# 2. SYNOPSIS

| ***Name of Sponsor/Company*** Janssen Pharmaceutica NV and McNeil AB, Johnson & Johnson<br>***Name of Finished Product:*** Benzocaine 8 mg lozenge<br>***Name of Active Ingredient:*** Benzocaine (JNJ-129649-AAA) | ***Individual Study Table Referring to Part of the Dossier***<br>***Volume:***<br>***Page:*** | (For National Authority Use Only) |
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***Title of Study:***

A multi-center, double-blind, randomized, parallel-group, placebo-controlled study to determine the efficacy and safety of a benzocaine lozenge for symptomatic treatment of sore throat caused by acute upper respiratory tract infection in adults

***Investigators:***

Nineteen investigators from 19 investigative sites in the Russian Federation:
Vladimir Popov; Olga Kropova; Tatiana Stepanova; Irina Sinitsina; Ekaterina Mirzabekyan; Marina Ballyuzek; Alexander Gofman; Andrey Obrezan; Tatiana Pak; Zhanna Paltsman; Rodion Oseshnyuk; Polina Khlyabova; Elena Pavlysh; Ekaterina Filippova; Irina Sedavnykh; Veronika Popova; Elena Reznik; Alina Agafina; and Svetlana Berns.

***Study Centers:***

Nineteen investigators from 19 sites in the Russian Federation

***Publication (reference):***

Not Applicable

***Study Period:*** ***Phase of Development:*** 3

***Date of first enrollment:*** 2 February 2018

***Date of last completed:*** 21 April 2018

***Objective:***

Primary Efficacy Objective:

- To evaluate the therapeutic effect of a benzocaine 8 mg lozenge versus placebo during a single dose assessment period of 3 hours with respect to time to meaningful pain relief.

Secondary Objectives:

- To evaluate onset of therapeutic effect of a benzocaine 8 mg lozenge versus placebo in terms of time to perceptible pain relief.
- To evaluate the therapeutic effect of a benzocaine 8 mg lozenge versus placebo in terms of self-assessed pain intensity.
- To evaluate the therapeutic effect of a benzocaine 8 mg lozenge versus placebo in terms of self-assessed difficulty in swallowing.
- To evaluate the duration of therapeutic effect of benzocaine 8 mg lozenge versus placebo in terms of period of time with perceptible pain relief.
- To evaluate the duration of meaningful pain relief of a benzocaine 8 mg lozenge versus placebo in terms of period of time with meaningful pain relief.

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- To compare subject ratings of their sore throat condition in a subject questionnaire at baseline and after 2 and 72 hours of treatment with benzocaine 8 mg lozenge versus placebo.
- To compare global evaluation of study treatments by subject at the end of the single dose treatment and after 72 hours of treatment with benzocaine 8 mg lozenge versus placebo.
- To evaluate the compliance with dosing regimen during the study.

Safety Objective:

- To evaluate the safety and tolerability of study medication based on adverse events (AEs) reporting throughout the study.

***Methodology:***

This multi-center, double-blind, randomized, parallel-group, placebo-controlled study consisted of two parts: an initial single-dose efficacy and safety part performed at the clinic on the first treatment day and a safety follow-up part with an intermediate site visit during home-based treatment.

Following screening and randomization, subjects suffering from throat pain caused by an acute upper respiratory tract infection received a single dose of either, benzocaine 8 mg or placebo lozenge, and were followed for a 3-hour assessment period where primary and secondary efficacy measurements were collected. Upon intake of the investigational product dose, by the subject, study personnel were responsible for starting the timers that were used to assess subject-reported pain relief. Subjects were instructed to immediately inform the appropriate member of study personnel once they had experienced perceptible pain relief (onset of therapeutic effect) and meaningful pain relief. The responsible member of study personnel stopped the relevant timer (specifically set for onset of perceptible or meaningful pain relief) as soon as the subjects announced that they had experienced either perceptible or meaningful pain relief.

Subjects were also instructed to immediately inform study personnel the moment that they no longer experienced perceptible or meaningful pain relief so that the relevant timer could be stopped. The time points collected by use of the timers were used to derive the onset and duration of both perceptible and meaningful pain relief.

The subjects assessed their pain intensity and the degree of difficulty swallowing during multiple assessment time points throughout the 3-hour period on 11-point numerical rating scales (NRS) where 0=no pain/not difficult, and 10=very severe pain/very difficult. Pain intensity assessments were conducted at screening. Assessments for both pain intensity and degree of difficulty swallowing were conducted at baseline, 2.5, 5, 7.5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60 minutes and then every 10 minutes up to and including 180 minutes (3-hour) after intake.

The subjects rated their sore throat condition in a subject questionnaire at baseline and after 2 and approximately 72 hours of treatment. The subjects also rated how satisfied they were with the investigational product as a treatment for sore throat by way of the global evaluation assessment at the end of the 3-hour assessment period and after approximately 72 hours of treatment.

After initiation of treatment and the initial efficacy part of the study (Day 1), the subjects were released for home-based treatment according to the investigational label to complete the safety part of the study. The subjects were equipped with diaries, to record number of investigational product doses taken per day, and additional benzocaine 8 mg lozenges or placebo, according to randomization. The subjects were instructed to follow the treatment label and return to the site for safety follow up at study Day 4 (target approximately 72 hours of treatment) and at the end of treatment, at Day 6 (target approximately 120 hours of treatment).

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***Number of Subjects (planned and analyzed):***

Planned: 260 subjects (benzocaine 8 mg lozenge group: 130 subjects; placebo lozenge group: 130 subjects); Analyzed: 259 subjects (benzocaine 8 mg lozenge group: 128 subjects; placebo lozenge group: 131 subjects) for efficacy and safety data sets.

***Diagnosis and Main Criteria for Inclusion:***

Subjects aged 18 years or older, suffering from throat pain caused by acute upper respiratory tract infection.

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

Benzocaine lozenge, 8 mg, Lot Number TG1002A. One lozenge to be dissolved slowly in the mouth every 2 hours as needed, maximum 6 lozenges per day (48 mg benzocaine per day) up to a maximum of 5 days.

***Duration of Treatment:***

Maximum of 5 days

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

Non-medicated (Placebo) lozenge indistinguishable in appearance and dosing schedule from the active 8 mg medicated benzocaine lozenge, Lot Number TI1008A.

***Criteria for Evaluation:***

***Efficacy:***

Primary Efficacy Endpoint:

- Time to meaningful pain relief.

Secondary Endpoints:

- Time to perceptible pain relief (onset of therapeutic effect).
- Continuous period of time within the 3-hour test period with perceptible pain relief.
- Continuous period of time within the 3-hour test period with meaningful pain relief.

Endpoints to assess the therapeutic effect in terms of subjects' self-ratings of pain intensity:

- Change from baseline in sore throat pain intensity self-ratings at 2.5, 5, 7.5, 10 and 15 minutes after intake, respectively.
- Mean change from baseline in sore throat pain intensity self-ratings based on all assessments up to 15, 30, 60, 120, and 180 minutes after intake as well as during the second (60+ to 120 minutes) and third hour (120+ to 180 minutes) after intake, respectively.

Endpoints to assess the therapeutic effect in terms of subjects' self-ratings of difficulty swallowing:

- Change from baseline in self-ratings of difficulty swallowing at 2.5, 5, 7.5, 10 and 15 minutes after intake, respectively.
- Mean change from baseline in self-ratings of difficulty swallowing based on all assessments up to 15, 30, 60, 120, and 180 minutes after intake as well as during the second (60+ to 120 minutes) and third hour (120+ to 180 minutes) after intake, respectively.

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Subjects' self-ratings of their sore throat condition:

- Change from baseline in self-ratings, referring to the time period since start of treatment, of the extent to which the sore throat condition diverts the subject's concentration, assessed after 2 and 72 hours of treatment, respectively.
- Change from baseline in self-ratings, referring to the time period since start of treatment, of the extent to which the sore throat condition made it difficult for the subject to speak, assessed after 2 and 72 hours of treatment, respectively.
- Subject ratings with respect to the degree of experienced improvement in their sore throat condition, assessed after 2 and 72 hours of treatment, respectively.
- Subject ratings with respect to the extent to which they were able to forget their sore throat condition, assessed after 2 and 72 hours of treatment, respectively.
- Subject ratings with respect to the degree of overall satisfaction with their assigned study medication for sore throat, rated at the end of the 3-hour assessment period and 72 hours of treatment, respectively.
- 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.
- Occurrence of serious AEs, and AEs resulting in premature withdrawal from the study.

## *Statistical Methods:*

All statistical tests were 2-sided with significance level of 5%. Presented confidence intervals (CIs) were 2-sided and had CI level 95%.

Sample Size: Treatment differences in the distribution of the primary efficacy endpoint, time to meaningful pain relief, as measured during a single dose assessment period of 3 hours were evaluated statistically using survival analysis methods. Time to 'worthwhile pain relief' with benzocaine lozenges has previously been studied in a placebo-controlled setting. An 8 mg benzocaine lozenge was compared to placebo and the results indicated a clear difference between treatments. For example, the estimated median time to 'worthwhile pain relief' was 20 minutes with active treatment, (95% CI = [16, 27]), whereas the lower bound of the corresponding CI for placebo lozenge was 45 minutes with somewhat less than 50% of placebo subjects reaching 'worthwhile pain relief' within 120 minutes. Data on time to 'worthwhile pain relief' as recorded in this study has been used to estimate a reasonable size for the current study. Specifically, using the observed proportions of placebo subjects reaching 'worthwhile pain relief' by time in the study as a basis, it was assumed that at least 50% of the observed differences in success proportions between the active lozenge and placebo was to be retained in the current study. Under this assumption the expected median time to meaningful pain relief was approximately 35 minutes or below for the active treatment arm and thus, would constitute a clinically relevant advantage relative to placebo. Based on 10,000 simulations of this scenario (Nquery Advisor® 7.0), a two-sided log rank test at significance level 5% would require 128 subjects in each treatment arm for a statistical power of 90%, assuming no drop-outs. After including some allowance for drop-outs, in total 260 subjects were to be included in the study with 130 subjects in each treatment arm.

## Efficacy Analyses

Primary Endpoint:

The primary endpoint was evaluated statistically using survival analysis methods. Specifically, treatment differences in the distributions of time to meaningful pain relief was statistically evaluated within the framework of a Cox proportional hazards model including adjustment for baseline pain intensity score. The estimated hazard ratio from the fitted model, benzocaine lozenge 8 mg versus placebo, was presented together with a 95% CI. Kaplan-Meier estimates of the proportion of subjects having reached meaningful pain relief was calculated by treatment with 95% CI at 1, 2.5, 5, 7.5, 10, 15, 20, 25, 30, 45, 60, 90, 120, 150, and 180 minutes post administration. Estimated quartiles with 95% CIs were calculated separately for the 2 study treatments.

Secondary Endpoints:

Time to perceptible pain relief was evaluated statistically and analogously to the analysis of the primary efficacy endpoint. Treatment differences in the distributions of the continuous period of time within the 3-hour test period with meaningful pain relief and perceptible pain relief, (duration of therapeutic effect), as assessed by the subject using a dedicated timer, were statistically evaluated with a Mann-Whitney test stratified for baseline pain intensity (van Elteren test).

Mean treatment differences in change from baseline in sore throat pain intensity self-ratings at 2.5, 5, 7.5, 10, and 15 minutes after intake, respectively, were for each assessment time point analyzed within the framework of an Analysis-of-Covariance (ANCOVA) model adjusted for baseline pain intensity score.

Mean treatment differences in mean change from baseline in sore throat pain intensity self-ratings based on all assessments up to 15, 30, 60, 120, and 180 minutes after intake as well as during the second (60+ to 120 minutes) and third hour (120+ to 180 minutes) after intake, respectively, were in each case analyzed within the framework of an ANCOVA model adjusted for baseline pain intensity score.

Mean treatment differences in change from baseline in self-ratings of difficulty swallowing at 2.5, 5, 7.5, 10, and 15 minutes after intake, respectively, were for each assessment time point analyzed within the framework of an ANCOVA model adjusted for baseline difficulty of swallowing score.

Mean treatment differences in mean change from baseline in self-ratings of difficulty swallowing based on all assessments up to 15, 30, 60, 120, and 180 minutes after intake as well as during the second (60+ to 120 minutes) and third hour (120+ to 180 minutes) after intake, respectively, were in each case analyzed within the framework of an ANCOVA model adjusted for baseline difficulty swallowing score.

Mean treatment differences in change from baseline in self-ratings, referring to the time period since start of treatment, of the extent to which the sore throat condition diverted the subject's concentration, assessed after 2 and 72-hour of treatment, respectively, were in both cases analyzed within the framework of an ANCOVA model adjusted for the baseline rating.

Mean treatment differences in change from baseline in self-ratings, referring to the time period since start of treatment, of the extent to which the sore throat condition makes it difficult for the subject to speak, assessed after 2 and 72-hour of treatment, respectively, were in both cases analyzed within the framework of an ANCOVA model adjusted for the baseline rating.

The distribution of subjects' ratings with respect to the extent to which they were able to forget their sore throat condition and the degree of experienced improvement in their sore throat condition, assessed after 2 and 72-hour of treatment, respectively, were in both cases compared statistically between the treatments using a Mann-Whitney test stratified for baseline pain intensity, (a van Elteren test).

The distribution of subjects' ratings with respect to the degree of overall satisfaction with their assigned investigational product for sore throat, rated at the end of the 3-hour assessment period and after approximately 72-hour of treatment, respectively, was in both cases compared statistically between the treatments using a Mann-Whitney test stratified for baseline pain intensity, (a van Elteren test).

In application of the van Elteren test stratified by baseline pain intensity, the following 4 strata based on the baseline pain intensity records were used: Baseline pain score=5, Baseline pain score=6, Baseline pain score=7, and Baseline pain score ≥8.

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Other Endpoints: Diary data on compliance, ie, the number of doses taken were summarized descriptively by treatment and study day.

### Safety Analyses

All AEs reported during the AE reporting period were listed by subject ID. Serious AEs were to be listed. The number and percentage of subjects experiencing treatment-emergent AEs were tabulated by treatment, system organ class (SOC), and preferred term (PT). In addition, the number and percentage of subjects experiencing treatment-emergent AEs were also tabulated by treatment, SOC, PT, and worst recorded severity. Any subjects who discontinued the study due to a treatment-emergent AEs were separately listed by treatment including descriptions of the AEs leading to withdrawal. Heart rate, systolic and diastolic blood pressure, and axillary body temperature data summaries were presented by treatment and assessment time point. Measurements of the clinical laboratory parameters were also listed. Previous and concomitant medications were listed.

## *SUMMARY – CONCLUSIONS*

A total of 271 subjects were screened; 11 subjects failed screening. Overall, 260 subjects were randomized: benzocaine 8 mg group; 129 subjects and placebo group; 131 subjects. Two hundred and fifty-six (256) subjects completed study treatment and 4 subjects discontinued (benzocaine 8 mg group: 1 subject withdrew consent and 1 subject was discontinued due to an AE of white blood cells count increased; placebo group: 2 subjects discontinued due to unspecified reasons mentioned as “other”).
The mean (S.D.) age of the study population was 37.9 (14.58) years in the benzocaine 8 mg group and 38.2 (14.86) years in the placebo group; more than 97% of subjects in both groups were white. Overall, 55.8% of subjects were female, with a slightly higher proportion of female subjects in the placebo group (59.5%) than in the benzocaine group (51.9%).

### *Efficacy Results:*

This study demonstrated that benzocaine 8 mg lozenge was efficacious in symptomatic treatment of sore throat caused by acute upper respiratory tract infection in adults as compared with a placebo lozenge with respect to:

- Time to meaningful and perceptible pain relief.
- Duration of meaningful and perceptible pain relief.
- Change from baseline in sore throat pain intensity scores at 5, 7.5, 10, and 15 minutes post dose as well as with respect to mean change from baseline in throat pain at all evaluated assessment time intervals up to 120+ to 180 minutes.
- Change from baseline in difficulty swallowing scores at 5, 7.5, 10 and 15 minutes post dose as well as with respect to mean change from baseline in difficulty swallowing scores at all evaluated assessment time intervals up to 60+ to 120 minutes.
- Change from baseline in self-ratings for diverted concentration after 2 and 72 hours of investigational product intake.
- Self-ratings of experienced improvement and ability to forget condition after 2 and 72 hours of investigational product intake.
- Self-ratings of overall satisfaction after 3 and 72 hours of investigational product intake.
- Change from baseline in self-ratings of difficulty in speaking at 2 hours.

No statistically significant differences were observed between benzocaine 8 mg lozenge when compared with placebo lozenge for change in pain intensity scores at 2.5 minutes, mean change in self-ratings of difficulty

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swallowing at 2.5 minutes, the mean change in self- ratings of difficulty swallowing during the120+ to 180 minutes interval, or change from baseline in self-ratings of difficulty in speaking at 72 hours.

### *Safety Results:*

Both investigational products were well tolerated, and no safety issues were identified. The two treatment groups did not differ significantly with respect to severity or occurrence of AEs.

- Overall, 15.6% of subjects reported treatment-emergent AEs in the benzocaine 8 mg group and 9.9% subjects in the placebo group.
- The most common treatment-emergent AEs included white blood cell count increased (2.3% of subjects in each group) and white blood cell urine positive (2.3% of subjects in the benzocaine group and 1.5% of subjects in the placebo group). All other treatment-emergent AEs occurred at frequencies of less-than 2%.
- Treatment-related AEs were reported by 6.3% of subjects in the benzocaine 8 mg group and 3.1% in the placebo group.
- No deaths or other serious AEs were reported.
- All treatment-emergent AEs were mild or moderate in severity, and all treatment-related AEs were mild in severity.
- Discontinuation from study was reported for 1 subject due to an AE of white blood cell count increased in benzocaine 8 mg group.

### *Conclusions:*

- This study demonstrated that benzocaine 8 mg lozenge is efficacious in symptomatic treatment of sore throat caused by acute upper respiratory tract infection in adults as compared with a placebo lozenge with respect to the primary endpoint of time to meaningful pain relief.
- The estimated hazard ratio (HR) for achieving meaningful pain relief from benzocaine lozenge when compared with placebo during the 3 hour treatment single-dose assessment period was 2.98 (95% CI: 2.15, 4.12); $p<0.001$.
- The results for the secondary endpoints of time to perceptible pain relief, duration of meaningful and perceptible pain relief, changes in sore throat pain intensity and difficulty swallowing scores, self-ratings for diverted concentration, experienced improvement, and ability to forget condition, self-ratings for overall satisfaction, and for difficulty in speaking strongly support the efficacy of benzocaine 8 mg lozenge for the symptomatic treatment of sore throat.
    - The estimated HR for achieving perceptible pain relief from benzocaine lozenge when compared with placebo during the 3 hour treatment single-dose assessment period was 1.51 (95% CI: 1.16, 1.96); p=0.002.
    - Timer assessments demonstrated median time to perceptible and meaningful pain relief of 3.69 minutes (95% CI: 2.92, 4.28) and 10.35 (95% CI: 8.75, 12.35) minutes, respectively, for the benzocaine group. The estimated median duration of perceptible and meaningful pain relief for the benzocaine group as measured by timer assessments was 58.79 and 27.63 minutes, respectively.
    - The benzocaine group demonstrated a statistically significantly greater decrease in pain intensity from baseline as early as 5 minutes post-dose when compared with the placebo group. The difference between treatment groups was maintained for all time intervals evaluating mean decrease from baseline including the 60+ to 120 minutes and 120+ to 180 minutes intervals.

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- A larger reduction in difficulty swallowing scores was seen in the benzocaine group than in the placebo group as early as 5 minutes post-dose and for all time intervals evaluating mean decrease from baseline except 120+ to 180 minutes interval.
- Change from baseline in self-ratings of diverted concentration after 2 and 72 hours of investigational product intake, self-ratings of experienced improvement and ability to forget condition after 2 and 72 hours of investigational product intake and self-ratings of overall satisfaction after 3 and 72 hours of investigational product intake, and change from baseline in self-ratings of difficulty in speaking at 2 hours were statistically significantly better for subjects who received benzocaine lozenges when compared with those that received placebo.

- Benzocaine 8 mg lozenges were well tolerated. No deaths or serious AEs were reported during the course of the study, and all AEs were mild or moderate in severity. No safety issues or new safety signals were identified. Overall, the AEs observed in this study were consistent with the established safety profile of benzocaine 8 mg lozenges.

***Date of the Report:*** 27 September 2018