2. SYNOPSIS

Name of company Galapagos NV
Name of finished product Not applicable
Name of active ingredient GLPG3970 (compound code: G1567970)
Title of study A Phase 1, non-randomized, fixed sequence, open-label, drug-drug interaction study to evaluate the effect of GLPG3970 on the pharmacokinetics of methotrexate in adult, healthy subjects Study Number: GLPG3970-CL-103; EudraCT Number: 2020-000391-37; ClinicalTrials.gov identifier: Not applicable; IND Number: Not applicable
Principal investigator name, number of study center and countries Maria Velinova, MD, PhD, single-center study, The Netherlands
Publication (reference) None at the time of the clinical study report
Study period First informed consent form (ICF) signed: 27 August 2020 Last subject's last visit (LSLV): 8 December 2020
Reporting period The reporting period was the same as the study period (see first ICF signed and LSLV dates above).
Phase of development of study Phase 1
Background and rationale for the study GLPG3970 is an oral, selective, small-molecule serine/threonine salt-inducible kinase 2 and 3 inhibitor with a broad therapeutic potential in various immune inflammatory disorders. Inhibition of this target has been shown in a non-clinical setting to block the production of pro-inflammatory cytokines, such as tumor necrosis factor α, and simultaneously increase the production of interleukin-10, which has an immune-regulatory role. In vitro studies suggest that GLPG3970 is an inhibitor of breast cancer resistance

protein (BCRP) and, based on the predicted human maximum observed plasma concentration at steady-state ($C_{max,ss}$) free exposures at the anticipated highest therapeutic dose relative to the in vitro half maximal inhibitory concentration, there is a potential risk of an interaction between GLPG3970 and substrates of BCRP. Methotrexate (MTX), a BCRP substrate, is a common background therapy that will be used by subjects enrolling into future clinical studies with GLPG3970. Therefore, this study will be conducted in order to determine if GLPG3970 can be safely coadministered with MTX.

In the original GLPG3970-CL-103 protocol, 2 treatment groups were planned: Group 1 (MTX/GLPG3970) and Group 2 (sulfasalazine/GLPG3970). Due to operational reasons, Group 2 was not performed during this study. The current clinical study report (CSR) only describes the safety and pharmacokinetic (PK) profile of subjects in Group 1. To evaluate sulfasalazine, a separate protocol has been written (GLPG3970-CL-117) and a separate CSR will be prepared to present safety and PK results. All protocol text referring to Group 2 can be found in the original protocol and will not be included in this CSR.

Objectives and endpoints

Objectives	**Endpoints**
Primary	
To evaluate the effect of GLPG3970 on the PK of MTX and its active metabolite 7-hydroxymethotrexate (7-OH-MTX) in healthy subjects.	MTX and 7-OH-MTX PK parameters: maximum observed plasma concentration (C_{max}) and area under the plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$).
Secondary	
To evaluate the safety and tolerability of the coadministration of GLPG3970 with MTX in healthy subjects.	Safety and tolerability, assessed by the incidence and severity of treatment-emergent adverse events (TEAEs)
To evaluate the PK of GLPG3970 in presence of MTX in healthy subjects	GLPG3970 PK parameters such as trough concentrations (C_{trough}), C_{max}, time of occurrence of C_{max} (t_{max}), and area under the plasma concentration-time curve from time zero till the last observed quantifiable concentration (AUC_{0-t})

Methodology

This was a Phase 1, non-randomized, fixed sequence, open-label, drug-drug interaction (DDI) study designed to assess the impact of concomitant administration of GLPG3970, a potential in vivo BCRP inhibitor, on the PK of MTX, a BCRP substrate.

A total of 15 subjects were planned to be enrolled in the MTX group, as follows:

- Study Period 1: On Day 1, subjects received a single oral dose of 7.5 mg of MTX in the morning, after an overnight fast of at least 10 hours and remained fasted up to 4 hours postdose
- Study Period 2: On Day 5 in the morning, after an overnight fast of at least 10 hours, subjects first received a single dose of GLPG3970 (350 mg) immediately followed by a single dose of 7.5 mg of MTX; subjects remained fasted up to 4 hours postdose. On Days 6, 7, and 8, subjects had to be fasted for at least 2 hours in the morning before they received a single dose of GLPG3970; breakfast was allowed as of 1 hour after the dose.

Subjects were planned to be in the study for approximately 10 weeks (screening to follow-up [FU]).

There was a screening period of up to 6 weeks (Days -42 to -3), an 11-day study period (Days -2 to 9), and a FU period of 2 weeks following the last GLPG3970 administration. Subjects were confined to the site during the entire treatment and PK blood collection period, from Day -2 up to Day 9.

Number of subjects

A total of 15 subjects were enrolled in the MTX group and 14 of them completed the study. One subject discontinued the study due to an adverse event (AE).

Main criteria for inclusion and exclusion

Inclusion Criteria

- Male or female Caucasian between 18–55 years of age (extremes included), on the date of signing the ICF.
- A body mass index (BMI) between 18–30 kg/m^2, inclusive.
- A BCRP c421C/C genotype.
- Judged to be in good health by the investigator based upon the results of a medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG), and fasting clinical laboratory safety tests, available at screening and prior to the first MTX administration. Bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) must be no greater than 1.5x upper limit of normal range (ULN). Other clinical laboratory safety test results must be within the reference ranges or test results that are outside the reference ranges need to be considered not clinically significant in the opinion of the investigator.

Exclusion Criteria

- Known hypersensitivity to GLPG3970, or MTX, or to their ingredients, or history of a significant allergic reaction to GLPG3970 or MTX ingredients as determined by the investigator.

Test Product, dose, mode of administration, batch numbers

GLPG3970 powder and solvent for oral solution formulated in 1 strength, i.e. 35 mg/mL of the active pharmaceutical ingredient G1567970 (G1567970 is the compound code for GLPG3970), was the investigational product (IP).

Subjects received a single dose of GLPG3970 (350 mg) in the morning of Days 5, 6, 7, and 8 (powder for solution: batch number: 5148804, expiry: 28 February 2021; solvent for solution: batch number 5148810, expiry: 31 August 2021).

Subjects received a single oral dose of MTX (7.5 mg) in the morning of Days 1 and 5 (batch number: 106241, expiry: 30 November 2024).

Duration of treatment

GLPG3970: 4 consecutive days (from Days 5 to 8)

MTX: 2 days (on Days 1 and 5)

Statistical methods

Pharmacokinetic analyses

Descriptive statistics were calculated by treatment for the plasma concentrations and the listed PK parameters. Mean (± standard deviation, SD) plasma concentrations for GLPG3970, MTX, and 7-OH-MTX versus time were plotted per treatment group.

The DDI assessment was made on ln-transformed MTX and 7-OH-MTX PK parameters (C_{max} and AUC) by means of a mixed-effect model with subject as random effect. Point estimate was calculated as the geometric mean of the individual ratios of each parameter for the test/reference treatments and expressed as a percentage. The 90% confidence interval (CI) of the point estimates were calculated using the mean square error of the analysis of variance. Point estimate and 90% CI were calculated for the following comparison: MTX and GLPG3970 (test treatment) versus MTX alone (reference treatment).

Safety analyses

All safety data collected on or after the first dose of GLPG3970/MTX administration up to the last FU visit after the last dose of GLPG3970, unless specified otherwise, were summarized by treatment group according to the actual GLPG3970/MTX received. All safety analyses were performed using the Safety Analysis Set. Clinical safety was addressed by assessing AEs, laboratory assessments, physical examinations, vital signs, and 12-lead ECGs.

Summary of results and conclusions

Subject disposition

A total of 15 subjects were included and 14 of them completed the study. One subject discontinued the study prematurely due to an AE of upper respiratory tract infection.

Demography and baseline characteristics

The median age of the subjects was 24.0 years (range 18 to 49 years) and all subjects were White males. The median BMI was 25.4 kg/m².

Pharmacokinetic results

The PK parameters of MTX, 7-OH-MTX, and GLPG3970, after MTX administered alone and after coadministration with GLPG3970, and related statistical assessments are summarized in the table below.

- The exposure of MTX was not affected by coadministration with GLPG3970, while a slight reduction of 20% and 23% was noted for C_{max} and AUC_{0-t} of 7-OH-MTX, respectively.
- GLPG3970 exposure after coadministration of MTX with GLPG3970 on Day 5 was as expected, based on previous studies with GLPG3970 administered alone.

	Descriptive Statistics PK Parameters Arithmetic Mean (CV%)		Inferential Statistics PK Parameters LS Geometric Mean Ratio (90% CI)[1]
	MTX 7.5 mg (N=15)	GLPG3970 350 mg + MTX 7.5 mg (N=14)	GLPG3970 350 mg + MTX 7.5 mg vs MTX 7.5 mg
MTX Parameters			
$AUC_{0-\infty}$ (ng.h/mL)[2]	684 (15.1)	636 (22.3)	91 (83 ; 99)
C_{max} (ng/mL)	183 (20.6)	199 (24.3)	108 (96 ; 121)
7-OH-MTX Parameters[3]			
AUC_{0-t} (ng.h/mL)	498 (18.1)	417 (29.7)	80 (69 ; 92)
C_{max} (ng/mL)	35.6 (18.6)	28.0 (22.6)	77 (72 ; 82)
GLPG3970 Parameters			
AUC_{0-t} (ng.h/mL)	NAP[4]	7660 (18.8)	NAP[4]
C_{max} (ng/mL)	NAP[4]	1750 (23.1)	NAP[4]
C_{trough} Day 6 (ng/mL)	NAP[4]	52.2 (33.0)	NAP[4]
C_{trough} Day 7 (ng/mL)	NAP[4]	68.1 (46.2)	NAP[4]
C_{trough} Day 8 (ng/mL)	NAP[4]	70.1 (45.5)	NAP[4]

[1] Point estimate and 90% CI of the least-squares geometric mean ratio, expressed as percentage, from a mixed-effects model on ln-transformed values with treatment as a fixed effect and subject as a random effect.
[2] N=13 for MTX 7.5 mg and N=12 for GLPG3970 350 mg + MTX 7.5 mg.
[3] $AUC_{0-\infty}$ could not be estimated for 7-OH-MTX due to insufficient sampling time points and AUC_{ext} >20%.
[4] NAP: Not applicable.

Safety results

- There were no deaths or serious adverse events (SAEs) during the study.
- There was 1 TEAE of upper respiratory tract infection that led to study discontinuation after administration of a single dose of MTX 7.5 mg.
- All TEAEs were mild in severity.
- The proportion of subjects with at least 1 TEAE was similar when MTX was administered alone or coadministered with GLPG3970.
- Headache was the most frequently reported TEAE (by Preferred Term [PT]) during the study and was only reported when MTX was coadministered with GLPG3970.
- No notable observations over time in (mean/median) actual values or changes from baseline were reported for clinical laboratory, vital signs, ECG, or physical examination parameters.
- No treatment-emergent abnormalities in safety parameters were reported as AEs and thus none were considered clinically significant by the investigator.

Conclusions

- There was no relevant effect on MTX exposure when coadministered with GLPG3970 350 mg q.d.
- GLPG3970 coadministered with MTX was well tolerated and the safety profile was consistent with the known safety profile of GLPG3970.
- The observations on the safety of MTX were consistent with the MTX labeling information, and were similar when administered alone or in combination with GLPG3970.

Date and version of this report

Final, 22 April 2021