2. SYNOPSIS

Name of Sponsor/Company McNeil AB ***Name of Finished Product:*** Combination tablet with paracetamol, guaifenesin and phenylephrine hydrochloride ***Name of Active Ingredient:*** Paracetamol, guaifenesin, phenylephrine	***Individual Study Table Referring to Part of the Dossier*** ***Volume:*** ***Page:***	(For National Authority Use Only)

Title of Study:

A single-dose, randomized, two-period, crossover bioequivalence study between a Combination tablet with paracetamol, guaifenesin and phenylephrine hydrochloride (Wrafton Laboratories Limited, United Kingdom) and Vicks Active SymptoMax Plus, powder for oral solution (Wrafton Laboratories Limited, United Kingdom) in healthy adult volunteers

Investigator:

[redacted]

Study Center:

[redacted] Saint-Petersburg, Russian Federation

Publication (reference):

None

Study Period:

Date of first subject enrollment 02 July 2017

Date of last subject enrollment 05 July 2017

Date of last subject completed study 13 July 2017

Phase of Development:

Bioequivalence study

Objective:

Primary Objective:

Comparison of pharmacokinetics and assessment of bioequivalence between the following treatments:

- Two tablets of Combination tablet with paracetamol, guaifenesin, and phenylephrine hydrochloride containing 250 mg paracetamol, 100 mg guaifenesin, 5 mg phenylephrine hydrochloride, and
- One sachet Vicks Active SymptoMax Plus containing 500 mg paracetamol, 200 mg guaifenesin, and 10 mg phenylephrine hydrochloride with respect to the single-

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dose pharmacokinetics of paracetamol, guaifenesin, and phenylephrine (based on total phenylephrine concentration), respectively.

Secondary Objectives:

- To compare study treatments with respect to single-dose pharmacokinetics of unconjugated phenylephrine.
- To compare data on adverse events after single-dose administration of combination tablet with paracetamol, guaifenesin, and phenylephrine hydrochloride (two tablets) and Vicks Active SymptoMax Plus (one sachet, powder for oral solution).

Methodology:

This was a single-dose, randomized, two-period cross-over study with 72 healthy male and female subjects. The investigational products were given at separate visits separated by 7±3 days. The total duration of each subject's participation was up to 3.5 weeks.

A total of 72 subjects (36 subjects per sequence) were randomized to one of two dosing sequences, AB or BA, where A - Test product Combination tablet with paracetamol, guaifenesin and phenylephrine hydrochloride [redacted] 2x (250/100/5 mg); B - Reference product Vicks Active SymptoMax Plus containing paracetamol, guaifenesin and phenylephrine hydrochloride 1x (500/200/10 mg).

Number of Subjects (planned and analyzed):

Screened: 85. Randomized: 72. Planned: 72. Analyzed: 72.

Included in the bioequivalence assessment for paracetamol (evaluable C_{max} and AUC_t values for both study products): 69

Included in the bioequivalence assessment for guaifenesin (evaluable C_{max} and AUC_t values for both study products): 68

Included in the bioequivalence assessment for phenylephrine total (evaluable C_{max} and AUC_t values for both study products): 67

Diagnosis and Main Criteria for Inclusion:

Healthy male or female subjects between the ages of 18 and 45 years, inclusive. The subjects had to have a Body Mass Index (BMI) between 18.5 and 30 kg/m^2. Subjects smoke no more than 10 cigarettes per day and had no uncontrollable habit of chewing or inhaling nicotine products. Male or non-pregnant, non-lactating female agreed to the contraceptive requirements (including female partner's use of a highly effective method of

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birth control for at least 3 months before the study, during the study, and for 30 days after the last dose of study drug 3 months before the study, during the study and for 30 days after the last dose of study drug.

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

Compound Name Paracetamol + Guaifenesin + Phenylephrine Hydrochloride

Product Name Combination tablet with paracetamol, guaifenesin and phenylephrine hydrochloride [redacted]

Dosage Form Film coated tablet

Unit Dose Paracetamol 250 mg Guaifenesin 100 mg Phenylephrine hydrochloride 5 mg

Route of Administration Oral

Physical Description White capsule shaped tablet, embossed with the letters "PGP", free from specks and blemishes

Manufacturer Wrafton Laboratories limited [redacted] United Kingdom

Batch number [redacted]

Following an overnight fast, two tablets were administered orally with 250 mL of ambient temperature water. Tablets were to be swallowed whole without prior chewing.

Duration of Treatment:

The investigational products were given at separate visits separated by 7±3 days. The total duration of each subject's participation was up to 3.5 weeks.

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

Compound Name Paracetamol + Guaifenesin + Phenylephrine Hydrochloride

Product Name Vicks Active SymptoMax Plus

Dosage Form Powder for oral solution

Unit Dose Paracetamol 500 mg Guaifenesin 200 mg Phenylephrine hydrochloride 10 mg

Route of Administration Oral

Physical Description Fine crystalline powder, off white or white with yellowish or

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grayish hue, free of large aggregates or inclusions, with typical lemon and menthol flavor

Manufacturer Wrafton Laboratories Limited, [redacted] United Kingdom

Batch number [redacted]

Following an overnight fast, the contents of one sachet were dissolved in 250 mL of hot (not boiling) water. It was allowed to cool to tolerable temperature, and then ingested promptly by the subject.

Criteria for Evaluation:

Pharmacokinetics:

Blood samples were drawn within 5 minutes before dosing (pre-dose), and at 5, 10, 15, 20, 25, 30, 40, 60, 75, 90, 105 minutes, as well as 2, 2.25, 2.5, 3, 4, 6, 8, and 12 hours after drug administration. A ± 2 minutes window was allowed for sampling during the first hour, and up to ± 10 minutes during the sampling period thereafter.

The frozen plasma samples (3 aliquots of each sample) were transported to [redacted] for analysis.

Paracetamol and guaifenesin were assessed simultaneously in the same plasma sample, whereas phenylephrine (total and free) was measured separately. All assessments were performed by LC MS/MS (liquid chromatography with tandem mass spectrometry) analysis, with Lower Limits of Quantification (LLOQ) being 100 ng/ml, 5000 ng/ml, 5 ng/ml and 5 pg/ml, for paracetamol, guaifenesin, phenylephrine (total) and phenylephrine (unconjugated), respectively.

Primary endpoints:

The following pharmacokinetic (PK) parameters for paracetamol, guaifenesin, and phenylephrine:

- the maximum observed plasma concentrations (C_{max}),
- the area under the plasma concentration-vs.-time curves from start of drug administration until the time of the last measurable concentration (AUC_t),

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- the area under the concentration-vs.-time curve extrapolated to infinity (AUC_{inf}),
- the extrapolated part of AUC_{inf}, AUC_{Extrap},
- the time at which the maximum plasma concentration is observed (t_{max}),
- the terminal elimination rate constant (λz) and half-life ($t_{1/2}$),
- the mean residence time (MRT).

Secondary endpoints:

- C_{max}, AUC_t, AUC_{inf}, AUC_{Extrap}, t_{max}, λz, $t_{1/2}$, and MRT for unconjugated phenylephrine

Safety:

- The occurrence of Adverse Events (AEs)

Statistical Methods:

For subject-level analyses, plasma concentrations below the LLOQ that occurred at times before t_{max} were set to zero, whereas concentrations below the LLOQ and observed after t_{max} were omitted.

The PK calculations were performed using Phoenix WinNonlin (version 6, Pharsight). Output was checked against the bioanalytical data. For descriptive statistics and safety evaluation SAS software version 9.4 (SAS Institute, USA) was used.

Statistical tests were based on two one-sided t-tests at a significance level of 5% each. No imputation of missing data was performed.

The Full Analysis Set includes all randomized subjects who have any valid PK endpoint values from at least one investigational product. PK data from the Full Analysis Set are summarized descriptively. However, only data from randomized subjects who have valid PK endpoint values from both the Test and Reference products were included in the statistical model.

Statistical comparisons of the test and the reference products with respect to C_{max}, AUC_t, and AUC_{inf}, respectively, for paracetamol, guaifenesin, and phenylephrine were based on a linear model for log transformed (natural log) PK parameter data. Product was included as

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a fixed factor in the statistical model. For each parameter evaluation, the statistical model also included covariate adjustments for period and sequence and subject, nested within sequence as fixed effects. Carry-over effects were assumed ignorable. Point and interval estimates of parameter geometric mean ratios were derived using estimated means and residual variance estimates from the fitted model.

The extrapolated part of AUC_{inf} (AUC_{Extrap}), the time to C_{max} (t_{max}), the estimated terminal elimination constant (λz), the estimated terminal half-life ($t_{1/2}$) and the mean residence time (MRT) are summarized descriptively.

Bioequivalence Analysis:

All statistical analyses were conducted at the end of the trial after data base closure. No interim statistical analysis was conducted.

Bioequivalence between test and reference products was to be concluded if the model-based 90% confidence intervals (CI) for the geometric mean ratios, μTest/μReference, of the primary parameters, i.e., C_{max} and AUC_t of paracetamol, guaifenesin, and phenylephrine were in the equivalence interval (0.8000, 1.2500).

Safety analysis:

All subjects who received at least one dose of investigational product were included in the Safety Analysis Set. In each case, dosing status was determined by the last treatment administered before the AE. The number and percentage of subjects experiencing AE were tabulated by treatment, system organ class, and preferred term. In addition, number and percentage of subjects experiencing AE that were considered treatment-related, i.e., either very likely, probably, or possibly related, were tabulated separately by treatment, system organ class, preferred term, and worst recorded severity. The latest version of the Medical Dictionary for Regulatory Activities (MedDRA) 19.0 was employed as AE classification system.

SUMMARY – CONCLUSIONS

A total of 85 subjects were screened. A total of 72 subjects (36 subjects per sequence) were randomized to one of two dosing sequences, AB or BA, where A - Test product Combination tablet with paracetamol, guaifenesin and phenylephrine hydrochloride [redacted] 2x (250/100/5 mg); B - Reference

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product Vicks Active SymptoMax Plus containing paracetamol, guaifenesin and phenylephrine hydrochloride 1x (500/200/10 mg).

Sixty-nine (69) subjects completed the study and 3 subjects withdrew from the study before the second dosing visit (one subject due to withdrawal consent and 2 subjects due to positive alcohol test).

None of the subjects had conditions or a medical history that the Principal Investigator considered would affect the conduct of the study or to represent a potential risk to the subject during study participation. None of the subjects received concomitant medications during the study.

The mean (SD) age of the study population was 24.4 (4.78) years; 100.0% of subjects were white; 65.3% (47) subjects were male.

Pharmacokinetics Results:

The estimated geometric mean ratio between Combination tablet with paracetamol, guaifenesin and phenylephrine hydrochloride and Vicks Active SymptoMax Plus and 90% CI for the geometric mean ratios of the primary parameters, i.e., C_{max} and AUC_t were:

- For paracetamol: 91.93% (86.69%, 97.48%) for C_{max}, 97.70% (95.17%, 100.30%) for AUC_t;
- For guaifenesin: 100.52% (91.07%, 110.96%) for C_{max}, 99.82% (94.04%, 105.96%) for AUC_t;
- For phenylephrine: 111.02% (106.39%, 115.86%) for C_{max}, 99.06% (96.01%, 102.21%) for AUC_t.

These intervals were entirely contained within the interval 80.00% - 125.00%. Thus, in this study bioequivalence was demonstrated between Combination tablet with paracetamol, guaifenesin and phenylephrine hydrochloride and Vicks Active SymptoMax Plus with respect to single-dose PK parameters for paracetamol, guaifenesin and phenylephrine.

The rate and extent of exposure of unconjugated phenylephrine were higher with the new Combination tablet with paracetamol, guaifenesin and phenylephrine hydrochloride than with Vicks Active SymptoMax Plus powder for oral solution. The estimated geometric mean ratio between Combination tablet with paracetamol, guaifenesin and phenylephrine

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hydrochloride and Vicks Active SymptoMax Plus and 90% CI for the geometric mean ratios of the C_{max} and AUC_t, for phenylephrine unconjugated, were: 215.15% (189.62%, 244.11%) for C_{max}, 160.52% (144.14%, 178.77%) for AUC_t.

Safety Results:

In this study four AEs were reported: two AEs after single-dose administration of Combination tablet with paracetamol, guaifenesin and phenylephrine hydrochloride and two AEs after Vicks Active SymptoMax Plus; all AEs were mild severity. Two AEs (2 subjects with dizziness after single-dose administration of Combination tablet with paracetamol, guaifenesin and phenylephrine hydrochloride) were considered related to the study product, and dizziness is listed in expected adverse reactions to paracetamol. No serious adverse events were reported in this study.

Conclusions:

Bioequivalence was demonstrated between the new Combination tablet with paracetamol, guaifenesin and phenylephrine hydrochloride and Vicks Active SymptoMax Plus powder for oral solution with respect to single-dose PK parameters for paracetamol, guaifenesin and phenylephrine.

The rate and extent of exposure of unconjugated phenylephrine were higher with the new Combination tablet with paracetamol, guaifenesin and phenylephrine hydrochloride than with Vicks Active SymptoMax Plus powder for oral solution.

The study products were well tolerated, with only mild AEs. Reported AEs were consistent with the known safety profiles of the active ingredients (paracetamol, guaifenesin and phenylephrine).

Date of the Report: 03 July 2018