2 SYNOPSIS

Name of Sponsor/Company: Milestone Pharmaceuticals Inc. 1111 Dr.-Frederik-Philips Blvd., Ste. 420 H4M 2X6 Canada **Name of Drug Product:** Etripamil (MSP-2017) **Name of Drug Substance:** Benzoic acid, 3-[2-[[(4S)-4-cyano-4-(3,4-dimethoxyphenyl)-5-methylhexyl]methylamino]ethyl]-, methyl ester	Individual Study Table Referring to Clinical Part of the Dossier Volume: Page:	*(For National Authority Use only)*

Title of Study:

An open-label, mass balance study to investigate the absorption, distribution, metabolism and excretion of [^{14}C]-etripamil nasal spray after a single dose to healthy male subjects

Investigator:

Christine Voors-Pette, MD
QPS Netherlands B.V.

Study Center: QPS Netherlands BV Hanzeplein 1, entrance 53 9713 GZ, Groningen, The Netherlands	**Publication (reference):** Not applicable
Study Period: 06 October 2020 (first subject, first visit) - 09 November 2020 (last subject completed)	**Phase of Development:** Phase 1

Objectives:

Primary objectives:

- To determine the ratio of parent drug to metabolite MSP-2030 in the circulation.
- Profiling of [^{14}C]-etripamil metabolites in blood, urine and feces.
- To determine the mass balance of drug-related materials following intranasal administration.
- To determine the primary route of excretion of drug-related materials.
- To determine the total radioactivity versus time profile in plasma and whole blood.

Secondary objectives:

- To evaluate the safety and tolerability of [^{14}C]-etripamil after a single intranasal dose.
- To determine the pharmacokinetics (PK) of total radioactivity, etripamil and its inactive metabolite MSP-2030 in plasma and urine after a single dose of [^{14}C]-etripamil nasal spray to healthy male subjects.

Exploratory objective:

- To determine the PK of metabolites, if any and data available.

Methodology:

Eligibility was assessed during a screening period of up to 4 weeks. Subjects checked into the clinic one day prior to dosing (Day -1) for baseline assessments and to (re-)confirm eligibility. The study drug was administered on Day 1. After study drug administration, the nose and face were wiped/cleaned and the wipes/tissues were collected.

Plasma, blood, urine and fecal samples were collected until discharge criteria were met and discharge was allowed by the principal investigator. Exhaled air samples and tissues used to wipe the face were collected as well. Discharge criteria were evaluated starting on Day 4, based on the results of Day 3. When the discharge criteria were not met, blood, urine and fecal samples were collected in 24-hour intervals until the discharge criteria were met and discharge was allowed by the principal investigator.

Subjects were discharged from the clinic no sooner than Day 4, provided discharge was allowed by the principal investigator and radioactivity had reached the following threshold values:

- Plasma and/or whole blood radioactivity reached levels below the lower limit of quantification (LLOQ) in 2 consecutive samples **and**
- Total excreted radioactivity reached ≥90% of the administered dose; **or**
  - Two (2) consecutive urine collection intervals were ≤1% of the administered dose **and**
  - Two (2) consecutive fecal collection intervals were ≤1% of the administered dose.

In case discharge criteria were met but total recovery remained low, discharge was allowed upon mutual agreement between the principal investigator and the Sponsor.

If the discharge criteria were not met on Day 7, subjects could be discharged at the discretion of the principal investigator and eventual consultation of the Sponsor.

Number of Subjects (Planned and Analyzed):

A total of 8 subjects were planned, 7 subjects were enrolled and analyzed in this study. All subjects completed the study without any major protocol deviations or violations.

Main Criteria for Inclusion:

Subjects were eligible for the study if they met the following main inclusion criteria:

- Healthy and free from clinically significant illness or disease as determined by medical history, physical examination, laboratory and other tests at Screening.
- Caucasian male subjects, aged 18 to 65 years (inclusive) at Screening.
- A body weight of ≥60 kg and a body mass index ranging from 18.0 to 30.0 kg/m^2 at Screening.

Test Product, Dose and Mode of Administration, Batch Number:

The test product containing 70.2 mg etripamil was prepared using the following:

- Cold etripamil batch number: 19MM-078
- Hot etripamil batch number: AC0206207
- Batch number test product [^{14}C]-etripamil: 2020J26-03

The planned radioactivity dose per subject was 100 µCi, the actual dose contained 96.9 µCi of radioactivity.

The study drug was administered intranasally.

Duration of Treatment:

The total duration of the study, from screening to follow-up, was approximately 5 weeks.

Criteria for Evaluation:

Primary endpoints

The following radioactivity parameters were calculated, whenever possible and appropriate, taking into account the last time point where detectable radioactivity counts were observed:

Whole blood and plasma:

- Maximum observed total radioactivity (C_{max}).
- Time from time zero to peak total radioactivity (t_{max}).
- Area under the total radioactivity-time curve from time zero to the last measurable concentration of total radioactivity (AUC_{0-t}).
- Area under the total radioactivity-time curve from time zero to infinity (AUC_{0-inf}).
- Total radioactivity half-life ($t_{1/2}$).
- Apparent terminal elimination rate constant (λ_z).
- Apparent total radioactivity clearance (CL/F) and volume of distribution (V_z/F).
- [^{14}C]-metabolic profile and identification of metabolites in plasma and/or blood.

Urine:

- Total radioactivity amount excreted in urine (A_{eu}).
- Total radioactivity excreted in urine as a percentage of the radioactive dose.
- [^{14}C]-metabolic profile and identification of metabolites in urine.
- Major radioactive peak/metabolite(s) in the urine radiochromatogram(s) as a percentage of the radioactive dose.

Feces:

- Total radioactivity amount excreted in feces (A_{ef}).
- Total radioactivity percentage dose excreted.
- [^{14}C]-metabolic profile and identification of metabolites in feces.
- Major radioactive peak/metabolite(s) in the fecal radiochromatogram(s) as a percentage of the radioactive dose.

Secondary endpoints

Safety and tolerability endpoints

The following were defined as safety/tolerability parameters:

- Adverse events (AEs);
- Vital signs (blood pressure, pulse rate, temporal temperature);
- 12-lead ECG;
- Telemetry;
- Clinical laboratory parameters;
- Physical examination.

Pharmacokinetic endpoints

The following PK parameters were calculated for etripamil (MSP-2017) and its inactive metabolite MSP-2030, whenever possible and appropriate:

Plasma:

- Maximum observed concentration (C_{max}).
- Time from time zero to peak concentration (t_{max}).
- Area under the concentration-time curve from time zero to the last measurable concentration (AUC_{0-t}).
- Area under the concentration-time curve from time zero to infinity (AUC_{0-inf}).
- Terminal half-life ($t_{1/2}$).
- Apparent terminal elimination rate constant (λ_z).
- Apparent clearance (CL/F) and volume of distribution (V_z/F).

Urine:

- Amount excreted unchanged in urine (A_{eu}).
- Fraction of dose excreted in urine (etripamil only) (f_{eu}).
- Renal clearance (CL_R).

Statistical Methods:

Pharmacokinetic

PK parameters were listed and descriptive statistics were calculated for the PK parameters.

Safety and tolerability

AEs were coded with MedDRA and a summary frequency table of adverse events is provided. The severity and relationship to study drug of adverse events were summarized as well.

Vital signs parameters were listed with any values outside the normal range and/or evaluated by the investigator as abnormal flagged. Descriptive statistics of absolute values of systolic and diastolic blood pressure, pulse rate, and body temperature at each time point, were tabulated.

Twelve-lead ECG parameters were listed with any values outside the normal range and/or evaluated by the investigator as abnormal flagged. Summary of overall interpretation were analyzed by count and percentage. Descriptive statistics of absolute values of heart rate, PR interval, QRS interval, QT interval, and QTc (Fridericia) interval at each time point were tabulated.

Clinical laboratory data were listed with any values outside the normal range and/or evaluated by the investigator as abnormal flagged. Descriptive statistics of hematology, chemistry and urinalysis were tabulated.

Summary and Conclusions:

Pharmacokinetics:

Following a single intranasal administration of 70.2 mg [^{14}C]-etripamil containing 96.9 µCi radioactivity to 7 healthy male subjects, a mean recovery of total radioactivity of 70.8% (ranging from 41.4% to 92.4%) was reached.

An average of 28.9% of radioactivity was recovered in urine, 25.6% in feces and 16.3% in tissues/wipes.

Following a single intranasal dose, the peak total radioactivity in plasma was achieved at a median of 90.00 minutes post-dose with mean maximum concentration (C_{max}) of 463 ng-Eq/mL. The mean value of AUC_{0-t} in plasma was 2230 h·ng-Eq/mL.

The peak total radioactivity in whole blood was achieved at a median of 90.00 minutes post-dose with mean maximum concentration (C_{max}) of 311 ng-Eq/mL. The mean value of AUC_{0-t} in whole blood was 890 h·ng-Eq/mL.

The peak plasma etripamil concentration was achieved at a median of 5.00 minutes post-dose with mean maximum concentration (C_{max}) of 67.3 ng/mL. The mean values of AUC_{0-t} and AUC_{0-inf} were 78.6 h·ng/mL, and 84.5 h·ng/mL, respectively. The mean $t_{1/2}$ was 2.92 h, V_z/F was 3500 L, and CL/F was 1070 L/h.

The peak plasma MSP-2030 concentration was achieved at a median of 25.00 minutes post-dose with mean maximum concentration (C_{max}) of 59.9 ng/mL. The mean values of AUC_{0-t} and AUC_{0-inf} were 288 h·ng/mL, and 318 h·ng/mL, respectively. The mean $t_{1/2}$ was 7.10 h, and the ratio of metabolite to parent (M/P; MSP-2030/etripamil) was 4.02.

The amount of etripamil excreted in urine (A_{eu}) was 0.00873 mg, the fraction excreted in urine (f_{eu}) was 0.0124%, and the renal clearance (CL_R) was 0.173 L/h.

Metabolite profiling, identification and radio-quantitation of [^{14}C]-etripamil

The metabolites of [^{14}C]-etripamil in male human subjects following a single intranasal dose of 70.2 mg (96.9 µCi) of [^{14}C]-etripamil were profiled.

Unchanged parent, etripamil; MSP-2030; metabolites M455 b, M601 d and three unknowns (Unk 8, Unk 9, Unk 10) were the only quantifiable radioactive components observed in plasma. In the samples that were time point-pooled across subjects, etripamil, MSP-2030, and Unk 10 accounted for <16%, <47.7%, and <36.3% of the plasma AUC_{0-6h}, respectively. In the AUC-pooled plasma (pooled by subject), etripamil, MSP-2030, and Unk 10 were the major (≥10%) components circulating in plasma, accounting for 27.8%, 32.1%, and 24.3% of the AUC_{0-6h}, respectively.

Several attempts were undertaken to identify the human plasma metabolite Unk 10, but this component could not be identified successfully. However, it seemed to indicate that Unk 10 would likely be formed in vivo and would not be an artifact of sample processing. Unfortunately, due to the limited amount of sample available, additional experiments to identify Unk 10 could not be conducted in the specific context of this study.

The mean dose recovered in feces across the seven subjects (0-168 h post-dose for subjects 1 through 5, and 0-240 h post-dose for subjects 6 and 7) from 0-240 h post-dose was 25.6%.

Unchanged parent was below the level of quantitation in feces, and there were no major metabolites (≥ 10% of the administered dose).

The mean dose recovered in urine across the seven subjects from 0-144 h post-dose was 28.9% (ranging from 9.4 - 48.5%). Unchanged parent was below the level of quantitation in urine and M179 was the only major (≥ 10% of the administered dose) metabolite accounting for 18.8% of the total dose administered.

Safety:
All 7 subjects reported treatment-emergent adverse events (TEAEs), but no treatment-emergent serious adverse event (TESAEs) were reported. All TEAEs were considered mild and resolved without action taken.

The following related TEAEs were reported by more than 2 subjects:

- Nasal congestion (7 subjects, 100%)
- Epistaxis (5 subjects, 71.43%)
- Nasal dryness (4 subjects, 57.14%)
- Headache (5 subjects, 71.43%)
- Lacrimation increased (3 subjects, 42.86%)

Based on the assessment of clinical and laboratory adverse experiences as well as all other safety parameters, a single intranasal dose of 70.2 mg [^{14}C]-etripamil containing 96.9 μCi radioactivity administered to healthy adult male subjects was well tolerated. Only non-serious TEAEs were reported.

Date of Report: 21 June 2022