2. SYNOPSIS

Name of Sponsor/Company McNeil AB ***Name of Finished Product:*** Xylometazoline+Dexpanthenol metered nasal spray (0.1 mg+5 mg/dose) ***Name of Active Ingredient:*** Xylometazoline 1 mg/ml and dexpanthenol 50 mg/ml	***Individual Study Table Referring to Part of the Dossier*** ***Volume:*** N/A ***Page:*** N/A	(For National Authority Use Only)

Title of Study:

An observer-blind, multi-centre, randomized, parallel-group study to compare the efficacy and safety of two formulations of xylometazoline/dexpanthenol nasal spray for the treatment of nasal congestion caused by an acute upper respiratory tract infection in adults

Investigators:

Five investigators from 5 investigative sites:

Dmitry A. Lioznov (site #1001); Tatiana E. Morozova (site #1002); Vladimir V. Popov (site #1003); Zhanna M. Sizova (site #1004); Konstantin A. Zakharov (site #1005)

Study Centers:

Five investigative sites in the Russian Federation:

Site #1001: First St. Petersburg State Medical University n.a. I. P. Pavlov, located at 6/8 Lev Tolstoy st., 197022, St. Petersburg, Russia.

Site #1002: First Moscow State Medical University n. a. I. M. Sechenov, University Clinical Hospital #1, located at 6 build 1, Bolshaya Pirogovskaya str., Moscow, 119991, Russia.

Site #1003: Railway Clinical Hospital n.a. Semashko at Lublino station JSC "Russian Railways", located at 23, bld. 1, Stavropolskaya str., Moscow, 109386, Russia.

Site #1004: City Polyclinic #2 of Healthcare Department of city of Moscow, located at 12, Fruktovaya str., Moscow, 117556, Russia.

Site #1005: Research centre Eco-safety Limited Liability Company, located at 65, Yuri Gagarina , St. Petersburg, 196143, Russia.

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Publication (reference):

Not applicable

Study Period: ***Phase of Development: III***

Date of first enrollment: 26 February 2018

Date of last completed: 2 May 2018

Objective:

Primary Efficacy Objective:

- To demonstrate non-inferiority of a xylometazoline/dexpanthenol formulation versus a marketed reference product, on self-assessed **nasal congestion** after 72 hours of treatment.

Secondary Efficacy Objectives:

- To compare self-assessments of **nasal congestion** following treatment with a xylometazoline/dexpanthenol formulation versus a marketed reference product, after 24 and 120 hours of treatment.
- To compare self-assessments of **rhinorrhoea** following treatment with xylometazoline/dexpanthenol formulation versus a marketed reference product after 24, 72 and 120 hours of treatment.
- To evaluate assessments of **crust formation** following treatment with xylometazoline/dexpanthenol formulation versus a marketed reference product after 24 hours and 72 hours of treatment and at the end of treatment (120 hours).
- To evaluate assessments of **dryness of nasal mucosa** following treatment with xylometazoline/dexpanthenol formulation versus a marketed reference product

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after 24 hours and 72 hours of treatment and at the end of treatment (120 hours).

- To evaluate assessments of **redness of nasal mucosa** following treatment with xylometazoline/dexpanthenol formulation versus a marketed reference product after 24 hours and 72 hours of treatment and at the end of treatment (120 hours).
- To evaluate assessments of **edema of nasal mucosa** following treatment with xylometazoline/dexpanthenol formulation versus a marketed reference product after 24 hours and 72 hours of treatment and at the end of treatment (120 hours).
- To evaluate the global evaluations of study treatments by the subjects after 72 hours of treatment.

Other Secondary objective:

- To evaluate the compliance with dosing regimen during the study.

Methodology:

This observer-blind, multi-center, randomized, parallel-group study in adults was designed to demonstrate non-inferiority between two formulations of xylometazoline/dexpanthenol nasal sprays in terms of efficacy and safety, when the products were used according to labeled instructions in a home based setting.

After the baseline assessments, the subjects received xylometazoline/dexpanthenol nasal spray or marketed reference nasal spray according to randomization and diaries for the full study period of in total five days (five 24 hour periods). The first dose was taken at the site under supervision. The study nurse scheduled visits for 24 hours, 72 hours and 120 hours after this first dose and the subjects were released for home based treatment. At the 72 hours visit, the primary and secondary efficacy endpoints were assessed by the subject and the Investigator, safety was followed up and subjects also evaluated the treatment in a global assessment. At the 24 hours visit and at the final visit, after a maximum of 5 full

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days (120 hours) of treatment, all secondary endpoints were assessed and safety was followed up.

Number of Subjects (planned and analyzed):

Planned: 140 Analyzed: 140 (Per-Protocol analysis set – 140 subjects; Safety analysis set - 140)

Diagnosis and Main Criteria for Inclusion:

Subjects of 18 years of age or older, suffering from nasal congestion with a clinical diagnosis of acute upper respiratory tract infection where symptoms of nasal congestion persisted for minimum of 3 hours and maximum of 36 hours.

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

Xylometazoline+Dexpanthenol metered nasal spray (0.1 mg+5 mg/dose), each dose/spray contains xylometazoline 0.1 mg and dexpanthenol 5 mg. One spray into each nostril, 3 times daily. Lot Number 17FD0020.

Duration of Treatment:

Maximum of 5 days.

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

Nasic® nasal spray - xylometazoline 1 mg/ml and dexpanthenol 50 mg/ml nasal spray, each dose/spray contained xylometazoline 0.1 mg and dexpanthenol 5 mg. One spray into each nostril, 3 times daily. Lot number: 929116.

Criteria for Evaluation:

Efficacy:

Primary endpoint:

- Change from baseline in self-assessment of **nasal congestion** after 72 hours of treatment.

Secondary endpoints:

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- Change from baseline in self-assessment of **nasal congestion** at 24 and 120 hours post dose.
- Change from baseline in self-assessment of **rhinorrhea** after 24 hours, 72 and 120 hours post dose.
- Assessment of **nasal crusting** after 24 hours, 72 hours and 120 hours post dose.
- Assessment of **dryness of nasal mucosa** after 24 hours, 72 hours and 120 hours post dose.
- Assessment of **redness of nasal mucosa** after 24 hours, 72 hours and 120 hours post dose.
- Assessment of **edema of nasal mucosa** after 24 hours, 72 hours and 120 hours post dose.
- Global evaluation assessments by subjects at 72 hours post dose.

All assessments were subjective and performed by the subjects for nasal congestion and rhinorrhea using five-point scales (0-4) and by Investigator (anterior rhinoscopy) for crust formation and for dryness and edema of nasal mucosa using a binary scale (absent/present). The Investigator assessed the redness of mucosa on a three-point scale (0-2).

Other secondary endpoint:

- Subject compliance with the study medication dosing regimen by reporting of doses taken in subject diary.

Safety:

Safety endpoints:

- Frequency and severity of treatment emergent AEs reported during the study.
- Frequency and severity of AEs possibly, probably, or very likely related to the study drug during study treatment.

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- Occurrence of serious AEs (SAEs), and AEs resulting in pre-mature withdrawal from the study.

Statistical Methods:

Success Criteria:

For each efficacy variable, treatment comparisons were performed at the three post baseline visits, 24, 72 and 120 hours, respectively. Non-inferiority was to be concluded if the upper bound of a two-sided 95% confidence interval for the difference in mean change from baseline in self-assessment of nasal congestion after 72 hours of treatment, study product vs. reference therapy, was below 0.35.

Primary Endpoint:

Between-treatment comparison of the change from baseline in the nasal congestion symptom score 72 hours after baseline post dose was based on the Per-protocol analysis set. A repeated measures linear model, jointly including data for the two treatment arms from the three post baseline visits in the analysis, and including terms for treatment and visit and the corresponding baseline value as a covariate was used. The within-subject covariance structure was assumed unstructured. Treatment-by-visit and baseline-by-visit terms were included in order to compare the treatments at a specific visit. A 95% confidence interval for the treatment mean value difference was calculated. Summary statistics was provided by treatment.

Secondary Endpoints:

Change from baseline in self-assessment of nasal congestion at 24 and 120 hours post dose and in self-assessment of rhinorrhea after 24 hours, 72 and 120 hours post dose was evaluated statistically as described above.

The distribution of subjects' ratings with respect to Investigator subjective assessment of nasal crusting, nasal mucosa dryness, redness of nasal mucosa and presence of edema were tabulated with the number and percentage for each category and treatment and time-point.

Global evaluation assessments by subjects at 72 hours post dose were tabulated with the number and percentage for each category and treatment.

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Other endpoint:

Diary data on compliance, the number of doses taken was summarized descriptively by treatment and study day.

Safety endpoints:

The safety analysis was based on subjects in the Safety analysis set.

All adverse events reported during the AE reporting period were listed by subject ID and treatment.

The number and percentage of subjects experiencing treatment emergent AEs and treatment-related AEs were tabulated by treatment using the MedDRA coding dictionary. Subjects experiencing an SAE were listed separately. Treatment-related AEs included events marked as being at least possibly related to study treatment. Subjects were counted only once for each system organ class and preferred term.

SUMMARY – CONCLUSIONS

A total of 140 subjects were randomized, 140 were included in the Per-Protocol analysis set, and 140 were included in the Safety analysis set. The mean (standard deviation, S.D.) age of the study population was 36.2 (12.10) years in the J & J nasal spray group and 33.5 (12.19) in the Nasic® group. Almost all subjects were white, only 1 (1.4%) subject in the J & J nasal spray group and 2 (2.8%) in the Nasic® group were Asian. 37.7% (26) and 53.5% (38) of subjects in test product and reference product groups, respectively, were male.

Efficacy Results:

- Primary efficacy endpoint: score of nasal congestion calculated by self-assessment scale was decreased after 72 hours of treatment in both study groups. The mean (S.D.) change was -1.4 (0.72) in the test product group and -1.5 (0.77) in the reference product group. After 72 hours after start of treatment, the mean difference between study groups together with a 95% confidence interval was -0.04 [-0.254; 0.178]. Non-inferiority of Xylometazoline+Dexpanthenol metered nasal spray

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(0.1 mg+5 mg/dose) versus the reference product Nasic® is confirmed, as the upper bound of a two-sided 95% confidence interval for the difference is below 0.35.

- Secondary endpoint: score of nasal congestion calculated by self-assessment scale was decreased after 24 and 120 hours of treatment in both study groups as well. The mean changes was -0.4 (0.55) in both groups after 24 hours and -2.1 (0.62) in the J & J nasal spray group and -2.2 (0.79) in the Nasic® group after 120 hours.
- Rhinorrhea score was decreased during the study in both groups. There were no patients with moderate or higher degree of this symptom at the Day 6 (end of treatment); while at Day 1 almost all patients (64 (92.8%) in the test product and 65 (91.6%) in the reference group) had these degrees of rhinorrhea.
- Secondary endpoints which were evaluated by Investigator subjective assessment were nasal crusting, mucosal dryness, presence of edema of nasal mucosa and the redness of nasal mucosa. The frequency of nasal crusting was presented in 10.1% (7) of subjects and in 14.1% (10) of subjects at the Day 1, and in 1.9% (1) of subjects and in 5.5% (3) of subjects at the Day 6 in the test and reference product groups, respectively. Mucosal dryness was presented in 31.9% (22) and in 35.2% (25) of subjects at Day 1 and in 5.6% (3) of subjects and in 3.6% (2) of subjects at Day 6 in test and reference product groups, respectively. Presence of edema of nasal mucosa was determined in 84.1% (58) of subjects in test product group and in 81.7% (58) of subjects in the reference product group at Day 1. At the end of the study (Day 6) this sign was found in 5.6% (3) in the J & J nasal spray group and in 16.4% (9) of subjects in the Nasic® group. The hyperemic nasal mucosa was defined in 84.1% (58) of subjects and in 84.5% (60) of subjects at Day 1 in the test and reference product groups, respectively, and only in 1.9% (1) of subjects in the J & J nasal spray group and in 5.5% (3) of subjects in the Nasic® group at Day 6.
- The subject global evaluation of study treatment was performed. It was found that 54 (78.3%) of subjects in the J & J nasal spray group and 56 (78.8%) of subjects in the Nasic® group were satisfied or very satisfied with the treatment. The quantity of

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subjects who experienced easiness in breathing to a good or great extent was 53 (76.8%) and 55 (77.5%) in test and reference product groups, respectively. A feeling of recovery from dryness (a good deal recovered and a great deal recovered together) were experienced in 50 (72.5%) in the J & J nasal spray group and in 44 (62.0%) in the Nasic® group after six days of treatment.

Safety Results:

All study medications were well tolerated and no safety issues were identified.

- Overall, 12 (17.4%) subjects in the J & J nasal spray group and 8 (11.3%) subjects in the Nasic® group had adverse events.

Treatment-related adverse events (including adverse events with relation to treatment of probable, possible or very likely) were reported by 3 (4.3%) of subjects in the test product group and 3 (4.2%) of subjects in the reference product group.

- The most common adverse events were in the blood and lymphatic system (mainly eosinophilia) and were reported by 5.8% of study subjects only in the J & J nasal spray group.
- No deaths or other serious adverse events were reported.
- There was no reported withdrawal from study.

Conclusions:

This study demonstrated that, after 72 hours of treatment, the test product Xylometazoline+Dexpanthenol metered nasal spray (0.1 mg+5 mg/dose) dosed three times daily was non-inferior to the reference product Nasic® (containing the same dose of active ingredients as the test product) dosed three times daily in the treatment of nasal congestion in adults. After the investigational treatment a decrease of such symptoms of acute respiratory tract infection as nasal congestion and rhinorrhea was determined. Other evaluated symptoms, which were investigated by Investigator (anterior rhinoscopy), were improved after the study treatment. It seemed to follow the same pattern in both groups for all symptoms.

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All study medications were well tolerated. The treatment-related adverse events were present in 4.3% of subjects in test product group and in 4.2% of subjects in the reference product group. No deaths or other serious adverse events that would require subject withdrawal or changes of the study treatment were reported. ***Date of the Report:*** 27 September 2018		