2. SYNOPSIS

Name of Sponsor/Company McNeil AB ***Name of Finished Product:*** Combination caplet with loperamide hydrochloride 2 mg and simethicone 125 mg ***Name of Active Ingredient:*** Loperamide hydrochloride and simethicone	***Individual Study Table Referring to Part of the Dossier*** ***Volume:*** ***Page:***	(For National Authority Use Only)

Title of Study:

An open-label, randomized, fasting, two-period, single-dose, crossover study to assess bioequivalence between a Combination caplet with loperamide hydrochloride and simethicone [redacted] and Imodium® Express tablets-lyophilizate [redacted] co-administered with Espumisan® capsule [redacted], in healthy volunteers

Investigators:

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Study Centers:

"Scientific and Research Centre Eco-safety" Limited Liability Company;
Russian Federation, 196143, Saint-Petersburg, Yuriya Gagarina prospect, 65

Publication (reference):

None

Study Period:

Date of first enrollment: 28 November 2019

Date of last completed: 26 December 2019

Phase of Development:

Bioequivalence study

Objectives:

Primary Objective:

- To assess bioequivalence between a Combination caplet with loperamide HCl 2 mg and simethicone 125 mg, and Imodium® Express tablets-lyophilizate with loperamide HCl 2 mg (co-administered with Espumisan® capsules with simethicone 40 mg), with respect to the single-dose pharmacokinetics of loperamide HCl (the maximum observed concentration, C_{max}, and the area under the concentration-vs.-time curve until the last measurable concentration, AUC_t, were used to assess bioequivalence).

Name of Sponsor/Company McNeil AB ***Name of Finished Product:*** Combination caplet with loperamide hydrochloride 2 mg and simethicone 125 mg ***Name of Active Ingredient:*** Loperamide hydrochloride and simethicone	***Individual Study Table Referring to Part of the Dossier*** ***Volume:*** ***Page:***	(For National Authority Use Only)

Secondary Objectives:

- To further describe the single-dose pharmacokinetics of loperamide;
- To compare data on adverse events (AEs) after single-dose administration of Combination caplet with loperamide HCl and simethicone, and Imodium® Express tablet co-administered with Espumisan® capsules.

Methodology:

The study was a randomized, single-dose, two-period crossover, open-label bioequivalence study in 48 healthy male and female volunteers under fasting conditions. The investigational products (IPs) were given at separate visits separated by a 7 day wash-out period. The total subject participation duration was 17 days from randomization to end of study safety evaluation.

Overall, 52 subjects were screened and 48 subjects were randomized to one of two dosing sequences, AB or BA (A – test treatment – Combination caplet with loperamide hydrochloride and simethicone [redacted] B – reference treatment – Imodium® Express tablets-lyophilizate [redacted] co-administered with Espumisan® capsules ([redacted] 24 subjects per sequence.

Blood samples were collected at specific time points following each designated dose, i.e. before IP dosing (pre-dose) within 5 min before administration and 0.5, 1, 2, 3, 4, 5, 6, 7, 10, 14, 24, 30, 36, 48, 72 hours after administration of the IP. At the end of the study, the well frozen plasma samples (one of each duplicate sample) were transported by a qualified courier to [redacted], Garrycastle, [redacted] for pharmacokinetic analysis. [redacted] operated according to Good Clinical Practice, Good Laboratory Practice and Good Manufacturing Practice quality standards. Loperamide was determined in human plasma by a fully validated bioanalytical method – liquid chromatography with tandem mass spectrometric detection (LC/MS-MS), with lower limit of quantification (LLOQ) for loperamide in plasma of 0.02 ng/ml.

Individual plasma concentration data from each subject and IP administration and the corresponding blood sampling times were the basic data for the pharmacokinetic analysis. For subject-level analyses, plasma concentrations below the LLOQ that occurred

Name of Sponsor/Company McNeil AB ***Name of Finished Product:*** Combination caplet with loperamide hydrochloride 2 mg and simethicone 125 mg ***Name of Active Ingredient:*** Loperamide hydrochloride and simethicone	***Individual Study Table Referring to Part of the Dossier*** ***Volume:*** ***Page:***	(For National Authority Use Only)

at times before T_{max} were set to zero, whereas concentrations below the LLOQ and observed after T_{max} were omitted.

Number of Subjects (planned and analyzed):

Planned number of subjects – 48.

Number of screened subjects – 52.

Number of randomized subjects – 48.

Number of completed subjects – 44.

Number of subjects in bioequivalence assessment – 42.

Diagnosis and Main Criteria for Inclusion:

Male or female subjects between the ages of 18 and 45 years, inclusive, who were verified as "Healthy" ("Healthy" was defined as absence of any diseases or abnormalities on the basis of physical examination, standard clinical laboratory and instrumental examinations performed at the screening visit). Body Mass Index (BMI) between 18.5 and 30.0 kg/m^2, inclusive, and a total body weight ≥50.0 kg. For females of childbearing potential – a negative urine pregnancy test at the baseline visit. Agreement of males or non-pregnant, non-lactating females to the contraceptive requirements (including female partner's use of a highly effective method of birth control for at least 3 months before the study during the study and for 30 days after the last dose of IP; except for use of hormonal contraceptives for females as per exclusion criterion #7). A personally signed and dated informed consent document before participating in any study-specific procedures, indicating that the subject has been informed of all pertinent aspects of the study. Willingness and ability to comply with scheduled visits, laboratory tests, and other study procedures specified in the protocol e.g. swallowing of tablets.

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

Two combination caplets with Loperamide HCl 2 mg and Simethicone 125 mg [redacted] for oral administration, batch # [redacted]

Reference Therapy, Dose and Mode of Administration, Batch Number:

Six Espumisan® capsules [redacted] for oral administration, batch # [redacted], followed by two Imodium Express tablets-lyophilizate [redacted]

Name of Sponsor/Company McNeil AB	***Individual Study Table Referring to Part of the Dossier***	(For National Authority Use Only)
Name of Finished Product: Combination caplet with loperamide hydrochloride 2 mg and simethicone 125 mg	***Volume:***	
Name of Active Ingredient: Loperamide hydrochloride and simethicone	***Page:***	

[redacted] for oral administration, batch #[redacted]

Duration of Treatment:

Following a minimum 10-hour overnight fasting period (from around 8 pm) at the investigational site an oral dose of the assigned IP was administered to subjects in the morning (around 8 am) according to the randomization scheme under the supervision of site personnel.

Criteria for Evaluation:

Pharmacokinetic Endpoints:

The following pharmacokinetic parameters were determined by means of non-compartmental analysis for each subject and treatment:

C_{max}	maximal observed plasma concentration;
T_{max}	time from IP administration to occurrence of C_{max};
AUC_t	area under the plasma concentration-vs.-time curve from IP administration until the time of the last measurable plasma concentration;
AUC_∞	area under the plasma concentration-vs.-time curve from IP administration extrapolated to infinity;
AUC_{extrap}	extrapolated part of AUC_∞;
λ_z	elimination rate constant;
$t_{1/2}$	elimination half-life (= $\ln 2/\lambda_z$).

Safety Endpoints (according to the Statistical Analysis Plan):

Occurrence of self-reported and observed AEs;

Occurrence of serious AEs (SAEs);

Occurrence of AEs leading to subject discontinuation from the study;

Name of Sponsor/Company McNeil AB ***Name of Finished Product:*** Combination caplet with loperamide hydrochloride 2 mg and simethicone 125 mg ***Name of Active Ingredient:*** Loperamide hydrochloride and simethicone	***Individual Study Table Referring to Part of the Dossier*** ***Volume:*** ***Page:***	(For National Authority Use Only)

The number and percentage of subjects experienced treatment-emergent AEs;

The number and percentage of subjects experienced treatment related AEs, i.e. AEs with a possible, probable, or very likely relation to the IP;

Vital signs (heart rate, systolic blood pressure, diastolic blood pressure) measured at Screening, Pre- and Post-Treatment administration (at -5, 30 and 60 min, 2, 3, 4, 5 and 6 hours) and End-of-Study;

Clinical laboratory parameters measured at Screening and End-of-Study.

Statistical Methods:

The FAS includes all randomized subjects who had any valid pharmacokinetic parameter values from at least one of the two IPs. However, in statistical comparisons of the geometric means of C_{max}, AUC_t, and AUC_∞ of loperamide HCl, in each case only data from subjects with valid parameter values for both IPs were included in the statistical model-fitting process. Safety Analysis Set included all subjects who received at least one dose of study treatment.

For treatment comparisons of C_{max} and AUC_t with respect to loperamide HCl, in each case the parameter geometric mean ratio, $\Psi = \mu_{Test}/\mu_{Reference}$ was estimated. Bioequivalence between the Combination caplet with loperamide HCl 2 mg and simethicone 125 mg (test product) and Imodium® Express tablets-lyophilizate with loperamide HCl 2 mg (co-administered with Espumisan® capsules with simethicone 40 mg; reference product) with respect to single-dose pharmacokinetics of loperamide HCl was concluded if the model-based 90% confidence intervals for the geometric mean ratios, $\Psi = \mu_{Test}/\mu_{Reference}$, of C_{max} and AUC_t, were both entirely within the equivalence interval (0.8000, 1.2500). This procedure is equivalent to rejecting the null hypothesis of non-equivalence at significance level alfa = 5% for each of the two primary pharmacokinetic parameters. For concluding bioequivalence, the bioequivalence criteria had to be fulfilled for both primary parameters.

No imputation of missing data was performed. All statistical analyses were conducted after data base lock. No interim statistical analysis was conducted.

The statistical treatment comparisons with respect to C_{max}, AUC_t, and AUC_∞ of loperamide HCl were, in each case, based on a linear model for log transformed (natural log)

Name of Sponsor/Company McNeil AB	***Individual Study Table Referring to Part of the Dossier***	(For National Authority Use Only)
Name of Finished Product: Combination caplet with loperamide hydrochloride 2 mg and simethicone 125 mg	***Volume:***	
Name of Active Ingredient: Loperamide hydrochloride and simethicone	***Page:***	

pharmacokinetic parameter data. For each parameter evaluation, the statistical model included covariate adjustments for period, treatment sequence, and subject, nested within sequence, as fixed effects. Carryover effects were assumed ignorable.

Descriptive statistics (e.g. mean, standard deviation, median, minimum and maximum for continuous variables; frequency and percentage for categorical variables) were presented for demographic and baseline characteristics. For all pharmacokinetic parameters, descriptive summary measures were presented by treatment. Measured plasma nicotine values were summarized by treatment and measurement time point. For continuous variables statistical summaries included mean values, standard deviations, medians and maximum as well as minimum values. In addition, geometric mean values and coefficients of variation were calculated for C_{max}, AUC_t, and AUC_∞. For T_{max} the frequency distribution additionally was tabulated by treatment.

Descriptive statistics of pharmacokinetic endpoints were presented based on all subjects in the FAS. A comparative statistical analysis of C_{max}, AUC_t, and AUC_∞ of loperamide HCl was performed. In each case an interval estimate, with confidence level 90% for the log-scale treatment mean difference, was derived using estimated means and residual variance estimates from the fitted model. The calculated interval was then back transformed to the original measurement scale to obtain a 90% confidence interval for the ratio of geometric means.

Safety analyses were based on the Safety Analysis Set. The Safety Analysis Set included all subjects who received at least one dose of IP. All AEs reported during the AE reporting period were listed by subject ID and last treatment administered before the AE. Any SAE were listed separately. The number and percentage of subjects experienced AEs were tabulated by IP, AE system organ class, and AE preferred term. In addition, number and percentage of subjects experiencing AEs that are considered IP-related, i.e., either very likely, probably, or possibly related, were tabulated separately by IP, AE system organ class, AE preferred term, and worst recorded severity. Any subjects who discontinued the study due to a treatment-emergent AE were also separately listed by treatment including descriptions of the AEs leading to withdrawal.

SUMMARY – CONCLUSIONS

An open-label, randomized, fasting, two-period, single-dose, crossover study was performed at one investigational site in the Russian Federation from 28 November 2019

Name of Sponsor/Company McNeil AB	***Individual Study Table Referring to Part of the Dossier***	(For National Authority Use Only)
Name of Finished Product: Combination caplet with loperamide hydrochloride 2 mg and simethicone 125 mg	***Volume:***	
Name of Active Ingredient: Loperamide hydrochloride and simethicone	***Page:***	

(first subject screened) to 26 December 2019 (last subject last visit performed).

A total of 48 subjects were randomized to one of two dosing sequences, AB or BA (A – test treatment – Combination caplet with loperamide hydrochloride and simethicone [redacted] B – reference treatment – Imodium® Express tablets-lyophilizate co-administered with Espumisan® capsules [redacted] 24 subjects per sequence.

All 48 randomized subjects received at least one dose of IP, had valid pharmacokinetic parameter values for at least one of the two IPs, and, therefore, were included in FAS.

Among them 42 subjects, who received both IPs, completed the study and had evaluable C_{max} and AUC_t for both study treatments were included in statistical comparisons of main pharmacokinetic parameters of loperamide HCl and bioequivalence assessment.

Four (4) subjects were withdrawn during the conduct of the study: in 2 cases the reason for discontinuation was AE development; while the other 2 subjects were withdrawn due to protocol violation. Another 2 subjects, who received both IPs and completed the study, were excluded from the statistical comparisons and bioequivalence assessment due to the absence of evaluable pharmacokinetic parameters (in blood plasma obtained from subject # [redacted] the pre-dose concentration of loperamide HCl was non-zero, while subject # [redacted] was prescribed concomitant medication 3 hours after IP administration).

None of the subjects had conditions or a medical history that the Principal Investigator considered potentially affecting the conduct of the study or representing a potential risk to the subject during study participation. Two (2) subjects received concomitant medications during the study in order to treat AE, data obtained from both of them, were not used in statistical comparisons and bioequivalence assessment.

The mean (SD) age of the study population was 26.1 (6.42) years and 100% of subjects were white. Overall, 25 (52.1%) of subjects were male. The mean (SD) BMI was 22.3 (3.04) kg/m^2.

Pharmacokinetic Results:

The estimated geometric mean ratios and corresponding 90% confidence intervals for the geometric mean ratios of the primary pharmacokinetic parameters (C_{max} and AUC_t)

Name of Sponsor/Company McNeil AB	***Individual Study Table Referring to Part of the Dossier***	(For National Authority Use Only)
Name of Finished Product: Combination caplet with loperamide hydrochloride 2 mg and simethicone 125 mg	***Volume:***	
Name of Active Ingredient: Loperamide hydrochloride and simethicone	***Page:***	

between Combination caplet with loperamide hydrochloride and simethicone and Imodium® Express tablets-lyophilizate co-administered with Espumisan® capsules were:

- 107.47% [99.10%, 116.56%] for C_{max};
- 113.98% [105.29%, 123.40%] for AUC_t.

These intervals were entirely within the interval 80.00%-125.00%. Thus, this study demonstrated bioequivalence between test product Combination caplet with loperamide hydrochloride and simethicone ([redacted] and reference product Imodium® Express tablets-lyophilizate [redacted] co-administered with Espumisan® capsules [redacted] with respect to loperamide HCl single-dose pharmacokinetic parameters.

Safety Results:

In this study overall 10 (21.7%) subjects reported AEs after administration of Imodium® Express tablets-lyophilizate co-administered with Espumisan® capsules and 10 (21.7%) subjects reported AEs after administration of Combination caplet with loperamide hydrochloride and simethicone.

No deaths and pregnancies were reported during the study.

One SAE (case of cellulitis) developed in 1 subject (#[redacted]) after administration of Imodium® Express tablets-lyophilizate co-administered with Espumisan® capsules. The clinical diagnosis was "Phlegmon in the area of left elbow joint". This SAE was severe, required hospitalization and surgical intervention and resulted in subject's withdrawal. Subject was hospitalized, received surgical incision and drainage of the phlegmon and prescribed antibacterial therapy. As a result of treatment full recovery was observed and SAE outcome was assessed as resolved. SAE was considered not related to study treatment.

Another AE (case of acute pharyngitis of mild severity developed after Combination caplet with loperamide hydrochloride and simethicone), also assessed as not related to study therapy resulted in subject withdrawal from the study due to medical reasons based on investigator's opinion.

Name of Sponsor/Company McNeil AB	***Individual Study Table Referring to Part of the Dossier***	(For National Authority Use Only)
Name of Finished Product: Combination caplet with loperamide hydrochloride 2 mg and simethicone 125 mg	***Volume:***	
Name of Active Ingredient: Loperamide hydrochloride and simethicone	***Page:***	

Overall, at least one treatment-related AE developed in 3 (6.5%) subjects after administration of test product and in 4 (8.7%) subjects after administration of reference products. Among AEs occurred after test product administration there were 2 cases (4.3%) of headache and 1 case (2.2%) of nausea. Among those related to reference products administration were headache, abdominal distension, abnormal erythrocyte sedimentation rate and hypotension – in 1 case (2.2%) each.

All AEs except for 1 case of cellulitis (SAE) were mild, including all cases of treatment-related AEs. Two (2) cases (SAE cellulitis and AE pharyngitis) resulted in subject's withdrawal. Another case of acute pharyngitis was revealed during the second dosing period and required prescription of concomitant therapy 3 hours after second IP administration, therefore, subject was not withdrawn, but pharmacokinetic data obtained from this subject were not used in statistical comparisons of pharmacokinetic parameters and in bioequivalence assessment.

In conclusion, both of the study products were well tolerated. Reported treatment-related AEs were mild and consistent with the known safety profile of the active ingredient (loperamide HCl).

Conclusions:

This study demonstrated the bioequivalence between the test product Combination caplet with loperamide hydrochloride and simethicone [redacted] and reference product Imodium® Express tablets-lyophilizate ([redacted] co-administered with Espumisan® capsules [redacted] with respect to single-dose pharmacokinetic parameters for loperamide HCl.

The study products were well tolerated, with only mild treatment-related AEs. Reported treatment related AEs were consistent with the known safety profiles of the active ingredient (loperamide HCl). One SAE (cellulitis) was documented in a healthy subject with possible causal relationship with performed venipuncture. This SAE resulted in hospitalization, was treated with surgical intervention and antibacterial therapy, and resolved completely. No deaths or pregnancies were registered.

Date of the Report: 31 July 2020