Study Patients

For the duration of the study, the patients should be informed and reminded of the restrictions outlined in this section.

5.1 Fasting

After an 8-hour fasting overnight, patients will have a light breakfast in the morning at least an hour before the IMP administration.

5.2 Contraception requirements

Women of childbearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, they should agree that in order to participate in the study they must adhere to the highly effective contraception requirements outlined in the Section 4.3 Exclusion criteria.

If there is any question that a patient will not reliably comply, the patient should not be entered or continue in the study.

6 Treatment

6.1 Study treatment

PPSGG and placebo is manufactured for Polyneuron by BAG Healthcare GmbH, Amtsgerichtsstraße 1 - 5, 35423 Lich, Germany. QP release is carried out by BAG Healthcare GmbH, which holds appropriate cGMP authorization.

Polyneuron will provide the site with investigational products manufactured and tested according to applicable good manufacturing practice (GMP) requirements for clinical trial supplies together with a certificate of analysis (CoA) and a confirmation that the investigational products are released for human use in clinical trials.

Polyneuron will ensure that the drugs, PPSGG and placebo, to be applied during the MAD phase, are identical in their appearance (colorless solution). Thus, neither the patient nor the investigators will be aware of whether the drug administered is the test or the reference drug.

Handling Requirements:

The designated person (e.g. pharmacist) at the study site will be responsible for ensuring that the study drugs are stored in compliance with GMP in a locked refrigerator (+2ºC to +8ºC) prior to administration with limited access and in accordance with the instructions on the study medication labels.

Patients will receive 1 infusion (SAD phase) or up to maximum 11 infusions (MAD phase) for 6 weeks during the study. Drug administrations will take place in the morning. The respective treatments will consist of the following:

Table 4 Dose regimen during SAD phase

Cohort No	IMP Single dose	Dose Level (mg) per patient	Dose volume (mL)	Dose concentration (mg/mL)
1	PPSGG	200	20	10
2	PPSGG	400	40	10
3	PPSGG	800	80	10
4	PPSGG	1600	160	10

An additional cohort of 3200 mg per patient may be included if the relative reductions in anti- MAG antibody titers have not reached the target of 50% relative reduction, no stopping rule for safety has been met and the end of cohort review by the IDMC from the previous patients considers proceeding to the final cohort justified by the previous safety and tolerability profile.

The specific Dose regimen during the MAD phase will be based on the data (PK / PD) derived from the SAD phase.

PPSGG will be provided to the sites in sufficient quantity. The IMP is supplied as liquid solution in 50 mL vials containing 10 mg/mL as solution for infusion. IMPs will be stored at the site in a refrigerator/refrigeration unit at 5±3°C (2-8°C). The IMP must not be allowed to freeze. The solution should be visually inspected prior to use. Only clear solutions without particles should be used. A single administration of PPSGG in the SAD phase and up to 11 infusions of PPSGG or placebo in the MAD phase will be given by intravenously over 60 minutes to the patient.

Detailed information on IMP handling will be provided in an IMP manual that is based on information provided in Polyneuron's pharmaceutical instruction. Immediately prior to administration, the assigned personnel dispense the study drug according to the cohort and dose of the patient. The dispensing of medication for administration will follow the randomization list.

The study medication will be prepared based on Table 5. The pump syringes will be filled with the study medication and the IV line filled up completely before the start of the infusion. Treatment with study drug will be administered intravenously into the arm contralateral to the arm used for blood collection. Infusions of the sterile solutions will be given through an infusion set and an IV catheter with the rate controlled by the infusion pump. At the end of the infusion, the IV catheter will be flushed with a saline solution.

Table 5 Study medication

Dose	Original concentration in mg/mL	Original Volume in mL	Infusion Speed in 60 min in mL/min
200	10	20	0,333
400	10	40	0,667
800	10	80	1,333
1600	10	160	2.667

6.1.1 Identity of Investigational treatment PPSGG

The drug product, PPSGG solution for infusion is a sterile, clear, and colorless solution filled in a sterile Type I glass vial. Concentration is expressed in terms of the amount of PPSGG free and pure acid per mL.

The solution contains PPSGG sodium as the active ingredient and a standard phosphate buffered saline (PBS) solution for pH 7.4, as inactive ingredient.

Component	Function	Quantity per Unit (40 mL)
		10 mg/mL
PPSGG sodium	Drug substance	400 mg
PBS solution	Solvent	40 mL, q.s.

Batch number	P01997
Route	IV
Retest date	Shelf life controlled by Interactive Voice Response System (IVRS)

6.1.2 Identity of Placebo

Strength	10 mg/mL
Route	intravenous
Batch number	P01963
Retest date	Shelf life controlled by IVRS

Placebo is a standard PBS solution, pH 7.4, composed of disodium hydrogen phosphate dodecahydrate, potassium dihydrogen phosphate, sodium chloride, and water for injection. An adjustment of the pH is not necessary. It is the same composition as used for the inactive ingredient for the PPSGG solution.

Component	Quality Reference	Molecular Weight	Concentration (mg/mL)
$Na_2HPO_4 \bullet 2H_2O^*$	Ph.Eur./USP	177.99	1.43
KH_2PO_4	Ph.Eur./USP	136.08	0.20
KCl	Ph.Eur./USP	74.55	0.20
NaCl	Ph.Eur./NF	58.44	8.00
Water for injection (WFI)	Ph.Eur./USP/In-House	-	1 mL (q.s)

Ph. Eur/USP = Pharmacopoeia Europaea/United States Pharmacopeia; Ph. Eur/NF = Pharmacopoeia Europaea/National Formulary

6.2 Labelling

The study drug will be provided by Polyneuron with appropriate labelling. Polyneuron will supply sufficient trial medication. The medication will be identified by project and protocol number, vial number, expiry date, storage requirements and contents. Polyneuron will provide a CoA.

The study products will be labelled in accordance with the Good Clinical Practice (GCP) ordinance and local regulatory requirements.

The labels on the vial and secondary packaging (box) of the IMP will contain the following information

- Polyneuron's study code.
- Polyneuron's name, address and phone number.
- European Union Drug Regulating Authorities Clinical Trials (EudraCT) number.
- Product name, strength and dosage form.
- Application form.
- Content by weight, volume, number of units.
- Route of administration.
- Directions for use.
- Batch number.
- Expiry date.
- Storage instructions.
- The term "For clinical trial use only".

Each manufacturing/packaging process will be performed and documented in conformity with GMP.

6.3 Treatment assignment

At the end of the SAD phase, a randomization will be done for the MAD phase. In total there will be two randomization lists created in this study, one per cohort of the MAD phase. During the SAD phase, all patients will receive PPSGG.

During the MAD phase only, patients will be randomized to receive either PPSGG or placebo. Blinded treatment with PPSGG and placebo is used to reduce potential bias during data collection and evaluation of clinical efficacy endpoints during the MAD phase.

The randomization during the MAD phase will be done via IVRS. The randomization schedule will link sequential numbers to treatment assignment allocated to treatment with PPSGG and placebo. The randomization number will be used to link the patient to a treatment arm and specify a unique medication number for the first package of investigational treatment to be dispensed to the patient.

Patients allocated to one of the groups within a cohort will receive a randomization number.

Each patient must be given only the study treatment assigned to their randomization number by the IVRS. The investigator must document the randomization number on the patient's eCRF.

These randomization numbers are linked to the different cohorts, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Polyneuron using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

6.4 Treatment blinding

SAD is an open label phase. MAD is a double-blind phase (patient and investigator blinded). Patients and investigators will remain blinded to study treatment throughout the MAD phase, except where indicated below.

The identity of treatments will be concealed by the use of study drugs that are all identical in packaging, labelling, schedule of administration, appearance, and odor.

Site staff: All site staff (including study investigator and study nurse) will be blinded to study treatment throughout the MAD phase.

Unblinding a single patient at a site for safety reasons (necessary for patient management) during the MAD phase, will occur via the process defined in place at the site (see Section 6.8 Emergency breaking of assigned treatment code).

Polyneuron staff: Polyneuron clinical staff is required to assist in the management and re-supply of the IMP. These individuals are not provided with randomization lists directly during the MAD phase.

During the MAD phase the sample analysts handling PK samples will receive a copy of the randomization schedule, to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team in a way that does not unblind individuals who are meant to be blinded.

Personnel involved in the analysis and the IDMC: An independent data analysis team of will be employed to produce the analysis results and to communicate with the IDMC at the time of safety review for the dose continuation and escalation meetings.

Polyneuron staff responsible for decision making at the clinical program development level will receive the aggregated unblinded results at the treatment group level at the time of the analysis at the end of the SAD phase. The team will not have access to the individual patient treatment codes during the MAD phase.

6.4.1 Unblinding plan for the MAD phase

See Table 6 for an overview of the blinding/unblinding plan.

Table 6 Unblinding plan for the study applicable for the MAD phase only

Role	Randomization list generated	Treatment allocation & dosing	Safety event	IDMC Safety review	Interim Analysis at end of treatment in MAD
Patients	B	B	UI	B	B
Site staff	B	B	UI	B	B
IVRS of Clinipace	UI	UI	UI	UI	UI
IDMC	B	B	UI	UI	UI
Independent analysis team	B	B	UI	UI	UI
Polyneuron team	B	B	B	B	UG

B=Blinded; UG = Unblinded at the group level; UI = Unblinded at the individual level; SAD = Single Ascending Dose; IDMC = Independent Data Monitoring Committee; MAD = Multiple Ascending dose

6.5 Treating the patient

PPSGG will be administered to the patient intravenously over a 60-minute infusion.

Polyneuron's qualified medical personnel will be readily available to advise on trial related medical questions or problems.

6.6 Patient identification

Each patient for whom an ICF is obtained will be assigned a unique 6-digit patient number xxx - yyy (country and site - patient number) strictly in chronological order of enrolment within each study site. Patients who withdraw from the study will keep their screening respective patient number even if the withdrawal occurs before randomization. The screening number corresponds to the patient number and will be documented on the eCRF and used to identify the patient throughout the study.

6.7 Permitted dose adjustments and interruptions of study treatment

Dose adjustments of study drug treatment are not permitted.

6.8 Emergency breaking of assigned treatment code

During the MAD phase, emergency code breaks must only be undertaken when it is required to safely treat the patient. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IVRS. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the study monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IVRS at any time in case of emergency. The investigator will need to provide:

- Protocol number.
- Study drug name (if available).
- Patient number.

In addition, the investigator must provide to the patient with oral and written information on how to contact his/her backup in cases of emergency when he/she is unavailable to ensure that un- blinding can be performed at any time.

An assessment will be done by the appropriate site personnel and Polyneuron after an emergency unblinding to assess whether or not study treatment should be discontinued for a given patient.

6.9 Treatment exposure and compliance

PK parameters (measures of treatment exposure) will be determined in all patients treated with PPSGG and placebo during the MAD phase, as detailed in Section 8.6 Pharmacokinetics.

The investigator must promote compliance by properly infusing the patient according to dose cohort.

All study treatment dispensed must be recorded on the Drug Accountability Log.

6.10 Recommended treatment of adverse events

At present, there is insufficient information to provide specific recommendations regarding treatment of AEs. There is no treatment that can reverse the activity of PPSGG. PPSGG has a relatively short half-life potential. AEs should therefore be treated symptomatically at the discretion of the investigator. Medication used to treat AEs must be recorded on the concomitant medications/significant non-drug therapies page of the eCRF. For treatment of IRR refer to Section 3.6.3 Management of Infusion Related Reactions (IRR).

6.11 Concomitant therapy

The investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study.

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the appropriate page of the eCRF.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication (see Section 6.12 Prohibited concomitant treatment). If in doubt, the investigator should contact Polyneuron before enrolling a patient or, if the patient is already enrolled, to determine if the patient should continue participation in the study.

6.12 Prohibited concomitant treatment

Any prescribed medication, over-the-counter drugs and significant non-drug therapies (plasmapheresis) known to have a possible impact in the clinical status of anti-MAG neuropathy are prohibited.

7 Study completion and discontinuation

7.1 Study completion and post-study treatment

All efforts will be done to facilitate the patients to complete the study in its entirety and thereafter no further study treatment will be made available to them.

An EOS visit, for each patient, is scheduled at the end of each corresponding phase (SAD and MAD phases).

Study Completion (SC) is defined as when the last patient completes their EOS visit at the end of the MAD phase, or at the end of SAD, if the patient decides not to continue with the MAD, and any repeated assessments associated with this visit have been followed-up appropriately by the investigator, or in the event of an early study termination decision, the date of that decision.

7.2 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study treatment is stopped earlier than the protocol planned duration.

Study treatment must be discontinued under the following circumstances:

- Patient decision - patients may choose to discontinue study treatment for any reason at any time.
- The investigator believes that continuation would negatively impact the safety of the patient or the risk/benefit ratio of trial participation.
- Any protocol deviation that results in a significant risk to the patient's safety.
- Pregnancy (see Section 9.4 Pregnancy reporting).
- Use of prohibited treatment as described in Section 6.12.
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the patient's overall status, prevents the patient from continuing participation in the study

If discontinuation of study treatment occurs, investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the patient's eCRF.

7.3 Withdrawal of informed consent

A patient can decide to withdraw from the study participation at any time, for any reason, specified or unspecified, and without penalty or loss of benefits to which the patient is otherwise entitled. In this case, the patient must immediately contact the investigator and state that it is his/her desire to withdraw from the study. The patient should be informed of the possibility to withdraw consent without giving any reason and to require that all previously retained identifiable samples will be destroyed to prevent future analyses, according to national provisions. The consent should include a statement that the consequence of the patient's withdrawal of consent will be that no new information will be collected from the patient and added to existing data or a database.

Patients who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their

consent (see Section 7.3 Withdrawal of informed consent). Where possible, they should return for EOS visit within 14 days after last study medication administration. If they fail to return for EOS visit for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the patient/pre-designated contact as specified in Section 7.4 Lost to follow-up. This contact should preferably be done according to the study visit schedule.

Withdrawal of consent from the study is defined as when a patient:

- Does not want to participate in the study anymore,
- Does not want to participate in any further visits or assessments,
- Does not want any further study related contacts or,
- Does not allow analysis of already obtained biologic material.

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the patient's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued, and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing. In the event of a patient deciding to stop participation in the study, he/she is requested to take part in the final medical examination including the required blood withdrawal (for the laboratory tests). This final examination is for the patient's safety. It is only by this examination that any impairment to the patient's health which may require treatment and could be related to the patient's participation in the study can be detected. If the patient is withdrawn for safety reasons, the investigator will make thorough efforts to document the final AE/SAE outcome.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

Patients can also be withdrawn from study at the description of the investigator for safety, compliance, behavioral or administrative reasons.

As the aim of this study is to generate information on the safety and tolerability, preliminary efficacy, and PD properties of the substance under investigation as well as PK data, patients who are withdrawn from the study for reasons other than safety issues may be replaced at the discretion of Polyneuron and the Investigator.

7.4 Lost to follow-up

For patients whose status is unclear because they fail to return for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents the steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. At least 3 attempts should be documented. A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the site for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.

- Before a patient is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.

Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

7.5 Study Stopping rules

During and after the administration of PPSGG, the patient will be closely monitored, in particular for signs and symptoms of IRRs, including skin reactions (urticaria, erythema, facial edema, facial rash, pruritus, eruptions), hypotension or hypertension, drop in oxygen saturation, respiratory problems (laryngospasm, laryngeal edema, bronchospasm, dyspnea), pain (joint pain, back pain, abdominal pain, chest pain) or other manifestations of hypersensitivity (fever, chills, rigors, diaphoresis, nausea, vomiting, neurological changes). One-lead ECG will be monitored continuously during the infusion, and 12-lead ECG pre-dose and at the end of infusion and at 2h and 8h after start of infusion. In the absence of symptoms, or in case of mild (asymptomatic with only incidental findings) or moderate (symptomatic without intervention required), the infusion should be stopped until the AE resolves to grade 1 and may be restarted with a lower infusion rate and treatment with antihistamines or methyl prednisolone may be initiated. If not resolved, Polyneuron shall be contacted and the patient withdrawn from the trial.

The IDMC will perform reviews of safety data throughout the study.

Enrolment in the study will be placed on hold and no further dosing will occur pending a full safety review if:

- One fatal or life-threatening SAE occurs, that is considered by the Investigator as potentially or possibly related to PPSGG and later confirmed the patient received IMP.
- Polyneuron, investigators and/or the IDMC considers that the number and/or severity of AEs, abnormal safety monitoring tests or abnormal laboratory findings justify putting the study on hold. Examples are:
    - One severe systemic infusion-related reaction occurs and does not resolve within 24 hours.
    - Three or more similar severe AEs occur as defined by the CTCAE v5.0, which are judged related to PPSGG.
    - Two SAEs which are judged related to PPSGG.

The IDMC can recommend (i) for the study to continue without amendment, (ii) to continue the study with modifications to the protocol (iii) to stop the study.

The study may continue after the safety review, if the IDMC and Polyneuron agree it is safe to proceed.

7.6 Individual stopping rules

Infusion related adverse events

If a patient experiences an infusion related adverse event that judged to be related or possibly related to the study drug, and is graded as severe or SAE, no further doses of study drug will be administered to the patient concerned.
If a patient experiences an infusion related adverse event that judged to be related to the study drug, and is graded as mild or moderate, the patient may receive a further dose of study drug following discussion with the investigator and sponsor, dependent on the nature of the AEs reported. For example, an asymptomatic localised erythematous rash would be less concerning that mild bronchospasm. If patients are to receive a further dose (i.e. re-challenged), an oral or IV antihistamine and oral acetaminophen will be administered approximately 30-60 minutes prior to the start of the infusion.

Non-Infusion related adverse events
If a patient experiences an adverse event following administration of study drug (i.e. post-treatment) that judged to be related to the study drug, and is graded as severe or SAE, no further doses of study drug will be administered.
If a patient experiences an adverse event that judged to be related to the study drug, and is graded as mild or moderate, the patient may receive a further dose of study drug following discussion with the investigator and sponsor, dependent on the nature of the AEs reported. The number of subjects reporting similar AEs and reports of the same or similar AE/s in an individual patient, will form part of the assessment to determine if patients should be re-challenged..

7.7 Early study termination by the sponsor

The study may be terminated by Polyneuron at any time for any reason. This may include reasons related to the benefit/risk assessment of participating in the study, practical reasons (including slow enrolment), or for regulatory, medical, scientific or ethical reasons. Should this be necessary, patients must be seen as soon as possible and treated as a prematurely discontinued patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the institutional review boards/independent ethics committees (IRBs/IECs) of the early termination of the trial.

8 Procedures and assessments

8.1 Repeat and additional assessments

Should it become necessary to repeat an assessment (e.g. ECG, laboratory tests, vital signs, etc.), the results of the repeated evaluation should be entered on the appropriate section of the eCRF, including date and hour of the repeated assessment. A statement should be included in the comments section explaining why the repeated or additional evaluation was performed.

8.2 Schedule of Assessments

Patients should be seen for all visits/assessments as outlined in the schedule of assessments or as close to the designated day/time as possible.

Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the AEs and concomitant medications recorded on the eCRF.

Table 7 Schedule of Assessments for the SAD phase

Period	Screening	Baseline	Treatment											EOS	FU[5]
Visit numbers	**1**	**2**	**3**								**4**	**5**	**6**	**7**	**8**
Study Day	**-14 to -1**	**-1**	**1**							**2**	**4**	**8±1**	**14±2**	**28±2**	**42±2**
Time			**Predose**	**5min**	**30min**	**60min**	**2h**	**6h**	**8h**						
Informed consent	X														
Biobank consent (optional)	X														
Inclusion/Exclusion criteria	X	X													
Medical history/current med condition	X														
Eligibility assessment	X														
Demography	X														
Physical Examination	X	X									X	X		X	
Serum creatinine	X														
HbA1c test	X														
Pregnancy test	X	X												X	
Vital signs (BP, PR, body temp)	X		X			X	X		X	X				X	
12-lead ECG	X	X	X			X	X		X	X				X	
1-lead ECG					X										
Hematology	X	X										X		X	
Clinical chemistry[1]	X	X										X		X	
Urinalysis	X	X										X		X	
Study Drug administration					X										
PK blood collection		X		X	X	X	X	X	X	X	X	X	X		
PD blood collection[2, 6]	X	X		X	X	X	X	X	X	X	X	X	X	X	X
ADA blood collection[3]		X											X	X	X
Biobank sampling (optional)		X													
Scores[4]	X												X	X	X
Exploratory biomarkers[7]		X								X				X	
Hospitalization						X									

Period	Screening	Baseline	Treatment											EOS	FU[5]
Visit numbers	1	2	3								4	5	6	7	8
Study Day	-14 to -1	-1	1							2	4	8±1	14±2	28±2	42±2
Time			Predose	5min	30min	60min	2h	6h	8h						
Concomitant medication	X														
Infusion related AE assessment				X	X	X	X	X	X	X					
Adverse events	X														X
Serious adverse events	X														X
Study completion information														X	

EOS = End of study; FU = Follow up; BP = Blood pressure; PR = Pulse rate; PK = Pharmacokinetics; PD = Pharmacodynamics; ADA = anti-drug antibodies; AE = Adverse event; ECG = electrocardiogram
1 Including liver safety monitoring (ALT, AST, ALP, TBL, PT/INR, GGT level assessment)
2 Including Bühlmann test and HNK-1 antibodies
3 will be combined with PD blood collection
4 Includes ONLS, RODS, INCAT sensory sum score, mRS, time to 10 m walking test, ataxia score. MUNIX and grip strength
5 The follow up (FU) period will depend on the anti-MAG antibody levels and will be extended until the levels reach baseline
6 In case of a reaction during infusion, the PD samples will be used to analyze tryptase, histamine, classical complement pathway, and cytokines
7 including assessment of neurofilament light chain and BAFF, indirect immunofluorescence assay, classical pathway complement cascade

Table 8 **Schedule of Assessments for the MAD phase during each infusion day**

Visit name	Treatment						
Study Day	Infusion Day						
Time	Predose	5 min	30 min	60 min	2h	6h	8h
Vital signs (BP, PR, body temp)	X			X	X		X
12-lead ECG	X			X	X		X
1-lead ECG	X						
Urinalysis	X						
PK blood collection	X	X	X	X	X	X	X
PD blood collection	X	X	X	X	X	X	X
Study Drug administration		X					
Infusion related AE assessment		X	X	X	X	X	X
Adverse events	X						
Serious adverse events	X						

Table 9 Schedule of Assessment (MAD)

Visit name	Screening	Baseline	Treatment														EOS	FU[6]
Study Day	**-14 to -1**	**-1**	**1**	**2**	**3**	**4**	**5**	**8±1**	**14±2**	**21±3**	**28±3**	**35±3**	**42±3**	**56±3**	**70±4**	**98±4**	**150±8**	**180±8**
*Informed consent	X																	
*Biobank consent (optional)	X																	
Inclusion/Exclusion criteria	X	X																
*Medical history/current med condition	X																	
Eligibility assessment	X																	
*Demography	X																	
Physical Examination	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum creatinine	X																	
HbA1c test	X																	
Pregnancy test	X	X									X			X		X	X	
Vital signs (BP, PR, body temp)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology	X	X						X			X		X			X	X	
Clinical chemisrty[1]	X	X						X			X		X			X	X	
Urinalysis	X	X	X													X	X	
Study Drug administration[5]			X	X	X	X	X	X	X	X	X	X	X					
PK blood collection[7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PD blood collection[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Visit name	Screening	Baseline	Treatment														EOS	FU[6]
Study Day	**-14 to -1**	**-1**	**1**	**2**	**3**	**4**	**5**	**8±1**	**14±2**	**21±3**	**28±3**	**35±3**	**42±3**	**56±3**	**70±4**	**98±4**	**150±8**	**180±8**
ADA blood collection[3]		X							X	X	X	X				X	X	X
Biobank sampling (optional)		X													X		X	
Scores[4]	X								X				X			X	X	X
Exploratory biomarkers[8]		X					X		X				X				X	
Concomitant medication	X																	
Infusion related AE assessment			X	X	X	X	X	X	X	X	X	X	X					
Adverse events	X																	X
Serious adverse events	X																	X
Study completion information																	X	

EOS = End of study; FU = Follow up; BP = Blood pressure; PR = Pulse rate; PK = Pharmacokinetics; PD = Pharmacodynamics; ADA = anti-drug antibodies; AE = Adverse event; ECG = electrocardiogram

1 Including liver safety monitoring (ALT, AST, ALP, TBL, PT/INR, GGT level assessment)
2 Including Bühlmann test and HNK-1 antibodies
3 will be combined with PD blood collection
4 Includes ONLS, RODS, INCAT sensory sum score, mRS, time to 10 m walking test, ataxia score. MUNIX and grip strength
5 Study Days and dosing schedule to be confirmed based on data from SAD phase
6 The follow up (FU) period will depend on the anti-MAG antibody levels and will be extended until the levels reach baseline
7 In case of a reaction during infusion, the PD samples will be used to analyze tryptase, histamine, classical complement pathway, and cytokines
8 including assessment of neurofilament light chain and BAFF, indirect immunofluorescence assay, classical pathway complement cascade

*Just newly recruited patients need to follow this assessment

8.3 Patient screening (Day -14 to -1, Visit no 1)

It is allowed to re-screen a patient if s/he fails the initial screening; however, each case must be discussed and agreed with Polyneuron on a case-by-case basis.

In each of the two study phases described in this protocol, all patients will undergo a screening examination to evaluate their health status and to check for inclusion and exclusion criteria. This examination will be conducted not more than 14 days prior to the planned first drug administration. Only patients meeting the inclusion and exclusion criteria will be admitted to the study.

During the screening examination, the patients are identified by a 6-digit patient number.

In addition, before inclusion into the study all patients screening data will be entered into the database to be assessed by the medical monitor.

This screening examination will consist of the following:

- Medical history, including collection of demographic data.
- Complete physical examination: respiratory rate, review of systems (eyes, ears, nose and throat [EENT], cardiac, peripheral vascular, pulmonary, musculoskeletal, neurologic, abdominal, lymphatic, dermatologic).
- Vital signs (blood pressure, pulse rate, and body temperature).
- Assessment of compliance with inclusion/exclusion criteria.
- ECG (12-lead).
- Evaluation of laboratory results.
- Blood sampling for pharmacodynamic markers.
- Blood for PD, including Bühlmann test, HNK-1 antibodies
- Laboratory tests, to include hematology, biochemistry, coagulation, serology, urinalysis, and exclusion tests (see Section 8.5 Safety for details).
- scores (ONLS, RODS, INCAT and mRS, ataxia), time to 10 meters walking test, MUNIX and grip strength
- concomitant medication

Patients entering the MAD, who completed the SAD phase need not to perform all assessments as new recruited patients, according to the list in the Schedule of Assessment. The following assessments could only be left out for patients entering the MAD phase after completion of the SAD phase:

- Informed consent
- Biobank consent (optional)
- Medical history/current med condition
- Demography

8.3.1 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data will be collected on all patients during screening. Relevant medical history/current medical conditions data will also be collected until signature of informed consent.

Patient demographics will include, following and adapted local regulations: age, sex, race, ethnicity. Other baseline disease characteristics will include relevant medical history, current medical conditions, results of laboratory screens, transplant history, donor characteristics (e.g., age, sex, race, type) and any other relevant information.

Investigators have the discretion to record abnormal test findings on the medical history eCRF, if in their judgment, the test abnormality occurred prior to the informed consent signature.

8.3.2 Eligibility review

An eligibility review will be performed based on the data entered during the screening by the medical monitor to assess the eligibility of the potential patient. The site will be informed about the decision in due time.

8.3.3 Study performance

The patients willing to participate in the study will only be included when all screening examination procedures have demonstrated that all inclusion criteria and none of the exclusion criteria apply. The patients will be assigned a patient number within the study. For detailed information about the procedure of assigning patient numbers please refer to Section 6.3. Treatment assignment.

8.3.4 Baseline (Day -1, Visit no 2)

During the Baseline visit, defined as one day before the start of the infusion, the following assessments will be performed:

- Confirmation of inclusion and exclusion criteria.
- Physical examination.
- Pregnancy test in women of childbearing potential.
- 12-lead ECG.
- Blood collection for hematology and clinical chemistry.
- Blood collection for PPSGG PK.
- Blood collection for PD, including Bühlmann test, HNK-1 antibodies
- Blood collection for ADA
- Exploratory biomarkers: assessment of neurofilament light chain and BAFF, indirect immunofluorescence assay and classical pathway complement cascade.
- Urine collection for urinalysis.
- Blood for biobanking (optional).

8.3.5 Treatment period (starting on Day 1, from Visit no 3)

The treatment period consists of 4 visits in the SAD and of up to 11 visits in the MAD phase. After screening and baseline assessment enrolment the treatment period will be performed. The interval between screening and the start of the IMP administration must not exceed 14 days. Patients meeting all inclusion and none of the exclusion criteria will be enrolled.

Patients will then receive one single administration of the IMP through IV infusion, on Day 1 in the SAD phase and for 6 weeks in the MAD phase with a maximum of 11 infusions. The patient will be closely observed during and after the administration of the IMP. Appropriate medical treatment will be kept available in case of an IRR during or following the administration of the IMP. The following procedures and assessments will be performed during and after the treatment: Please refer to the Schedule of Assessment

- Monitor vital signs during the infusion up to 8 hours after start of infusion.
- Monitor 1-lead ECG continuously during the infusion and for a total of 8 hours.

- 12-lead ECG at predose, during the infusion of the IMP at 60 min and then at 2 hours and 8 hours after start of infusion.
- Blood collection for PPSGG PK during baseline (Day -1), on infusion Day 1 (at 5 min, 30 min, 60 min, 2h, 6h, and 8h after start of administration), and on Day 2, 4, 8 and 14 of the SAD phase. In the MAD phase just before first infusion on infusion Day 1 (at 5 min, 30 min, 60 min, at 2h, 6h, and 8h after start of administration) then trough levels before each infusion and on each infusion day (Day 1 to 5, Day 8, 14, 21, 28, 35 and 42) and on Day 53, 70, 98 and EOS.
- Blood collection for PD, including Bühlmann test, HNK-1 antibodies on Day on infusion Day 1 (at 5 min, 30 min, 60 min, 2h, 6h, and 8h after start of administration), and on Day 2, 4, 8 and 14 of the SAD phase. In the MAD phase just before first infusion on infusion Day 1 and on Day 5, 14, 42 and EOS.
- Exploratory biomarkers: assessment of neurofilament light chain and BAFF, indirect immunofluorescence assay, and classical pathway complement cascade.
- Blood collection for hematology and clinical chemistry on Day 8, 28 and EOS visits during the SAD and on Day 8, 28, 42, 98 and EOS during the MAD.
- scores (ONLS, RODS, INCAT and mRS, ataxia), time to 10 meters walking test, MUNIX and grip strength at Day 14 and EOS (Visit no 6) during SAD phase, on Day 14, 98 and EOS for the MAD phase.
- Pregnancy test on Day 28, 56 and 96
- AEs (including infusion related AEs) and SAEs.
- Check for signs of infusion-related reactions, including clinical signs and symptoms, changes in diastolic or systolic blood pressure, heart rate, oxygen saturation, and skin reactions or local reactions at the infusion site during the infusion.

All the assessments are to be performed at the clinical site, except for the safety laboratory, PD biomarkers (blood) and the PPSGG pharmacokinetic (blood).

8.3.6 End-Of-Study (EOS) and optional Follow-up period

The length of the follow-up period will depend on the anti-MAG antibody levels and will last from Day 28 until EOS (Day 42) for the SAD phase. In exceptional cases, when the anti-MAG antibody levels did not reach the baseline level, the patient will be asked to come for an additional visit to check for these levels. In the MAD phase the schedule of assessments will be defined based on the outcome data of the SAD phase. The following assessments will be done on Days 28 and 42 for SAD, according to the schedule specified in Section 8.2 Schedule of Assessments.

The following assessments will be performed in each patient/phase at the EOS visit:

- Physical examination.
- Pregnancy test in all women of child-bearing potential.
- Vital signs.
- 12-lead ECG.
- Blood collection for hematology, clinical chemistry and urine collection for urinalysis.

- Blood collection for PD
- Blood collection for ADA
- scores (ONLS, RODS, INCAT and mRS, ataxia), time to 10 meters walking test, MUNIX and grip strength
- Exploratory biomarkers: assessment of neurofilament light chain and BAFF, indirect immunofluorescence assay, and classical pathway complement cascade
- Collection of AEs and SAEs.

The following assessments will be performed during the follow-up visit:

- Blood collection for PD and ADA.
- scores (ONLS, RODS, INCAT and mRS, ataxia), time to 10 meters walking test, MUNIX and grip strength.
- AE/SAE reporting

All assessments are to be performed at the hospital. The analysis of the PD biomarkers (blood) and the PPSGG PK (blood) will be done at the dedicated laboratories.

The EOS assessments are required on Day 28 for the SAD phase or whenever a patient discontinues or is discontinued from the study prematurely (see section 7.2); they should be performed on the last available study day.

8.4 Safety

Hematology, clinical chemistry will be performed at the local laboratory. Urine dipstick will be performed locally. Values considered clinically significant and/or IMP-related will be noted in the comments of the eCRF with reference to the date, study day and time (using the 24-hour clock), if applicable. The Investigator will record his/her medical opinion on the clinical significance of each laboratory value outside of the reference range both on the laboratory report and the eCRF. This decision will be based upon the nature and degree of the observed abnormality. The Investigator may choose to repeat any abnormal result, but only once, in order to rule out a laboratory error.

Clinically relevant deviations of laboratory test results from the normal range that occur during the course of the study or at a post-study examination will be reported. Repeated assessments are mandatory until their normalization or until the time course and reason of the underlying process are clearly determined. In case of doubt, Polyneuron's medical monitor must be contacted

Safety assessments are specified in the Section 8.2 Schedule of Assessments detailing when each assessment is to be performed.

8.4.1 Vital signs

This assessment of vital signs will include heart rate, systolic and diastolic blood pressure and core body temperature. The core temperature can be assessed orally, tympanically, or rectally. If patient is in hypothermia (< 35ºC), the temperature will be measured rectally, or via pulmonary artery thermistor catheters or bladder thermistor catheters.

8.4.2 1- lead Electrocardiogram

The 1-lead ECG will be assessed for occurrence of or change to abnormal ECG patterns (change in 1-lead ECG "yes/no", clinically relevant ""yes/no"; only monitoring; recording and

printout is not requested unless clinical significant abnormalities) and documented on the eCRF.

8.4.3 12- lead Electrocardiogram (ECG)

The 12-lead ECG recordings (I, II, III, aVR, aVL, aVF, V1-V6) will be recorded as follows: normal or abnormal (with specification of finding reported in the eCRF), ventricular rate and RR (msec), PR (msec), QRS (msec), QT (msec) and QTc (with Bazett's and Fridericia's QT corrections) intervals.

The tracings will be printed out, clinically assessed, dated and signed prior to submission to the Sponsor. Scanned tracings will be uploaded in the eCRF. The patient's identification number, the date and time of the tracing must appear on the printout of the tracing.

8.4.4 Hematology

Hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differentials and platelet count will be measured. Coagulation tests including prothrombin time (PT) also reported as INR and activated partial thromboplastin time (aPTT).

8.4.5 Clinical Chemistry

Albumin, alkaline phosphatase, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, gamma-glutamyl-transferase, lactate dehydrogenase, bicarbonate, calcium, magnesium, phosphorus, chloride, sodium, potassium, creatinine, creatine kinase, direct bilirubin, indirect bilirubin, total bilirubin, total cholesterol (including low density lipoprotein (LDL) and high density lipoprotein (HD) fractions), triglycerides, total protein, blood urea nitrogen (BUN) or urea, uric acid, amylase, lipase, and glucose will be measured in the local laboratory.

8.4.6 Urinalysis

Routine analysis at the hospital with a dipstick will be performed including glucose, protein, bilirubin, urobilinogen and nitrite.

8.4.7 Pregnancy and assessments of fertility

In any woman of childbearing potential, i.e. not > 1 year postmenopausal or surgically sterilized, a urine dipstick pregnancy test will be performed at screening, Day 28, 56, 98 and end-of-study visits. If the dipstick test indicates a positive result, a human chorionic gonadotropin (hCG) laboratory blood test will be performed to confirm pregnancy.

A woman of childbearing potential cannot be included in the study if any of the following occurs:

- The urine dipstick pregnancy test indicates a positive result and the pregnancy has been not yet been ruled out by the following hCG blood test.
- No urine dipstick pregnancy test has been performed at screening.
- The urine dipstick pregnancy test indicates a negative result, but a pregnancy is suspected by the Investigator based on clinical elements and cannot be ruled out by further investigation.

If a positive urine dipstick pregnancy test occurs at end-of-study, or if a pregnancy is suspected at any time during the study, a hCG blood test will be performed to confirm the pregnancy.

Refer to Section 9.4 Pregnancy reporting for details on pregnancy reporting.

8.4.8 Physical Examination

A complete physical examination should include the examination of general appearance, skin, neck (including thyroid), EENT, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological systems.

If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed (this information for all physical examinations must be included in the source documentation at the study site but it will not be recorded on the eCRF).

Significant findings that are present prior to informed consent are included in the CRF capturing Medical History. Significant findings observed after informed consent signature which meet the definition of an AE must be appropriately recorded on the appropriate CRF capturing AEs.

8.5 Pharmacokinetics

PK samples will be collected at the time points defined the Section 8.2 Schedule of Assessments.

PK samples will be obtained and evaluated in all patients at all dose levels.

PPSGG in serum will be determined by an ELISA/chromatography method. Concentrations below the lower limit of quantification (LLOQ) will be reported as “zero” and missing data will be labelled as such in the Bioanalytical Data Report.

Serum samples remaining after completion of the determination of PPSGG may be used for exploratory purposes to further characterize the PK or PK/PD of PPSGG. These analyses may include assessment of for example protein binding, or other bioanalytical purposes (e.g. cross check between different sites, stability assessment).

The following PK parameters of PPSGG will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.3 or later):

$AUC_{0\text{-}t}$, AUC_{inf}, C_{max}, CL, T_{max}, $T_{1/2}$ and V_{ss} and other PK parameters will be measured as appropriate. To denote parameters determined at steady state “ss” will be used.

8.6 Pharmacodynamics

Pharmacodynamic samples will be collected at the time points defined in the Section 8.2 Schedule of Assessments.

PD samples will be obtained and evaluated in all patients at all dose levels, including the placebo group.

PD assessments will include, but not be limited to: reduction of anti-MAG IgM antibody levels by at least 50% and time to anti-MAG IgM rebound (pre-treatment BTU), paraprotein levels (g/L), total IgM levels (g/L), and anti-HNK1) IgM titers.

PD evaluations will be performed primarily in the PD analysis set of patients, who completed the study according to the protocol (i.e., without serious deviations, such as more than 3 missing samples per profile). The PD population is specified in Section Study populations 11.1.

8.7 Efficacy assessments

Clinical efficacy assessments will be performed at screening, and Day 14, and EOS during SAD and during MAD then every 8 weeks. Efficacy assessments will include physical exam and the following scores:

Clinical efficacy outcome for the SAD and MAD phases

- ONLS score.
- Time to walk 10 meters.
- RODS.
- Ataxia score.

Endpoints for the MAD phase only

All the above and then additionally every 8 weeks from Day 14 the following ones:

- INCAT sensibility score and modified INCAT.
- Motor Unit Number Index (MUNIX).
- Grip Strength.

Endpoints for the MAD phase only

- Neurofilament light chain (NfL) to measure the degree of axonal damage.
- B-cell activating factor (BAFF).
- Indirect immunofluorescence on sciatic nerves.
- Classical pathway of the complement.

8.8 Other assessments

The study includes an optional biobank research component which requires a separate informed consent signature if the patient agrees to participate. As permitted by local governing regulations and by IRB/EC, it is required as part of this protocol that the Investigator presents these options to the patient.

The aim is to collect additional blood for a biobank to obtain serum and cells. This should help to better characterize the disease, its pathology and the antibody producing cells in anti-MAG neuropathy patients.

8.9 Use of residual biological samples

Any residual samples remaining after the protocol-defined analysis has been performed may be used for additional exploratory analysis. This may include, but is not limited to, using residual samples for protein binding, metabolite profiling, biomarkers of transporters or metabolic enzyme activity or other bioanalytical purposes (e.g., cross check between different sites and/or stability assessment). Given the exploratory nature of the work, the analytical method used for those assessments will not be validated. As such, the results from this exploratory analysis will not be included in the clinical study report.

9 Adverse Events and Serious Adverse Events

9.1 Definitions

9.1.1 Adverse Events

An **AE** is defined as any untoward medical occurrence in a clinical study patient to whom an IMP has been administered and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of an IMP, whether or not considered related to the IMP.

Events Meeting the AE definition

- Other safety assessments (e.g., physical examination, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events Not Meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient’s condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

9.1.2 Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death.

b. Is life-threatening.

   The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization:

   - In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications (except hospitalization due to

planned study procedure) that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

9.1.3 Abnormal Laboratory Parameters

Abnormal laboratory findings (e.g., clinical chemistry, hematology, urinalysis) or other abnormal assessments (e.g., vital signs) will be judged by the investigator as "clinically significant/relevant" or "not clinically significant/relevant" based on the investigator's medical and scientific expertise.

Clinically significant abnormal findings or other clinically significant abnormal assessments that are detected during the clinical study or that were present at baseline and significantly worsen during the study will be recorded as an AE. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with a medical condition already documented as medical history or AE will not be recorded separately, unless judged by the investigator as more severe than expected for the patient's condition.

If during treatment with the IMP abnormal laboratory findings occur which were not present before the treatment started and which were judged by the investigator as "clinically relevant" and recorded as AE in the eCRF, further clinical or laboratory tests must be carried out by the investigator until the values return to the normal range or until a plausible explanation is given by the investigator (e.g., disease) of the change of the laboratory values.

9.1.4 Overdose, Abuse, Misuse, Medication Errors and other Uses Outside what is foreseen in this Protocol

There are situations that may present a risk to the patients or conduct of the study even if no immediate AE is noted. Such events (i.e., drug overdose, drug abuse, drug misuse, medication errors, and other uses outside what is foreseen in the protocol) should be reported in the same format and within the same timelines as a SAE even if they may not result in an adverse outcome.

Overdose: Administration of a quantity of an IMP given per administration or cumulatively that is above the maximum recommended dose according to the protocol dosing instructions or authorized product information. Clinical judgment should always be applied.

Abuse: Persistent or sporadic, intentional excessive use of an IMP that is accompanied by harmful physical or psychological effects.

Misuse: Situations where the IMP is intentionally and inappropriately used not in accordance with the protocol dosing instructions or authorized product information.

Medication error: Unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

9.1.5 Recording and Follow-Up of Adverse Events and/or Serious Adverse Events

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information on the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Polyneuron/Clinipace Pharmacovigilance in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by Polyneuron/Clinipace Pharmacovigilance. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to Polyneuron/Clinipace Pharmacovigilance.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will assess intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- **Mild:** An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- **Moderate:** An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe:** An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the causal relationship between study treatment and each occurrence of each AE/SAE according to the available data as:
    - **Related:** There is a reasonable causal relationship, which means that there are facts, evidence, and/or arguments to suggest a causal relationship. The AE could medically (pharmacologically/clinically) be attributed to the IMP in this study.
    - **Not related:** There is no reasonable causal relationship, which means that there is no evidence to suggest a causal relationship. The AE could not medically (pharmacologically/clinically) be attributed to the IMP in this study.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the IB in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to Polyneuron/Clinipace Drug Safety. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Polyneuron/Clinipace Drug Safety.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Events and Serious Adverse Events

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Polyneuron/Clinipace Pharmacovigilance to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a patient dies during participation in the study, the investigator will provide Polyneuron/Clinipace Pharmacovigilance with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to Polyneuron/Clinipace Pharmacovigilance within 24 hours of receipt of the information.

9.1.6 Reporting of Serious Adverse Events

Serious Adverse Events Reporting to Polyneuron/Clinipace Drug Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Polyneuron/Clinipace Drug Safety will be the electronic data collection (EDC) tool.
- The site will enter the SAE data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor by telephone.

SAE Reporting to Sponsor/Clinipace Pharmacovigilance via Paper eCRF only if EDC system is unavailable

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Sponsor/Clinipace Pharmacovigilance within 24 hours. Fax number: +49 6196 7709-112.
- In rare circumstances, and in the absence of facsimile equipment, notification by email is acceptable. Reports should be emailed to: Safety@clinipace.com

9.1.7 Rapid communication plan of serious adverse events and suspected unexpected serious adverse reactions (SUSARs) between the sponsor, the investigators of all sites and the patients

If an event is reported as 'serious' in the eCRF database, an automatic SAE notification e-mail will inform the CRO's Pharmacovigilance team and the Sponsor. In the event a SUSAR is confirmed, this will be reported in all countries where the trial is approved, according to local requirements. SUSARs associated with the IMP undergo expedited reporting to Regulatory Authorities, ECs/ Autonomous Communities (for Spain) and investigators according to the following timelines:

SUSARs: within 15 calendar days
Fatal or life threatening SUSAR: within 7 calendar days
SAE: Annual report

If the CRO's Pharmacovigilance team is notified of very severe, unanticipated, suspected adverse reactions during the study (e.g., anaphylactic reaction to IMP, Stevens Johnson syndrome, acute organ failure), the report will be rapidly escalated to the Pharmacovigilance management team and the Sponsor Medical Monitor for immediate action.

9.2 Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information

All SAEs and AEs will be collected from the signing of the ICF until the end of the study including Follow-up.

All SAEs will be recorded and reported to Polyneuron or designee immediately and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to Polyneuron within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Polyneuron/Clinipace Pharmacovigilance.

9.3 Documentation and Reporting of Adverse Events

The occurrence of AEs will be assessed by non-directive questioning of the patient at each visit. Further, AEs reported by the patient during or between visits or detected through observation, physical examination, laboratory test or other assessments will be documented. AEs that were ongoing at the end of the previous visit should be queried for resolution or change in severity or seriousness until resolution or until Follow-up, whichever comes first.

The patients will be instructed that they must report any AE, patientive complaints or objective changes in their well-being to the investigator or the clinic personnel, regardless of the perceived relationship between event and IMP.

All AEs must be documented in the patient's eCRF. If in one patient the same AEs occur on several occasions, then the AE in question must be documented and assessed as new each time.

For any AE, the following data must be recorded on the eCRF:

- **Description of the AE** in medical terms (preferably: diagnosis), not as reported by the patient.

  Note: Every attempt should be made to describe the AE in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent a typical or extreme manifestation of the diagnosis, in which case they should be reported as separate AE.

- **Date of onset** (start date and time) and **date of recovery** (stop date and time).

- **Intensity of the AE** as assessed by the investigator according to the following definitions
    - **Mild**: The AE is easily tolerated and does not interfere with routine activities/ normal functioning of the patient.
    - **Moderate**: The AE causes discomfort and affects the patient's normal activities, i.e., interferes with routine activities, but are not hazardous, uncomfortable or embarrassing to the patient.
    - **Severe**: The AE causes considerable interference with the patient's usual activities, e.g., inability to work.

- **Causal relationship** between the occurrence of an AE and the administration of the IMP as assessed by the investigator according to the available data as:
    - **Related**: There is a reasonable causal relationship, which means that there is evidence to suggest a causal relationship. The AE could medically (pharmacologically/clinically) be attributed to the IMP in this study.
    - **Not related**: There is no reasonable causal relationship, which means that there is no evidence to suggest a causal relationship. The AE could not medically (pharmacologically/clinically) be attributed to the IMP in this study.

- **Actions taken on the IMP**
    - e.g., corrective treatment.

- **Outcome**
    - **Recovered/ resolved**: The AE had stopped completely, and the stop date is recorded.

- **Recovered/ resolved with sequelae**: No further changes are expected due to the AE and residual symptoms are assumed to persist.
- **Not recovered/ not resolved**: The AE is ongoing; the event is followed up.
- **Fatal**: The patient died as a consequence of the AE; date of death is recorded as stop date of the AE.
- **Unknown**: Unknown to the investigator (e.g., patient lost to follow-up).

- **Seriousness** according to the definition given in Section 9.1.2 Definition of Serious Adverse Events.

9.3.1 Notification of Serious Adverse Events

Prompt notification by the investigator to the Polyneuron/Clinipace Pharmacovigilance of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study treatment under clinical investigation are met.

The Polyneuron/Clinipace Pharmacovigilance has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Polyneuron/Pharmacovigilance will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Any SAE will be reported immediately (i.e., within 24 hours after receipt) by the investigator to the Drug Safety of Polyneuron/Pharmacovigilance (for details, see Section 9.1.6 Reporting of Serious Adverse Events). The initial SAE report must be as complete as possible. The report should include at least the following information:

- **Patient identification** (e.g., assigned patient number, year of birth).
- **Identifiable reporting source** (e.g., site number, name of investigator, telephone number, fax and/ or e-mail address).
- **Identification of the clinical study** (e.g., study code) or IMP.
- **SAE term** (preferably: diagnosis; if possible, also including description and course of the SAE).
- **Seriousness criterion** according to the definition given in Section 9.1.2 Definition of Serious Adverse Events.
- **Causal relationship** between the occurrence of an AE and the administration of the IMP as assessed by the investigator according to the available data. If based on follow-up information the investigator changes his/her initial causality assessment, this should be submitted to sponsor/CRO Drug Safety immediately (i.e., within 24 hours after receipt).
- **Signature of the investigator**

If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying the Polyneuron/Clinipace Pharmacovigilance of the event and completing the SAE report form. Information not available at the time of the initial report (e.g., an end date for the AE or laboratory values received after the report) will be documented on a follow-up SAE report form and reported immediately (i.e., within 24 hours after receipt) to Polyneuron/Clinipace Pharmacovigilance.

Additional information not covered by the SAE report form, including copies of hospital reports, autopsy reports or other relevant documents, will be requested, if necessary, by either the

clinical monitor or the Polyneuron/Clinipace Pharmacovigilance for a detailed description and a final evaluation of the case. All personal identifiers (e.g., name, detailed birth of date, address) must be pseudonymized prior to submission by blinding personal data and using the assigned identification code of the study patient.

The investigator should institute any supplementary investigations of SAE based on their clinical judgment of the likely causative factors. This may include seeking further opinion from a specialist in the field of the AE.

If the SAE information is incomplete or inconsistent and directly affects the sponsor's reporting obligation to health authorities, the Polyneuron/Clinipace Pharmacovigilance may directly contact the investigator for clarification.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary. The sponsor will be responsible for notification of the competent authorities, Ethics Committees (ECs) and investigators in the event of SUSAR and any other important safety issues requiring expedited reporting.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Polyneuron/Clinipace Pharmacovigilance will review and then file it along with the IB, and will notify the IRB/IEC, if appropriate according to local requirements.

9.4 Pregnancy reporting

No embryo-fetal development studies have been performed. Therefore, this study excludes enrolment of women of child-bearing potential unless they are using highly effective methods of contraception, thus pregnancy is not an expected outcome for any female study patient. However, in the case that a pregnancy in a female study patient should occur, please follow the below reporting guidelines.

To ensure patient safety, each pregnancy occurring after signing the informed consent must be **reported to Polyneuron within 24 hours** of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Polyneuron. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on an SAE form.

The study drug must be discontinued, though the patient may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The patient may continue all other protocol assessments.

9.5 Early phase safety monitoring

The Investigator will monitor AEs in an ongoing manner and inform Polyneuron of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing Polyneuron and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Polyneuron and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, Polyneuron will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

10 Quality assurance and quality control

All patient data relating to the study will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IEC review, and regulatory agency inspections and provide direct access to source data documents.

This study will be monitored regularly by Clinipace according to ICH-GCP and their monitoring SOPs. Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

Clinipace is responsible for the data management of this study including data quality checking.

Polyneuron assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

Monitoring will be done by personal visits from a representative of Clinipace. Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patient are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, International Council on Harmonization (ICH) GCP, and all applicable regulatory requirements.

Patient confidentiality must be maintained in accordance with local requirements. The monitoring standards also require full verification for the presence of ICF, adherence to the inclusion/exclusion criteria, documentation of SAEs, and recording of the main efficacy and safety endpoints.

In addition to the monitoring visits, frequent communications (letter, telephone, and fax) by the clinical monitor will ensure that the investigation is conducted according to the clinical protocol and regulatory requirements.

The results of monitoring visits will be documented in monitoring reports. Issues arising will be escalated and dealt with in a timely manner. The escalation process is defined in the respective SOPs of Clinipace.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion. If source documents are not durable as long as needed (e.g. printouts on thermo labile paper), they must be preserved as certified copy. No records may be destroyed during the retention period without the written

approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1 Data collection

Data capture and management will be conducted using the Clinipace clinical management and EDC/eCRF system. The processes and responsibilities of data collection, management and quality assurance will be specified in the Data Management Plan.

All applicable study data collected on each patient will be entered by approved site personnel into the eCRF. Instructions for the completion and submission of eCRFs will be provided to the sites in a separate document.

Authorized personnel will verify all data entered into eCRFs for completeness and accuracy with reference to the source documents and records and will issue data queries to correct missing data or discrepancies found against the source within the EDC system. Data validation will consist of automated and manual edit checks that are created directly in the EDC system. Edit checks will be executed on all data points defined and documented by the study team and data management will be able to issue manual queries as needed to the eCRF. Study metrics will be reported from the EDC system. Only authorized site personnel will be able to enter/modify/correct data in the eCRF.

10.2 Independent Data Monitoring Committee

An IDMC will review the safety data and anti-MAG antibodies results and will provide its recommendations to Polyneuron.

The membership of the IDMC and the responsibilities of the IDMC and Polyneuron will be defined in a separate document entitled the “Independent Data Monitoring Committee Charter”. The IDMC Charter will include information about data flow, purpose and timing of IDMC meetings, guidance in the decision-making process, communication strategy, procedures for ensuring confidentiality, and procedures to address conflicts of interest.

11 Data analysis

The analysis will be conducted on all patients at the time the study ends. Any data analysis carried out independently by the investigator should be submitted to Polyneuron at least 30 days before submission for publication or presentation to enable review for Intellectual Property matters. Descriptive statistics (number (N), mean, SD, median and ranges for continuous variables, frequencies and percentages for categorical variables) will be provided by treatment group and/or by visit, if applicable. All data will be listed by patient, treatment group and, where applicable, by visit. Full details of the analyses will be provided in the Statistical Analysis Plan (SAP).

11.1 Analysis sets (study populations)

The statistical analysis will be based on separate analysis populations, defined as follows:

The two study phases SAD and MAD described in this protocol form an exploratory investigation without any formal statistical hypotheses. All results will be interpreted descriptively only from the following analyses sets:

Safety population (SP): All patients who receive at least one dose of study medication. The SP will be the primary analysis set for the safety and tolerability analyses.

Intent-to-treat (ITT) population: all patients who were enrolled. The ITT population will be used as analysis set to confirm efficacy.

Per-protocol (PP) population: all patients, who meet the inclusion/exclusion criteria, received full-course of the study drug as per enrolment and have completed the main relevant visits (at least one visit one week and one month during SAD after study drug dosing is needed to assess biomarker and scores. During MAD at least one visit one month after the last dosing), for safety and efficacy assessment and who satisfactorily completed a pharmacodynamic blood sampling period without any major protocol violations which would render the data unreliable. The PP population will be used as analysis set to confirm the efficacy analyses and will constitute the primary analysis set for the PD and PK analyses. At least one visit one week and one month during SAD after dosing is needed to assess biomarker and scores. During MAD at least one visit one month after the last dosing.

Pharmacokinetic (PK) population: all patients who are included in the Safety population and who satisfactorily completed a pharmacokinetic blood sampling period without any major protocol violations which would render the data unreliable.

Pharmacodynamic (PD) population: all patients who are included in the PP and who satisfactorily completed a pharmacodynamic blood sampling period without any major protocol violations which would render the data unreliable.

11.2 Statistical hypothesis

The two study phases SAD and MAD described in this protocol form an exploratory investigation without any formal statistical hypotheses. All results will be interpreted descriptively only.

11.3 Protocol Deviation

Important deviations from the protocol, such as deviations from inclusion and exclusion criteria, relevant deviations in sampling times or from the planned time schedule of safety assessments will be reported in the clinical study report.

If an unexpected important deviation from the study protocol occurs, the investigator will consult Polyneuron to make a decision on how this deviation can be handled.

11.4 Patient demographics and other baseline characteristics

All data for background and demographic variables will be listed by dose group and patient. Summary statistics will be provided by dose group.

Relevant medical history, current medical conditions and other relevant information will be listed by treatment group and patient.

11.5 Treatments

Data for study drug administration and concomitant therapies will be summarized by dose group.

Total duration of time on study drug (Exposure) and reasons for discontinuation of study drug will be summarized by treatment group.

11.6 Analysis of safety

Safety endpoints will be summarized by treatment:

- Frequency, duration, severity and outcome of TEAEs.
- Changes in physical examination.

- Changes in clinical signs and scores.
- Signs of IRRs.
- Vital signs and ECGs.
- Hematology, clinical chemistry and urinalysis.

TEAEs are all AEs that that first appear during or after treatment with the IMP including those that worsened relative to the pre-treatment state.

Signs of IRRs include clinical signs and symptoms, changes in diastolic or systolic blood pressure, heart rate, oxygen saturation, and skin reactions or local reactions at the infusion site, which are monitored during and shortly after the administration of the IMP.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 22.0 or higher and summarized in frequency tables according to Preferred Term (PT) and System Organ Class (SOC). AEs will also be summarized according to their severity and causality. When an AE occurs more than once in the same patient, maximal severity and strongest causality will be counted. All SAEs and AEs leading to premature withdrawal from the study will be listed. Laboratory variables will be examined using mean changes from baseline. Laboratory values will also be categorized according to CTCAE toxicity grade and tabulated by their highest on-study toxicity grade. Shift tables will present numbers and percentages of patients with high / normal / low (or normal / abnormal) laboratory results at baseline and the last measurement available. Use of concomitant medications and of rescue antibiotics will be summarized.

Vital signs

All vital signs data will be listed by treatment, patient, and time point and abnormalities will be flagged. Summary statistics will be provided by treatment and time.

To assess the effect of PPSGG on blood pressure after dosing with PPSGG, blood pressure and heart rate on each infusion day (see Schedule of Assessments) expressed as change from baseline will be summarized. This represents the blood pressure at the approximate time of C_{max} after first dose and at steady state. The relationship between changes in blood pressure and heart rate and the C_{max} concentrations will also be investigated graphically.

ECG

All ECG data will be listed by treatment, patient, and time point and abnormalities will be flagged. Summary statistics will be provided by treatment and time and the number of patients with values above key threshold values will be displayed.

Clinical laboratory evaluations

All laboratory data will be listed by treatment, patient and time point and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and time point.

Adverse events

All information obtained on AEs will be displayed by treatment and patient.

The number and percentage of patients with AEs will be tabulated by SOC and PT with a breakdown by treatment. A patient with multiple AEs events within a SOC is only counted once towards the total of this SOC.

Summaries of SAEs will be provided in a similar manner.

Further displays of AEs may be produced in order to appropriately describe the outcomes seen in this trial.

11.6.1 Sample Handling procedures

All the safety analysis will be performed in local laboratory.

Sample handling is described separately in a Laboratory Manual.

Each sample will be labelled to indicate not less than: Polyneuron, study number, patient number, and sampling time.

All sample handling procedures, including the time of each sample collection, the time of placement into frozen storage (at the end of the sample workup), and the date of transfer or shipment of the samples to the responsible analyst will be documented in detail. Any missing blood draws must be reported in the eCRF. The exact time (using the 24-hour clock) of sample collection and possible problems occurring during the sampling will be entered in the respective sections of the eCRF.

All samples will be stored for a period of 6 months after submission of the final report to Polyneuron. If no separate contract for further storage has been agreed by Polyneuron, the samples will then be destroyed or shipped to Polyneuron. Both, return and destruction of samples requires Polyneurons approval.

Each sample will be labelled to indicate the study number, patient number, period number (MAD phase only), and sampling time.

All sample handling procedures, including the time of each sample collection, the time of placement into frozen storage (at the end of the sample workup), and the date of transfer or shipment of the samples to the responsible analyst will be documented in detail.

After sampling, blood and urine samples will be worked up and analyzed in a central laboratory, all results will be judged by a physician individually and commented as follows:

- Values within the reference ranges will not be commented. A '*' representing the value will be plotted within the brackets representing the reference range.
- For values slightly outside the reference ranges without clinical relevance a '*' representing the value will be plotted outside the brackets representing the reference range.
- For values outside the reference ranges with major deviation and/or possible pathological relevance a '*' representing the value will be plotted outside the brackets representing the reference range. In addition, the respective parameter will be shaded.

For all findings with major deviation and/or possible pathological relevance, follow-up examinations will be carried out until the deviation returns to normal or the absence of pathological relevance can be confirmed. If a deviation considered clinically relevant has not returned to a normal or not clinically relevant value when it is checked during the screening laboratory tests, the patient will not be included in the study.

The investigator has to decide whether a laboratory abnormality represents an adverse event

11.7 Analysis of Pharmacodynamics

Secondary variables supporting the secondary objective to assess the effect of PPSGG on reduction of anti-MAG IgM levels, change reduction of anti-MAG IgM antibody levels and time to anti-MAG IgM rebound (pre-treatment BTU), paraprotein levels (g/L), total IgM levels (g/L),

and anti-HNK-1 IgM titers will be analyzed. Descriptive summary statistics will be provided by dose and dosing frequency. Appropriate transformations will be detailed in the SAP. Estimates of the differences between each does of PPSGG and placebo will be calculated.

11.8 Analysis of Pharmacokinetics

PPSGG concentration data will be listed by dose, patient and time point (described in Section 8.6). Descriptive summary statistics will be provided by treatment and time, including the frequency (n, %) of samples collected. Sample concentrations below the LLOQ will be reported and used in PK calculation as zero.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. An exception to this is T_{max}. Since T_{max} is generally evaluated by a nonparametric method, median values and ranges will be given for this parameter. A geometric mean will not be reported if the dataset includes zero values.

The relationship between doses of PPSGG and the PK parameters AUC and C_{max} will be explored and used to calculate PPSGG half-life (T1/2, volume of distribution (Vd) and CL rate. Descriptive summary statics will also be provided for $T_{1/2}$, Vd and CL.

Graphical methods will be employed to show mean and individual concentration-time profiles and dose-exposure proportionality.

11.9 Analysis of exploratory variables (if applicable)

Statistical analysis for exploratory variables will be described in more detail in the Statistical Analysis Plan.

11.9.1 Exploratory endpoints

- NfL to measure the degree of axonal damage.
- BAFF.
- Indirect immunofluorescence on sciatic nerves.
- Classical pathway of the complement.

All biomarker data will be listed by treatment, patient, and time. Summary statistics will be provided by doses and time. Change from baseline until EOS will be summarized.

Graphical measures will be used to explore relationships between PPSGG treatment and biomarkers.

11.10 Sample size calculation

The sample size per cohort in this SAD and MAD study is representative of other FiH studies and based on feedback from EMA for a scientific advice.

It is anticipated that the specified number of patients should complete the study in accordance with this protocol. An insufficient number of evaluable cases might impair the aim of the study.

To allow for a drop-out rate of up to 20% in MAD phase, 30 patients will be enrolled with the aim of having at least 24 patients complete each phase.

11.11 Interim analyses

No formal interim analysis is planned for this study. Safety data will be gathered and reviewed by the IDMC on continuous basis. The data will be frozen after the SAD phase to define the schedule and doses for the MAD phase based on the SAD data as described previously.

12 Regulatory and Ethical considerations

12.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki.

12.2 Responsibilities of the investigator and Institutional Review Board/Independent Ethics Committee

Before the start of the study Polyneuron or authorized applicant will apply for approval for the performance of the study at the Competent Authority. The sites will apply for approval for the performance of the study at the respective EC. All documents required by the EC and by the Competent Authority will be submitted.

Any notification / submission has to be dated and to contain sufficient information to identify the respective protocol.

The study will only be started after receipt of the written approval of the respective EC and Competent Authority.

The Principal Investigator and Clinipace are responsible for maintaining the approval documents in the study documentation files.

The Principal Investigator or Clinipace will report promptly to the EC new information that may adversely affect the safety of the patients or the conduct of the trial.

Polyneuron (or authorized applicant), should submit a written report about the safety of the patients as well as a list of occurred suspected serious adverse drug reactions caused by the investigational medicinal product of the clinical study to the EC and the Competent Authority annually, or more frequently if requested by the EC or the Competent Authority.

A declaration of the end of trial should be forwarded by Polyneuron (or authorized applicant), to the Competent Authority and to the EC within 90 days after the study has been completed or in the event of premature termination of the study within 15 days.

Polyneuron (or authorized applicant) should provide a summary of the clinical study report to the EC and Competent Authority within 1 year after completion of the study

The reporting to the EC and the Competent Authority is clearly defined in the Quality Agreement and responsibility list for clinical study.

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation) informed consent.

12.3 Informed consent procedure

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Clinipace will provide to investigators a proposed ICF that complies with the ICH E6 GCP guideline and regulatory requirements and is considered appropriate for this study. The procedures set out in the main consent form concerning the storage, maintenance of privacy, and release of the data or specimens for the main study will also be adhered to for any future research. Any changes to the proposed consent form suggested by the investigator must be agreed to by Polyneuron before submission to the IRB/IEC.

The investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.
Patients must be informed that their participation is voluntary. Patients will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative

Information about potential side effects in humans about the investigational drug can be found in the IB. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and then must be discussed with the patient.

Ensure patients are informed of the contraception requirements outlined in the Section (Exclusion criteria) and in Section (Contraception requirements).

A separate consent for an optional Biobanking component will be obtained. The Investigator presents this option to the patient, as permitted by local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in this biobank collection will in no way affect the patient's ability to participate in the main research study.

A copy of the approved version of all consent forms must be provided to the Polyneuron monitor after IRB/IEC approval.

12.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

12.5 Quality Control and Quality Assurance

Audits of investigator sites, vendors, and Polyneuron systems are performed or overseen by Polyneuron Pharma Auditing and Compliance Quality Assurance (or contract research organization [CRO] working on behalf of Polyneuron), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk-based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Polyneuron processes.

13 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study patients. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Polyneuron and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

13.1 Protocol Amendments

Neither the investigator nor the sponsor will alter this clinical study protocol without obtaining the written agreement of the other party. Once the study has started, amendment should be made only in exceptional cases. The changes then become part of the clinical study protocol.

Substantial amendment, i.e., changes in the clinical study protocol which may have a significant impact on the safety of the patients, or on the scientific value of the study, or on the conduct or management of the study, may not be implemented without a favorable opinion of the ECs/IRBs unless the changes consist of urgent safety measures to protect study patients. In such a case, approval must be obtained as soon as possible after implementation.

Amendments which are minor and/or refer to changes regarding logistical and administrative aspects of the study (i.e., change in telephone numbers) are always sent to the ECs for information.

14 References

1. Latov N, Braun PE, Gross RB et al. Plasma cell dyscrasia and peripheral neuropathy: identification of the myelin antigens that react with human paraproteins. Proc. Natl. Acad. Sci. U. S. A. 1981; 78(11):7139–7142.

2. Braun PE, Frail DE, Latov N. Myelin-associated glycoprotein is the antigen for a monoclonal IgM in polyneuropathy. J. Neurochem. 1982; 39(5):1261–1265.

3. Steck AJ, Stalder AK, Renaud S. Anti-myelin-associated glycoprotein neuropathy. Curr. Opin. Neurol. 2006; 19(5):458–463.

4. Rison RA, Beydoun SR. Paraproteinemic neuropathy: a practical review. BMC Neurol. 2016; 16:13.

5. Ritz MF, Erne B, Ferracin F et al. Anti-MAG IgM penetration into myelinated fibers correlates with the extent of myelin widening. Muscle Nerve 1999; 22(8):1030–1037.

6. Dalakas MC. Pathogenesis of immune-mediated neuropathies. Biochim. Biophys. Acta 2015; 1852(4):658–666.

7. Talamo G, Mir MA, Pandey MK et al. IgM MGUS associated with anti-MAG neuropathy: a single institution experience. Ann. Hematol. 2015; 94(6):1011–1016.

8. Vallat J-M, Magy L, Ciron J et al. Therapeutic options and management of polyneuropathy associated with anti-MAG antibodies. Expert Rev. Neurother. 2016; 16(9):1111–1119.

9. Nobile-Orazio E, Baldini L, Barbieri S et al. Treatment of patients with neuropathy and anti-MAG IgM M-proteins. Ann. Neurol. 1988; 24(1):93–97.

10. Lunn MP, Nobile-Orazio E. Immunotherapy for IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies. Cochrane Database Syst. Rev. 2016; 10:CD002827.

11. Dalakas MC. Advances in the diagnosis, immunopathogenesis and therapies of IgM-anti-MAG antibody-mediated neuropathies. Ther. Adv. Neurol. Disord. 2018; 11:1756285617746640.

12. Pestronk A, Florence J, Miller T et al. Treatment of IgM antibody associated polyneuropathies using rituximab. J. Neurol. Neurosurg. Psychiatry 2003; 74(4):485–489.

13. Benedetti L, Briani C, Franciotta D et al. Long-term effect of rituximab in anti-mag polyneuropathy. Neurology 2008; 71(21):1742–1744.

14. Dalakas MC. Pathogenesis and Treatment of Anti-MAG Neuropathy. Curr. Treat. Options Neurol. 2010; 12(2):71–83.

15. Latov N. Diagnosis and treatment of chronic acquired demyelinating polyneuropathies. Nat. Rev. Neurol. 2014; 10(8):435–446.

16. Quarles RH, Weiss MD. Autoantibodies associated with peripheral neuropathy. Muscle Nerve 1999; 22(7):800–822.

17. Tatum AH. Experimental paraprotein neuropathy, demyelination by passive transfer of human IgM anti-myelin-associated glycoprotein. Ann. Neurol. 1993; 33(5):502–506.

18. Crickx E, Weill JC, Reynaud CA, et al. Anti-CD20-mediated B-cell depletion in autoimmune diseases: successes, failures and future perspectives. Kidney Int. 2020 Jan 30. pii: S0085-2538(20)30108-3. doi: 10.1016/j.kint.2019.12.025. [Epub ahead of print].

19. Svahn J, Petiot P, Antoine JC, et al. Anti-MAG antibodies in 202 patients: clinicopathological and therapeutic features. J Neurol Neurosurg Psychiatry. 2018 May;89(5):499-505. doi: 10.1136/jnnp-2017-316715. Epub 2017 Oct 25.

20. Polyneuron; PN-1007 (PPSGG) IB, version 2, April 2020.

21. Herrendorff R, Hänggi P, Pfister H et al. Selective in vivo removal of pathogenic anti-MAG autoantibodies, an antigen-specific treatment option for anti-MAG neuropathy. Proc. Natl. Acad. Sci. U. S. A. 2017; 114(18):E3689–E3698.

22. Katopodis AG, Warner RG, Duthaler RO et al. Removal of anti-Galalpha1,3Gal xenoantibodies with an injectable polymer. J. Clin. Invest. 2002; 110(12):1869–1877.

23. Cook L, Macdonald DHC. Management of paraproteinaemia. Postgrad. Med. J. 2007; 83(978):217–223.

24. Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. [http://www.fda.gov/regulatory-information/search-fda-guidance-documents/estimating-maximum-safe-starting-dose-initial-clinical-trials-therapeutics-adult-healthy-volunteers].

25. Strategies to identify and mitigate risks for first-in-human early clinical trials with investigational medicinal products. [https://www.ema.europa.eu/en/strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational-medicinal].

26. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of paraproteinemic demyelinating neuropathies. Report of a Joint Task Force of the European Federation of Neurological Societies and the Peripheral Nerve Society--first revision. J. Peripher. Nerv. Syst. JPNS 2010; 15(3):185–195.

27. F. Alexis, E. Pridgen, L. K. Molnar, O. C. Farokhzad, Factors affecting the clearance and biodistribution of polymeric nanoparticles. Mol Pharm 5, 505-515 (2008).

28. M. Liu, H. Li, G. Luo, Q. Liu, Y. Wang, Pharmacokinetics and biodistribution of surface modification polymeric nanoparticles. Arch Pharm Res 31, 547-554 (2008).

15 Appendices

15.1 Common Terminology Criteria for Adverse Events v5.0 (CTCAE)

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Introduction

The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

SOC

System Organ Class (SOC), the highest level of the MedDRA1 hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v5.0 term is a MedDRA LLT (Lowest Level Term).

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1

Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2

Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental Activities of Daily Living (ADL)*.

Grade 3

Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

Grade 4

Life-threatening consequences; urgent intervention indicated. Grade 5 Death related to AE. A Semi-colon indicates ‘or’ within the description of the grade. A single dash (-) indicates a Grade is not available. Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Definitions

A brief Definition is provided to clarify the meaning of each AE term. A single dash (-) indicates a Definition is not available.

Navigational Notes

A Navigational Note is used to assist the reporter in choosing a correct AE. It may list other AEs that should be considered in addition to or in place of the AE in question. A single dash (-) indicates a Navigational Note has not been defined for the AE term.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

15.2 Overall Neuropathy Limitations Scale (ONLS)

Name:
Date:

Overall Neuropathy Limitations Scale (ONLS)

Instructions: The examiner should question **and** observe the patient in order to determine the answers to the following questions. Note should be made of any other disorder other than peripheral neuropathy which limits function at the foot of the page.

ARM SCALE

Does the patient have any symptoms in their hands or arms, eg tingling, numbness or weakness? **Yes** ☐ **No** ☐
(if "no", please go to "legs" section)

Is the patient affected in their ability to:	Not affected	Affected but not prevented	Prevented
Wash and brush their hair	☐	☐	☐
Turn a key in a lock	☐	☐	☐
Use a knife and fork together (or spoon, if knife and fork not used)	☐	☐	☐
Do or undo buttons or zips	☐	☐	☐
Dress the upper part of their body excluding buttons or zips	☐	☐	☐

If all these functions are prevented can the patient make purposeful movements with their hands or arms? Yes ☐ No ☐ Not applicable ☐

Arm Grade
0–Normal
1–Minor symptoms in one or both arms but not affecting any of the functions listed **SCORE=____**
2–Disability in one or both arms affecting but not preventing any of the functions listed
3–Disability in one or both arms preventing at least one but not all functions listed
4–Disability in both arms preventing all functions listed but purposeful movement still possible
5–Disability in both arms preventing all purposeful movements

LEG SCALE

	Yes	No	Not applicable
Does the patient have difficulty running or climbing stairs?	☐	☐	☐
Does the patient have difficulty with walking?	☐	☐	☐
Does their gait look abnormal?	☐	☐	☐
How do they mobilise for about 10 metres (ie 33 feet)?			
Without aid	☐	☐	☐
With one stick or crutch or holding to someone's arm	☐	☐	☐
With two sticks or crutches or one stick or crutch holding onto someone's arm or frame	☐	☐	☐
With a wheelchair	☐	☐	☐
If they use a wheelchair, can they stand and walk 1 metre with the help of one person?	☐	☐	☐
If they cannot walk as above are they able to make some purposeful movements of their legs, eg reposition legs in bed?	☐	☐	☐
Does the patient use **ankle foot orthoses/braces?** (please circle)	☐	☐ **If yes:** (please circle) **right/left**	

Leg grade
0–Walking/climbing stairs/running not affected
1–Walking/climbing stairs/running is affected, but gait does not look abnormal **SCORE=____**
2–Walks independently but gait looks abnormal
3–Requires unilateral support to walk 10 metres (stick, single crutch, one arm)
4–Requires bilateral support to walk 10 metres (sticks, crutches, crutch and arm,frame)
5–Requires wheelchair to travel 10 metres but able to stand and walk 1 metre with the help of one person
6–Restricted to wheelchair, unable to stand and walk 1 metre with the help of one person, but able to make some purposeful leg movements
7–Restricted to wheelchair or bed most of the day, unable to make any purposeful movements of the legs

Overall Neuropathy Limitation Scale–arm scale (range 0 to 5)+leg scale (range 0 to 7);
(range: 0 (no disability) to 12 (maximum disability)) **TOTAL SCORE=____**
Is there any disorder, other than peripheral neuropathy, which affects the above functions **Yes** ☐ **No** ☐
If **yes** please describe:

15.3 Inflammatory Neuropathy Cause and Treatment (INCAT) Sensory Sum Score (ISS)

The ISS ranges from 0 (normal sensation) to 20 (most severe sensory deficit) and is composed of the summation of the following sensation qualities:

- Pinprick arm grade (range 0-4).
- Vibration arm grade (range 0-4).
- Pinprick leg grade (range 0-4).
- Vibration leg grade (range 0-4).
- Two-point discrimination grade (range 0-4).

Pinprick is tested with the sharp end of an esthesiometer, patients indicate normal or abnormal. Paresthesia, dysesthesia or hyperesthesia are to be scored as abnormal. Normal reference point: face.

Vibration sense is tested using the graduated Rydel-Seiffer tuning fork, measures obtained are compared with the reported normative threshold values.

Pinprick and vibration sense examination take place distal to proximal and only the highest extension of dysfunction of the most affected arm and leg are recorded separately for both qualities.

Pinprick sensation (sites of examination and corresponding grades)		**Vibration sensation (sites of examination and corresponding grades)**		**Two-point discrimination (sites of examination and corresponding grades)**
Arms	Legs	Arms	Legs	Index finger [K]
Normal sense 0, at index finger A	Normal sense 0, at hallux F	Normal sense 0, at index finger A	Normal sense 0, at hallux F	Normal sense 0, <4 mm
Abnormal sense	Abnormal sense	Abnormal sense	Abnormal sense	Abnormal sense
1, at index finger [B]	1, at hallux [G]	1, at index finger [B]	1, at hallux [G]	1, 5-9 mm
2, at wrist [C]	2, at ankle [H]	2, at wrist [C]	2, at ankle [H]	2, 10-14 mm
3, at elbow [D]	3, at knee [I]	3, at elbow [D]	3, at knee [I]	3, 15-19 mm
4, at shoulder [E]	4, at groin [J]	4, at shoulder [E]	4, at groin [J]	4, > 20 mm

A,B: index finger (dorsum distal interphalangeal joint); C: ulnar styloid process; D: medial humerus epicondyle; E: acromioclavicular joint; F,G: hallux (dorsum inter-phalangeal joint); H: medial malleolus; I: patella; J: anterior superior iliac spine; K: index finger (ventral side: distal phalanx).

15.4 Rasch-built Overall Disability Scale (RODS) Scale

INSTRUCTIONS: This is a questionnaire about the relationship between daily activities and your health. Your answers give information about how your polyneuropathy affects your daily and social activities and to what degree you are able to perform your usual activities.

Answer each question by marking the correct box ("x"). If you are not sure about your ability to perform a task, you are still requested to mark an answer that comes as close as possible to your judged ability to complete such a task. All questions should be completed. You can only choose one answer to each question. If you situation fluctuates, your answer should be based on how you *usually* perform the task.

If you need assistance or you are using special devices to perform the activity, you are requested to mark "possible, but with some difficulty ". In case you never perform the activity due to your polyneuropathy mark "not possible".

Are you able to	Mark the best option with "x"		
Task	Not possible to perform [0]	Possible, but with some difficulty [1]	Possible, without any difficulty [2]
1. read a newspaper/book?	☐	☐	☐
2. eat?	☐	☐	☐
3. brush your teeth?	☐	☐	☐
4. wash upper body?	☐	☐	☐
5. sit on a toilet?	☐	☐	☐
6. make a sandwich?	☐	☐	☐
7. dress upper body?	☐	☐	☐
8. wash lower body?	☐	☐	☐
9. move a chair?	☐	☐	☐
10. turn a key in a lock?	☐	☐	☐
11. go to the general practitioner?	☐	☐	☐
12. take a shower?	☐	☐	☐
13. do the dishes?	☐	☐	☐

14. do the shopping?	☐	☐	☐
15. catch an object (e.g., ball)?	☐	☐	☐
16. bend and pick up an object?	☐	☐	☐
17. walk one flight of stairs?	☐	☐	☐
18. travel by public transportation?	☐	☐	☐
19. walk and avoid obstacles?	☐	☐	☐
20. walk outdoor < 1 km?	☐	☐	☐
21. carry and put down a heavy object?	☐	☐	☐
22. dance?	☐	☐	☐
23. stand for hours?	☐	☐	☐
24. run?	☐	☐	☐

15.5 Hand Grip Strength Test

With the Martin Vigorimeter, the patient squeezes a rubber ball that is connected to a manometer with rubber tubing.

The patient's grip strength is expressed in kilopascal (kPa), with a range of 0–160 kPa.

The same dynamometer will be used for a patient throughout the study. When performing the test, patients will stand, holding the dynamometer in dominant hand, with their arm parallel to the body without squeezing the arm against the body. This assessment will be performed in triplicate on same day at each time point.

15.6 The Modified Rankin Scale (mRS)

The scale runs from 0-6, running from perfect health without symptoms to death.

0 - No symptoms.

1 - No significant disability. Able to carry out all usual activities, despite some symptoms.

2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.

3 - Moderate disability. Requires some help, but able to walk unassisted.

4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.

5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent.

6 - Dead.

15.7 Motor Unit Number Index (MUNIX)

MUNIX will be performed on the tibialis anterior (TA), abductor digiti mini (ADM) and abductor pollicis brevis (APB) muscles as previously reported (Delmont et al. 2016).

Supramaximal distal stimulations of the corresponding nerves will be performed to achieve maximal CMAP amplitude with minimum rise time and sharp negative take-off. The recordings will be assessed on a 300ms window with filter setting of 3Hz-3000Hz. Ten isometric contractions will be recorded as surface interference pattern (SIP) ranging from 10 to 100% of contraction. The degree of the force increment will be estimated by the resistance given by the examiner and by the amplitude and the fullness of the SIP. SIP epochs will be accepted if SIP area >20mV/ms, ideal case motor unit count (ICMUC) <100 and SIP area/CMAP area >1. A MUNIX sumscore will be calculated by adding the results of the ADM, APB and TA muscles.

APB: Place hand upon flat surface, palm up. Place recording electrode on thenar eminence just lateral to mid-point of first metacarpal, aligned with first metacarpal. Place reference electrode distally at the thumb. Grounding electrode is placed on the dorsum of the hand. Place stimulator at wrist between flexor carpi radialis and palmaris longus tendons. Avoid partial abduction of the thumb and pronation of the forearm. Counter resistance: place your hand over the patient's hand, with your thumb giving resistance to the patient's thumb.

ADM: Place hand upon flat surface, palm up. Place recording electrode on ADM at midpoint fifth metacarpal. Place reference electrode distally at the little finger. Grounding electrode is placed on the dorsum of the hand. Place stimulator at wrist adjacent to flexor carpi ulnaris tendon. In some subjects, maximal compound muscle action potential (CMAP) is achieved with more proximal placement of the recording electrode. Be aware of initial baseline shift due to electrode movement on the skin while increasing force levels. Counter resistance: stabilize with your fingers/thumb. Do not allow abduction of digit V.

TA: Lower leg is positioned naturally with sole of the foot on the floor, knee flexed approximately 90 degrees. Place recording electrode lateral to tibial crest, one-third of distance between ankle and knee (closer to knee). Place reference electrode over the patellar tendon. Grounding electrode should be places above at the level of the fibular head. Place stimulator one to two fingerbreadths inferior to fibular head. Counter resistance: use your hand to give resistance with the foot positioned at 90 degrees. Avoid pronation/supination of the foot.

15.8 Ataxia Score

- normal posture with closed eyes (0).
- slight postural alteration with closed eyes (1).
- severe postural alteration with closed eyes (2).
- inability to stand with closed eyes (3).

15.9 Timed 10-Meter Walk Test Instructions

Description:

Individual walks without assistance 10 meters (32.8 feet) and the time is measured.

Set-up

- Measure and mark a 10-meter indoor walkway, along a flat, quiet corridor with a non-carpeted surface.
- Place chairs at the start and finish of the walkway.

Site instructions:

- Patients should be evaluated for lower limb injury immediately prior the test.
- A 10-minute rest period should always be given prior to the start of the test.
- Start timing when the toes of the leading foot crosses the 0-meter mark.
- Stop timing when the toes of the leading foot crosses thee 10-meter mark
- Ambulatory aids such as cones and walkers are permitted.
- No support may be given by an assistant unless the patient needs help to rise from a fall or to sit down.
- Subjects may not touch the walls.
- Due to possibility of subject falls, the course should be within easy access of appropriate medical assistance.
- Test results should be recorded on the 10 Meter Walk Test Worksheet.

Patient instructions

- Patients should wear comfortable clothing and appropriate shoes for walking. Since patients will be tested at multiple time points, they should make an effort to wear the same type of shoes each time.
- The tester will say ”Ready, Set, Go”. When the tester says go, begin walking at your normal comfortable pace.

CLINICAL STUDY PROTOCOL

Study title	First in Human study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy of PPSGG (PN-1007) in anti-MAG neuropathy patients.
Investigational Medicinal Product	PPSGG (PN-1007).
Study Number	PN-1007-001.
EudraCT number	2020-000067-23.
Study phase	Phase I/IIa.
Version and Date of protocol	Version 2.0, 08 July 2020.
Sponsor	Polyneuron Pharmaceuticals AG Hochbergerstrasse 60C CH-4057 Basel, Switzerland.
Coordinating Investigator	Emilien Delmont, MD.

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SPONSOR SIGNATURE PAGE

Protocol Title: First in Human Study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy of PPSGG (PN-1007) in anti-MAG neuropathy patients.

Protocol Number: PN-1007-001.

Sponsor: Polyneuron Pharmaceuticals AG.

I approve the contents of this clinical protocol for Study No. PN-1007-001 Version 2.0 , 08July 2020 and agree to meet all obligations of Polyneuron Pharmaceuticals as detailed in all applicable regulations and guidelines. In addition, I will inform the Coordinating Investigator and all other investigators of all relevant information that becomes available during the conduct of this study.

Sponsor Signatory:

Debra Barker, MD
CMO, Polyneuron Pharmaceuticals AG
Hochbergerstrasse 60C
CH-4057 Basel, Switzerland.

Signature

8th July 2020

Date

Coordinating Investigator:

Emilien Delmont, MD
APHM Hopital La Timone Adultes
264 Rue Saint Pierre,
F- 13005 Marseille, France.

Signature

8 July 2020

Date

PROTOCOL INVESTIGATOR AGREEMENT

As Investigator of this study, I agree:

- To conduct the study in compliance with this protocol, and with mutually agreed future protocol amendments, protocol administrative changes, other study conduct procedures and study conduct documents provided by Polyneuron Pharmaceuticals AG.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of, and will comply with, 'Good Clinical Practice' (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study (my Staff) are adequately informed about the investigational medicinal product and other study-related duties and functions as described in the protocol and have the necessary skill and competencies to manage them.
- To co-operate with the representative of Polyneuron Pharmaceutical AG's appointed Contract Research Organization (CRO) in the monitoring of the study and resolution of queries about the data.
- That I have been informed that the agency and Ethics Committee may require the sponsor to obtain and supply, as necessary, details about the Investigator's ownership interest in the sponsor or the investigational product, and more generally about the financial ties with the sponsor. Polyneuron Pharmaceuticals AG will use and disclose the information solely for the purpose of complying with regulatory requirements.
- To provide Polyneuron Pharmaceuticals AG or CRO with a current Curriculum Vitae and other documents required by the Ethics or authorities for this study.

Study title	First in Human Study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy of PPSGG in anti-MAG neuropathy patients.
EudraCT number	2020-000067-23.
Versions and Date of protocol	Version 2.0 08 July 2020.
Protocol code number	PN-1007-001.
Name and address of Investigator	

_____ _____

Signature **Date**

Amendment 2 (July 2020)

Amendment rationale

The purpose of this amendment is to address questions raised by different health authorities. The changes are summarized below.

Changes to the protocol

The following changes have been implemented throughout the protocol:

1. Recent apheresis/plasmapheresis has been added as exclusion criterion in Section 4.3.
2. The limit for creatinine clearance at inclusion has been raised to 60 mL/min. The inclusion criterion in the protocol in Section 4.3. has been adapted accordingly.
3. Additional pregnancy tests on a monthly basis (on Days 28, 56 and 98) in the MAD phase have been added. The Assessment schedule in Section 8.1. has been updated accordingly.
4. The exclusion criterion (Section 4.4) has been updated to specify that progesterone containing hormonal tablets must be associated with inhibition of ovulation in order to qualify as highly effective.
5. The durations of contraceptive use between males and females have been aligned to one week.
6. In Section 7.6 the study stopping rules have been adapted.
7. The plan for rapid communication of serious adverse events and suspected unexpected serious adverse reactions (SUSARs) between the sponsor, the investigators of all sites and the patients has been described in Section 9.1.7.
8. Section 1.8 has been updated to provide some clarification on the justification of the doses.
9. The wording of the starting dose of MAD phase has been adapted. The dosing of both cohorts in the MAD phase will not exceed the exposures achieved in the SAD phase (Cmax and AUC0-tau), and will commence at a dose at least one dose level lower than safely completed in the SAD.
10. A back-up system in support of IVRS in case of the necessity for the investigator to unblind study treatment during MAD part of the study in has been implemented and is described in Section 6.8.
11. A section “Reference safety information (RSI) has been added and is reflected in Section 9.1.8.
12. Motor Unit Number Index (Munix) will be defined as exploratory endpoint in selected sites only, as not all sites are able to perform this score. Section 2.3 and Synopsis have been updated.
13. As only patients capable of discernment will be enrolled in this study, there is no need to dispatch a copy of the ICF to the participant’s legal representative. The Section 12.3. has been adapted accordingly.
14. An additional section (Section 13.2.) has been added to describe particular measures related to Covid-19 pandemic.

15. Minor changes were made throughout the protocol for improved clarity, better alignment between protocol sections and to correct minor consistency error.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through font for deletions~~ and underlined for insertions. A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

Synopsis

Study Number and Title	First in Human Study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy of PPSGG (PN-1007) in anti-MAG neuropathy patients.
Study Phase	Phase I/IIa.
Study Duration	Overall planned study duration is Q2 2020 – Q2 2022. Up to 2 months and 8 visits per patient in the single ascending dose (SAD) phase and up to 6 months and 17 visits per patient in the multiple ascending dose (MAD) phase.
Indication	Anti-myelin-associated glycoprotein (MAG) neuropathy.
Rationale for the study	This is a Phase I/IIa, First in Human (FiH), multicenter, single and multiple ascending dose escalation trial of PPSGG, an antibody scavenger of pathogenic anti-MAG immunoglobulin M (IgM) autoantibodies for treatment of anti-MAG neuropathy. The aim of the study is to assess the safety and tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of PPSGG in a SAD and a MAD phase in an adaptive trial in anti-MAG neuropathy patients. The safety and tolerability of PPSGG has been demonstrated in different animal species, for up to 11 single doses given over 15 min IV infusion. Currently, there is no treatment for anti-MAG neuropathy approved by the European Medicines Agency (EMA) or by the US Food and Drug Administration (FDA). However, off-label treatments are used for treatment of anti-MAG neuropathy, including various immunomodulatory and immunosuppressive treatments used to manage anti-MAG neuropathy. Nonetheless, these treatments are of limited efficacy and may induce side effects. Clinical improvement of neuropathic symptoms in patients with anti-MAG neuropathy correlates with reduced serum levels of anti-MAG IgM autoantibodies and disease worsening is associated with increasing anti-MAG IgM levels during treatment follow-up. Knowledge of the biological role of the MAG protein, the inhibitory activity of PPSGG on anti-MAG IgM antibodies, and the clinical correlation between anti-MAG IgM levels and clinical outcomes support the hypothesis that a reduction in anti-MAG IgM levels by PPSGG can be associated with clinical improvements for patients. During the SAD phase, PPSGG will be administered via intravenous (IV) infusion to patients with confirmed anti-MAG neuropathy. Based on the safety and PK/PD data of the SAD phase, PPSGG will be administered up to 11 times during the MAD phase of this study for a maximum of 6 weeks.

Objectives

Primary objective

To assess the safety and tolerability after single and multiple intravenous administrations of PPSGG in patients suffering from anti-MAG neuropathy.

Secondary objectives

- To evaluate the PK of PPSGG after single and multiple intravenous administrations.
- To investigate PD of PPSGG in reducing anti-MAG IgM levels.
- To obtain preliminary efficacy data from neurological evaluations and clinical outcomes using different clinical scores

Study design

Phase Description

Phase I: FiH, open label, SAD escalation study in anti-MAG neuropathy patients to assess the safety, tolerability, PK and PD parameters of PPSGG.

After completion and evaluation of the SAD phase a MAD phase will follow.

Phase IIa: randomized, dose escalation, double blind (patient and investigator blinded), placebo-controlled, MAD in anti-MAG neuropathy patients to assess the safety, immunogenicity, tolerability, PK, PD and preliminary efficacy parameters of PPSGG.

- Phase I: Single Ascending Dose (SAD)

The single rising dose escalation phase will enroll 6 patients in each of the 4 or 5 ascending dose cohorts. The first administration of PPSGG of any cohort will be provided to a single patient (sentinel patient). The decision to continue dosing the remaining patients in a given cohort will be based on all available safety data collected during the first 72 hours after treatment of the sentinel patient. The decision to escalate to the following dose (once a cohort is completed) will be based on all available safety data, collected during a minimum of 72 hours after the start of the infusion for all patients, where no stopping rules are met and analyzed by an Independent Data Monitoring Committee (IDMC). The study drug will be administered as a 60 min (120 min for optional 3200 mg dose) IV infusion.

In the SAD phase each patient will have, within 2 months, the following 8 visits: Screening, Baseline, Treatment (4 visits), end of study (EOS) and Follow-up.

- Phase IIa: Multiple Ascending Dose (MAD)

The multiple rising dose phase will enroll 2 dose cohorts of at least 12 patients each (10 on active and 2 on placebo). Dose

levels will be determined based on the safety, tolerability, PK and PK/PD outcome (anti-MAG IgM titers) from the SAD phase. The dosing of both cohorts in the MAD phase will not exceed the exposures achieved in the SAD phase (C_{max} and $AUC_{0\text{-}tau}$), and will commence at a dose at least one dose level lower than safely completed in the SAD. The dosing frequency will be defined based on the PK/PD relationship established during the SAD phase (PPSGG half-life, anti-MAG IgM kinetic) and simulation of it. The study drug will be administered for up to 11 times (as a 60 min (120 min for optional 3200 mg dose) IV infusion) for six weeks to explore the effect on anti-MAG antibody levels. For safety purposes the first 2 patients in each cohort of the MAD phase will be randomized to receive active or placebo treatment in a double-blind fashion. The decision to continue dosing in a given cohort will be based on safety data of the first 2 patients collected during 2 weeks (minimum) after the start of the infusion. The decision to escalate to the following dose will be based on safety data collected during the first 2 weeks after the start of infusion and analyzed by an IDMC.

In the MAD phase each patient will have, within 6 months, up to 17 visits: Screening, Baseline, Treatment (up to 14 visits), EOS and Follow-up.

The MAD phase dosing regimen will be adapted for in accordance with PK/PD modelling, safety and tolerability data collected during the SAD phase. The dosing of both cohorts in the MAD phase will not exceed the exposures achieved in the SAD phase (C_{max} and $AUC_{0\text{-}tau}$), and will commence at a dose at least one dose level lower than safely completed in the SAD. Dosing regimen includes the dose level administered, the frequency of dosing and the duration of dosing, i.e. the number of doses administered.. Based on the safety toxicology studies performed in animals the maximum number of doses is 11 infusions in 6 weeks. The goal is to define a potential dose and regime to reliably, safely and sustainably reduce anti-MAG IgM antibody levels by at least 50%

The following assessments will be performed in each of the two phases (SAD and MAD):

- Safety and tolerability (adverse events (AEs), vital signs, laboratory data, electrocardiograms (ECGs), and local tolerability assessment).
- Blood sampling for anti-drug antibodies (ADA) development (immunogenicity).
- Blood sampling for PPSGG pharmacokinetics.
- Blood sampling for pharmacodynamics: (anti-MAG titers (Bühlmann Titer Units), paraprotein levels, anti-human

natural killer- 1 antibodies (anti-HNK-1 Titers) and total IgM.

- Clinical assessments based on overall neuropathy limitations scale (ONLS) score, time to walk 10 meters, and Rasch-built overall disability scale (RODS) and Ataxia scores.

The following assessments will be performed in the MAD phase only :

- INCAT sensory sum score (ISS)
- Motor Unit Number Index (MUNIX) in selected sites only.
- Grip strength
- Neurofilament light chain (NfL) to measure the degree of axonal damage.
- B-cell activating factor (BAFF).
- Indirect immunofluorescence on sciatic nerves.

Each phase (SAD and MAD) will be split in two parts: (1) an active administration phase with single (SAD) or multiple (MAD) infusions and (2) an observation phase of 1 and 3 months respectively for the SAD and MAD.
After this, patients whose antibody levels have not returned to baseline will enter in the follow-up phase, the duration of which will depend on the evolution of the anti-MAG IgM antibody levels.

Number of patients

Approximately 48 patients will participate. Six patients per cohort (4 or more cohorts) in Phase I (SAD) and 12 patients (10 active and 2 placebo) per cohort (total 2 cohorts) in Phase IIa (MAD) respectively. In order to have enough evaluable patients, up to 2 additional patients per cohort will be recruited. Patients from the SAD phase will be eligible to enroll in the MAD phase once their anti-MAG antibody levels have returned to baseline.

Sites

Approximately 8 sites from 5 European countries are planned to participate.

Inclusion criteria

- Written informed consent.
- Age between 18 and 80 years, male and female.
- Patient with a confirmed diagnosis of monoclonal IgM associated with monoclonal gammopathy of undetermined significance (MGUS) with anti-MAG activity (titer of >10’000 Bühlmann Titer units (BTU)) and demyelinating neuropathy defined by electrophysiological criteria according to European Federation of Neurological Societies/Peripheral Nervous System paraproteinemic demyelinating neuropathy (EFNS/PNS PDN) guideline, 2010.

- Clear clinical signs of disability: with at least ONLS ≥ 2 in lower extremities.
- Inflammatory Neuropathy Cause and Treatment sensory sum score (ISS) ≥2
- Patients must have adequate hepatic function as evidenced by total bilirubin < 26 µmol/l (1.5 mg/dL), and alkaline phosphatase and aspartate transaminase/alanine aminotransferase <2X the upper limit of normal (ULN).
- Absence of cause of neuropathy independent from anti- MAG activity: e.g. diabetes, hypothyroidism, past or current dependence on alcohol, past or current treatment with neurotoxic drugs.
- Patients must have adequate renal function as evidenced by serum creatinine <2 mg/dL or calculated creatinine clearance of ≥60 mL/min within 28 days before the first investigational medicinal product (IMP) administration using the Modification of Diet in Renal Disease (MDRD) formula.
- Capability to meet the requirements of the study.

Exclusion criteria

- Patients with total serum IgM levels >30 g.
- Hematological malignancy (e.g. known multiple myeloma or confirmed Waldenström's macroglobulinemia based on bone marrow analysis).
- Patients with any history of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
- Previous immunosuppressive treatment with intravenous immunoglobulin (IVIG) or apheresis/plasmapheresis in the preceeding 3 months, and cyclophosphamide and/or biologicals (e.g. rituximab): in the preceeding 6 months prior to enrolment.
- Other neurological, neuromuscular, rheumatologic or orthopedic conditions with significant impact on the capability of walking preventing evaluation of neurological scores.
- Anti-MAG neuropathy patients with persistent clinically significant laboratory abnormalities not related to the anti-MAG neuropathy, such as significant renal dysfunction, hepatic dysfunction, cardiac disease or other significant neurological disorder.

- Anti-MAG neuropathy patients with a modified Rankin Scale (mRS) score >4.
- Participation in another interventional clinical trial.
- Any other significant finding that would increase, according to the Investigator, the risk of having an adverse outcome from participating in the study.
- Any other medical condition, including mental illness or substance abuse deemed by the investigator(s) to likely interfere with the patient's ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results.
- Patients who have undergone major surgery ≤ 2 weeks prior to starting study drug or who have not recovered from the side-effects of surgery.
- A history of clinically significant ECG abnormalities, or any of the following ECG abnormalities at screening:
    - PR >200 msec.
    - QRS complex >120 msec.
    - QTcF >450 msec (males).
    - QTcF >460 msec (females).
    - History of familial long QT syndrome or known family history of Torsades de Pointes.
    - Use of agents known to prolong the QT interval unless they can be permanently discontinued for the duration of the study.
- Sexually active males must use a condom during intercourse after the start of the IMP administration and for at least one week after stopping study medication and should not father a child in this period after completion of the study medication (SAD and MAD phases). A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. In addition, male participants should not donate sperm for the time period specified above.
- Use of other investigational drugs at the time of enrolment, or within 5 half-lives of enrolment, or within 30 days, whichever is longer; or longer if required by local regulations.
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 1 week after discontinuation of the investigational drug. Highly effective contraception methods include:

- Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking the investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
- Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure <1%), for example hormone vaginal ring or transdermal hormone contraception. Progesterone containing hormonal tablets must be associated with inhibition of ovulation in order to qualify as highly effective.

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking the investigational drug. If local regulations deviate from the contraception methods listed above and require more extensive measures to prevent pregnancy, local regulations apply and will be described in the informed consent form (ICF).

Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking the investigational drug. In case of oophorectomy alone the reproductive status of the woman must be confirmed by follow up hormone level assessment.

Investigational Medicinal Product IMP	**Formulation**	Liquid formulation 10 mg/mL for IV administration.
	Name	Test product: PPSGG: Poly phenyl (disodium 3-O-sulfo-beta-D-glucopyranuronate)-(1-3)-beta-D-galactopyranoside. Reference product: Placebo (phosphate buffered saline (PBS).

Route	IV infusion over 60 minutes (the potential dose of 3200 mg will require a 120 minutes infusion).
Dose	SAD phase: Single IV infusion of 200, 400, 800 mg and 1600 mg per patient in 4 cohorts. A higher dose (3200 mg) may be administered if safe to do and satisfactory antibody reduction has not been demonstrated in previous cohorts MAD phase: Multiple intravenous infusions for 6 weeks (up to 11 administrations) of PPSGG over 2 dose levels (dose level and frequency determined from SAD results). The dosing of both cohorts in the MAD phase will not exceed the exposures achieved in the SAD phase (C_{max} and $AUC_{0\text{-}tau}$), and will commence at a dose at least one dose level lower than safely completed in the SAD.

Safety endpoints

The following parameters will be monitored throughout the study or as specified:

- Frequency, duration, severity and outcome of AEs, treatment emergent AEs (TEAEs), and Serious AEs (SAEs) from time of informed consent signature to the EOS visit including follow-up as required.
- Any concomitant medications and relevant non-drug therapies.
- Signs and symptoms of infusion-related reactions on infusion days continuously during the infusion of the study drug until 1 hour after the end of infusion, and at 8 and 24 hours (Day 2) after the start of administration.
- Physical examination from screening, baseline, on infusion day (before dosing with the IMP), and Day 8 during SAD and EOS visit and during MAD during each visit until the EOS visit.
- Vital signs with the 12-lead ECG at screening, on infusion days predose, during the infusion of the IMP at 60 min (120 min for optional 3200 mg dose) and then at 2 hours and 8 hours after start of infusion during SAD and EOS visit. During the MAD, vital signs with the 12-lead ECG at each day of visit until the EOS.
- 1-lead ECG on infusion days continuously during the infusion of the IMP until 2 hours after start of infusion for both the SAD and MAD.
- Safety hematology, clinical chemistry and urinalysis at screening, baseline, on Day 8, and EOS during the SAD and on Day 8, 28, 42, 98 and EOS during the MAD.

- Blood sampling for anti-drug-antibodies (ADA) (immunogenicity) at screening and predosing, then Day 28 (EOS) in the SAD and Days 42 and EOS in the MAD.

Pharmacokinetic endpoints	**Timing of sampling**	PPSGG's PK will be determined in serum in the SAD phase on infusion Day 1 (at 30 min, 60 min, 2h, 6h, and 8h after start of administration), and on Day 2, 4, 8 14 and 28 of the SAD phase. The sampling for the potential 3200 mg dose would be at 30 min, 60 min, 2h, 3h, 6h, 8h and 10h after start of infusion. In the MAD phase on each of Days 1, 3, 5, and 42 at predose, at 30 min, 60 min, at 2h, 6h, and 8h after start of infusion. An additional PK sample will be taken on Day 150 (EOS). The time points for PK sampling for the MAD phase will be confirmed based on the PK data collected during SAD phase.
	Method	Enzyme-Linked Immunosorbent Assay (ELISA)/chromatography.
Pharmacodynamic endpoints	**Timing of sampling**	PPSGG's PD biomarkers will be determined in serum in the SAD phase during screening, baseline, on infusion day (30 min, 60 min, 2h, 8h after start on infusion) and on Day 2, 4, 8, 14 and EOS (Day 28). During the MAD phase on each of Days 1, 3, 5 and 42 at predose, at 30 min, 60 min, at 2h, and 8h after start of infusion. Then PD samples taken on Days 2, 4, 6, 7, 8, 9, 10 and Day 11 at predose and 2h after start of infusion.
	Methods	ELISA, capillary electrophoresis, indirect immunoassay.

Efficacy endpoints

Clinical efficacy assessments will be performed at screening, and Day 14, and EOS during SAD and during MAD then every 8 weeks.

Clinical efficacy outcome for the SAD and MAD phases

- ONLS score.
- Time to walk 10 meters.
- RODS.
- Ataxia score.

Endpoints for the MAD phase only

All the above and then additionally every 8 weeks from Day 14 the following ones:

- INCAT sensory sum score.
- Grip Strength.

Exploratory endpoints

Endpoints for the MAD phase only

- Neurofilament light chain (NfL) to measure the degree of axonal damage.
- B-cell activating factor (BAFF).
- Indirect immunofluorescence on sciatic nerves.
- Motor Unit Number Index (MUNIX) in selected sites.

Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will review the safety data and will provide its recommendations to Polyneuron to escalate to the next higher dose cohort (Dose Escalation) in both SAD and MAD phases and to continue within a given cohort after the sentinel patient dosing (Dose continuation, MAD phase only).

Analyses populations

The two study phases SAD and MAD described in this protocol form an exploratory investigation without any formal statistical hypotheses. All results will be interpreted descriptively only from the following analyses sets:

Safety population (SP): All patients who receive at least one dose of study medication. The SP will be the primary analysis set for the safety and tolerability analyses.

Intent-to-treat (ITT) population: all patients who were enrolled. The ITT population will be used as analysis set to confirm the efficacy.

Per-protocol (PP) population: all patients, who meet the inclusion/exclusion criteria, received full-course of the study drug as per randomization during the MAD and have completed the main relevant visits (at least 1 visit, 1 week, and 1 month during the SAD phase after dosing is needed to assess biomarker and scores. During the MAD phase, at least 1 visit 1 month after the last dosing, for safety and efficacy assessments and who satisfactorily completed a PD blood sampling period without any major protocol violations which would render the data unreliable. The PP population will constitute the primary analysis set for the PD and PK, and efficacy analyses.

Pharmacokinetic (PK) population: all patients who satisfactorily completed a PK blood sampling period without any major protocol violations which would render the data unreliable.

Pharmacodynamic (PD) population: all patients who satisfactorily completed a PD blood sampling period without any major protocol violations which would render the data unreliable.

An evaluable patient is defined as a patient that meets the criteria to be included in the Per-protocol (PP) population.

Statistical Method

Sample size

This is a FiH study of PPSGG which its primary objective is to assess its safety and tolerability. The total number of at least 24 evaluable planned patients per phase (SAD and MAD) to be included in this study is thought to be sufficient for an early assessment of the safety and tolerability of PPSGG. No previous PK nor PD data for single or multiple doses of PPSGG in patients are available.

Patients who withdraw for reasons other than safety can be substituted in agreement with Polyneuron.

Statistical analysis

Physical examination, ECG and vital signs (blood pressure assessments, pulse rate, body temperature), signs of infusion-related reactions, laboratory assessments and AEs, TEAEs and SAEs will be analyzed. Signs of infusion-related reactions include clinical signs and/or symptoms, changes in diastolic or systolic blood pressure, heart rate, and skin reactions or local reactions at the infusion site. TEAEs will be summarized in frequency tables according to Preferred Term (PT) and System Organ Class (SOC). TEAEs will also be summarized according to their severity and causality regarding the IMP. When a TEAE occurs more than once in the same patient, maximal severity and strongest causality will be counted. All SAEs and TEAEs leading to premature withdrawal from the study will be listed. Laboratory variables will be examined using mean changes from baseline. Laboratory values will also be categorized according to the updated Common Terminology Criteria for Adverse Events (CTCAE) toxicity grade version and tabulated by their highest on-study toxicity grade. Shift tables will present numbers and percentages of patients with high / normal / low (or normal/abnormal) laboratory results at baseline and last measurement available. Non-TEAEs will be listed only. Use of concomitant medications will be summarized.

Descriptive statistics will be provided for the PK parameters and scatter plots may be used to investigate PK/PD or efficacy relationships. Statistical general linear model procedures and regression analysis will be applied for the analysis of the PK and PD parameters when applicable.

Descriptive statistics will also be used for the PD assessments.

Efficacy analysis

The efficacy analysis will be performed separately for the SAD and MAD phase. In the SAD phase changes in the following parameters will be assessed on Day 14, 28 and at EOS visit:

- Clinical scores.
- PK/PD.

- Evolution of anti-MAG antibodies (time to reach the lowest level after starting IMP treatment and time to achieve baseline values).

The MAD phase, in addition to all the above, will also include clinical and score assessments every 8 weeks until the EOS visit.

Statistical methods

Descriptive statistics (n, mean, standard deviation (SD), median and ranges for continuous variables, frequencies and percentages for categorical variables) will be provided by treatment group and/or visit, if applicable. All data will be listed by patient, treatment group and, where applicable, visit. Data from all placebo treated patients in MAD will be pooled for comparison with active cohorts. Further technical details will be described in the Statistical Analysis Plan (SAP).

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List of Tables

List of abbreviations

ADA	Anti-drug antibody
ADL	Activities of Daily Living
ADM	Abductor digiti minimi
AE	Adverse event
ALT	Alanine aminotransferase
Anti-HNK1	Anti-human natural killer-1
APB	Abductor pollicis brevis
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC0-t	The area under the concentration-time curve from time zero to time ‘t’
AUCinf	The AUC from time zero to infinity
BAFF	B-cell activating factor
BTU	Bühlmann Titer Units
BUN	Blood urea nitrogen
BW	Body weight
CHMP	Committee for Medicinal Products for Human Use
CL	The total body clearance of drug from the serum
C_{max}	The maximum (peak) observed serum, blood, serum, or other body fluid drug concentration after dose administration
CMAP	Compound muscle action potential
CNS	Central nervous system
CoA	Certificate of Analysis
CRO	Contract research organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DRF	Dose Range Finding
EC	Ethics Committee
ECG	Electrocardiogram

eCRF	Electronic Case Report Form
EDC	Electronic data collection
EFNS/PNS PDN	European Federation of Neurological Societies/Peripheral Nervous system Paraproteinemic Demyelinating Neuropathy
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EENT	Eye, ears, nose and throat
EOS	End-of-study
EudraCT	European union drug regulating authorities Clinical Trials
FDA	Food and Drug Administration
FiH	First-in-Human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HgA1c	Hemoglobin A1c
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDL	High density lipoprotein
HED	Human equivalent dose
HIPPA	Health Insurance Portability and Accountability Act
HNK-1	Human natural killer-1
IB	Investigators' Brochure
ICF	Informed consent form
ICH	International Council on Harmonization
ICMUC	Ideal case motor unit count
IDMC	Independent Data Monitoring Committee
IgE	Immunoglobulin E
IgG	Immunoglobulin G

IgM	Immunoglobulin M
IL	Interleukin
IMP	Investigational Medicinal Product
INCAT	Inflammatory Neuropathy Cause and Treatment Sensory Scale
INR	International normalized ratio
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRR	Infusion-related reaction
ISS	INCAT Sensory sum score
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous
IVIG	Intravenous immunoglobulin
IVRS	Interactive Voice Response System
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LLOQ	Lower limit of quantification
MABEL	Minimum anticipated biological effect level
MAD	Multiple Ascending Dose
MAG	Myelin-associated glycoprotein
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MFD	Maximum feasible dose
MGUS	Monoclonal gammopathy of undetermined significance
mRS	modified Rankin Scale
MRSD	Maximum recommended starting dose
MPS	Mononuclear Phagocyte System
MUNIX	Motor Unit Number Index
N	number
NfL	Neurofilament light chain

NOAEL	No Observed Adverse Effect Level
ONLS	Overall Neuropathy Limitations Scale
PBMC	Peripheral blood mononuclear cells
PBS	Phosphate buffered saline
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per protocol
PPSGG (PN-1007)	Poly (phenyl disodium 3-O-sulfo-ß-D-glucopyranuronate-(1→3)-ß-D-galactopyranoside)
PT	Preferred Term
RBC	Red blood cell count
RODS	Rasch-built Overall Disability Scale
SAF	Safety population
SAD	Single Ascending Dose
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SC	Study Completion
SD	Standard deviation
SF-36	36-Item Short Form Survey
SGOT	Serum glutamic oxaloacetic transaminase (= AST)
SGPT	Serum glutamic pyruvic transaminase (= ALT)
SIP	Surface interference pattern
SM	Sphingomyelin
SOC	System Organ Class
SOP	Standard Operating Procedure
SP	Safety population
SUSAR	Suspected unexpected serious adverse reaction
$T_{1/2}$	The elimination half-life associated with the terminal slope of a semi logarithmic concentration-time curve
TA	Tibilis anterior

TEAE	Treatment-emergent adverse event(s)
Tmax	The time to reach maximum (peak) serum, blood, serum, or other body fluid drug concentration after dose administration
TNF	Tumor necrosis factor
TPE	Therapeutic Plasma Exchange
Vd	Volume of distribution
Vss	The apparent volume of distribution at steady state
WBC	White blood cell count
WOCP	Women of child bearing potential
γ-GT	Gamma-Glutamyltransferase

1 Introduction

1.1 Background

Anti-myelin-associated glycoprotein (MAG) neuropathy is a demyelinating polyneuropathy associated with a monoclonal immunoglobulin M (IgM) gammopathy with anti-MAG activity. Patients with anti-MAG neuropathy suffer from sensorimotor deficits, sensory ataxia, paresthesias, muscle weakness, neuropathic pain, and tremor. Anti-MAG neuropathy is an autoimmune disease strongly associated with monoclonal IgM autoantibodies (anti-MAG IgM) with reactivity against MAG [1],[2],[3],[4]. Anti-MAG IgM antibodies have been demonstrated to be causally related to the neuropathy in a number of animal models. IgM and complement are deposited on the myelin sheath, splitting the myelin lamellae causing demyelination, and eventually axonal damage. During the last few years, much progress has been made in understanding the pathophysiological mechanism of the disease [5],[6] and adoptive transfer of patient sera into susceptible host animals has been demonstrated to cause sensory ataxia and reproduce the human pathology [11], [17]. The prevalence of this rare disease is about 1 in 100,000 [7]. Anti-MAG neuropathy is an age-related disease and typically, the disease onset occurs after the age of 50 years. The disease is 2.7 times more frequent in men than in women [8].

Currently there is no treatment for anti-MAG neuropathy approved by the European Medicines Agency (EMA) or the US Food and Drug Administration (FDA). However, off-label treatments are used for treatment of anti-MAG neuropathy, which are discussed below. The primary objective of the treatment is to reduce the pathogenic anti-MAG autoantibody titers [9]. Therefore, various immunomodulatory and immunosuppressive treatments have been used to manage anti-MAG neuropathy. Nonetheless, these treatments are of limited efficacy and have potential side effects [10],[11].

Clinical improvement of neuropathic symptoms in patients with anti-MAG neuropathy correlates with reduced serum levels of anti-MAG IgM [9],[12],[3],[13] and disease worsening is associated with increasing anti-MAG IgM levels during treatment follow-up [13,14]. The therapeutic goal is a reduction in anti- MAG IgM levels (Bühlmann titers) by at least 50% from individual baseline level [15].

1.2 Current Treatment Options for anti-MAG neuropathy

The pathogenic role of the monoclonal anti-MAG IgM antibody in anti-MAG neuropathy, based on clinical studies that show correlations between disease outcomes and anti-MAG IgM levels, is widely accepted [14],[16], and therapeutic approaches are therefore generally directed at reduction of antibody levels.

No therapies have yet been approved for this serious disease due to the lack of evidence from well- controlled clinical trials. Anecdotally, rituximab has been the most successful but shows some benefit in only 30-50% of patients with a variable impact on anti-MAG antibody levels and occasionally causes a paradoxical worsening. Clinical improvement is typically associated with at least a 50% decrease in IgM [15]. The target antigen of rituximab, CD20 is a lineage restricted molecule and is expressed on B cells throughout B-Cell differentiation prior to terminal differentiation of B cells to plasma cells. Primary failure of rituximab in a proportion of patients as above may be associated with the presence of CD 20 negative plasma cells in the spleen and tissues [18] but in these patients, removal of the pathogenic autoantibodies could be expected to provide a therapeutic benefit.

A number of chemotherapeutic and targeted agents used in Waldenstroms and other haematological malignancies have been tried [11], therapeutic benefit has been limited and

the associated toxicities of these agents are substantial. Patients with an underlying malignancy are excluded from the proposed clinical trial thus the intended patient population is one with neurological symptoms but a normal life expectancy.

Severe adverse events with rituximab, Ibrutinib (Bruton Kinase inhibitor) and other agents used in haematological malignancies are noted to be more frequent in patients over 65 years of age. Given that 65 is the median age of onset of anti-MAG neuropathy the patient population in the proposed study would be one with increased risk.

Therefore, given that responses to agents used to treat malignancies are limited and associated with substantial myelotoxicity and increased mortality in this patient group [19] there remains an unmet medical need for a more effective and less toxic treatment for these patients. Targeted removal of the pathogenic antibodies rather than broad immunosuppression remains an approach to address this unmet need in this orphan disease. This antigen specific approach could offer both initial symptomatic relief and disease modification if treatment can maintain antibody levels below pathogenic levels.

1.3 PPSGG (PN-1007)

The active substance is poly (phenyl disodium 3-O-sulfo-ß-D-glucopyranuronate)-(1→3)-ß-D-galactopyranoside and will be referred to as poly(phenyl sulfoglucuronate galactoside) (PPSGG) throughout the document. PPSGG is a glycopolymer consisting of two structural units coupled to a poly-L-lysine backbone, glycan and thioglycerol units.

PPSGG is a fully synthetic molecule obtained from (disodium 3-O-sulfo-ß-D-glucopyranuronate)-(1→3)-β-D-galactopyranoside that binds to a chloroacetylated poly-L-lysine hydrobromide backbone through a tyramine-based thiol-linker. Multiple copies of the active part of the molecule, phenyl (disodium 3-O-sulfo-ß-D-glucopyranuronate)-(1→3)-ß-D-galactopyranoside, are coupled to the chloroacetylated poly-L-lysine; the remaining chloroacetylated poly-L-lysine polymers are coupled with thioglycerol, which promotes the solubility of the overall molecule. 25-45% of the poly-L-lysine backbone is coupled to glycan units, and 55-75% are coupled to thioglycerol units [20].

PPSGG is formulated as a solution ready to use drug product for intravenous (IV) infusion.

PPSGG is intended to bind anti-MAG IgM autoantibodies, the underlying cause of anti-MAG neuropathy, in a highly selective manner, resulting in their neutralization and removal from the circulation. While the anti-MAG IgM autoantibodies do not cross the blood-brain barrier, they can cross the blood-nerve barrier to enter the peripheral nervous system. In contrast, based on tissue distribution studies and the physico-chemical properties of the glycopolymer [21, 22], PPSGG does not cross the blood-nerve barrier; therefore, binding of PPSGG to the anti-MAG IgM antibodies occurs in the blood. This allows specific targeting of anti-MAG IgM in the circulation and circumvents unspecific immunosuppression associated with current treatment strategies.

1.4 Nonclinical data

It has been demonstrated that PPSGG prevented the binding of patients' anti-MAG IgM autoantibodies to MAG at low nanomolar concentrations in a competitive enzyme-linked immunosorbent assay (ELISA) and selectively bound to anti-MAG IgM. PPSGG efficiently reduced the anti-MAG IgM antibody titers in an immunological mouse model for anti-MAG neuropathy at a dose range of 2- 10 mg/kg [19] and was able to efficiently inhibit the binding of patients' anti-MAG IgM to sciatic nerve myelin of non-human primates ex vivo within the

same concentration range. In vitro experiments and in a dose titration study in mice, showed that the binding stoichiometry of PPSGG:anti-human natural killer-1 (anti-HNK-1) IgM is 1:1 to 1:2. Based on an estimated average patient population with 1-10 g/L of monoclonal anti-MAG IgM, doses of 120-1200 mg should remove most circulating autoantibodies [10, 23]. Moreover, no signs of large immune complex formation (in vitro) or immune complex related toxicity (in vivo) were observed in mice.

PPSGG has a short half-life at pharmacological doses (approximately 20 to 30 min in 2 rodent and 1 non-rodents' species) with a low volume of distribution in rats and dogs, distributing only within the vascular system and is cleared through the mononuclear phagocyte system (MPS). PPSGG, once cleared by phagocytes, is most likely broken down in the liver to different natural components which may be recycled or eliminated: for instance, the poly-L-lysine backbone to shorter poly-L-lysine chains and then recycled in protein synthesis; the glycomimetic part is cleaved into monosaccharides and may enter the catabolic pathway or is excreted; and the thioglycerol part is expected to be eliminated by renal excretion or, similar to glycerol, by hepatic metabolism. In humans, clearance (CL), metabolism and distribution are expected to be similar to that observed in animal models since these pathways are highly conserved among mammalian species.

Exploratory non-GLP and repeat-dose GLP toxicology and safety studies did not identify a target organ of toxicity which is not unexpected given the low volume of distribution, rapid clearance and low systemic dosing from weekly administrations. Dose escalation was limited by infusion-related findings in the rat and dog (tremors, decreased activity, flushing). Clinically PPSGG was well tolerated in dogs with up to 200 mg/kg/dose (no-observed-adverse-effect level (NOAEL)) with intravenous (IV) infusion over 15 min administered intermittently over six weeks in GLP repeat dose toxicology studies. In rats, initial DRF studies demonstrated 400 mg/kg/dose infused over 15 min was not tolerated, with clinical signs consistent with a mast cell degranulation (of unknown mechanism). Repeat dose GLP toxicology studies with up to 150 mg/kg/dose with 15 min IV infusion administered intermittently over 6 weeks was well tolerated without adverse findings (NOAEL). A subsequent exploratory non-GLP study examining the dose versus infusion rate relationship found that the clinical tolerability in rats was highly dependent on the time/length of infusion, with Cmax of PPSGG driving the observed clinical findings. In this study, no increase in histamine or tryptase levels were evident 1 h after infusion, and there was no binding of IgE to PPSGG. PPSGG does not affect neurological behaviour (Modified Irwin) or respiratory function in rats and has no clinically relevant effect on human cardiac channels up to the physiological limits of solubility for the molecule. PPSGG did not induce an innate immune response (cytokine release) in human peripheral blood mononuclear cells (PBMC) or induce the formation of anti-drug antibodies over repeat administration in rats.

Based on these results, the NOAEL was considered to be 200 mg/kg/dose for dogs and 150 mg/kg for rats, respectively.

The potential of PPSGG to interact with co-administered medication has not been assessed. No formal drug interaction studies have been conducted with PPSGG in humans.

No reproductive or developmental toxicity studies using PPSGG have been conducted to date.

1.5 Clinical data

1.5.1 Human safety and tolerability data

This is the first in human (FiH) study, therefore no clinical data are available.

1.6 Study rationale

This is a FiH Phase I/IIa multicenter, single ascending dose (SAD) and multiple ascending dose (MAD) study, to assess the safety and preliminary efficacy of PPSGG, an antibody scavenger of pathogenic anti-MAG IgM autoantibodies, for treatment of anti-MAG neuropathy. The safety and tolerability of PPSGG has been demonstrated in different animal species, for 6 weeks with 11 single doses via slow IV infusion over 15 min in rats and dogs during the non- clinical toxicology studies.

The design has been chosen as a classical Dose Escalation design as required in this type of trial with the starting dose calculated following the recommendations from the EMA Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products (September 2007) and FDA Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (July 2005) [24, 25].

The unique therapeutic approach of PPSGG is intended to bind to anti-MAG IgM autoantibodies in a highly selective manner, resulting in their neutralization and removal from the circulation. While the anti-MAG IgM autoantibodies do not pass the blood-brain barrier, they can pass the blood-nerve barrier to enter the peripheral nervous system. In contrast, based on tissue distribution study data and established physico-chemical properties of the glycopolymer [19, 20], PPSGG does not pass the blood-nerve barrier; therefore, binding of PPSGG to the anti-MAG IgM antibodies occurs in the blood. This allows specific targeting of anti-MAG IgM in the circulation, the underlying cause of the disease. This concept has been verified in vitro and in vivo. Currently, there is no treatment for anti-MAG neuropathy approved by the EMA or FDA. However, some medicinal products are used off-label for management of anti-MAG neuropathy; these products employ either an immunomodulatory or immunosuppressive approach to reduce the pathogenic anti- MAG autoantibody are summarized below.

- Immunomodulatory approaches include intravenous immunoglobulins (IVIG), therapeutic plasma exchange (TPE) and apheresis, and treatment with interferon alpha. However, none of the immunomodulatory treatments consistently demonstrated satisfactory short- and long-term efficacy in clinical studies.

- Immunosuppressive approaches include rituximab, corticosteroids and chemotherapeutic drugs, such as cladribine, fludarabine, cyclophosphamide and chlorambucil. These treatments cause a general immune suppression by lymphocyte depletion, which includes a reduction of disease-causing anti-MAG autoantibodies. However, immunosuppressive treatments have failed to demonstrate efficacy consistently in clinical trials and are associated with severe side effects, including anemia, neutropenia, thrombocytopenia, gastrointestinal distress, and opportunistic infections.

Since these alternative off-label treatment approaches are unspecific, their efficacy for treatment of anti-MAG neuropathy has not been convincingly demonstrated, and some of these treatments are associated with severe side effects. The unmet medical need remains and requires new approaches of treatment for the anti-MAG neuropathy.

1.7 Rationale for study design

Data from toxicological studies with PPSGG have shown a benign safety profile. The design of the SAD phase of this study (open label, single ascending dose) efficiently addresses the primary objective to assess the safety and tolerability of PPSGG and will also provide

information on its pharmacokinetics (PK), and pharmacodynamics (PD); while very little can be expected in terms of efficacy (short term reduction of levels of anti-MAG antibodies, only, may be expected) with minimal clinical impact on the disease. Since these autoantibodies are only present in patients with anti-MAG neuropathy, but not in healthy humans, information obtained from a study in healthy subjects would be limited in respect to PK, and any potential target related toxicities.

In the MAD phase, the study drug is compared in a double-blind design with placebo. Placebo is chosen to enable a proper efficacy assessment as well as safety evaluation of PPSGG in patients with anti-MAG neuropathy

Clinical endpoints including assessments of signs and symptoms on neurological scales will be included as secondary endpoints in the MAD cohorts. Given the potential for bias in such evaluations the placebo control is necessary to enable an unbiased evaluation of any potential early signs of efficacy in these cohorts.

An Independent Data Monitoring Committee (IDMC) will provide recommendations about stopping, modifying or continuing the study; the decision to continue and/or to escalate the dose of PPSGG will be based on the review of safety and tolerability results. Given the short half-life of PPSGG shown in preclinical studies and assuming a short half-life in humans, a 72-hour safety review in the SAD phase and a 2-week safety data review in the MAD phase for Dose Escalation are considered adequate.

1.8 Rationale for dose/regimen, route of administration and duration of treatment

The maximum recommended starting dose (MRSD) of the FiH trial of PPSGG was calculated following both the “FDA Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers” (July 2005) and the “EMA Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products” (September 2007) [22, 23]. Taking both guidelines into account the NOAEL of PPSGG was determined in non-clinical toxicological studies. Based on the findings of these studies the surrogate NOAEL of PPSGG was established at 200 mg/kg in dogs and 150 mg/kg in rats. In a next step the human equivalent dose (HED) was calculated applying the allometric scaling factor of 1.8 for dogs and 6.2 for rats as outlined in Table 1. The planned starting dose is a flat dose of 200 mg, which corresponds to approximately 2.8 mg/kg body weight (BW) for a patient of 70 kg. Flat dosing is most appropriate for treatment as the target and route of elimination are largely independent of body weight. Hence the surrogate NOAEL determined in non-clinical safety studies translates to a maximum recommended starting dose of maximum 111.1 mg/kg BW, which leads to a safety factor of 39.7 without considering the safety factor of 10.

Table 1 Starting dose of PPSGG based on the NOAEL from non-clinical safety studies

Species tested	Determined surrogate NOAEL	Allometric scaling factor	Calculated HED human equivalent dose applying a safety factor of 10	Planned starting dose	Safety Factor
Dog	200 mg/kg	1.8	200 mg/kg / 1.8 / 10 = 11.11 mg/kg BW	2.8 mg/kg	39.7
Rat	150 mg/kg	6.2	150 mg/kg / 6.2 / 10 = 2.42 mg/kg BW	2.8 mg/kg	8.6

BW = Body weight; HED = Human equivalent dose; NOAEL + No-observed-adverse-effect-level

The planned PPSGG dose range and regimen of the proposed study covers the efficacious dose range demonstrated in the pre-clinical efficacy studies and offers a large safety margin according to the in vivo toxicology studies conducted in rat and dogs.

In order to predict the human exposure (Cmax and AUC) at the proposed doses in this clinical trial protocol, PK and TK data from the preclinical studies have been used to develop a PK/PD model. Based on this model, the predicted exposures and resultant margins of safety are shown in Table 2.

Table 2 PK/PD model based on PK / TK data for predicted exposures

Parameter	Dose (mg)	Species for prediction	Human prediction (70 kg)		Predicted fold difference[1]	
			Estimated β	Theoretical β	Estimated β	Theoretical β
AUC_{0-inf} (mg*h/mL)	200	Rat	0.04	0.13	NA[2]	NA[2]
		Dog		0.06	923	615
	1600	Rat	0.33	1.01	NA[2]	NA[2]
		Dog		0.47	112	79
	3200	Rat	1.85	6.71	NA[2]	NA[2]
		Dog		3.05	20	12
C_{max} (mg/mL)	200	Rat	0.05	0.04	70	88
		Dog		0.05	71	71
	1600	Rat	0.40	0.33	8.8	11
		Dog		0.37	8.9	9.6
	3200	Rat	0.55	0.96	6.4	3.6
		Dog		0.71	6.5	5.0

[1] Relative to observed mean at day 1 at highest dose in GLP TOX study:
Rat GLP Tox 150 mg/kg : C_{max} = 3.50 mg/mL, AUC_{0-inf} = Not reported
Dog GLP Tox 200 mg/kg : C_{max} = 3.55 mg/mL, AUC_{0-inf} = 36.90 mg*h/mL
[2] AUC_{0-inf} not reported at 150 mg/kg in rat GLP tox study

At the proposed dose of 200 mg total, the estimated safety margins are ≥70 for Cmax and ≥600 for AUC whilst at the highest optional dose proposed (3200mg), the estimated safety margin is ≥3.6 for Cmax and ≥12 for AUC.

While animals were treated with a 15 min IV infusion, the minimum infusion duration in this study is 1hr. As a result of the slower infusion rate, it is expected the predicted Cmax values are higher than those that will be observed in patients, thus adding to the safety margin for this parameter.

During the SAD part of the study, PK and PD data will be reviewed on an ongoing basis and the predicted exposure for a subsequence dosing cohort will be calculated, based on all available data from previous cohort/s.

Despite the limitation regarding calculating the minimum anticipated biological effect level (MABEL) it is still possible to consider other PD effects when defining the clinical starting dose in humans (e.g. dose response curves of the in vivo efficacy model experiments).

To corroborate that the dose range of 2-10 mg/kg in the in vitro and in vivo pharmacodynamics studies would be sufficient to deplete circulating anti-MAG autoantibodies in anti-MAG neuropathy patients, a dose titration study, using passive immunization with a monoclonal anti-HNK-1 IgM was performed. The IV injection of 5 µg PPSGG was sufficient to bind 89.43% (±1.33 SD) of the 60 µg anti-MAG IgM and 10 µg PPSGG was sufficient to bind 93.28% (±0.50 SD) of the 120 µg anti-HNK-1 IgM. Based on these findings, a dose of 80 mg PPSGG would be sufficient to bind and remove 1 g of anti-MAG IgM autoantibodies in humans. Of note, since no antibody-signal was detected at later time points after administration the anti-HNK-1 IgM antibodies have been eliminated and not only bound by the glycopolymer. The pentameric IgM has a molecular weight of 900-1000 kDa and is therefore approximately five times heavier than PPSGG with a calculated average weight of 194 kD. In general, the paraprotein (anti-MAG IgM) levels in anti-MAG neuropathy patients are in the range of 1–10 g/L or in some patients even higher [10, 23]. Clinical improvement in anti-MAG neuropathy has been correlated with a sustained reduction of anti-MAG autoantibody levels at least 50% [10, 24].

Based on a range of 1-10 g/L of monoclonal anti-MAG IgM, 240 mg to 2400 mg of PPSGG should remove the circulating anti-MAG IgM antibodies in the majority of the patients. Based on an estimated average patient with 4 g/L anti-MAG IgM in a plasma volume of 3 L, the estimated dose of PPSGG is 960 mg.

Beginning from the proposed starting dose for PPSGG, all subsequent doses that will be used during Dose Escalation will be calculated by applying an escalation factor of 2. The dose of 1600 mg per patient has been selected to achieve at least 2-fold the predicted exposure needed for efficacy based on relative reductions in titers of anti-MAG autoantibodies and would be anticipated to reduce by 50% the relative titers of patients with very high pre-dose anti-MAG levels. An additional cohort of 3200 mg per patient may be included if the relative reductions in anti-MAG antibody titers do not reach the target of 50%. Based on this consideration the dose groups of the FiH study of PPSGG are defined as outlined in Table 3.

Table 3 Foreseen Dose Escalation groups in the single ascending dose phase

Cohort 1	Cohort 2	Cohort 3	Cohort 4	Optional Cohort 5
200 mg	400 mg	800 mg	1600 mg	3200 mg

SAD: The design of the SAD phase of this study allows evaluation of the safety of the low dose of PPSGG (200 mg) before proceeding to the administration of higher doses. During each cohort of the SAD phase after treatment of the first patient (sentinel patient), Polyneuron and investigator will review the safety data from 72 hours after the starting dose before agreeing to dose the remaining patients in the given cohort. Dosing can only commence for the next cohort (Dose Escalation) after satisfactory review of the safety data from the proceeding cohort by the IDMC.

MAD: During each cohort of the MAD phase after treatment of the first 2 patients, the IDMC will review 2 week safety data after administration of the first dose before the rest of the given cohort will be dosed (cohort completion). Dosing can only commence for the next cohort (Dose Escalation) after satisfactory review of the safety data from the proceeding cohort by the IDMC.

1.9 Rationale for choice of comparator

As there is no approved therapy for anti-MAG neuropathy, and PPSGG is a first in class compound, patients will be randomized to receive either PPSGG or placebo in the MAD phase to reduce bias in safety and efficacy assessments

2 Objectives and endpoints

2.1 Primary objective(s)

Primary objective(s)	Endpoints related to primary objective(s)
To assess the safety and tolerability of PPSGG after single and multiple IV administrations in patients with anti- MAG neuropathy.	Assessment of safety based on vital signs, physical examination, electrocardiograms (ECGs), laboratory assessments, Signs of infusion-related reactions (IRRs), including clinical signs and symptoms, changes in diastolic or systolic blood pressure, heart rate, oxygen saturation, and skin reactions or local reactions at the infusion site and collection of adverse events (AEs) assessed from consent signature until the end of the study visit. Presence of anti-drug antibodies (ADA) will also be investigated.

2.2 Secondary objective(s)

Secondary objective(s)	Endpoints related to secondary objective(s)
To evaluate the PK of PPSGG after single and multiple IV administrations	Non-compartmental parameters related to PPSGG, including but not limited to T_{max}, C_{max}, as well as trough (pre-dose) levels after multiple dose
To investigate PD of PPSGG in reducing anti-MAG IgM levels	• Reduction of anti-MAG antibodies (Anti-MAG IgM Titers (BTU), Paraprotein levels (g/l), and total IgM (g/L)Time to anti-MAG IgM rebound (time until antibody levels are reach individual pre-treatment/baseline levels again). • Paraprotein levels (g/L). • Total IgM levels (g/L). • Anti-HNK1 titers.
To investigate the preliminary efficacy of PPSGG in SAD and MAD	• Change in the Overall Neuropathy Limitations scale (ONLS) score. • Time to walk 10 meters. • Rasch-built Overall Disability Scale (RODS). • Ataxia score. •
To investigate the preliminary efficacy of PPSGG in MAD only	• INCAT sensory sum score ISS. • Grip Strength.

2.3 Exploratory objective(s)

Exploratory objective(s)	Endpoints related to exploratory objective(s)
To assess the effect of PPSGG on other biomarkers of mode of action in MAD only	• Neurofilament light chain (NfL) to measure the degree of axonal damage. • B-cell activating factor (BAFF). • Indirect immunofluorescence on sciatic nerves. • • Motor Unit Number Index (MUNIX) in selected sites only.

3 Investigational plan

3.1 Study design

This protocol describes the planned conduct of a SAD phase and a MAD phase to be performed with PPSGG. These two phases will be conducted sequentially.

In each phase (SAD and MAD) the cohorts will be executed in a sequential order after the review of the safety data by an IDMC.

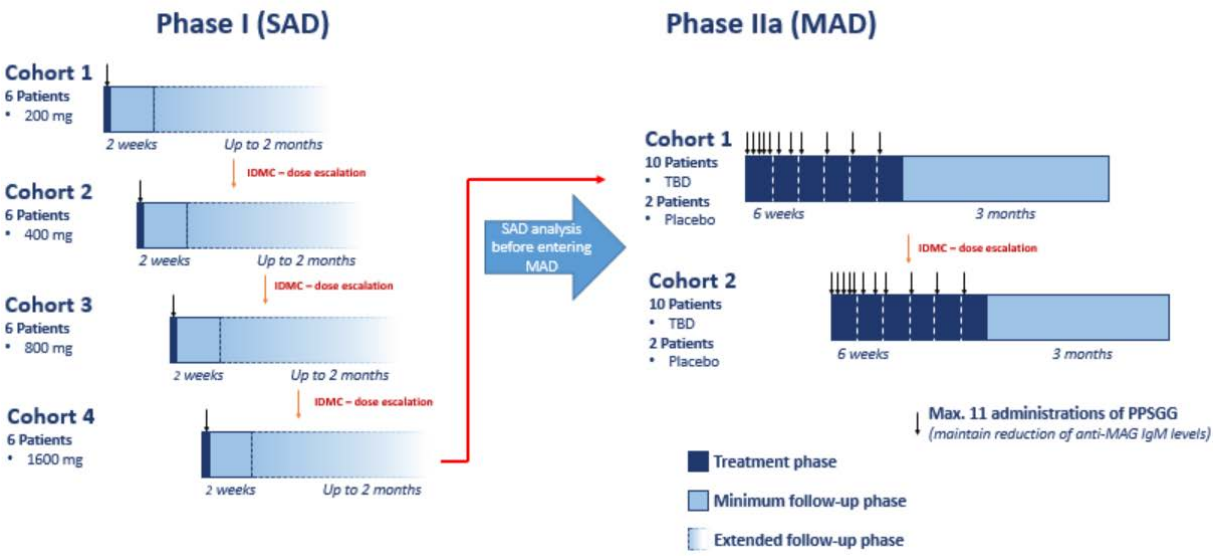
In the SAD phase each patient will have the following 8 visits: Screening, Baseline, Treatment (4 visits), end of study (EOS) and Follow-up.

In the MAD phase each patient will have up to 17 visits: Screening, Baseline, Treatment (up to 14 visits), EOS and Follow-up.

The MAD phase will be adapted for dosing regimen in accordance with PK, PD, safety and tolerability data collected during the SAD phase. The dosing of both cohorts in the MAD phase will not exceed the exposures achieved in the SAD phase (Cmax and AUC0-tau), and will commence at a dose at least one dose level lower than safely completed in the SAD. Dosing regimen includes the dose level administered, the frequency of dosing and the duration of dosing, i.e. the number of doses administered. Based on the safety toxicology studies performed in animals the maximum number of dosing is 11 infusions for 6 weeks. The goal is to define a potential dose and regime to reliably and safely reduce anti-MAG IgM antibody levels by at least 50%.

Patients to be screened must have a confirmed diagnosis of monoclonal IgM associated with monoclonal gammopathy of undetermined significance (MGUS) with anti-MAG activity (titer of > 10’000 BTU) and demyelinating neuropathy defined by electrophysiological criteria according to European Federation of Neurological Societies/Peripheral Nervous System Paraproteinemic Demyelinating Neuropathy (EFNS/PNS PDN) guideline, 2010. [26]

Patients fulfilling the inclusion and exclusion criteria will be sequentially assigned to a cohort starting with the lowest dose in the SAD phase. In the MAD phase the patient will be randomly assigned to active or placebo treatment in a given dose cohort. Please refer to the scheme below:



3.2 Design of the single ascending dose phase (Phase I)

The first phase, SAD, is a FiH, open label, single dose escalation study in anti-MAG neuropathy patients to establish safety, tolerability, PK, and PD parameters of PPSGG. The study will enroll 6 patients per cohort (4 or 5 cohorts), up to a maximal dose of 3200 mg. The first dose of any cohort will be provided to a single patient first (sentinel patient). The decision to complete a given dose cohort of the sentinel patient will be based on the safety data, collected during the first 72 hours after the start of the infusion and reviewed by Polyneuron and the investigator The study will be halted after the completion of each cohort (6 patients), for the evaluation of all safety- relevant data from these 6 patients, collected within the first 72 hours from the start of the investigational medicinal product (IMP) and additional data as available (with particular focus on events occurring immediately after the start of treatment) by an IDMC. The decision to escalate to the following dose will be based on the safety data from these 6 patients provided no study stopping rules are met and the recommendations from the IDMC.

The study drug will be administered as a single 60 min (120 min for optional 3200 mg dose) IV infusion on Day 1 in the morning. Patients will be hospitalized from the day before (Day -1), unless they live in the vicinity of the hospital and could be there early in the morning, until 24 hours after the start of the infusion.

The SAD phase will involve the following assessments after all inclusion and exclusion criteria have been checked during the screening and baseline visits (see Section 8.2 Schedule of Assessments):

- Vital signs.
- Blood and urine sampling for clinical safety laboratory.
- Blood sampling for PK.
- Blood sampling for PD markers anti-MAG IgM and time to anti-MAG IgM rebound (pre-treatment BTU) paraprotein levels (g/L), total IgM levels (g/L), and anti-HNK1 IgM titers.
- Blood sampling for anti-drug antibodies (ADA) responses (immunogenicity).
- 12-lead ECG.
- Physical examination.
- Optional blood sampling for biobanking.

- Clinical efficacy assessments: ONLS score, time to walk 10 meters, RODS, and Ataxia score

The study duration per patient is up to 2 months. Each patient will have the following 8 visits: Screening, Baseline, Treatment (4 visits), EOS and Follow-up.

3.3 Single ascending dose/Multiple ascending dose transition

Following the completion of the SAD phase which includes assessments of safety and tolerability, anti-MAG antibodies PK, PD responses and ADA responses, a pharmacokinetic/ pharmacodynamic model will be established and evaluation of all these data will be performed by Polyneuron in collaboration with the IDMC to decide doses and schedules of PPSGG in the MAD phase. The goal is to define a potential dose and regime to reliably and safely reduce anti-MAG IgM antibody levels by at least 50%.

3.4 Design of the multiple ascending dose phase (Phase IIa)

Up to thirty patients will be enrolled in the MAD phase, to allow for a drop-out rate of 20% to have 24 patients to complete this phase of the study.

The MAD phase that consists of two sequential and ascending cohorts will establish the safety and tolerability, immunogenicity, PK parameters, and PD effects after repeated escalated doses.

Many of the same patients involved in the SAD phase will enter the MAD phase. If “new” patients need to be recruited, they will need to undergo the complete screening procedure (see Section 8.3 Study performance).

The Dose Escalation will follow the same rules as for the SAD phase. The first 2 patients per cohort will be randomized to receive PPSGG or placebo in a double-blind fashion. At the end of each cohort a Dose Escalation assessment will be performed by the IDMC based on the safety data collected after 2 weeks of the start of the PPSGG administration.

The MAD phase will be adapted for dosing regimen in accordance with PK, PD, safety and tolerability data collected during the SAD phase. The dosing of both cohorts in the MAD phase will not exceed the exposures achieved in the SAD phase (Cmax and AUC0-tau), and will commence at a dose at least one dose level lower than safely completed in the SAD. Dosing regimen includes the dose level administered, the frequency of dosing and the duration of dosing, i.e. the number of doses administered. Based on the safety toxicology studies performed in animals the maximum number of doses is 11 infusions. The goal is to define a potential dose and regime to reliably and safely reduce anti-MAG IgM antibody levels by at least 50%.

In the first week, all patients may receive a maximum of 1 dose per day for 5 consecutive days until the desired reduction of anti-MAG IgM antibody titers is achieved. For the following 5 weeks we aim to maintain the antibody levels below the 50% of baseline. The exact dosing regimen for the MAD phase will be adjusted based on PK data from the SAD phase.

The MAD phase will last for maximum 11 infusions for 6 weeks, with a 3-month observation phase, which can be extended until the anti-MAG IgM titers reach pre-treatment levels (up to 6 months after end of treatment). The MAD phase will involve the following assessments:

For safety (time points indicated in the Schedule of Assessments):

- Vital signs.
- Blood and urine sampling for clinical safety laboratory.
- Blood sampling for PK.

- Blood sampling for ADA responses (immunogenicity).
- ECG.
- Physical examination.

For efficacy (time points indicated in the Schedule of Assessment):

- Blood sampling for PD markers anti-MAG IgM and time to anti-MAG IgM rebound (pre-treatment BTU), paraprotein levels (g/L), total IgM levels g/L), and anti-HNK-1 IgM titers.
- Scores for clinical efficacy assessment: ONLS score, time to walk 10 meters, RODS, Ataxia score, INCAT sensory sum score, Grip strength.
- Munix as exploratory endpoint in selected sites only

Blood sampling for assessment of exploratory biomarkers will be collected. The study duration per patient is 6 months. Each patient will have up to 17 visits: Screening, Baseline, Treatment (up to 14 visits covering 11 infusions for 6 weeks), EOS and Follow-up.

3.5 Cohort completion and Dose Escalation

As this is the first time of administration of PPSGG in humans, the design of this study is similar to a Phase I FiH study in which 3 or more different increasing single doses (cohort 1, cohort 2, cohort 3, cohort 4 and optional cohort 5) in the SAD phase will be tested. Six patients per cohort will be dosed via an IV infusion over 60 minutes (120 min for optional 3200 mg dose) with PPSGG.

Cohort 1 (SAD)

Dose
1 sentinel patient

→

Dose
All remaining patients of the cohort after review of 72h safety data

→

IDMC meeting
Dose escalation to next higher cohort based on at least 72h safety data from all patients

During the MAD phase 2 different multiple ascending doses will be administered in a double- blinded manner. Each cohort in the MAD phase also includes 2 patients that will receive placebo. Each dose of PPSGG or placebo will be administered via an IV infusion over 60 minutes (120 min for optional 3200 mg dose). After treatment of the first 2 patients in each cohort and after treatment of all patients in that cohort, a safety analysis will be performed. The dosing cohorts and safety assessments are schematically represented below.

Cohort 1 (MAD)

Dose
1 active patient
1 placebo patient

→

IDMC
Dose remaining patients of the cohort after IDMC review of 2 weeks safety data

→

IDMC meeting
Dose escalation to next higher cohort based on 2 at least weeks safety data from all patients

→

Cohort 2 (MAD)

Dose
1 active patient
1 placebo patient

IDMC
Dose remaining patients of the cohort after IDMC review of 2 weeks safety data

As there is no placebo in the SAD phase only a single sentinel patient in each cohort is required for safety review. In the MAD phase the first 2 patients (sentinel) in each cohort will be randomized as follows: 1 patient will be treated with PPSGG and 1 patient with placebo. The following safety data, obtained from the sentinel patient(s) during the first 72 hours post study drug administration in the SAD phase and 2 weeks post drug administration in the MAD phase, will be checked by Polyneuron and will consist of:

- AEs.
- Baseline characteristics.
- Vital signs, including core temperature, blood pressure and heart rate.
- Laboratory data including hematology, clinical chemistry and urinalysis.
- ECG.

This review will be based on data entered in the electronic case report form (eCRF).

The remaining patients of the cohort will be dosed if no safety concerns are observed after reviewing the safety data of the sentinel patient in the SAD phase and the first 2 patients in the MAD phase, as listed above. The treating investigator might be involved in the review of the data for clarification in case of medical questions.

The decision to escalate to the following dose (once a cohort is completed) will be based on the safety data, as listed above collected during the first 72 hours after the start of the infusion in the SAD phase and after 2 weeks for the MAD phase, where no stopping rules are met and agreed by an IDMC.

If the SAD phase is stopped at one dose level due to clinically relevant toxicity, the maximum dose appropriate for the MAD phase will be defined as the dose level below the dose inducing the relevant toxicity.

- No transition to the next dose cohort during the SAD and/or MAD phases can occur before the review of all safety data of the previous cohort by the IDMC
- Usage of the next higher dose level in the study will be suspended if any of the following occurs:
    - 3 or more patients in a dose cohort meet one of the individual stopping criteria (see Section 7.5 Study Stopping rules).
    - 4 or more patients in a dose cohort experience a treatment related (i.e. moderate and/or severe) AEs.
    - 1 or more patients in a dose cohort experience a treatment related serious adverse event (SAE)

In the Dose Escalation Assessments, the Polyneuron staff and the IDMC will review blinded data during the MAD phase.

3.6 Risks and benefits

This study is the first administration of PPSGG in humans; therefore, no prior human safety and tolerability data are available. As with any drug, it is possible that adverse reactions are caused by PPSGG. There may be unknown or unforeseeable risks. However, the risk to patients in this study will be minimized by adherence to the inclusion/exclusion criteria, close clinical monitoring in an hospital setting, strict adherence to standard practice including training of staff and provision of manuals for study procedures, infusion procedure, stopping rules for an individual patient (see Section 7.5 Study Stopping rules), as well as a safety review after the first part of the study and monitoring by an IDMC (see Section 10.2 Independent Data Monitoring Committee). In addition, sentinel dosing is included in both the SAD and MAD phases of the study.

Evaluation of the safety of PPSGG in dogs and rats demonstrated a favorable toxicity profile (see IB). In a repeat-dose GLP study in rats and dogs with doses up to 150 and 200 mg/kg respectively, eleven 15 min infusions over 36 days (followed by a 2-week recovery), resulted in no toxicities. There were no clinical signs, no effects on organ weight or macroscopic observations, no adverse effects seen in clinical chemistry or hematology and no histopathological changes were observed. Safety pharmacology found no clinically relevant effects on the cardiovascular system.

Based on the experimental animal studies that were carried out, investigation of the safety and tolerability of PPSGG showed no special dangers for humans. Therefore, based on the safety profile of PPSGG the risks in participating in the trial are considered acceptable. However, they include the usual risks of participating in clinical trials, which are related to possible allergic reactions, infusion related adverse event, blood drawing via venepuncture. Patients' safety will be observed during all study phases. Before the drug administration, participants will be informed about the potential and/or observed adverse effects, if any, that occurred in the previous cohort.

Medical progress is based on research which ultimately must rest in part on experimentation involving humans. Eligible patients may consider participation in this clinical trial because they want to contribute to the advancement of medical knowledge. Still, considerations related to the well-being of the individual patients enrolled into this clinical study must take precedence over the interests of science and society. Based on the available information and the design of the study, Polyneuron and the Principal investigator consider the trial to be ethically acceptable. The duration of hospitalization and the medical surveillance are considered adequate to ensure safety of the patients

There may be unknown risks of PPSGG which may be serious.

3.6.1 Blood sample volumes

Approximately 150 mL of blood is planned to be collected during the whole SAD phase and approximately 440 mL during the whole MAD phase, from each patient as part of the study. Additional samples may be required for safety monitoring.

The timing of blood sample collections is outlined in the Schedule of Assessments (see Section 8.2 Schedule of Assessments).

3.6.2 Risk mitigation strategy

There are preclinical findings of undetermined clinical relevance that will be mitigated by careful clinical monitoring. Thus, vital signs and ECG will be monitored before and after the first dose during the SAD phase and before and after the doses during the MAD phase and at other visits throughout the study.

Patients will return to the study site on a regular basis. During these visits, safety, tolerability, efficacy, and PK/PD data will be collected. Standard safety assessments will include vital signs, ECGs, clinical laboratory evaluations (hematology, blood chemistry and urinalysis), and AEs as outlined in the Schedule of Assessments (see Section 8.2 Schedule of Assessments). In addition to the standard clinical laboratory assessments, patients will be regularly monitored for signs and symptoms, inflammation, and hematologic and hepatic function. Patients will be informed to report any symptoms to the clinical staff to assure proper assessment and so that care can be administered in a timely manner.

In addition, the clinical opinion of the Investigator will be used to protect individual patient safety during the trial.

Finally, key safety data will be reviewed by Polyneuron in a blinded manner on an ongoing basis. An IDMC will regularly review safety data to assess whether the benefit/risk of each treatment arm remains acceptable.

3.6.3 Management of Infusion Related Reactions (IRR):

In case of occurrence of an IRR, the following measures are to be taken:

- PPSGG infusion should be interrupted and vital signs monitored until the IRR resolves to the Common Terminology Criteria for Adverse Events (CTCAE) Grade ≤1 and then the infusion can be restarted at a slower rate
- Treatment with oral acetaminophen, antihistamines and methylprednisolone can be initiated, or other treatments can be given as necessary in line with the patient's condition and local standard of care.
- The patient can be pre-treated with antihistamines prior to the next PPSGG infusion during the MAD phase in cases with mild reactions. In case of a moderate, severe or serious reaction the patients will be withdrawn.
- When anaphylaxis is suspected and/or confirmed, treatment with epinephrine must be initiated immediately. In case of severe reactions during the infusion of PPSGG the treatment should be stopped immediately and discontinued permanently.

AEs of IRRs and hypersensitivity must be captured on the patient's source data and on the AE page of the eCRF, along with their signs and symptoms. If dosing is interrupted, discontinued or the patient is withdrawn from the study as a result of an infusion site reaction, this must be recorded in the patient's source data and the eCRF. In the event of IRRs, blood samples taken at the end of infusion will be analyzed for complement, histamine, and cytokines to elucidate the mechanism.

4 Study Population

4.1 Anti-MAG neuropathy patients

PPSGG is targeting anti-MAG IgM autoantibodies, which are the underlying cause of anti-MAG neuropathy. Since these autoantibodies are only present in patients with anti-MAG neuropathy, but not in healthy humans, information obtained from a study in healthy patients would be limited in respect to PK, PD and any potential target related toxicities.

Moreover, since PPSGG acts as a mimetic of the antigen, the potential for immunogenicity is an important safety concern in healthy volunteers. Potential ADAs resulting from exposure of healthy individuals to PPSGG may bind to the human natural killer-1 (HNK-1) epitope in the PNS and trigger the development of the anti-MAG neuropathy. Of note, no immunogenicity was detected in the non-clinical development so far (see Section 1.1 Background) [19].

However, it is acknowledged that it is not possible to fully predict immunogenicity in humans based on non-clinical studies. Therefore, the sponsor considers a FiH study directly in a small number of patients with anti-MAG neuropathy the most appropriate approach to minimize the potential risk for immunogenicity, as also confirmed by the EMA during a scientific advice meeting.

The following inclusion and exclusion criteria are chosen to select the appropriate study population regarding homogeneity in order to meet the requirements for reliable evaluation of the data collected.

Eligible patients will be included in the study after having given voluntary written informed consent before the first screening examination procedure takes place.

A confirmed diagnosis of anti-MAG neuropathy should be available. Sites will provide documentation of disease confirmation (i.e. previously performed tests) to the medical monitor for review. A formal process for eligibility review for any patients recommended by the investigator is done by the medical monitor based on the data entered during the screening visit.

4.2 Inclusion criteria

Anti-MAG neuropathy patients eligible for inclusion in this study must fulfill **all** of the following criteria:

- Written informed consent.
- Age between 18 and 80 years, male and female.
- Patient with a confirmed diagnosis of monoclonal IgM associated with monoclonal gammopathy of undetermined significance (MGUS) with anti-MAG activity (titer of >10’000 Bühlmann Titer units (BTU) and demyelinating neuropathy defined by electrophysiological criteria according to European Federation of Neurological Societies/Peripheral Nervous System paraproteinemic demyelinating neuropathy EFNS/PNS PDN guideline, 2010.
- Clear clinical signs of disability: with at least ONLS ≥2 in lower extremities.
- Inflammatory Neuropathy Cause and Treatment sensory sum score (ISS) ≥2.
- Patients must have adequate hepatic function as evidenced by total bilirubin <26 µmol/l (1.5 mg/dL), and alkaline phosphatase and aspartate transaminase/alanine aminotransferase <2X the upper limit of normal (ULN).
- Absence of cause of neuropathy independent from anti- MAG activity: e.g. diabetes, hypothyroidism, past or current dependence on alcohol, past or current treatment with neurotoxic drugs.
- Patients must have adequate renal function as evidenced by serum creatinine <2mg/dL or calculated creatinine clearance of ≥60 mL/min within 28 days before first investigational medicinal product (IMP) administration using Modification of Diet in Renal Disease (MDRD) formula.
- Capability to meet the requirements of the study.

4.3 Exclusion criteria

Anti-MAG neuropathy patients fulfilling any of the following criteria are <u>not</u> eligible for inclusion in this study:

- Patients with total serum IgM levels >30 g.
- Hematological malignancy (e.g. known multiple myeloma or confirmed Waldenström's macroglobulinemia based on bone marrow analysis).
- Patients with any history of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
- Previous immunosuppressive treatment with intravenous immunoglobulin (IVIG) or apheresis/plasmapheresis in the preceeding 3 months, and cyclophosphamide and/or biologicals (e.g. rituximab): in the preceeding 6 months prior to enrolment.
- Other neurological, neuromuscular, rheumatologic or orthopedic conditions with significant impact on the capability of walking preventing evaluation of neurological scores.
- Anti-MAG neuropathy patients with persistent clinically significant laboratory abnormalities not related to the anti-MAG neuropathy, such as significant renal dysfunction, hepatic dysfunction, cardiac disease or other significant neurological disorder.
- Anti-MAG neuropathy patients with a modified Rankin Scale (mRS) score >4.
- Participation in another Interventional clinical trial.
- Any other significant finding that would increase, according to the investigator, the risk of having an adverse outcome from participating in the study.
- Any other medical condition, including mental illness or substance abuse deemed by the investigator(s) to likely interfere with the patient's ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results.
- Patients who have undergone major surgery ≤ 2 weeks prior to starting study drug or who have not recovered from the side-effects of surgery.
- A history of clinically significant ECG abnormalities, or any of the following ECG abnormalities at screening:
    - PR >200 msec.
    - QRS complex >120 msec.
    - QTcF >450 msec (males).
    - QTcF >460 msec (females).
    - History of familial long QT syndrome or known family history of Torsades de Pointes.
    - Use of agents known to prolong the QT interval unless they can be permanently discontinued for the duration of the study.
- Sexually active males must use a condom during intercourse after the start of IMP administration and for at least one week after stopping study medication and should not father a child in this period after completion of the study medication (SAD and MAD phases). A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. In addition, male participants should not donate sperm for the time period specified above.

- Use of other investigational drugs at the time of enrolment, or within 5 half-lives of enrolment, or within 30 days, whichever is longer; or longer if required by local regulations.
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 1 week after discontinuation of the investigational drug. Highly effective contraception methods include:
    - Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking the investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
    - Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure <1%), for example hormone vaginal ring or transdermal hormone contraception. Progesterone containing hormonal tablets must be associated with inhibition of ovulation in order to qualify as highly effective.

  In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug. If local regulations deviate from the contraception methods listed above and require more extensive measures to prevent pregnancy, local regulations apply and will be described in the informed consent form (ICF).

  Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking the investigational drug. In case of oophorectomy alone, the reproductive status of the woman must be confirmed by follow up hormone level assessment.

4.4 Patients participating in SAD and MAD phases

Patients that have participated in the SAD phase may enter the MAD phase but not all the screening and tests procedures performed in the SAD phase during screening need to be repeated. Just “newly” recruited patients need to go through the complete screening assessment as described in Section 8.3 Patient screening.

5 Restrictions for Study Patients

For the duration of the study, the patients should be informed and reminded of the restrictions outlined in this section.

5.1 Fasting

After an 8-hour fasting overnight, patients will have a light breakfast in the morning at least an hour before the IMP administration.

5.2 Contraception requirements

Women of childbearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, they should agree that in order to participate in the study they must adhere to the highly effective contraception requirements outlined in the Section 4.3 Exclusion criteria.

If there is any question that a patient will not reliably comply, the patient should not be entered or continue in the study.

6 Treatment

6.1 Study treatment

PPSGG and placebo is manufactured for Polyneuron by BAG Healthcare GmbH, Amtsgerichtsstraße 1 - 5, 35423 Lich, Germany. QP release is carried out by BAG Healthcare GmbH, which holds appropriate cGMP authorization.

Polyneuron will provide the site with investigational products manufactured and tested according to applicable good manufacturing practice (GMP) requirements for clinical trial supplies together with a certificate of analysis (CoA) and a confirmation that the investigational products are released for human use in clinical trials.

Polyneuron will ensure that the drugs, PPSGG and placebo, to be applied during the MAD phase, are identical in their appearance (colorless solution). Thus, neither the patient nor the investigators will be aware of whether the drug administered is the test or the reference drug.

Handling Requirements:

The designated person (e.g. pharmacist) at the study site will be responsible for ensuring that the study drugs are stored in compliance with GMP in a locked refrigerator (+2ºC to +8ºC) prior to administration with limited access and in accordance with the instructions on the study medication labels.

Patients will receive 1 infusion (SAD phase) or up to maximum 11 infusions (MAD phase) for 6 weeks during the study. Drug administrations will take place in the morning. The respective treatments will consist of the following:

Table 4 Dose regimen during SAD phase

Cohort No	IMP Single dose	Dose Level (mg) per patient	Dose volume (mL)	Dose concentration (mg/mL)
1	PPSGG	200	20	10
2	PPSGG	400	40	10
3	PPSGG	800	80	10
4	PPSGG	1600	160	10

An additional cohort of 3200 mg per patient may be included if the relative reductions in anti- MAG antibody titers have not reached the target of 50% relative reduction, no stopping rule for safety has been met and the end of cohort review by the IDMC from the previous patients considers proceeding to the final cohort justified by the previous safety and tolerability profile.

The specific Dose regimen during the MAD phase will be based on the data (PK / PD) derived from the SAD phase.

PPSGG will be provided to the sites in sufficient quantity. The IMP is supplied as solution at a concentration of10 mg/mL.. IMPs will be stored at the site in a refrigerator/refrigeration unit at 5±3°C (2-8°C). The IMP must not be allowed to freeze. The solution should be visually inspected prior to use. Only clear solutions without particles should be used. A single administration of PPSGG in the SAD phase and up to 11 infusions of PPSGG or placebo in the MAD phase will be given by intravenously over 60 minutes (120 min for 3200 mg dose) to the patient.

Detailed information on IMP handling will be provided in an IMP manual that is based on information provided in Polyneuron's pharmaceutical instruction. Immediately prior to administration, the assigned personnel dispense the study drug according to the cohort and dose of the patient. The dispensing of medication for administration will follow the randomization list.

The study medication will be prepared based on Table 5. The pump syringes will be filled with the study medication and the IV line filled up completely before the start of the infusion. Treatment with study drug will be administered intravenously into the arm contralateral to the arm used for blood collection. Infusions of the sterile solutions will be given through an infusion set and an IV catheter with the rate controlled by the infusion pump. At the end of the infusion, the IV catheter will be flushed with a saline solution.

Table 5 Study medication

Dose	Original concentration in mg/mL	Original Volume in mL	Infusion Speed in 60 min in mL/min
200	10	20	0,333
400	10	40	0,667
800	10	80	1,333
1600	10	160	2.667
3200	10	320	5.222

6.1.1 Identity of Investigational treatment PPSGG

The drug product, PPSGG solution for infusion is a sterile, clear, and colorless solution filled in a sterile Type I glass vial. Concentration is expressed in terms of the amount of PPSGG free and pure acid per mL.

The solution contains PPSGG sodium as the active ingredient and a standard phosphate buffered saline (PBS) solution for pH 7.4, as inactive ingredient.

Component	Function	Quantity per Unit (40 mL)

		10 mg/mL
PPSGG sodium	Drug substance	400 mg
PBS solution	Solvent	40 mL, q.s.

Batch number	P01997
Route	IV
Retest date	Shelf life controlled by Interactive Voice Response System (IVRS)

6.1.2 Identity of Placebo

Strength	NA
Route	intravenous
Batch number	P01963
Retest date	Shelf life controlled by IVRS

Placebo is a standard PBS solution, pH 7.4, composed of disodium hydrogen phosphate dodecahydrate, potassium dihydrogen phosphate, sodium chloride, and water for injection. An adjustment of the pH is not necessary. It is the same composition as used for the inactive ingredient for the PPSGG solution.

Component	**Quality Reference**	**Molecular Weight**	**Concentration (mg/mL)**
$Na_2HPO_4 \bullet 2H_2O^*$	Ph.Eur./USP	177.99	1.43
KH_2PO_4	Ph.Eur./USP	136.08	0.20
KCl	Ph.Eur./USP	74.55	0.20
NaCl	Ph.Eur./NF	58.44	8.00
Water for injection (WFI)	Ph.Eur./USP/In-House	-	1 mL (q.s)

Ph. Eur/USP = Pharmacopoeia Europaea/United States Pharmacopeia; Ph. Eur/NF = Pharmacopoeia Europaea/National Formulary

6.2 Labelling

The study drug will be provided by Polyneuron with appropriate labelling. Polyneuron will supply sufficient trial medication. The medication will be identified by project and protocol number, vial number, expiry date, storage requirements and contents. Polyneuron will provide a CoA.

The study products will be labelled in accordance with the Good Clinical Practice (GCP) ordinance and local regulatory requirements.

The labels on the vial and secondary packaging (box) of the IMP will contain the following information

- Polyneuron’s study code.
- Polyneuron’s name, address and phone number.
- European Union Drug Regulating Authorities Clinical Trials (EudraCT) number.
- Product name, strength and dosage form.

- Application form.
- Content by weight, volume, number of units.
- Route of administration.
- Directions for use.
- Batch number.
- Expiry date controlled by IVRS.
- Storage instructions.
- The term “For clinical trial use only”.

Each manufacturing/packaging process will be performed and documented in conformity with GMP.

6.3 Treatment assignment

At the end of the SAD phase, a randomization will be performed for the MAD phase. In total there will be two randomization lists created in this study, one per cohort of the MAD phase. During the SAD phase, all patients will receive PPSGG.

During the MAD phase only, patients will be randomized to receive either PPSGG or placebo. Blinded treatment with PPSGG and placebo is used to reduce potential bias during data collection and evaluation of clinical efficacy endpoints during the MAD phase.

The randomization during the MAD phase will be done via IVRS. The randomization schedule will link sequential numbers to treatment assignment allocated to treatment with PPSGG and placebo. The randomization number will be used to link the patient to a treatment arm and specify a unique medication number for the first package of investigational treatment to be dispensed to the patient.

Patients allocated to one of the groups within a cohort will receive a randomization number.

Each patient must be given only the study treatment assigned to their randomization number by the IVRS. The investigator must document the randomization number on the patient’s eCRF.

These randomization numbers are linked to the different cohorts, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Polyneuron using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

6.4 Treatment blinding

SAD is an open label phase. MAD is a double-blind phase (patient and investigator blinded). Patients and investigators will remain blinded to study treatment throughout the MAD phase, except where indicated below.

The identity of treatments will be concealed by the use of study drugs that are all identical in packaging, labelling, schedule of administration, appearance, and odor.

Site staff: All site staff (including study investigator and study nurse) will be blinded to study treatment throughout the MAD phase.

Unblinding a single patient at a site for safety reasons (necessary for patient management) during the MAD phase, will occur via the process defined in place at the site (see Section 6.8 Emergency breaking of assigned treatment code).

Polyneuron staff: Polyneuron clinical staff is required to assist in the management and re-supply of the IMP. These individuals are not provided with randomization lists directly during the MAD phase.

During the MAD phase the sample analysts handling PK samples will receive a copy of the randomization schedule, to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team in a way that does not unblind individuals who are meant to be blinded.

Personnel involved in the analysis and the IDMC: An independent data analysis team will be employed to produce the analysis results and to communicate with the IDMC at the time of safety review for the dose continuation and escalation meetings.

Polyneuron staff responsible for decision making at the clinical program development level will receive the blinded results at the treatment group level at the time of the analysis. The team will not have access to the individual patient treatment codes during the MAD phase.

6.4.1 Unblinding plan for the MAD phase

See Table 6 for an overview of the blinding/unblinding plan.

Table 6 Unblinding plan for the study applicable for the MAD phase only

Role	Randomization list generated	Treatment allocation & dosing	Safety event	IDMC Safety review	Analysis at end of treatment in MAD
Patients	B	B	UI	B	B
Site staff	B	B	UI	B	B
IVRS of Clinipace	UI	UI	UI	UI	UI
IDMC	B	B	UI	UI	UI
Independent analysis team	B	B	UI	UI	UI
Polyneuron team	B	B	B	B	UG

B=Blinded; UG = Unblinded at the group level; UI = Unblinded at the individual level; SAD = Single Ascending Dose; IDMC = Independent Data Monitoring Committee; MAD = Multiple Ascending dose

6.5 Treating the patient

PPSGG will be administered to the patient intravenously over a 60-minute (120 min for 3200 mg dose) infusion.

Polyneuron's qualified medical personnel will be readily available to advise on trial related medical questions or problems.

6.6 Patient identification

Each patient for whom an ICF is obtained will be assigned a unique 6-digit patient number xxx - yyy (country and site - patient number) strictly in chronological order of enrolment within each study site. Patients who withdraw from the study will keep their screening respective patient number even if the withdrawal occurs before randomization. The screening number corresponds to the patient number and will be documented on the eCRF and used to identify the patient throughout the study.

6.7 Permitted dose adjustments and interruptions of study treatment

Dose adjustments of study drug treatment are not permitted.

6.8 Emergency breaking of assigned treatment code

During the MAD phase, emergency code breaks must only be undertaken when it is required to safely treat the patient. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IVRS. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the study monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IVRS at any time in case of emergency. The investigator will need to provide:

- Protocol number.
- Study drug name (if available).
- Patient number.

In addition, the investigator must provide to the patient with oral and written information on how to contact his/her backup in cases of emergency when he/she is unavailable to ensure that un- blinding can be performed at any time.

An assessment will be done by the appropriate site personnel and Polyneuron after an emergency unblinding to assess whether or not study treatment should be discontinued for a given patient.

6.9 Treatment exposure and compliance

PK parameters (measures of treatment exposure) will be determined in all patients treated with PPSGG and placebo during the MAD phase, as detailed in Section 8.5 Pharmacokinetics.

The investigator must promote compliance by properly infusing the patient according to dose cohort.

All study treatment dispensed must be recorded on the Drug Accountability Log.

6.10 Recommended treatment of adverse events

At present, there is insufficient information to provide specific recommendations regarding treatment of AEs. There is no treatment that can reverse the activity of PPSGG. We anticipate PPSGG will have a relatively short half-life. AEs should therefore be treated symptomatically

at the discretion of the investigator. Medication used to treat AEs must be recorded on the concomitant medications/significant non-drug therapies page of the eCRF. For treatment of IRR refer to Section 3.6.3 Management of Infusion Related Reactions (IRR):.

6.11 Concomitant therapy

The investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study.

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the appropriate page of the eCRF.

Medication entries should be specific to generic name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication (see Section 6.12 Prohibited concomitant treatment). If in doubt, the investigator should contact Polyneuron before enrolling a patient or, if the patient is already enrolled, to determine if the patient should continue participation in the study.

6.12 Prohibited concomitant treatment

Any prescribed medication, over-the-counter drugs and significant non-drug therapies (plasmapheresis) known to have a possible impact in the clinical status of anti-MAG neuropathy are prohibited.

7 Study completion and discontinuation

7.1 Study completion and post-study treatment

All efforts will be done to facilitate the patients to complete the study in its entirety and thereafter no further study treatment will be made available to them.

An EOS visit, for each patient, is scheduled at the end of each corresponding phase (SAD and MAD phases).

Study Completion (SC) is defined as when the last patient completes their EOS visit at the end of the MAD phase, or at the end of SAD, if the patient decides not to continue with the MAD, and any repeated assessments associated with this visit have been followed-up appropriately by the investigator, or in the event of an early study termination decision, the date of that decision.

7.2 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study treatment is stopped earlier than the protocol planned duration.

Study treatment must be discontinued under the following circumstances:

- Patient decision - patients may choose to discontinue study treatment for any reason at any time.
- The investigator believes that continuation would negatively impact the safety of the patient or the risk/benefit ratio of trial participation.
- Any protocol deviation that results in a significant risk to the patient’s safety.
- Pregnancy (see Section 9.4 Pregnancy reporting).

- Use of prohibited treatment as described in Section Prohibited concomitant treatment Section 6.12.
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the patient's overall status, prevents the patient from continuing participation in the study

If discontinuation of study treatment occurs, investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the patient's eCRF.

7.3 Withdrawal of informed consent

A patient can decide to withdraw from the study participation at any time, for any reason, specified or unspecified, and without penalty or loss of benefits to which the patient is otherwise entitled. In this case, the patient must immediately contact the investigator and state that it is his/her desire to withdraw from the study. The patient should be informed of the possibility to withdraw consent without giving any reason and to require that all previously retained identifiable samples will be destroyed to prevent future analyses, according to national provisions. The consent should include a statement that the consequence of the patient's withdrawal of consent will be that no new information will be collected from the patient and added to existing data or a database.

Patients who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 7.3 Withdrawal of informed consent). Where possible, they should return for EOS visit within 14 days after last study medication administration. If they fail to return for EOS visit for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the patient/pre-designated contact as specified in Section 7.4 Lost to follow-up. This contact should preferably be done according to the study visit schedule.

Withdrawal of consent from the study is defined as when a patient:

- Does not want to participate in the study anymore,
- Does not want to participate in any further visits or assessments,
- Does not want any further study related contacts or,
- Does not allow analysis of already obtained biologic material.

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the patient's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued, and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing. In the event of a patient deciding to stop participation in the study, he/she is requested to take part in the final medical examination including the required blood withdrawal (for the laboratory tests). This final examination is for the patient's safety. It is only by this examination that any impairment to the patient's health which may require treatment and could be related to the patient's participation in the study can be detected. If the patient is withdrawn for safety reasons, the investigator will make thorough efforts to document the final AE/SAE outcome.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

Patients can also be withdrawn from study at the description of the investigator for safety, compliance, behavioral or administrative reasons.

As the aim of this study is to generate information on the safety and tolerability, preliminary efficacy, and PD properties of the substance under investigation as well as PK data, patients who are withdrawn from the study for reasons other than safety issues may be replaced at the discretion of Polyneuron and the Investigator.

7.4 Lost to follow-up

For patients whose status is unclear because they fail to return for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents the steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. At least 3 attempts should be documented. A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the site for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient’s last known mailing address or local equivalent methods). These contact attempts should be documented in the patient’s medical record.

Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

7.5 Study Stopping rules

During and after the administration of PPSGG, the patient will be closely monitored, in particular for signs and symptoms of IRRs, including skin reactions (urticaria, erythema, facial edema, facial rash, pruritus, eruptions), hypotension or hypertension, drop in oxygen saturation, respiratory problems (laryngospasm, laryngeal edema, bronchospasm, dyspnea), pain (joint pain, back pain, abdominal pain, chest pain) or other manifestations of hypersensitivity (fever, chills, rigors, diaphoresis, nausea, vomiting, neurological changes). One-lead ECG will be monitored continuously during the infusion, and 12-lead ECG pre-dose and at the end of infusion and at 2h and 8h after start of infusion. In the absence of symptoms, or in case of mild (asymptomatic with only incidental findings) or moderate (symptomatic without intervention required), the infusion should be stopped until the AE resolves to grade 1 and may be restarted with a lower infusion rate and treatment with antihistamines or methyl prednisolone may be initiated. If not resolved, Polyneuron shall be contacted and the patient withdrawn from the trial.

The IDMC will perform reviews of safety data throughout the study.

Enrolment in the study will be placed on hold and no further dosing will occur pending a full safety review if:

- One fatal or life-threatening SAE occurs, that is considered by the Investigator as potentially or possibly related to PPSGG and later confirmed the patient received IMP.

- Polyneuron, investigators and/or the IDMC considers that the number and/or severity of AEs, abnormal safety monitoring tests or abnormal laboratory findings justify putting the study on hold. Examples are:
    - One severe systemic infusion-related reaction occurs and does not resolve within 24 hours.
    - Three or more similar severe AEs occur as defined by the CTCAE v5.0, which are judged related to PPSGG.
    - Two SAEs which are judged related to PPSGG.
- If 2 patients at any dose level discontinue treatment due to changes in vital signs, ECG intervals or findings on continuous ECG monitoring no further patients will be enrolled at this dose level pending review by IDMC.

The IDMC can recommend (i) for the study to continue without amendment, (ii) to continue the study with modifications to the protocol (iii) to stop the study.

The study may continue after the safety review, if the IDMC and Polyneuron agree it is safe to proceed.

7.6 Individual stopping rules

Infusion related adverse events

If a patient experiences an infusion related adverse event that judged to be related to the study drug, and is graded as severe or SAE, no further doses of study drug will be administered to the patient concerned.

If a patient experiences an infusion related adverse event that judged to be related to the study drug, and is graded as mild or moderate, the patient may receive a further dose of study drug following discussion with the investigator and sponsor, dependent on the nature of the AEs reported. For example, an asymptomatic localised erythematous rash would be less concerning that mild bronchospasm. If patients are to receive a further dose (i.e. re-challenged), an oral or IV antihistamine and oral acetaminophen will be administered approximately 30-60 minutes prior to the start of the infusion.

Non-Infusion related adverse events

If a patient experiences an adverse event following administration of study drug (i.e. post-treatment) that judged to be related to the study drug, and is graded as severe or SAE, no further doses of study drug will be administered.

If a patient experiences an adverse event that judged to be related to the study drug, and is graded as mild or moderate, the patient may receive a further dose of study drug following discussion with the investigator and sponsor, dependent on the nature of the AEs reported. The number of subjects reporting similar AEs and reports of the same or similar AE/s in an individual patient, will form part of the assessment to determine if patients should be re-challenged.

Changes in Vital Signs and ECG intervals

In MAD portion of study, patients will be discontinued if after repeated measurements, have pulse/heart rate, blood pressure or ECG interval measurements that fulfil one or more of the criteria listed below.

Vital signs

- pulse/heart rate < 40 or >120 BPM
- systolic BP < 90 or >180 mm Hg
- diastolic BP < 50 or >100 mm Hg

12 lead ECG

- PR interval < 170 or >260 msec
- QRS duration >150 msec
- QTc >500 msec (with Bazett's or Fridericia's QT correction)

Continuous ECG monitoring

- Run of supraventricular tachycardia of more than 20 complexes
- Run of ventricular tachycardia of more than 5 complexes
- Any other clinically significant arrhythmias

7.7 Early study termination by the sponsor

The study may be terminated by Polyneuron at any time for any reason. This may include reasons related to the benefit/risk assessment of participating in the study, practical reasons (including slow enrolment), or for regulatory, medical, scientific or ethical reasons. Should this be necessary, patients must be seen as soon as possible and treated as a prematurely discontinued patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the institutional review boards/independent ethics committees (IRBs/IECs) of the early termination of the trial.

8 Procedures and assessments

8.1 Repeat and additional assessments

Should it become necessary to repeat an assessment (e.g. ECG, laboratory tests, vital signs, etc.), the results of the repeated evaluation should be entered on the appropriate section of the eCRF, including date and hour of the repeated assessment. A statement should be included in the comments section explaining why the repeated or additional evaluation was performed.

8.2 Schedule of Assessments

Patients should be seen for all visits/assessments as outlined in the schedule of assessments or as close to the designated day/time as possible.

Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the AEs and concomitant medications recorded on the eCRF.

Table 7 Schedule of Assessments for the SAD phase

Period	Screening	Baseline	Treatment										EOS	FU[5]
Visit numbers	**1**	**2**	**3**						**4**	**5**	**6**		**7**	**8**
Study Day	**-14 to -1**	**-1**	**1**						**2**	**4**	**8±1**	**14±2**	**28±2**	**42±2**
Time			**Predose**	**30min**	**60min**	**2h**	**6h**	**8h**						
Informed consent	X													
Biobank consent (optional)	X													
Inclusion/Exclusion criteria	X	X												
Medical history/current med condition	X													
Eligibility assessment	X													
Demography	X													
Physical Examination	X	X									X		X	
Serum creatinine	X													
HbA1c test	X													
The modified ranking scale (mRS)	X													
Inflammatory Neuropathy Cause and Treatment sensory sum score (ISS)	X													
Pregnancy test in WOCP	X	X											X	
Vital signs (BP, PR, body temp)	X		X		X	X		X					X	
12-lead ECG	X		X		X	X		X					X	
1-lead Continuous ECG monitoring			X											
Hematology	X	X									X		X	
Clinical chemistry[1]	X	X									X		X	
Urinalysis	X	X									X		X	
Study Drug administration			X											
PK blood collection				X	X	X	X	X	X	X	X	X	X	
PD blood collection[2]	X	X		X	X	X		X	X	X	X	X	X	X
ADA blood collection[3]	X	X											X	
Biobank sampling (optional)		X												

Period	Screening	Baseline	Treatment										EOS	FU[5]
Visit numbers	1	2	3							4	5	6	7	8
Study Day	-14 to -1	-1	1						2	4	8±1	14±2	28±2	42±2
Time			Predose	30min	60min	2h	6h	8h						
Scores[4]	X											X	X	X
Hospitalization			X											
Concomitant medication	X													
Infusion related AE assessment				X X	X	X	X	X	X					
Adverse events	X													X
Serious adverse events	X													X
Study completion information													X	

EOS = End of study; FU = Follow up; BP = Blood pressure; PR = Pulse rate; PK = Pharmacokinetics; PD = Pharmacodynamics; ADA = anti-drug antibodies; AE = Adverse event; ECG = electrocardiogram
1 Including liver safety monitoring (ALT, AST, ALP, TBL, PT/INR, GGT level assessment)
2 Including anti-MAG titers (Bühlmann Titer Units), paraprotein levels, anti-human natural killer- 1 antibodies (anti-HNK-1 Titers) and total IgM.
3 will be combined with PD blood collection
4 Includes ONLS, RODS, time to 10 m walking test, ataxia score,
5 The follow up (FU) period will depend on the anti-MAG antibody levels and will be extended until the levels reach baseline
In case of a reaction during infusion, an additional samples will be taken to analyze tryptase, histamine, classical complement pathway, and cytokines

For the optional 3200 mg dose cohort the time for PK sampling will be the following: predose, 30 min, 60 min, 2h, 3h, 6h, 8h and 10h

Table 8 **Schedule of Assessments for the MAD phase during specified infusion days**

Visit name	Treatment					
Study Day	Infusion Day 1, 3, 5 and 42					
Time	Predose	30 min	60 min	2h	6h	8h
Vital signs (BP, PR, body temp)	X		X	X		
12-lead ECG	X		X	X		
1-lead Continuous ECG monitoring	X					
Urinalysis	X					
PK blood collection	X	X	X	X	X	X
PD blood collection[1]	X	X	X	X	X	X

Study Drug administration		X						
Infusion related AE assessment		X	X	X	X	X	X	
Adverse events	X							
Serious adverse events	X							

1 PD blood collection on all other days at predose and 2h only

Table 9 Schedule of Assessment (MAD)

Visit name	**SCR**	**Baseline**	**Treatment**														**EOS**	**FU[6]**
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Study Day	**-14 to -1**	**-1**	**1**	**2**	**3**	**4**	**5**	**8±1**	**14±2**	**21±3**	**28±3**	**35±3**	**42±3**	**56±3**	**70±4**	**98±4**	**150±8**	**180±8**
*Informed consent	X																	
*Biobank consent (optional)	X																	
Inclusion/Exclusion criteria	X	X																
*Medical history/current med condition	X																	
Eligibility assessment	X																	
*Demography	X																	
Physical Examination	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum creatinine	X																	
HbA1c test	X																	
Pregnancy test in WOCP	X	X									X			X		X	X	
Vital signs (BP, PR, body temp)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG evaluation	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
1-lead ECG monitoring			X	X	X	X	X	X	X	X	X	X	X					

Visit name	SCR	Baseline	Treatment														EOS	FU[6]
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Study Day	**-14 to -1**	**-1**	**1**	**2**	**3**	**4**	**5**	**8±1**	**14±2**	**21±3**	**28±3**	**35±3**	**42±3**	**56±3**	**70±4**	**98±4**	**150±8**	**180±8**
Hematology	X	X						X			X		X			X	X	
Clinical chemisrty[1]	X	X						X			X		X			X	X	
Urinalysis	X	X	X													X	X	
Study Drug administration[5]			X	X	X	X	X	X	X	X	X	X	X					
PK blood collection[7]			X		X		X						X				X	
PD blood collection[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ADA blood collection[3]	X	X											X				X	
Biobank sampling (optional)		X											X				X	
Scores[4]	X								X				X			X	X	X
Exploratory biomarkers[7]		X					X		X				X				X	X
Concomitant medication	X																	
Infusion related AE assessment			X	X	X	X	X	X	X	X	X	X	X					
Adverse events	X																	X
Serious adverse events	X																	X
Study completion information																	X	

EOS = End of study; FU = Follow up; BP = Blood pressure; PR = Pulse rate; PK = Pharmacokinetics; PD = Pharmacodynamics; ADA = anti-drug antibodies; AE = Adverse event; ECG = electrocardiogram

1 Including liver safety monitoring (ALT, AST, ALP, TBL, PT/INR, GGT level assessment)
2 Including anti-MAG titers (Bühlmann Titer Units), paraprotein levels, anti-human natural killer- 1 antibodies (anti-HNK-1 Titers) and total IgM
3 will be combined with PD blood collection
4 Includes ONLS, RODS, INCAT sensory sum score, time to 10 m walking test, ataxia score, and grip strength
5 Study Days and dosing schedule to be confirmed based on data from SAD phase
6 The follow up (FU) period will depend on the anti-MAG antibody levels and will be extended until the levels reach baseline

7 including assessment of neurofilament light chain and BAFF, indirect immunofluorescence assay, and MUNIX (in selected sites only)
In case of a reaction during infusion, an additional will be taken to analyze tryptase, histamine, classical complement pathway, and cytokines

*Just newly recruited patients need to follow this assessment

8.3 Patient screening (Day -14 to -1, Visit no 1)

It is allowed to re-screen a patient if s/he fails the initial screening; however, each case must be discussed and agreed with Polyneuron on a case-by-case basis.

In each of the two study phases described in this protocol, all patients will undergo a screening examination to evaluate their health status and to check for inclusion and exclusion criteria. This examination will be conducted not more than 14 days prior to the planned first drug administration. Only patients meeting the inclusion and exclusion criteria will be admitted to the study.

During the screening examination, the patients are identified by a 6-digit patient number.

In addition, before inclusion into the study all patients screening data will be entered into the database to be assessed by the medical monitor.

This screening examination will consist of the following:

- Medical history, including collection of demographic data.
- Complete physical examination: respiratory rate, review of systems (eyes, ears, nose and throat [EENT], cardiac, peripheral vascular, pulmonary, musculoskeletal, neurologic, abdominal, lymphatic, dermatologic).
- Vital signs (blood pressure, pulse rate, and body temperature).
- Assessment of compliance with inclusion/exclusion criteria.
- ECG (12-lead).
- Evaluation of laboratory results.
- Blood for PD markers: anti-MAG IgM and time to anti-MAG IgM rebound (pre-treatment BTU) paraprotein levels (g/L), total IgM levels (g/L), and anti-HNK1 IgM titers Laboratory tests, to include hematology, biochemistry, coagulation, serology, urinalysis, and exclusion tests (see Section 8.4 Safety for details).
- Scores in SAD and MAD (ONLS, RODS, mRS, ataxia), and time to 10 meters walking test, and in MAD only: INCAT sensory sum score and grip strength
- Concomitant medication

Patients entering the MAD, who completed the SAD phase need not to perform all assessments as new recruited patients, according to the list in the Schedule of Assessment. For patients who completed the SAD phase of the study, the following assessments may be omitted should they continue in the MAD phase:

- Informed consent
- Biobank consent (optional)
- Medical history/current med condition
- Demography

8.3.1 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data will be collected on all patients during screening. Relevant medical history/current medical conditions data will also be collected until signature of informed consent.

Patient demographics will include, following and adapted local regulations: age, sex, race, ethnicity. Other baseline disease characteristics will include relevant medical history, current medical conditions, results of laboratory screens, transplant history, donor characteristics (e.g., age, sex, race, type) and any other relevant information.

Investigators have the discretion to record abnormal test findings on the medical history eCRF, if in their judgment, the test abnormality occurred prior to the informed consent signature.

8.3.2 Eligibility review

An eligibility review will be performed based on the data entered during the screening by the medical monitor to assess the eligibility of the potential patient. The site will be informed about the decision in due time.

8.3.3 Study performance

The patients willing to participate in the study will only be included when all screening examination procedures have demonstrated that all inclusion criteria and none of the exclusion criteria apply. The patients will be assigned a patient number within the study. For detailed information about the procedure of assigning patient numbers please refer to Section 6.3. Treatment assignment.

8.3.4 Baseline (Day -1, Visit no 2)

During the Baseline visit, defined as one day before the start of the infusion, the following assessments will be performed:

- Confirmation of inclusion and exclusion criteria.
- Physical examination.
- Pregnancy test in women of childbearing potential.
- Blood collection for hematology and clinical chemistry.
- Blood collection for PPSGG PK.
- Blood collection for PD markers: anti-MAG IgM and time to anti-MAG IgM rebound (pre-treatment BTU) paraprotein levels (g/L), total IgM levels (g/L), and anti-HNK1 IgM titers
- Blood collection for ADA
- Blood collection for Exploratory biomarkers in MAD phase only
- Urine collection for urinalysis.
- Blood for biobanking (optional).

8.3.5 Treatment period (starting on Day 1, from Visit no 3)

The treatment period consists of 4 visits in the SAD and of up to 11 visits in the MAD phase. After screening and baseline assessment enrolment the treatment period will be performed. The interval between screening and the start of the IMP administration must not exceed 14 days. Patients meeting all inclusion and none of the exclusion criteria will be enrolled.

Patients will then receive one single administration of the IMP through IV infusion, on Day 1 in the SAD phase and for 6 weeks in the MAD phase with a maximum of 11 infusions. The patient will be closely observed during and after the administration of the IMP. Appropriate medical treatment will be kept available in case of an IRR during or following the administration of the IMP. The following procedures and assessments will be performed during and after the treatment: Please refer to the Schedule of Assessment

- Monitor vital signs during the infusion up to 8 hours after start of infusion.
- Monitor 1-lead Continuous ECG monitoring during the infusion and for a total of 2 hours on each infusion treatment.
- 12-lead ECG at predose, during the infusion of the IMP at 60 min (120 min at option 3200 mg dose) and then at 2 hours and 8 hours (in SAD) after start of infusion and at EOS. In MAD on infusion days and then on Day 56, 70, 98 and 150.

- Blood collection for PPSGG PK during SAD phase on infusion Day 1 (at 30 min, 60 min, 2h, 6h, and 8h after start of infusion), and on Day 2, 4, 8 14 and 28 of the SAD phase. The sampling for the potential 3200 mg dose would be at 30 min, 60 min, 2h, 3h, 6h, 8h and 10h after start of administration on the infusion day.
- Blood collection for PPSGG PK during the MAD phase on Days 1, 3, 5, and Day 42 (predose, at 30 min, 60 min, at 2h, 6h, and 8h after start of infusion) and on Day 150 (EOS). The time points for PK sampling for the MAD phase will be confirmed based on the PK data collected during SAD phase.
- Blood collection for PD during SAD on infusion day (30 min, 60 min, 2h, 8h after start on infusion) and on Day 2, 4, 8, 14 and EOS (Day 28). During the MAD phase on Days 1, 3, 5 and 42 (predose, at 30 min, 60 min, at 2h, and 8h after start of infusion) and on Days 2, 4, 6, 7, 8, 9, 10 and Day 11 at predose and 2h after start of infusion.
- Exploratory biomarkers in MAD phase only: assessment of neurofilament light chain and BAFF, indirect immunofluorescence assay and MUNIX (in selected sites only).
- Blood collection for hematology and clinical chemistry on screening, baseline and Day 8, 28 (EOS) during the SAD and on Day 8, 28, 42, 98 and 150 (EOS) during the MAD.
- Scores (ONLS, RODS, ataxia), time to 10 meters walking test, at Day 14 and EOS (Visit no 6) during SAD phase On Day 14, 98 and EOS for the MAD phase.
- Pregnancy test on Day 28 (SAD and MAD) and on Day 56, 96 and 150 (MAD only)
- AEs (including infusion related AEs) and SAEs.
- Check for signs of infusion-related reactions, including clinical signs and symptoms, changes in diastolic or systolic blood pressure, heart rate, oxygen saturation, and skin reactions or local reactions at the infusion site during the infusion.

All the assessments are to be performed at the clinical site, except for the safety laboratory, PD biomarkers (blood) and the PPSGG pharmacokinetic (blood).

8.3.6 End-Of-Study (EOS) and optional Follow-up period

The length of the follow-up period will depend on the anti-MAG antibody levels and will last from Day 28 until EOS (Day 42) for the SAD phase. In exceptional cases, when the anti-MAG antibody levels did not reach the baseline level, the patient will be asked to come for an additional visit to check for these levels. In the MAD phase the schedule of assessments will be defined based on the outcome data of the SAD phase. The following assessments will be done on Days 28 and 42 for SAD, according to the schedule specified in Section 8.2 Schedule of Assessments.

The following assessments will be performed in each patient/phase at the EOS visit:

- Physical examination.
- Pregnancy test in all women of child-bearing potential.
- Vital signs.
- 12-lead ECG.
- Blood collection for hematology, clinical chemistry and urine collection for urinalysis.
- Blood collection for PD
- Blood collection for ADA
- Scores in SAD phase: (ONLS, RODS, ataxia) and time to 10 meters walking test,
- Scores in MAD phase: ONLS, RODS, ISS , ataxia) and time to 10 meters walking test,

- Exploratory biomarkers in MAD phase only: MUNIX in selected sites only, assessment of neurofilament light chain and BAFF, indirect immunofluorescence assay on sciatic nerves
- Collection of AEs and SAEs.

The following assessments will be performed during the follow-up visit:

- Blood collection for PD and ADA.
- Scores in SAD phase: (ONLS, RODS, ataxia) and time to 10 meters walking test,
- Scores in MAD phase: ONLS, RODS, ISS, ataxia, time to 10 meters walking test and grip strength test.
- Exploratory assessments in MAD only: Neurofilament light chain (NfL), BAFF, Indirect immunofluorescence on sciatic nerves, and MUNIX in selected sites.
- AE/SAE reporting

All assessments are to be performed at the hospital. The analysis of the PD biomarkers (blood) and the PPSGG PK (blood) will be done at the dedicated laboratories.

The EOS assessments are required on Day 28 for the SAD phase or whenever a patient discontinues or is discontinued from the study prematurely (see section 7.2); they should be performed on the last available study day.

8.4 Safety

Hematology, clinical chemistry will be performed at the local laboratory. Urine dipstick will be performed locally. Values considered clinically significant and/or IMP-related will be noted in the comments of the eCRF with reference to the date, study day and time (using the 24-hour clock), if applicable. The Investigator will record his/her medical opinion on the clinical significance of each laboratory value outside of the reference range both on the laboratory report and the eCRF. This decision will be based upon the nature and degree of the observed abnormality. The Investigator may choose to repeat any abnormal result, but only once, in order to rule out a laboratory error.

Clinically relevant deviations of laboratory test results from the normal range that occur during the course of the study or at a post-study examination will be reported. Repeated assessments are mandatory until their normalization or until the time course and reason of the underlying process are clearly determined. In case of doubt, Polyneuron's medical monitor must be contacted

Safety assessments are specified in the Section 8.2 Schedule of Assessments detailing when each assessment is to be performed.

8.4.1 Vital signs

This assessment of vital signs will include heart rate, systolic and diastolic blood pressure and core body temperature. The core temperature can be assessed orally, tympanically, or rectally. If patient is in hypothermia (< 35ºC), the temperature will be measured rectally, or via pulmonary artery thermistor catheters or bladder thermistor catheters.

8.4.2 1- lead Electrocardiogram (ECG)

The 1-lead ECG will be assessed for occurrence of or change to abnormal ECG patterns (change in 1-lead ECG "yes/no", clinically relevant ""yes/no"; only monitoring; recording and printout is not requested unless clinical significant abnormalities) and documented on the eCRF.

8.4.3 12- lead Electrocardiogram (ECG)

The 12-lead ECG recordings will be recorded as follows: normal or abnormal (with specification of finding reported in the eCRF), ventricular rate and RR (msec), PR (msec), QRS (msec), QT (msec) and QTc (with Bazett's and Fridericia's QT corrections) intervals.

The tracings will be printed out, clinically assessed, dated and signed.The patient's identification number, the date and time of the tracing must appear on the printout of the tracing.

8.4.4 Hematology

Hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differentials and platelet count will be measured. Coagulation tests including prothrombin time (PT) also reported as INR (International Normalised Ratio) and activated partial thromboplastin time (aPTT).

8.4.5 Clinical Chemistry

Albumin, alkaline phosphatase, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, gamma-glutamyl-transferase, lactate dehydrogenase, bicarbonate, calcium, magnesium, phosphorus, chloride, sodium, potassium, creatinine, creatine kinase, direct bilirubin, indirect bilirubin, total bilirubin, total cholesterol (including low density lipoprotein (LDL) and high density lipoprotein (HD) fractions), triglycerides, total protein, blood urea nitrogen (BUN) or urea, uric acid, amylase, lipase, and glucose will be measured in the local laboratory.

8.4.6 Urinalysis

Routine analysis at the hospital with a dipstick will be performed including glucose, protein, bilirubin, urobilinogen and nitrite.

8.4.7 Pregnancy and assessments of fertility

In any woman of childbearing potential, i.e. not > 1 year postmenopausal or surgically sterilized, a urine dipstick pregnancy test will be performed at screening, Day 28 (EOS in SAD) and on Day 56, 98 and 150 (EOS) in MAD. If the dipstick test indicates a positive result, a human chorionic gonadotropin (hCG) laboratory blood test will be performed to confirm pregnancy.

A woman of childbearing potential cannot be included in the study if any of the following occurs:

- The urine dipstick pregnancy test indicates a positive result and the pregnancy has been not yet been ruled out by the following hCG blood test.
- No urine dipstick pregnancy test has been performed at screening.
- The urine dipstick pregnancy test indicates a negative result, but a pregnancy is suspected by the Investigator based on clinical elements and cannot be ruled out by further investigation.

If a positive urine dipstick pregnancy test occurs at end-of-study, or if a pregnancy is suspected at any time during the study, a hCG blood test will be performed to confirm the pregnancy.

Refer to Section 9.4 Pregnancy reporting for details on pregnancy reporting.

8.4.8 Physical Examination

A complete physical examination should include the examination of general appearance, skin, neck (including thyroid), EENT, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological systems.

If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed (this information for all physical examinations must be included in the source documentation at the study site but it will not be recorded on the eCRF).

Significant findings that are present prior to informed consent are included in the CRF capturing Medical History. Significant findings observed after informed consent signature which meet the definition of an AE must be appropriately recorded on the appropriate CRF capturing AEs.

8.5 Pharmacokinetics

PK samples will be collected at the time points defined the Section 8.2 Schedule of Assessments.

PK samples will be obtained and evaluated in all patients at all dose levels.

PPSGG in serum will be determined by an ELISA/chromatography method. Concentrations below the lower limit of quantification (LLOQ) will be reported as “zero” and missing data will be labelled as such in the Bioanalytical Data Report.

Serum samples remaining after completion of the determination of PPSGG may be used for exploratory purposes to further characterize the PK or PK/PD of PPSGG. These analyses may include assessment of for example protein binding, or other bioanalytical purposes (e.g. cross check between different sites, stability assessment).

The following PK parameters of PPSGG will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.3 or later):

$AUC_{0\text{-}t}$, AUC_{inf}, C_{max}, CL, T_{max}, $T_{1/2}$ and V_{ss} and other PK parameters will be measured as appropriate. To denote parameters determined at steady state “ss” will be used.

8.6 Pharmacodynamics

Pharmacodynamic samples will be collected at the time points defined in the Section 8.2 Schedule of Assessments.

PD samples will be obtained and evaluated in all patients at all dose levels, including the placebo group.

PD assessments will include, but not be limited to: reduction of anti-MAG IgM antibody levels by at least 50% and time to anti-MAG IgM rebound (pre-treatment BTU), paraprotein levels (g/L), total IgM levels (g/L), and anti-HNK1) IgM titers.

PD evaluations will be performed primarily in the PD analysis set of patients, who completed the study according to the protocol (i.e., without serious deviations, such as more than 3 missing samples per profile). The PD population is specified in Section 11.1.

8.7 Efficacy assessments

Clinical efficacy assessments will be performed at screening, and Day 14, and EOS during SAD and during MAD then every 8 weeks. Efficacy assessments will include physical exam and the following scores:

Clinical efficacy outcome for the SAD and MAD phases

- ONLS score.
- Time to walk 10 meters.
- RODS.
- Ataxia score.

Efficacy endpoints for the MAD phase only

All the above and then additionally every 8 weeks from Day 14 the following ones:

- INCAT sensory sum score.
- Grip Strength.

8.8 Exploratory assessments

Endpoints for the MAD phase only

- Neurofilament light chain (NfL) to measure the degree of axonal damage.
- B-cell activating factor (BAFF).
- Indirect immunofluorescence on sciatic nerves.
- Motor Unit Number Index (MUNIX) in selected sites.

8.9 Other assessments

The study includes an optional biobank research component which requires a separate informed consent signature if the patient agrees to participate. As permitted by local governing regulations and by IRB/EC, it is required as part of this protocol that the Investigator presents these options to the patient.

The aim is to collect additional blood for a biobank to obtain serum and cells. This should help to better characterize the disease, its pathology and the antibody producing cells in anti-MAG neuropathy patients.

8.10 Use of residual biological samples

Any residual samples remaining after the protocol-defined analysis has been performed may be used for additional exploratory analysis. This may include, but is not limited to, using residual samples for protein binding, metabolite profiling, biomarkers of transporters or metabolic enzyme activity or other bioanalytical purposes (e.g., cross check between different sites and/or stability assessment). Given the exploratory nature of the work, the analytical method used for those assessments will not be validated. As such, the results from this exploratory analysis will not be included in the clinical study report.

9 Adverse Events and Serious Adverse Events

9.1 Definitions

9.1.1 Adverse Events

An **AE** is defined as any untoward medical occurrence in a clinical study patient to whom an IMP has been administered and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of an IMP, whether or not considered related to the IMP.

Events Meeting the AE definition

- Other safety assessments (e.g., physical examination, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events Not Meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient’s condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

9.1.2 Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death.

b. Is life-threatening.

   The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization:

   - In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for

observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications (except hospitalization due to planned study procedure) that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

9.1.3 Abnormal Laboratory Parameters

Abnormal laboratory findings (e.g., clinical chemistry, hematology, urinalysis) or other abnormal assessments (e.g., vital signs) will be judged by the investigator as "clinically significant/relevant" or "not clinically significant/relevant" based on the investigator's medical and scientific expertise.

Clinically significant abnormal findings or other clinically significant abnormal assessments that are detected during the clinical study or that were present at baseline and significantly worsen during the study will be recorded as an AE. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with a medical condition already documented as medical history or AE will not be recorded separately, unless judged by the investigator as more severe than expected for the patient's condition.

If during treatment with the IMP abnormal laboratory findings occur which were not present before the treatment started and which were judged by the investigator as "clinically relevant" and recorded as AE in the eCRF, further clinical or laboratory tests must be carried out by the investigator until the values return to the normal range or until a plausible explanation is given by the investigator (e.g., disease) of the change of the laboratory values.

9.1.4 Overdose, Abuse, Misuse, Medication Errors and other Uses Outside what is foreseen in this Protocol

There are situations that may present a risk to the patients or conduct of the study even if no immediate AE is noted. Such events (i.e., drug overdose, drug abuse, drug misuse, medication errors, and other uses outside what is foreseen in the protocol) should be reported in the same format and within the same timelines as a SAE even if they may not result in an adverse outcome.

Overdose: Administration of a quantity of an IMP given per administration or cumulatively that is above the maximum recommended dose according to the protocol dosing instructions or authorized product information. Clinical judgment should always be applied.

Abuse: Persistent or sporadic, intentional excessive use of an IMP that is accompanied by harmful physical or psychological effects.

Misuse: Situations where the IMP is intentionally and inappropriately used not in accordance with the protocol dosing instructions or authorized product information.

Medication error: Unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

9.1.5 Recording and Follow-Up of Adverse Events and/or Serious Adverse Events

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information on the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Polyneuron/Clinipace Pharmacovigilance in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by Polyneuron/Clinipace Pharmacovigilance. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to Polyneuron/Clinipace Pharmacovigilance.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will assess intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- **Mild:** An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- **Moderate:** An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe:** An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the causal relationship between study treatment and each occurrence of each AE/SAE according to the available data as:
    - **Related:** There is a reasonable causal relationship, which means that there are facts, evidence, and/or arguments to suggest a causal relationship. The AE could medically (pharmacologically/clinically) be attributed to the IMP in this study.
    - **Not related:** There is no reasonable causal relationship, which means that there is no evidence to suggest a causal relationship. The AE could not medically (pharmacologically/clinically) be attributed to the IMP in this study.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the IB in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to Polyneuron/Clinipace Drug Safety. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Polyneuron/Clinipace Drug Safety.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Events and Serious Adverse Events

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Polyneuron/Clinipace Pharmacovigilance to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a patient dies during participation in the study, the investigator will provide Polyneuron/Clinipace Pharmacovigilance with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to Polyneuron/Clinipace Pharmacovigilance within 24 hours of receipt of the information.

9.1.6 Reporting of Serious Adverse Events

Serious Adverse Events Reporting to Polyneuron/Clinipace Drug Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Polyneuron/Clinipace Drug Safety will be the electronic data collection (EDC) tool.
- The site will enter the SAE data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor by telephone.

SAE Reporting to Sponsor/Clinipace Pharmacovigilance via Paper eCRF only if EDC system is unavailable

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Sponsor/Clinipace Pharmacovigilance within 24 hours. Fax number: +49 6196 7709-112.
- In rare circumstances, and in the absence of facsimile equipment, notification by email is acceptable. Reports should be emailed to: Safety@clinipace.com

9.1.7 Rapid communication plan of serious adverse events and suspected unexpected serious adverse reactions (SUSARs) between the sponsor, the investigators of all sites and the patients

If an event is reported as 'serious' in the eCRF database, an automatic SAE notification e-mail will inform the CRO's Pharmacovigilance team and the Sponsor. In the event a SUSAR is confirmed, this will be reported in all countries where the trial is approved, according to local requirements. SUSARs associated with the IMP undergo expedited reporting to Regulatory Authorities, ECs/ Autonomous Communities (for Spain) and investigators according to the following timelines:

SUSARs: within 15 calendar days

Fatal or life threatening SUSAR: within 7 calendar days

SAE: Annual report

If the CRO's Pharmacovigilance team is notified of very severe, unanticipated, suspected adverse reactions during the study (e.g., anaphylactic reaction to IMP, Stevens Johnson syndrome, acute organ failure), the report will be rapidly escalated to the Pharmacovigilance management team and the Sponsor Medical Monitor for immediate action.

9.2 Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information

All SAEs and AEs will be collected from the signing of the ICF until the end of the study including Follow-up.

All SAEs will be recorded and reported to Polyneuron or designee immediately and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to Polyneuron within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Polyneuron/Clinipace Pharmacovigilance.

9.3 Documentation and Reporting of Adverse Events

The occurrence of AEs will be assessed by non-directive questioning of the patient at each visit. Further, AEs reported by the patient during or between visits or detected through observation, physical examination, laboratory test or other assessments will be documented. AEs that were ongoing at the end of the previous visit should be queried for resolution or change in severity or seriousness until resolution or until Follow-up, whichever comes first.

The patients will be instructed that they must report any AE, patient complaints or objective changes in their well-being to the investigator or the clinic personnel, regardless of the perceived relationship between event and IMP.

All AEs must be documented in the patient's eCRF. If in one patient the same AEs occur on several occasions, then the AE in question must be documented and assessed as new each time.

For any AE, the following data must be recorded on the eCRF:

- **Description of the AE** in medical terms (preferably: diagnosis), not as reported by the patient.

  Note: Every attempt should be made to describe the AE in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent atypical or extreme manifestation of the diagnosis, in which case they should be reported as separate AE.

- **Date of onset** (start date and time) and **date of recovery** (stop date and time).
- **Intensity of the AE** as assessed by the investigator according to the following definitions
    - **Mild**: The AE is easily tolerated and does not interfere with routine activities/ normal functioning of the patient.
    - **Moderate**: The AE causes discomfort and affects the patient's normal activities, i.e., interferes with routine activities, but are not hazardous, uncomfortable or embarrassing to the patient.
    - **Severe**: The AE causes considerable interference with the patient's usual activities, e.g., inability to work.
- **Causal relationship** between the occurrence of an AE and the administration of the IMP as assessed by the investigator according to the available data as:
    - **Related**: There is a reasonable causal relationship, which means that there is evidence to suggest a causal relationship. The AE could medically (pharmacologically/clinically) be attributed to the IMP in this study.
    - **Not related**: There is no reasonable causal relationship, which means that there is no evidence to suggest a causal relationship. The AE could not medically (pharmacologically/clinically) be attributed to the IMP in this study.
- **Actions taken on the IMP**
    - e.g., corrective treatment.
- **Outcome**
    - **Recovered/ resolved**: The AE had stopped completely, and the stop date is recorded.

- **Recovered/ resolved with sequelae**: No further changes are expected due to the AE and residual symptoms are assumed to persist.
- **Not recovered/ not resolved**: The AE is ongoing; the event is followed up.
- **Fatal**: The patient died as a consequence of the AE; date of death is recorded as stop date of the AE.
- **Unknown**: Unknown to the investigator (e.g., patient lost to follow-up).

- **Seriousness** according to the definition given in Section 9.1.2 Definition of Serious Adverse Events.

9.3.1 Notification of Serious Adverse Events

Prompt notification by the investigator to the Polyneuron/Clinipace Pharmacovigilance of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study treatment under clinical investigation are met.

The Polyneuron/Clinipace Pharmacovigilance has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Polyneuron/Pharmacovigilance will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

Any SAE will be reported immediately (i.e., within 24 hours after receipt) by the investigator to the Drug Safety of Polyneuron/Pharmacovigilance (for details, see Section 9.1.6 Reporting of Serious Adverse Events). The initial SAE report must be as complete as possible. The report should include at least the following information:

- **Patient identification** (e.g., assigned patient number, year of birth).
- **Identifiable reporting source** (e.g., site number, name of investigator, telephone number, fax and/ or e-mail address).
- **Identification of the clinical study** (e.g., study code) or IMP.
- **SAE term** (preferably: diagnosis; if possible, also including description and course of the SAE).
- **Seriousness criterion** according to the definition given in Section 9.1.2 Definition of Serious Adverse Events.
- **Causal relationship** between the occurrence of an AE and the administration of the IMP as assessed by the investigator according to the available data. If based on follow-up information the investigator changes his/her initial causality assessment, this should be submitted to sponsor/CRO Drug Safety immediately (i.e., within 24 hours after receipt).
- **Signature of the investigator**

If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying the Polyneuron/Clinipace Pharmacovigilance of the event and completing the SAE report form. Information not available at the time of the initial report (e.g., an end date for the AE or laboratory values received after the report) will be documented on a follow-up SAE report form and reported immediately (i.e., within 24 hours after receipt) to Polyneuron/Clinipace Pharmacovigilance.

Additional information not covered by the SAE report form, including copies of hospital reports, autopsy reports or other relevant documents, will be requested, if necessary, by either the

clinical monitor or the Polyneuron/Clinipace Pharmacovigilance for a detailed description and a final evaluation of the case. All personal identifiers (e.g., name, detailed birth of date, address) must be pseudonymized prior to submission by blinding personal data and using the assigned identification code of the study patient.

The investigator should institute any supplementary investigations of SAE based on their clinical judgment of the likely causative factors. This may include seeking further opinion from a specialist in the field of the AE.

If the SAE information is incomplete or inconsistent and directly affects the sponsor's reporting obligation to health authorities, the Polyneuron/Clinipace Pharmacovigilance may directly contact the investigator for clarification.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary. The sponsor will be responsible for notification of the competent authorities, Ethics Committees (ECs) and investigators in the event of SUSAR and any other important safety issues requiring expedited reporting.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Polyneuron/Clinipace Pharmacovigilance will review and then file it along with the IB, and will notify the IRB/IEC, if appropriate according to local requirements.

9.4 Pregnancy reporting

No embryo-fetal development studies have been performed. Therefore, this study excludes enrolment of women of child-bearing potential unless they are using highly effective methods of contraception, thus pregnancy is not an expected outcome for any female study patient. However, in the case that a pregnancy in a female study patient should occur, please follow the below reporting guidelines.

To ensure patient safety, each pregnancy occurring after signing the informed consent must be **reported to Polyneuron within 24 hours** of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Polyneuron. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on an SAE form.

The study drug must be discontinued, though the patient may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The patient may continue all other protocol assessments.

9.5 Early phase safety monitoring

The Investigator will monitor AEs in an ongoing manner and inform Polyneuron of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing Polyneuron and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Polyneuron and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, Polyneuron will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

10 Quality assurance and quality control

All patient data relating to the study will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IEC review, and regulatory agency inspections and provide direct access to source data documents.

This study will be monitored regularly by Clinipace according to ICH-GCP and their monitoring SOPs. Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

Clinipace is responsible for the data management of this study including data quality checking.

Polyneuron assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

Monitoring will be done by personal visits from a representative of Clinipace. Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patient are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, International Council on Harmonization (ICH) GCP, and all applicable regulatory requirements.

Patient confidentiality must be maintained in accordance with local requirements. The monitoring standards also require full verification for the presence of ICF, adherence to the inclusion/exclusion criteria, documentation of SAEs, and recording of the main efficacy and safety endpoints.

In addition to the monitoring visits, frequent communications (letter, telephone, and fax) by the clinical monitor will ensure that the investigation is conducted according to the clinical protocol and regulatory requirements.

The results of monitoring visits will be documented in monitoring reports. Issues arising will be escalated and dealt with in a timely manner. The escalation process is defined in the respective SOPs of Clinipace.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion. If source documents are not durable as long as needed (e.g. printouts on thermo labile paper), they must be preserved as certified copy. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1 Data collection

Data capture and management will be conducted using the Clinipace clinical management and EDC/eCRF system. The processes and responsibilities of data collection, management and quality assurance will be specified in the Data Management Plan.

All applicable study data collected on each patient will be entered by approved site personnel into the eCRF. Instructions for the completion and submission of eCRFs will be provided to the sites in a separate document.

Authorized personnel will verify all data entered into eCRFs for completeness and accuracy with reference to the source documents and records and will issue data queries to correct missing data or discrepancies found against the source within the EDC system. Data validation will consist of automated and manual edit checks that are created directly in the EDC system. Edit checks will be executed on all data points defined and documented by the study team and data management will be able to issue manual queries as needed to the eCRF. Study metrics will be reported from the EDC system. Only authorized site personnel will be able to enter/modify/correct data in the eCRF.

10.2 Independent Data Monitoring Committee

An IDMC will review the safety data and anti-MAG antibodies results and will provide its recommendations to Polyneuron.

The membership of the IDMC and the responsibilities of the IDMC and Polyneuron will be defined in a separate document entitled the “Independent Data Monitoring Committee Charter”. The IDMC Charter will include information about data flow, purpose and timing of IDMC meetings, guidance in the decision-making process, communication strategy, procedures for ensuring confidentiality, and procedures to address conflicts of interest.

11 Data analysis

The analysis will be conducted on all patients at the time the study ends. Any data analysis carried out independently by the investigator should be submitted to Polyneuron at least 30 days before submission for publication or presentation to enable review for Intellectual Property matters. Descriptive statistics (number (N), mean, SD, median and ranges for continuous variables, frequencies and percentages for categorical variables) will be provided by treatment group and/or by visit, if applicable. All data will be listed by patient, treatment group and, where applicable, by visit. Full details of the analyses will be provided in the Statistical Analysis Plan (SAP).

11.1 Analysis sets (study populations)

The statistical analysis will be based on separate analysis populations, defined as follows:

The two study phases SAD and MAD described in this protocol form an exploratory investigation without any formal statistical hypotheses. All results will be interpreted descriptively only from the following analyses sets:

Safety population (SP): All patients who receive at least one dose of study medication. The SP will be the primary analysis set for the safety and tolerability analyses.

Intent-to-treat (ITT) population: all patients who were enrolled. The ITT population will be used as analysis set to confirm efficacy.

Per-protocol (PP) population: all patients, who meet the inclusion/exclusion criteria, received full-course of the study drug as per randomization during MAD and have completed the main relevant visits. Aat least 1 visit, 1 week and 1 month during the SAD after dosing is needed to assess biomarker and scores. During the MAD phase, at least 1 visit 1 month after the last dosing, for safety and efficacy assessment and who satisfactorily completed a PD blood sampling period without any major protocol violations which would render the data unreliable. The PP population will constitute the primary analysis set for the PD and PK, and efficacy analyses...

Pharmacokinetic (PK) population: all patients who satisfactorily completed a PK blood sampling period without any major protocol violations which would render the data unreliable.

Pharmacodynamic (PD) population: all patients who satisfactorily completed a PD blood sampling period without any major protocol violations which would render the data unreliable.

11.2 Statistical hypothesis

The two study phases SAD and MAD described in this protocol form an exploratory investigation without any formal statistical hypotheses. All results will be interpreted descriptively only.

11.3 Protocol Deviation

Important deviations from the protocol, such as deviations from inclusion and exclusion criteria, relevant deviations in sampling times or from the planned time schedule of safety assessments will be reported in the clinical study report.

If an unexpected important deviation from the study protocol occurs, the investigator will consult Polyneuron to make a decision on how this deviation can be handled.

11.4 Patient demographics and other baseline characteristics

All data for background and demographic variables will be listed by dose group and patient. Summary statistics will be provided by dose group.

Relevant medical history, current medical conditions and other relevant information will be listed by treatment group and patient.

11.5 Treatments

Data for study drug administration and concomitant therapies will be summarized by dose group.

Total duration of time on study drug (Exposure) and reasons for discontinuation of study drug will be summarized by treatment group.

11.6 Analysis of safety

Safety endpoints will be summarized by treatment:

- Frequency, duration, severity and outcome of TEAEs.
- Changes in physical examination.
- Changes in clinical signs and scores.
- Signs of IRRs.

- Vital signs and ECGs.
- Hematology, clinical chemistry and urinalysis.

TEAEs are all AEs that that first appear during or after treatment with the IMP including those that worsened relative to the pre-treatment state.

Signs of IRRs include clinical signs and symptoms, changes in diastolic or systolic blood pressure, heart rate, oxygen saturation, and skin reactions or local reactions at the infusion site, which are monitored during and shortly after the administration of the IMP.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 22.0 or higher and summarized in frequency tables according to Preferred Term (PT) and System Organ Class (SOC). AEs will also be summarized according to their severity and causality. When an AE occurs more than once in the same patient, maximal severity and strongest causality will be counted. All SAEs and AEs leading to premature withdrawal from the study will be listed. Laboratory variables will be examined using mean changes from baseline. Laboratory values will also be categorized according to CTCAE toxicity grade and tabulated by their highest on-study toxicity grade. Shift tables will present numbers and percentages of patients with high / normal / low (or normal / abnormal) laboratory results at baseline and the last measurement available. Use of concomitant medications and of rescue antibiotics will be summarized.

Vital signs

All vital signs data will be listed by treatment, patient, and time point and abnormalities will be flagged. Summary statistics will be provided by treatment and time.

To assess the effect of PPSGG on blood pressure after dosing with PPSGG, blood pressure and heart rate on each infusion day (see Schedule of Assessments) expressed as change from baseline will be summarized. This represents the blood pressure at the approximate time of C_{max} after first dose and at steady state. The relationship between changes in blood pressure and heart rate and the C_{max} concentrations will also be investigated graphically.

ECG

All ECG data will be listed by treatment, patient, and time point and abnormalities will be flagged. Summary statistics will be provided by treatment and time and the number of patients with values above key threshold values will be displayed.

Clinical laboratory evaluations

All laboratory data will be listed by treatment, patient and time point and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and time point.

Adverse events

All information obtained on AEs will be displayed by treatment and patient.

The number and percentage of patients with AEs will be tabulated by SOC and PT with a breakdown by treatment. A patient with multiple AEs events within a SOC is only counted once towards the total of this SOC.

Summaries of SAEs will be provided in a similar manner.

Further displays of AEs may be produced in order to appropriately describe the outcomes seen in this trial.

11.6.1 Sample Handling procedures

All the safety analysis will be performed in local laboratory.

Sample handling is described separately in a Laboratory Manual.

Each sample will be labelled to indicate not less than: Polyneuron, study number, patient number, and sampling time.

All sample handling procedures, including the time of each sample collection, the time of placement into frozen storage (at the end of the sample workup), and the date of transfer or shipment of the samples to the responsible analyst will be documented in detail. Any missing blood draws must be reported in the eCRF. The exact time (using the 24-hour clock) of sample collection and possible problems occurring during the sampling will be entered in the respective sections of the eCRF.

All samples will be stored for a period of 6 months after submission of the final report to Polyneuron. If no separate contract for further storage has been agreed by Polyneuron, the samples will then be destroyed or shipped to Polyneuron. Both, return and destruction of samples requires Polyneurons approval.

Each sample will be labelled to indicate the study number, patient number, period number (MAD phase only), and sampling time.

All sample handling procedures, including the time of each sample collection, the time of placement into frozen storage (at the end of the sample workup), and the date of transfer or shipment of the samples to the responsible analyst will be documented in detail.

After sampling, blood and urine samples will be worked up and analyzed in a central laboratory, all results will be judged by a physician individually and commented as follows:

- Values within the reference ranges will not be commented. A '*' representing the value will be plotted within the brackets representing the reference range.
- For values slightly outside the reference ranges without clinical relevance a '*' representing the value will be plotted outside the brackets representing the reference range.
- For values outside the reference ranges with major deviation and/or possible pathological relevance a '*' representing the value will be plotted outside the brackets representing the reference range. In addition, the respective parameter will be shaded.

For all findings with major deviation and/or possible pathological relevance, follow-up examinations will be carried out until the deviation returns to normal or the absence of pathological relevance can be confirmed. If a deviation considered clinically relevant has not returned to a normal or not clinically relevant value when it is checked during the screening laboratory tests, the patient will not be included in the study.

The investigator has to decide whether a laboratory abnormality represents an adverse event

11.7 Analysis of Pharmacodynamics

In addition to the secondary objective, the assessmentof the effect of PPSGG on reduction of anti-MAG IgM levels (in BTU), time to anti-MAG IgM rebound (compare to pre-treatment BTU), following secondary variables will be analyzed: paraprotein levels (g/L), total IgM levels (g/L), and anti-HNK-1 IgM titers. Descriptive summary statistics will be provided by dose and dosing

frequency. Appropriate transformations will be detailed in the SAP. Estimates of the differences between each does of PPSGG and placebo will be calculated.

11.8 Analysis of Pharmacokinetics

PPSGG concentration data will be listed by dose, patient and time point (described in Section 8.6). Descriptive summary statistics will be provided by treatment and time, including the frequency (n, %) of samples collected. Sample concentrations below the LLOQ will be reported and used in PK calculation as zero.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. An exception to this is T_{max}. Since T_{max} is generally evaluated by a nonparametric method, median values and ranges will be given for this parameter. A geometric mean will not be reported if the dataset includes zero values.

The relationship between doses of PPSGG and the PK parameters AUC and C_{max} will be explored and used to calculate PPSGG half-life (T1/2, volume of distribution (Vd) and CL rate. Descriptive summary statics will also be provided for $T_{1/2}$, Vd and CL.

Graphical methods will be employed to show mean and individual concentration-time profiles and dose-exposure proportionality.

11.9 Analysis of exploratory variables (if applicable)

Statistical analysis for exploratory variables will be described in more detail in the Statistical Analysis Plan.

11.9.1 Exploratory endpoints

- NfL to measure the degree of axonal damage.
- BAFF.
- Indirect immunofluorescence on sciatic nerves.
-
- MUNIX in selected sites

All biomarker data will be listed by treatment, patient, and time. Summary statistics will be provided by doses and time. Change from baseline until EOS will be summarized.

Graphical measures will be used to explore relationships between PPSGG treatment and biomarkers.

11.10 Sample size calculation

The sample size per cohort in this SAD and MAD study is representative of other FiH studies and based on feedback from EMA for a scientific advice.

It is anticipated that the specified number of patients should complete the study in accordance with this protocol. An insufficient number of evaluable cases might impair the aim of the study.

To allow for a drop-out rate of up to 20% in MAD phase, 30 patients will be enrolled with the aim of having at least 24 patients complete each phase.

11.11 Interim analyses

No formal interim analysis is planned for this study. Safety data will be gathered and reviewed by the IDMC on continuous basis. The data will be frozen after the SAD phase to define the schedule and doses for the MAD phase based on the SAD data as described previously.

12 Regulatory and Ethical considerations

12.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki.

12.2 Responsibilities of the investigator and Institutional Review Board/Independent Ethics Committee

Before the start of the study Polyneuron or authorized applicant will apply for approval for the performance of the study at the Competent Authority. The sites will apply for approval for the performance of the study at the respective EC. All documents required by the EC and by the Competent Authority will be submitted.

Any notification / submission has to be dated and to contain sufficient information to identify the respective protocol.

The study will only be started after receipt of the written approval of the respective EC and Competent Authority.

The Principal Investigator and Clinipace are responsible for maintaining the approval documents in the study documentation files.

The Principal Investigator or Clinipace will report promptly to the EC new information that may adversely affect the safety of the patients or the conduct of the trial.

Polyneuron (or authorized applicant), should submit a written report about the safety of the patients as well as a list of occurred suspected serious adverse drug reactions caused by the investigational medicinal product of the clinical study to the EC and the Competent Authority annually, or more frequently if requested by the EC or the Competent Authority.

A declaration of the end of trial should be forwarded by Polyneuron (or authorized applicant), to the Competent Authority and to the EC within 90 days after the study has been completed or in the event of premature termination of the study within 15 days.

Polyneuron (or authorized applicant) should provide a summary of the clinical study report to the EC and Competent Authority within 1 year after completion of the study

The reporting to the EC and the Competent Authority is clearly defined in the Quality Agreement and responsibility list for clinical study.

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation) informed consent.

12.3 Informed consent procedure

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Clinipace will provide to investigators a proposed ICF that complies with the ICH E6 GCP guideline and regulatory requirements and is considered appropriate for this study. The procedures set out in the main consent form concerning the storage, maintenance of privacy, and release of the data or specimens for the main study will also be adhered to for any future research. Any changes to the proposed consent form suggested by the investigator must be agreed to by Polyneuron before submission to the IRB/IEC.

The investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.
Patients must be informed that their participation is voluntary. Patients will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient.

Information about potential side effects in humans about the investigational drug can be found in the IB. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and then must be discussed with the patient.

Ensure patients are informed of the contraception requirements outlined in the Section (Exclusion criteria) and in Section (Contraception requirements).

A separate consent for an optional Biobanking component will be obtained. The Investigator presents this option to the patient, as permitted by local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in this biobank collection will in no way affect the patient’s ability to participate in the main research study.

A copy of the approved version of all consent forms must be provided to the Polyneuron monitor after IRB/IEC approval.

12.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

12.5 Quality Control and Quality Assurance

Audits of investigator sites, vendors, and Polyneuron systems are performed or overseen by Polyneuron Pharma Auditing and Compliance Quality Assurance (or contract research organization [CRO] working on behalf of Polyneuron), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk-based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Polyneuron processes.

13 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study patients. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Polyneuron and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

13.1 Protocol Amendments

Neither the investigator nor the sponsor will alter this clinical study protocol without obtaining the written agreement of the other party. Once the study has started, amendment should be made only in exceptional cases. The changes then become part of the clinical study protocol.

Substantial amendment, i.e., changes in the clinical study protocol which may have a significant impact on the safety of the patients, or on the scientific value of the study, or on the conduct or management of the study, may not be implemented without a favorable opinion of the ECs/IRBs unless the changes consist of urgent safety measures to protect study patients. In such a case, approval must be obtained as soon as possible after implementation.

Amendments which are minor and/or refer to changes regarding logistical and administrative aspects of the study (i.e., change in telephone numbers) are always sent to the ECs for information.

13.2 COVID-19 pandemic

As a result of the ongoing COVID-19 pandemic, several challenges have been identified as having an impact on the PN-1007-001 trial. These include restriction of possible visits to investigational sites, more importantly, assurance of patient safety during the pandemic. In addition, monitoring activities are impacted by investigator site staff availability and social distancing rules. These challenges could have an impact on the conduct of the trial, such as the completion of trial visits, safety and efficacy assessments, and compliance with required study procedures.
In response to the noted challenges resulting from the pandemic, Polyneuron has developed specific measures taking into account the published guidelines from Regulatory Authorities, to ensure the continuity of safety oversight and IMP dosing, while keeping patient confidentiality for enrolled patients who are unable to attend study visits in person.
It is important to note that the default study design and procedures are unchanged. This section provides only recommendations when a COVID-19-related deviation is unavoidable, on how to handle and document the exception**.**

Study Medication and Administration
In the SAD part of the study, dosing for patients that have passed all screening assessments and recruitment of new patients may be suspended. The decision to suspend these activities would be based on:

- The prevalence of Covid-19 infection in both the geographical area of investigational site and the residence of the patients concerned
- Government imposed restrictions

- Availability of study staff

Screening, recruitment and dosing may continue/resume when the risk to study participants is considered, by both the investigator and sponsor, to be no greater than minimal.
For the MAD it will depend on how many doses the patients had received and the COVID-19 situation. The protocol will be updated with the current state of COVID-19 knowledge.

Study Visits
In the event a patient is unable to attend a scheduled study visit onsite due to the COVID-19 pandemic, site personnel should endeavour, wherever possible, to contact the patient by video or telephone conference, for discussions focused on their safety including the review of the patient's RODS questionnaire, and change in co-medications, if applicable. Contact with patient should take place before any safety lab collection is instituted. Additionally, the visit should be rescheduled to a later date, if possible, within the timeframe provided below (for each visit), from the originally scheduled visit date. Any change to the schedule needs to be properly documented in the eCRF. The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study. The investigator should show "due diligence" by documenting in the source documents the steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. At least 3 attempts should be documented.
Subsequent visits should follow originally planned protocol schedule.
Visits, which cannot be performed according to the original schedule due to COVID-19, should be planned to maintain a similar time duration between visits:
approximately 6 to 8 days between visits up to Day 56,
after Day 56, the current schedule of visits will apply.
In the event of revised visit dates becoming very close together, the investigator will advise if a single visit should be performed. The Sponsor may be consulted if needed.
Patients should not be discontinued from the study if a scheduled visit is delayed or missed due to COVID-19.

Study Assessments
In case a scheduled study visit cannot be performed on site due to COVID-19 pandemic, the following study assessments should be performed by video or telephone call, and as close as possible to the scheduled date.

- Assessments of adverse events (AE); in the event of a suspected/confirmed case of COVID-19, the site personnel should notify the Sponsor Medical Monitor as soon as possible
- Review of concomitant medications

In exceptional circumstances Safety laboratory evaluations (hematology, blood chemistry) if scheduled and PD
Blood samples may be collected and analysed either at a local physician's office, local laboratory, or by a visiting nurse. The best option for a particular patient will be discussed on a case by case and country by country basis between sponsor and investigator. All measures taken need to be properly documented. Safety laboratory results are to be provided to the PI/designee to allow for the assessment of clinical significance. Additional blood samples for PD should be frozen and shipped to the investigator's site.

All results from local lab assessments must be available in the source documents. In the event there is a laboratory result that fulfils the criteria of an adverse event, such adverse event must be entered into the eCRF and a Serious Adverse Event (SAE) / Adverse Event of Special Interest (AESI) form completed, if the event is serious or qualifies as AESI. The protocol required laboratory assessments collected at each visit are referenced in Section 8.4.4 and 8.4.5 of the protocol, respectively.

Discontinuation/Withdrawal
Patient withdrawal due to reasons attributable to the COVID-19 pandemic will be recorded on the eCRF as per the updated eCRF completion guidelines.

Monitoring
Remote site monitoring visits will be conducted as per Monitoring Plan.
However, remote Source Data Verification (SDV), will not be conducted as it may potentially expose confidential patient information and require deviations from data protection regulations (e.g. GDPR).

14 References

1. Latov N, Braun PE, Gross RB et al. Plasma cell dyscrasia and peripheral neuropathy: identification of the myelin antigens that react with human paraproteins. Proc. Natl. Acad. Sci. U. S. A. 1981; 78(11):7139–7142.

2. Braun PE, Frail DE, Latov N. Myelin-associated glycoprotein is the antigen for a monoclonal IgM in polyneuropathy. J. Neurochem. 1982; 39(5):1261–1265.

3. Steck AJ, Stalder AK, Renaud S. Anti-myelin-associated glycoprotein neuropathy. Curr. Opin. Neurol. 2006; 19(5):458–463.

4. Rison RA, Beydoun SR. Paraproteinemic neuropathy: a practical review. BMC Neurol. 2016; 16:13.

5. Ritz MF, Erne B, Ferracin F et al. Anti-MAG IgM penetration into myelinated fibers correlates with the extent of myelin widening. Muscle Nerve 1999; 22(8):1030–1037.

6. Dalakas MC. Pathogenesis of immune-mediated neuropathies. Biochim. Biophys. Acta 2015; 1852(4):658–666.

7. Talamo G, Mir MA, Pandey MK et al. IgM MGUS associated with anti-MAG neuropathy: a single institution experience. Ann. Hematol. 2015; 94(6):1011–1016.

8. Vallat J-M, Magy L, Ciron J et al. Therapeutic options and management of polyneuropathy associated with anti-MAG antibodies. Expert Rev. Neurother. 2016; 16(9):1111–1119.

9. Nobile-Orazio E, Baldini L, Barbieri S et al. Treatment of patients with neuropathy and anti-MAG IgM M-proteins. Ann. Neurol. 1988; 24(1):93–97.

10. Lunn MP, Nobile-Orazio E. Immunotherapy for IgM anti-myelin-associated glycoprotein paraprotein-associated peripheral neuropathies. Cochrane Database Syst. Rev. 2016; 10:CD002827.

11. Dalakas MC. Advances in the diagnosis, immunopathogenesis and therapies of IgM-anti-MAG antibody-mediated neuropathies. Ther. Adv. Neurol. Disord. 2018; 11:1756285617746640.

12. Pestronk A, Florence J, Miller T et al. Treatment of IgM antibody associated polyneuropathies using rituximab. J. Neurol. Neurosurg. Psychiatry 2003; 74(4):485–489.

13. Benedetti L, Briani C, Franciotta D et al. Long-term effect of rituximab in anti-mag polyneuropathy. Neurology 2008; 71(21):1742–1744.

14. Dalakas MC. Pathogenesis and Treatment of Anti-MAG Neuropathy. Curr. Treat. Options Neurol. 2010; 12(2):71–83.

15. Latov N. Diagnosis and treatment of chronic acquired demyelinating polyneuropathies. Nat. Rev. Neurol. 2014; 10(8):435–446.

16. Quarles RH, Weiss MD. Autoantibodies associated with peripheral neuropathy. Muscle Nerve 1999; 22(7):800–822.

17. Tatum AH. Experimental paraprotein neuropathy, demyelination by passive transfer of human IgM anti-myelin-associated glycoprotein. Ann. Neurol. 1993; 33(5):502–506.

18. Crickx E, Weill JC, Reynaud CA, et al. Anti-CD20-mediated B-cell depletion in autoimmune diseases: successes, failures and future perspectives. Kidney Int. 2020 Jan 30. pii: S0085-2538(20)30108-3. doi: 10.1016/j.kint.2019.12.025. [Epub ahead of print].

19. Svahn J, Petiot P, Antoine JC, et al. Anti-MAG antibodies in 202 patients: clinicopathological and therapeutic features. J Neurol Neurosurg Psychiatry. 2018 May;89(5):499-505. doi: 10.1136/jnnp-2017-316715. Epub 2017 Oct 25.

20. Polyneuron; PN-1007 (PPSGG) IB, version 2, April 2020.

21. Herrendorff R, Hänggi P, Pfister H et al. Selective in vivo removal of pathogenic anti-MAG autoantibodies, an antigen-specific treatment option for anti-MAG neuropathy. Proc. Natl. Acad. Sci. U. S. A. 2017; 114(18):E3689–E3698.

22. Katopodis AG, Warner RG, Duthaler RO et al. Removal of anti-Galalpha1,3Gal xenoantibodies with an injectable polymer. J. Clin. Invest. 2002; 110(12):1869–1877.

23. Cook L, Macdonald DHC. Management of paraproteinaemia. Postgrad. Med. J. 2007; 83(978):217–223.

24. Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. [http://www.fda.gov/regulatory-information/search-fda-guidance-documents/estimating-maximum-safe-starting-dose-initial-clinical-trials-therapeutics-adult-healthy-volunteers].

25. Strategies to identify and mitigate risks for first-in-human early clinical trials with investigational medicinal products. [https://www.ema.europa.eu/en/strategies-identify-mitigate-risks-first-human-early-clinical-trials-investigational-medicinal].

26. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of paraproteinemic demyelinating neuropathies. Report of a Joint Task Force of the European Federation of Neurological Societies and the Peripheral Nerve Society--first revision. J. Peripher. Nerv. Syst. JPNS 2010; 15(3):185–195.

27. F. Alexis, E. Pridgen, L. K. Molnar, O. C. Farokhzad, Factors affecting the clearance and biodistribution of polymeric nanoparticles. Mol Pharm 5, 505-515 (2008).

28. M. Liu, H. Li, G. Luo, Q. Liu, Y. Wang, Pharmacokinetics and biodistribution of surface modification polymeric nanoparticles. Arch Pharm Res 31, 547-554 (2008).

15 Appendices

15.1 Common Terminology Criteria for Adverse Events v5.0 (CTCAE)

Publish Date: November 27, 2017

Introduction

The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

SOC

System Organ Class (SOC), the highest level of the MedDRA1 hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v5.0 term is a MedDRA LLT (Lowest Level Term).

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1

Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2

Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental Activities of Daily Living (ADL)*.

Grade 3

Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

Grade 4

Life-threatening consequences; urgent intervention indicated. Grade 5 Death related to AE. A Semi-colon indicates ‘or’ within the description of the grade. A single dash (-) indicates a Grade is not available. Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Definitions

A brief Definition is provided to clarify the meaning of each AE term. A single dash (-) indicates a Definition is not available.

Navigational Notes

A Navigational Note is used to assist the reporter in choosing a correct AE. It may list other AEs that should be considered in addition to or in place of the AE in question. A single dash (-) indicates a Navigational Note has not been defined for the AE term.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

15.2 Overall Neuropathy Limitations Scale (ONLS)

Name:
Date:

Overall Neuropathy Limitations Scale (ONLS)

Instructions: The examiner should question **and** observe the patient in order to determine the answers to the following questions. Note should be made of any other disorder other than peripheral neuropathy which limits function at the foot of the page.

ARM SCALE

Does the patient have any symptoms in their hands or arms, eg tingling, numbness or weakness? **Yes** ☐ **No** ☐
(if "no", please go to "legs" section)

Is the patient affected in their ability to:	Not affected	Affected but not prevented	Prevented
Wash and brush their hair	☐	☐	☐
Turn a key in a lock	☐	☐	☐
Use a knife and fork together (or spoon, if knife and fork not used)	☐	☐	☐
Do or undo buttons or zips	☐	☐	☐
Dress the upper part of their body excluding buttons or zips	☐	☐	☐

If all these functions are prevented can the patient make purposeful movements with their hands or arms? Yes ☐ No ☐ Not applicable ☐

Arm Grade
0=Normal
1=Minor symptoms in one or both arms but not affecting any of the functions listed **SCORE=____**
2=Disability in one or both arms affecting but not preventing any of the functions listed
3=Disability in one or both arms preventing at least one but not all functions listed
4=Disability in both arms preventing all functions listed but purposeful movement still possible
5=Disability in both arms preventing all purposeful movements

LEG SCALE

	Yes	No	Not applicable
Does the patient have difficulty running or climbing stairs?	☐	☐	☐
Does the patient have difficulty with walking?	☐	☐	☐
Does their gait look abnormal?	☐	☐	☐
How do they mobilise for about 10 metres (ie 33 feet)?			
Without aid	☐	☐	☐
With one stick or crutch or holding to someone's arm	☐	☐	☐
With two sticks or crutches or one stick or crutch holding onto someone's arm or frame	☐	☐	☐
With a wheelchair	☐	☐	☐
If they use a wheelchair, can they stand and walk 1 metre with the help of one person?	☐	☐	☐
If they cannot walk as above are they able to make some purposeful movements of their legs, eg reposition legs in bed?	☐	☐	☐
Does the patient use **ankle foot orthoses/braces?** (please circle)	☐	☐ **If yes:** (please circle) **right/left**	

Leg grade
0=Walking/climbing stairs/running not affected
1=Walking/climbing stairs/running is affected, but gait does not look abnormal **SCORE=____**
2=Walks independently but gait looks abnormal
3=Requires unilateral support to walk 10 metres (stick, single crutch, one arm)
4=Requires bilateral support to walk 10 metres (sticks, crutches, crutch and arm,frame)
5=Requires wheelchair to travel 10 metres but able to stand and walk 1 metre with the help of one person
6=Restricted to wheelchair, unable to stand and walk 1 metre with the help of one person, but able to make some purposeful leg movements
7=Restricted to wheelchair or bed most of the day, unable to make any purposeful movements of the legs

Overall Neuropathy Limitation Scale=arm scale (range 0 to 5)+leg scale (range 0 to 7);
(range: 0 (no disability) to 12 (maximum disability)) **TOTAL SCORE=____**
Is there any disorder, other than peripheral neuropathy, which affects the above functions **Yes** ☐ **No** ☐
If **yes** please describe:

15.3 Inflammatory Neuropathy Cause and Treatment (INCAT) Sensory Sum Score (ISS)

The ISS ranges from 0 (normal sensation) to 20 (most severe sensory deficit) and is composed of the summation of the following sensation qualities:

- Pinprick arm grade (range 0-4).
- Vibration arm grade (range 0-4).
- Pinprick leg grade (range 0-4).
- Vibration leg grade (range 0-4).
- Two-point discrimination grade (range 0-4).

Pinprick is tested with the sharp end of an esthesiometer, patients indicate normal or abnormal. Paresthesia, dysesthesia or hyperesthesia are to be scored as abnormal. Normal reference point: face.

Vibration sense is tested using the graduated Rydel-Seiffer tuning fork, measures obtained are compared with the reported normative threshold values.

Pinprick and vibration sense examination take place distal to proximal and only the highest extension of dysfunction of the most affected arm and leg are recorded separately for both qualities.

Pinprick sensation (sites of examination and corresponding grades)		**Vibration sensation (sites of examination and corresponding grades)**		**Two-point discrimination (sites of examination and corresponding grades)**
Arms	Legs	Arms	Legs	Index finger [K]
Normal sense 0, at index finger A	Normal sense 0, at hallux F	Normal sense 0, at index finger A	Normal sense 0, at hallux F	Normal sense 0, <4 mm
Abnormal sense	Abnormal sense	Abnormal sense	Abnormal sense	Abnormal sense
1, at index finger [B]	1, at hallux [G]	1, at index finger [B]	1, at hallux [G]	1, 5-9 mm
2, at wrist [C]	2, at ankle [H]	2, at wrist [C]	2, at ankle [H]	2, 10-14 mm
3, at elbow [D]	3, at knee [I]	3, at elbow [D]	3, at knee [I]	3, 15-19 mm
4, at shoulder [E]	4, at groin [J]	4, at shoulder [E]	4, at groin [J]	4, > 20 mm

A,B: index finger (dorsum distal interphalangeal joint); C: ulnar styloid process; D: medial humerus epicondyle; E: acromioclavicular joint; F,G: hallux (dorsum inter-phalangeal joint); H: medial malleolus; I: patella; J: anterior superior iliac spine; K: index finger (ventral side: distal phalanx).

15.4 Rasch-built Overall Disability Scale (RODS) Scale

INSTRUCTIONS: This is a questionnaire about the relationship between daily activities and your health. Your answers give information about how your polyneuropathy affects your daily and social activities and to what degree you are able to perform your usual activities.

Answer each question by marking the correct box ("x"). If you are not sure about your ability to perform a task, you are still requested to mark an answer that comes as close as possible to your judged ability to complete such a task. All questions should be completed. You can only choose one answer to each question. If you situation fluctuates, your answer should be based on how you *usually* perform the task.

If you need assistance or you are using special devices to perform the activity, you are requested to mark "possible, but with some difficulty ". In case you never perform the activity due to your polyneuropathy mark "not possible".

Are you able to	Mark the best option with "x"		
Task	**Not possible to perform** [0]	**Possible, but with some difficulty** [1]	**Possible, without any difficulty** [2]
1. read a newspaper/book?	☐	☐	☐
2. eat?	☐	☐	☐
3. brush your teeth?	☐	☐	☐
4. wash upper body?	☐	☐	☐
5. sit on a toilet?	☐	☐	☐
6. make a sandwich?	☐	☐	☐
7. dress upper body?	☐	☐	☐
8. wash lower body?	☐	☐	☐
9. move a chair?	☐	☐	☐
10. turn a key in a lock?	☐	☐	☐
11. go to the general practitioner?	☐	☐	☐
12. take a shower?	☐	☐	☐
13. do the dishes?	☐	☐	☐

14. do the shopping?	☐	☐	☐
15. catch an object (e.g., ball)?	☐	☐	☐
16. bend and pick up an object?	☐	☐	☐
17. walk one flight of stairs?	☐	☐	☐
18. travel by public transportation?	☐	☐	☐
19. walk and avoid obstacles?	☐	☐	☐
20. walk outdoor < 1 km?	☐	☐	☐
21. carry and put down a heavy object?	☐	☐	☐
22. dance?	☐	☐	☐
23. stand for hours?	☐	☐	☐
24. run?	☐	☐	☐

15.5 Hand Grip Strength Test

With the Martin Vigorimeter, the patient squeezes a rubber ball that is connected to a manometer with rubber tubing.

The patient's grip strength is expressed in kilopascal (kPa), with a range of 0–160 kPa.

The same dynamometer will be used for a patient throughout the study. When performing the test, patients will stand, holding the dynamometer in dominant hand, with their arm parallel to the body without squeezing the arm against the body. This assessment will be performed in triplicate on same day at each time point.

15.6 The Modified Rankin Scale (mRS)

The scale runs from 0-6, running from perfect health without symptoms to death.

0 - No symptoms.

1 - No significant disability. Able to carry out all usual activities, despite some symptoms.

2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.

3 - Moderate disability. Requires some help, but able to walk unassisted.

4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.

5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent.

6 - Dead.

15.7 Motor Unit Number Index (MUNIX)

MUNIX will be performed on the tibialis anterior (TA), abductor digiti mini (ADM) and abductor pollicis brevis (APB) muscles as previously reported (Delmont et al. 2016).

Supramaximal distal stimulations of the corresponding nerves will be performed to achieve maximal CMAP amplitude with minimum rise time and sharp negative take-off. The recordings will be assessed on a 300ms window with filter setting of 3Hz-3000Hz. Ten isometric contractions will be recorded as surface interference pattern (SIP) ranging from 10 to 100% of contraction. The degree of the force increment will be estimated by the resistance given by the examiner and by the amplitude and the fullness of the SIP. SIP epochs will be accepted if SIP area >20mV/ms, ideal case motor unit count (ICMUC) <100 and SIP area/CMAP area >1. A MUNIX sumscore will be calculated by adding the results of the ADM, APB and TA muscles.

APB: Place hand upon flat surface, palm up. Place recording electrode on thenar eminence just lateral to mid-point of first metacarpal, aligned with first metacarpal. Place reference electrode distally at the thumb. Grounding electrode is placed on the dorsum of the hand. Place stimulator at wrist between flexor carpi radialis and palmaris longus tendons. Avoid partial abduction of the thumb and pronation of the forearm. Counter resistance: place your hand over the patient's hand, with your thumb giving resistance to the patient's thumb.

ADM: Place hand upon flat surface, palm up. Place recording electrode on ADM at midpoint fifth metacarpal. Place reference electrode distally at the little finger. Grounding electrode is placed on the dorsum of the hand. Place stimulator at wrist adjacent to flexor carpi ulnaris tendon. In some subjects, maximal compound muscle action potential (CMAP) is achieved with more proximal placement of the recording electrode. Be aware of initial baseline shift due to electrode movement on the skin while increasing force levels. Counter resistance: stabilize with your fingers/thumb. Do not allow abduction of digit V.

TA: Lower leg is positioned naturally with sole of the foot on the floor, knee flexed approximately 90 degrees. Place recording electrode lateral to tibial crest, one-third of distance between ankle and knee (closer to knee). Place reference electrode over the patellar tendon. Grounding electrode should be places above at the level of the fibular head. Place stimulator one to two fingerbreadths inferior to fibular head. Counter resistance: use your hand to give resistance with the foot positioned at 90 degrees. Avoid pronation/supination of the foot.

15.8 Ataxia Score

- normal posture with closed eyes (0).
- slight postural alteration with closed eyes (1).
- severe postural alteration with closed eyes (2).
- inability to stand with closed eyes (3).

15.9 Timed 10-Meter Walk Test Instructions

Description:

Individual walks without assistance 10 meters (32.8 feet) and the time is measured.

Set-up

- Measure and mark a 10-meter indoor walkway, along a flat, quiet corridor with a non-carpeted surface.
- Place chairs at the start and finish of the walkway.

Site instructions:

- Patients should be evaluated for lower limb injury immediately prior the test.
- A 10-minute rest period should always be given prior to the start of the test.
- Start timing when the toes of the leading foot crosses the 0-meter mark.
- Stop timing when the toes of the leading foot crosses thee 10-meter mark
- Ambulatory aids such as cones and walkers are permitted.
- No support may be given by an assistant unless the patient needs help to rise from a fall or to sit down.
- Subjects may not touch the walls.
- Due to possibility of subject falls, the course should be within easy access of appropriate medical assistance.
- Test results should be recorded on the 10 Meter Walk Test Worksheet.

Patient instructions

- Patients should wear comfortable clothing and appropriate shoes for walking. Since patients will be tested at multiple time points, they should make an effort to wear the same type of shoes each time.
- The tester will say ”Ready, Set, Go”. When the tester says go, begin walking at your normal comfortable pace.

5.1.2 Signature of Sponsor's Responsible Medical Officer

Study Title:	First in Human study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy of PPSGG (PN-1007) in anti-MAG neuropathy patients
Study Number:	PN-1007-001
Version:	Final 1.0 03 FEB 2022

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

SPONSOR'S RESPONSIBLE MEDICAL OFFICER

Signed: Debra S Barker Date: 3rd Feb 2022

Debra Barker, MD
Polyneuron Pharmaceuticals AG

5.1.3 Council for International Organizations of Medical Sciences

PN-1007-001 POP19520_301_001_POP00001 FU1 Final CIOMS_12 FEB 2021

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year				Day	Month	Year	
PRIVACY	FRANCE		PRIVACY		70 Years	Female	72.00 kg	17	NOV	2020	

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [LOWER LEVEL TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
Infusion related reaction [Infusion related reaction]

Case Description: Information from France received on 17-Nov-2020 and additional information on 18-Nov-2020, 19-NOV-2020, 25-NOV-2020, 26-NOV-2020 and 30-NOV-2020.
Clinical trial case, serious, unexpected and related was received via Clinipace who first became aware of the case on 17-NOV-2020 (Site 301; Patient 001).

(Continued on Additional Information Page)

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) PPSGG (PPSGG) Liquid, 10 milligram {Lot # P01963/P01997}
(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☒ NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1) 200 milligram	#1) Intravenous

17. INDICATION(S) FOR USE
#1) Anti-myelin-associated glycoprotein ass
(Continued on Additional Information Page)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)	19. THERAPY DURATION
#1) 17-NOV-2020 11:25:00 / 17-NOV-2020 11:27:00	#1) 2 min

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1) GABAPENTINE (GABAPENTINE) Tablet ; 03-NOV-2020 / Ongoing

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
1990 to 1990	Procedure	Hysterectomy (Hysterectomy)
SEP-2020 to SEP-2020	Historical Condition	Fuchs' syndrome (Fuchs' syndrome)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Polyneuron Pharmaceuticals AG
Hochbergerstrasse 60C
Basel, CH-4057 SWITZERLAND

26. REMARKS
Medically Confirmed: Yes
World Wide #: FR-POP-POP00001
Patient ID: 301-001
Study ID: PN-1007-001(continued)

24b. MFR CONTROL NO.
POP00001

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
01-FEB-2021

24d. REPORT SOURCE
☒ STUDY ☐ LITERATURE
☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
12-FEB-2021

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Protocol Number/Title: PN-1007-001
First in Human study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy of PPSGG (PN-1007) in anti-MAG neuropathy patients.

Site ID: 301
Subject ID: 001
SAE Verbatim Term (AE No): Infusion related reaction
SAE MedDRA Lower Level Term: Infusion related reaction
SAE Relationship to Study Product: Related
Outcome: Recovered/ Resolved
Country of Origin: France

Subject 301-001 a 70-year-old female was enrolled in PN-1007-001, First in Human study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy of PPSGG (PN-1007) in anti-MAG neuropathy patients on 04-NOV-2020. Subject was in phase I (open label, single ascending dose escalation study. First IP dose was started on 17-NOV-2020 at 11:25 as an intravenous (IV) infusion at 200 mg (I=SAD).

While participating in this clinical study, the subject experienced a serious adverse event of Infusion related reaction.

The subject was diagnosed with monoclonal IgM associated with MGUS with anti-MAG activity (titer of > 10’000 BTU) and demyelinating neuropathy on 09-MAR-2020. The subject’s prior therapies included gabapentine 900 mg, daily, orally since 03-NOV-2020 for neuropathic pain.

The subject’s relevant surgical history included hysterectomy in 1990, Corneal transplant for Fuchs disease in SEP-2020 and intermittent insomnia since 2020. The site confirmed that patient had no history of atopy.

Concomitant medications included zopiclone

On 17-NOV-2020 at 11:27 (study day 1), 2 minutes after the first dose of the study drug, the subject experienced Infusion related reaction. Study drug was started on the same day at 11:25, as a single 60 min intravenous infusion at a dose of 200 mg. The subject felt a bitter taste in the mouth, facial erythrosis, a warmth feeling throughout the body with a feeling of losing consciousness but did not experience hypotension, bronchospasm, loss of consciousness, desaturation, or digestive disorder. It was confirmed that there was an increase in heart rate and grade 1 increase of systolic blood pressure at start of infusion:

Time	Heart rate (bpm)	Blood pressure (mmHg)
11:25	64	
11:27	67	
11:29	94	154 / 81
11:30	80	
11:31	78	
11:32	73	152 / 77
11:38	73	116 / 54
11:41	68	154 / 72
11:44	67	151 / 68
11:47	67	143 / 72
11:50	70	146 / 76

The event of infusion related reaction was considered resolved on 17-Nov-2020 at 11:47 by stopping the infusion at 11:27, elevation of lower limbs, O2 therapy, respiratory (inhalation) of 15 L/min as needed on 17-NOV-2020. Furthermore Polaramine (dexchlorpheniramine) 5 mg was administered intravenously on 17-NOV-2020 near 11:35 before the event resolution and just after lower limb elevation and O2 therapy.

There were no changes in routine haematology and clinical chemistry from 17-NOV-2020, 20-NOV-2020 and 24-Nov-2020 compared to baseline.
Tryptase was reported as 5.38 µg/l (range <11.5) on and as 5.16 µg/l on 18-NOV-2020. Histamine was reported as 6.40 nmol/l (range 0.00 - 10.00) on 17-NOV-2020 and as 8.00 nmol/l on 20-NOV-2020.

The action taken with the study drug due to the event was reported as drug withdrawn on 17-Nov-2020 at 11:27.

Follow-up 01 was received on 01-Feb-2021:
New laboratory values were reported (see other relevant tests).

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

The subject completed the SAD Phase of the study on 15-DEC-2020.

Company comment
Initial received on 17-Nov-2020 and additional information on 18-Nov-2020, 19-NOV-2020, 25-NOV-2020, 26-NOV-2020, 30-NOV-2020 and follow up received on 01-FEB-2021.

The sponsor's final assessment of Infusion related reaction based on new data (significant complement activation) is, that it was Serious, related to study drug, and unexpected.

Significant increase in complement activation product C5b9 was observed one hour post infusion as well as MIP-1a and MCP-1, IL-8 and TNF-alpha.

The complement activation is likely classical pathway subsequent to immune complex formation. This is being investigated further.

There was no basophil activation observed in the patient.

Case Comment: The investigator's assessment of infusion related reaction was that it was serious, event being medically significant and considered to be severe (Grade 3), related to study drug but not related to the disease under study. Grade 3 was confirmed by the site as intravenous intervention was indicated.

13. Relevant Tests

On 04-Nov-2020 (at screening): Blood pressure 140 / 71 mmHg, heart rate 80 bpm.
On 17-NOV-2020, 10:02 (pre-dose):Blood pressure 140 / 73 mmHg, heart rate 63 bpm.
On 17-NOV-2020, 12:25: Blood pressure 120 / 69 mmHg, heart rate 67 bpm
On 17-NOV-2020, 13:29: Blood pressure 130 / 59 mmHg, heart rate 63 bpm
On 17-NOV-2020, 19:27: Blood pressure 137 / 81 mmHg, heart rate 67 bpm

	C3 (g/l)	C4 (g/l)	CH50 (%)
04-NOV-2020 Serum	1.34	0.283	111
17-NOV-2020 Serum	1.26	0.224	97
18-NOV-2020 Serum	1.34	0.255	117
20-NOV-2020 Serum	1.33	0.285	126

	sC5b9(ng/ml)	C4d (ng/ml)	C5a (ng/ml)
04-NOV-2020 Plasma	133.9563	1.423775	14.4912
17-NOV-2020 Plasma	827.7842	2.460011	12.06082

	Eotaxin (pg/ml)	IP-10 (pg/ml)	MCP-1 (pg/ml)
04-NOV-2020 Serum	219.7194185	109.897826	301.699199
17-NOV-2020 Serum	243.009674	120.522801	478.888119

	MIP-1a (pg/ml)	IL17a (pg/ml)	VEGFa (pg/ml)
04-NOV-2020 Serum	34.3404329	0.15101323	124.005605
17-NOV-2020 Serum	250.713647	0.31789447	114.72297

	IFNgamma (pg/ml)	IL10 (pg/ml)	IL6 (pg/ml)
04-NOV-2020 Serum	1.677890512	0.1342247	0.81266504
17-NOV-2020 Serum	1.6578933	0.45559687	3.57117513

	IL8 (pg/ml)
04-NOV-2020 Serum	23.2306853
17-NOV-2020 Serum	239.211755

	IL1b (pg/ml)	IL2 (pg/ml)	TNFa (pg/ml)
04-NOV-2020 Serum	0.18446824	0.06180181	1.12905393
17-NOV-2020 Serum	0.39770344	0.13556916	18.6714534

Mfr. Control Number: POP00001

ADDITIONAL INFORMATION

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) PPSGG (PPSGG) Liquid, 10 milligram {Lot # P01963/P01997}; Regimen #1	200 milligram; Intravenous	Anti-myelin-associated glycoprotein associated polyneuropathy (Anti-myelin-associated glycoprotein associated polyneuropathy)	17-NOV-2020 11:25:00 / 17-NOV-2020 11:27:00; 2 min

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
SEP-2020 to SEP-2020	Procedure	Corneal transplant (Corneal transplant);
2020 to Unknown	Current Condition	Insomnia (Insomnia);

26. Remarks continued

Center ID: 301

5.1.4 Laboratory Reports

HNK1 IgG Laboratory Report dated 17 JAN 2022

HNK1-MAG-C3-C4-CH50 Laboratory Report dated 01 FEB 2022

Sample Number	Visit	Date	HNK1 IgG (%Cal)
NN0052000	V2	16/11/2020	84,1160221
NN0052006	V3 D1 30min	17/11/2020	91,77954227
NN0052005	V3 D1 1h	17/11/2020	84,77347034
NN0052004	V3 D1 2h	17/11/2020	68,61878453
NN0052003	V3 D1 8h	17/11/2020	NA
NN0052007	V3 D2	18/11/2020	66,87845304
NN0052289	V4	20/11/2020	99,06586
NN0052218	V5	24/11/2020	111,2564
NN0052509	V6	01/12/2020	174,8618785
NN0052518	V7	15/12/2020	154,9723757
		26/06/2021	188,6299

Date 27/07/2021
Buhlmann anti-HNK1 Antibodies ELISA
CatalogNumber : EK-HNK1-U
Lot Number : 3101.U

Dr Alexandre Brodovitch
Ingénieur Hospitalier
Laboratoire d'Immunologie, Hôpital de la Conception
147 Bd Baille, 13005 Marseille, France

Date: 17/01/2022
Signature:

Sampling

Date	TIME	DAY	TIMEPOINT	ID	SAMPLE NUMBER	Anti-MAG (BTU)	Anti-HNK1 (% Cal)	Dilution	C3 (g/l)	C4 (g/l)	CH50 (%)	CH50 (%)	
16/11/20	14:57	V2		301-001	NN0052000	42367	130	1/200	1,27	0,262	152	152	
18/11/20	11:30	V3 D2		301-001	NN0052007	39819	142	1/200	1,23	0,232	159	159	
20/11/20	11:13	V4		301-001	NN0052289	42700	149	1/200	1,29	0,256	QI	QI	
17/11/20	12:20	V3 D1	30min	301-001	NN0052006	40503	142	1/200	1,31	0,215	120	120	
17/11/20	12:20	V3 D1	1h	301-001	NN0052005	43222	141	1/200	QI	QI	QI	QI	
24/11/20	11:28	V5		301-001	NN0052218	44971	133	1/200	1,34	0,26	>156	>156	
17/11/20	12:20	V3 D1	2h	301-001	NN0052004	40799	134	1/200	1,26	0,208	QI	QI	
17/11/20	12:20	V3 D1	8h	301-001	NN0052003	42076	133	1/200	1,22	0,204	132	132	

Date		04/12/2020
Buhlmann anti-HNK1 Antibodies ELISA		
	CatalogNumber	EK-HNK1-U
	Lot Number	3101.U

Date		04/12/2020
Buhlmann anti-MAG Antibodies ELISA		
	CatalogNumber	EK-MAG
	Lot Number	1941

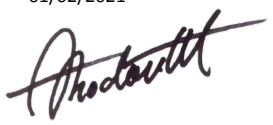
Date		04/12/2020
BindingSite Optilite C3c Kit		
	CatalogNumber	NK023.Opt
	Lot Number	471410

Date		04/12/2020
BindingSite Optilite C4 Kit		
	CatalogNumber	NK025.Opt
	Lot Number	467206

Date		04/12/2020
BindingSite Optilite CH50 Kit		
	CatalogNumber	NK095.Opt
	Lot Number	479794

Dr Alexandre Brodovitch
Ingénieur Hospitalier
Laboratoire d'Immunologie, Hôpital de la Conception
147 Bd Baille, 13005 Marseille, France

Date : 01/02/2021
Signature :



5.1.5 Pharmacokinetic Report

PN1007-039 Qualitative Analysis of PPSGG in the PK samples from the sentinel patient of PN1007-001 dated 23 APR 2021

Polyneuron Pharmaceuticals

Polyneuron Pharmaceuticals AG

Report number

PN1007-039

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info@polyneuron.com - www.polyneuron.com

ICBT Institute of Chemistry and Biotechnology
Bioanalytics Group

Zurich University of Applied Sciences

PPSGG in the serum of sentinel patient from PN1007-001

Qualitative Analysis of total PPSGG in anti-MAG neuropathy patient serum
Qualitative Analysis of PPSGG and IgM in soluble / insoluble serum fractions

Authors: Laure-Anne Bickel, Dr. Sabina Gerber
Date: 23.04.2021
Document: 2021-04-23_Polyneuron-ZHAW_PPSGG_QualitativeAnalysisSentinelPatient_Report.pptx

Western Blot analysis of total PPSGG in sentinel patient serum

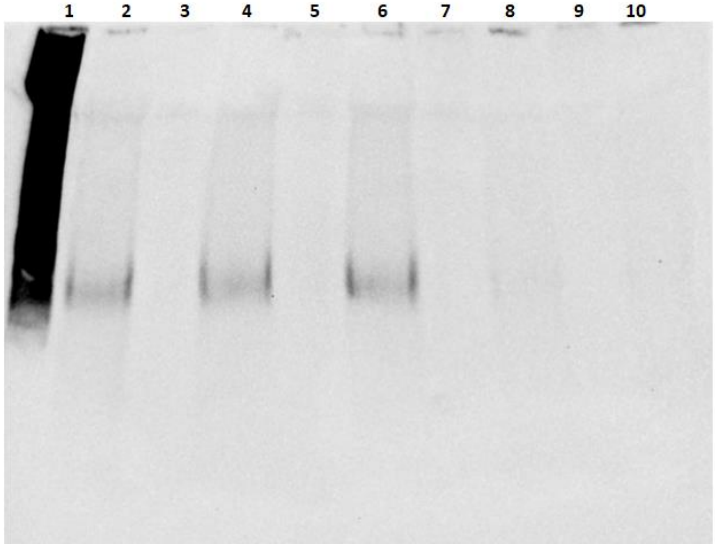
- **Analysis**
  - Anti-HNK-1 Western Blot of sentinel patient PK samples taken at 30 min, 1 h, 2 h, 6 h and 8 h

- **Samples analyzed**
  - PN-1007-001, ID: 301-001, NN0052**63**, *Y2684053030*, Total PK 30 min **4**
  - PN-1007-001, ID: 301-001, NN0052**55**, *Y2684053030*, Total PK 1 h **4**
  - PN-1007-001, ID: 301-001, NN0052**47**, *Y2684053030*, Total PK 2 h **4**
  - PN-1007-001, ID: 301-001, NN0052**39**, *Y2684053030*, Total PK 6 h **4**
  - PN-1007-001, ID: 301-001, NN0052**31**, *Y2684053030*, Total PK 8 h **4**

Western Blot analysis of total PPSGG in sentinel patient serum

- **Analysis procedure**
  - PK serum samples (30 min, 1 h, 2 h, 6 h, 8 h) thawed on ice, homogenized
  - Added 4 µg Thermolysine (protease) and 4 M Urea buffer to 10 µl serum sample
  - Incubated for 4 h, 70 °C
  - Added Lämmli buffer (reducing condition)
    - Inactivated for 10 min, 95 °C
  - SDS-PAGE and detection of total PPSGG by Western Blot (anti-HNK-1)

Western Blot analysis of total PPSGG in sentinel patient serum



Index

1. PPSGG Ref. 500 ng
2. Sentinel Patient Total PK 30 min
3. -
4. Sentinel Patient Total PK 1 h
5. -
6. Sentinel Patient Total PK 2 h
7. -
8. Sentinel Patient Total PK 6 h
9. -
10. Sentinel Patient Total PK 8 h

SDS-PAGE: 30 min, 200 V

Primary Antibody: **mouse anti-HNK-1 (IgG)**, Squarix (Lot: SQ19MAK109550)
Secondary Antibody: **goat anti-mouse IgG (HRP Conj.)**, Sigma (A3673)

Conclusions

- PPSGG detected in samples 30 min, 1 h and 2 h
- No PPSGG detected in samples 6 h and 8 h

Anti-PPSGG Western Blot analysis of soluble and insoluble fractions in sentinel patient serum

- **Analysis**
  - Anti-HNK-1 Western Blot of sentinel patient PK samples taken at 30 min, 1 h, 2 h, 6 h and 8 h

- **Samples analyzed**
  - PN-1007-001, ID: 301-001, NN0052**63**, *Y2684053030*, Total PK 30 min **4**
  - PN-1007-001, ID: 301-001, NN0052**55**, *Y2684053030*, Total PK 1 h **4**
  - PN-1007-001, ID: 301-001, NN0052**47**, *Y2684053030*, Total PK 2 h **4**
  - PN-1007-001, ID: 301-001, NN0052**39**, *Y2684053030*, Total PK 6 h **4**
  - PN-1007-001, ID: 301-001, NN0052**31**, *Y2684053030*, Total PK 8 h **4**
  - PN-1007-001, ID: 301-001, NN0052**64**, *Y2684053030*, Total PK 30 min **3**
  - PN-1007-001, ID: 301-001, NN0052**56**, *Y2684053030*, Total PK 1 h **3**
  - PN-1007-001, ID: 301-001, NN0052**48**, *Y2684053030*, Total PK 2 h **3**
  - PN-1007-001, ID: 301-001, NN0052**40**, *Y2684053030*, Total PK 6 h **3**
  - PN-1007-001, ID: 301-001, NN0052**32**, *Y2684053030*, Total PK 8 h **3**

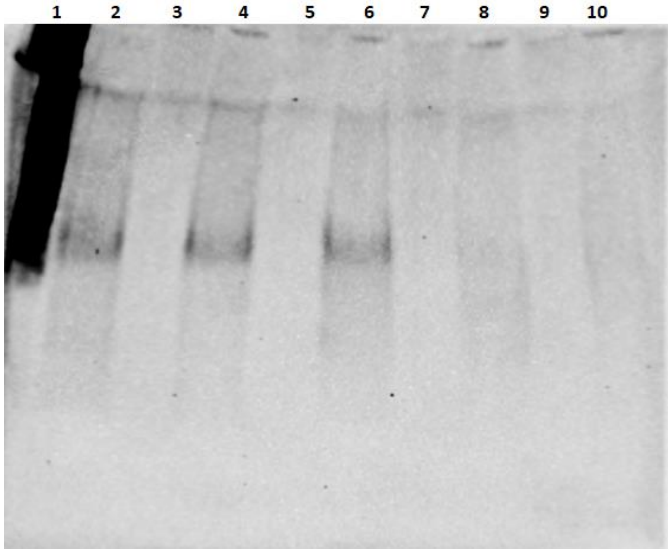
Anti-PPSGG Western Blot analysis of soluble and insoluble fractions in sentinel patient serum

- **Analysis procedure**
  - Centrifugation of 100 µl PK serum sample from each time point 30 min, 1 h, 2 h, 6 h, 8 h
    - 3 h, 4 °C, 18'000 x g

  →no pellet visible after centrifugation
  - Supernatant (SN) transferred in a new tube
    - 10 µl SN were digested with Thermolysine (4 µg) in Urea buffer (4 M) for 4 h at 70 °C
  - Pellet washed with 500 µl PBS
  - Repeated centrifugation
    - 3 h, 4 °C, 18'000 x g
    - Supernatant (after PBS wash) was discarded
  - Resuspension of pellet in Lämmli buffer (reducing condition)
  - SDS-PAGE of supernatants and pellets with detection of PPSGG by Western Blot (anti-HNK-1)

  - Load:
    - 10 µl supernatant →soluble fraction
    - Whole pellet →insoluble fraction

Anti-PPSGG Western Blot analysis of soluble fractions in sentinel patient serum



Primary Antibody: **mouse anti-HNK-1 (IgG)**, Squarix (Lot: SQ19MAK109550)
Secondary Antibody: **goat anti-mouse IgG (HRP Conj.)**, Sigma (A3673)

Index

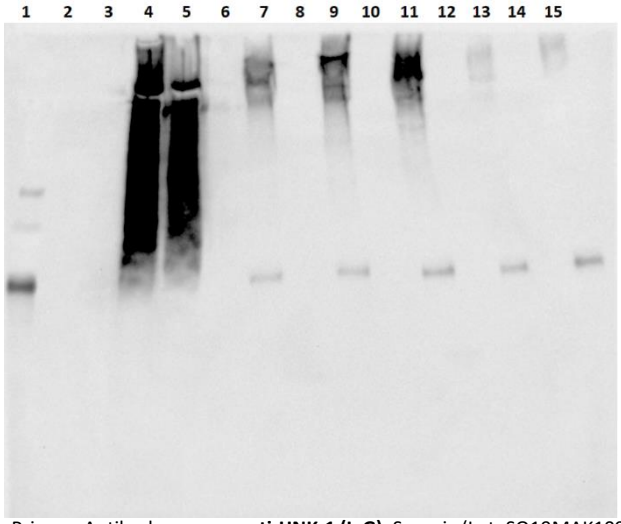
1. PPSGG Ref. 500 ng
2. SN Sentinel Patient 30 min
3. -
4. SN Sentinel Patient 1 h
5. -
6. SN Sentinel Patient 2 h
7. -
8. SN Sentinel Patient 6 h
9. -
10. SN Sentinel Patient 8 h

SDS-PAGE: 30 min, 200 V

Conclusions

- PPSGG detected in soluble fractions (supernatants) of samples 30 min, 1 h and 2 h
- No PPSGG detected in soluble fractions (supernatants) of samples 6 h and 8 h

Anti-PPSGG Western Blot analysis of insoluble fractions in sentinel patient serum



Primary Antibody: **mouse anti-HNK-1 (IgG)**, Squarix (Lot: SQ19MAK109550)
Secondary Antibody: **goat anti-mouse IgG (HRP Conj.)**, Sigma (A3673)

Index

1. Negative Control (Anti-MAG Serum), Pellet
2. -
3. Marker
4. PPSGG Ref. 500 ng
5. PPSGG Ref. 100 ng
6. -
7. Pellet Sentinel Patient 30 min
8. -
9. Pellet Sentinel Patient 1 h
10. -
11. Pellet Sentinel Patient 2 h
12. -
13. Pellet Sentinel Patient 6 h
14. -
15. Pellet Sentinel Patient 8 h

SDS-PAGE: 30 min, 200 V

Conclusions

- PPSGG detected in insoluble fractions (pellets) of samples 30 min, 1 h and 2 h
- No PPSGG detected in insoluble fractions (pellets) of samples 6 h and 8 h

Western Blot analysis of total IgM in supernatants and pellets of serum samples

- **Analysis**
  - Anti-human IgM Western Blot of sentinel patient PK samples taken at 6 h and 8 h, anti-MAG serum pool and human serum (Sigma)

- **Samples analyzed**
  - PN-1007-001, ID: 301-001, NN00522**30**, *Y2684053030*, Total PK 8 h **5**
  - PN-1007-001, ID: 301-001, NN00522**38**, *Y2684053030*, Total PK 6 h **5**
  - human serum Sigma, 4522
  - Pool anti-MAG patient serum
  - goat anti-human IgM (HRP Conj.) Abcam, ab98549

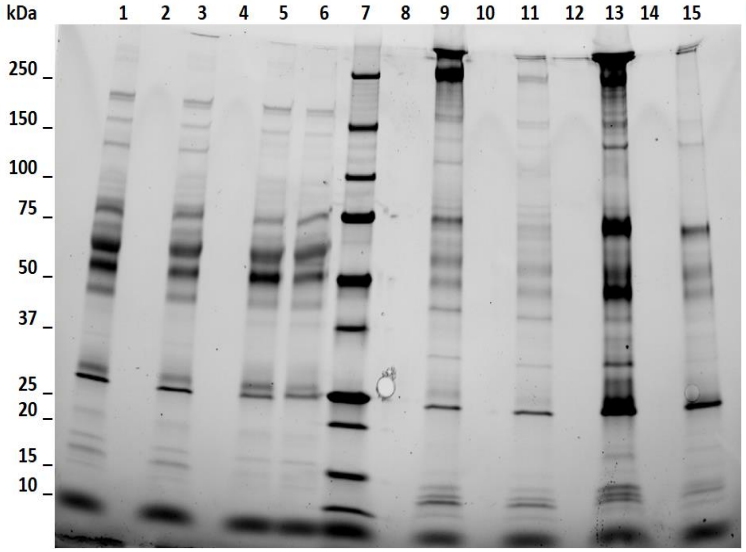
Western Blot analysis of total IgM in supernatants and pellets of serum samples

- **Analysis procedure**
  - Centrifugation of 100 µl serum sample (Total PK 6 h and 8 h, human serum, anti-MAG serum)
    - 3 h, 4 °C, 18'000 x g

  →no pellet visible after centrifugation
  - Supernatant (SN) transferred in a new tube
    - 1 : 20 dilution of SN
    - 1 µl diluted SN mixed with Lämmli buffer (reducing condition)
  - Pellet washed with 500 µl PBS
  - Repeated centrifugation
    - 3 h, 4 °C, 18'000 x g
    - Supernatant (after PBS wash) discarded
  - Resuspension of pellet in Lämmli buffer (reducing condition)
  - SDS-PAGE of supernatants and pellets
    - Stain-free detection
    - Western Blot detection (anti-human IgM)
  - Load:
    - 0.05 µl supernatant →soluble fraction
    - Whole pellet →insoluble fraction

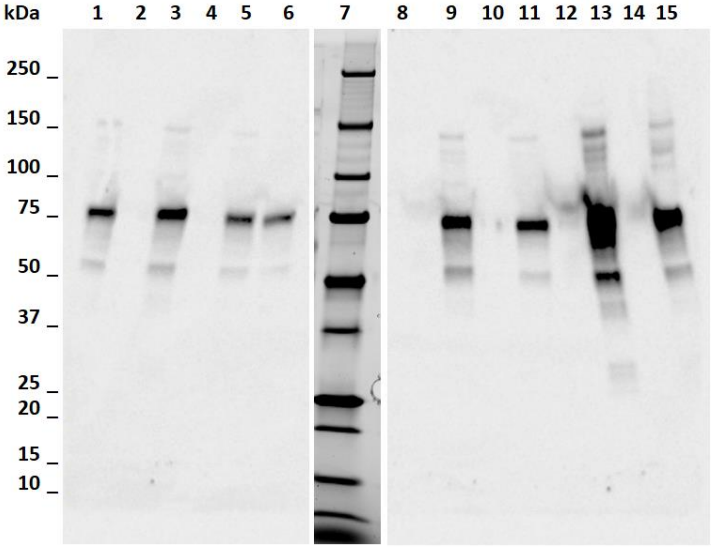
Western Blot analysis of total IgM in supernatants and pellets of serum samples

Total Protein, Stain-Free detection method



SDS-PAGE (4-15%): Stain-Free

Anti-human IgM Western Blot



Primary Antibody: **goat α-human IgM (HRP Conj.)**, Abcam

Index

1. SN Sentinel Patient, 8 h
2. -
3. SN Sentinel Patient, 6 h
4. -
5. SN Anti-MAG serum
6. SN Sigma serum
7. Marker
8. –
9. Pellet Sentinel Patient 8 h
10. –
11. Pellet Sentinel Patient 6 h
12. –
13. Pellet Anti-MAG serum
14. –
15. Pellet Sigma serum

Expected molecular mass IgM: 80 kDa (Heavy Chain)

Conclusions

- Total human IgM was detected by Western Blot in all sera samples of both supernatants and pellets, including Sigma serum and anti-MAG serum pool which did not contain any PPSGG