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Sponsor: Sanofi **Drug substance(s):** AMBROXOL HYDROCHLORIDE	**Study Identifiers:** U1111-1202-9392, NCT03583658 **Study code:** LPS15328
Title of the study: A randomised, double-blind, placebo controlled, parallel group, multicentre trial to assess the efficacy and safety of ambroxol lozenges 20 mg (hard boiled lozenges) versus placebo for the relief of sore throat pain in patients with acute pharyngitis (LPS15328) (DELICIOUS study)	
Study center(s): 11 centers in South Africa, each center screened and randomized at least 1 patient	
Study period: Date first patient enrolled: 30/Jun/2018 Date last patient completed: 02/Sep/2019	
Phase of development: 3	
Objectives: The primary objective of this study was to assess the efficacy of the new hard boiled ambroxol lozenges 20 mg for the relief of sore throat pain in patients with acute pharyngitis. The secondary objective of this study was to assess the safety of the new hard boiled ambroxol lozenges 20 mg in patients with acute pharyngitis.	
Methodology: This clinical trial was a Phase 3, randomized, double-blind, placebo controlled, parallel group, multicenter trial to assess the efficacy and safety of ambroxol lozenges 20 mg (hard boiled lozenges) versus matching placebo for the relief of sore throat pain in patients with acute pharyngitis of at least moderate intensity (score of 6 or greater on a 0-10 point ordinal numerical scale). Approximately 390 patients would be randomized into the trial (195 in each treatment group) in 11 trial sites.	
Number of patients**:**	Planned: 390 Randomized: 390 Treated: 390
Evaluated:	Efficacy: ITT: 390; mITT 388 Safety: 390
Diagnosis and criteria for inclusion: Inclusion criteria: Male and female patients at least 18 years of age with sore throat due to acute pharyngitis with an onset no more than 72 hours prior to Visit 1, and pain intensity score ≥ 6 on a 0-10-pont ordinal numerical rating scale who had signed a written informed consent. Key Exclusion criteria: Patients with a known allergy to and/or hypersensitivity to ambroxol or any other ingredients, patients with suspected drug dependency and/or alcohol abuse, and patients with symptoms of primarily bacterial pharyngitis or bacterial secondary infection (clinical findings, ie, fever).	

Study treatments

Investigational medicinal product(s): Ambroxol 20 mg hard boiled lozenges

Formulation: Ambroxol 20 mg hard boiled lozenges

Route(s) of administration: Oromucosal

Dose regimen: 1 lozenge up to 6 times per day, up to 3 days

Noninvestigational medicinal product(s): Placebo

Formulation: Lozenges (hard boiled lozenges)

Route(s) of administration: Oromucosal

Dose regimen: 1 lozenge up to 6 times per day, up to 3 days

Duration of treatment: Up to 3 days

Duration of observation: Up to 4 days

Criteria for evaluation:

Efficacy:

The primary endpoint was the time-weighted average of the pain intensity difference (PID) from pre-dose over the first 3 hours after the first lozenge, expressed as the ratio of the pre-dose baseline, sum of PID ($SPID_{norm,0-3h}$)

Secondary endpoints were:

- $SPID_{norm,0-24h}$
- 3-hour patient assessment of efficacy
- 24-hour patient assessment of efficacy

Exploratory endpoints were:

- Time course of PID from pre-dose baseline over the first 24h
- Time to perceptible pain relief after the first lozenge
- Time to the second lozenge after the first lozenge
- Number of lozenges taken during each treatment day
- Patient assessment of efficacy at the end of each treatment day
- Assessment of redness of the pharyngeal mucosa
- Number of patients who discontinued treatment due to lack of efficacy
- Final overall investigator and patient assessments of efficacy

Safety:

The safety endpoints were assessed by:

- Adverse events
- Patient's assessment of tolerability at 3h, 24h, and at the end of each treatment day
- Final overall investigator and patient assessments of tolerability at the end of the trial

Statistical methods: The primary efficacy endpoint was tested for the mITT population using an analysis of variance (ANOVA) including treatment as fixed effect. Treatment differences were estimated by reference to the adjusted least square means (LSmeans) and the corresponding 95% confidence intervals (CI).

All secondary efficacy endpoints were analyzed using the mITT population. ANOVA analysis on $SPID_{norm\ 0\text{-}24h}$) was performed using the same statistical model as defined above. A logistic regression model including the term of treatment, with baseline pain intensity (PI) as a covariate, was fitted to analyze the multinomial endpoints of 3-hour and 24-hour patient assessment of efficacy.

Exploratory efficacy endpoints were also analyzed or summarized using the mITT population. For the time course of PID from pre-dose baseline over the first 24 hours, restricted maximum likelihood estimation based on a mixed-effect model for repeated measures analysis was used to obtain adjusted means for the treatment effects. This model included treatment and time as discrete fixed effects, baseline PI as a continuous fixed effect, and interaction between time and treatment as well as baseline PIand time.

For the endpoints time to perceptible pain relief after the first lozenge and time to the second lozenge after the first lozenge, a Kaplan-Meier analysis was performed and the log-rank test was used.

A logistic regression model including the term of treatment, with baseline PI as a covariate was fitted to analyze the further endpoints of the daily and final overall patient assessment of efficacy as well as the final overall investigator assessment of efficacy.

For the assessment of redness of the pharyngeal mucosa, the percentage of patients with deterioration, stable or amelioration was analyzed using Chi-Squared Test p-value.

Descriptive statistics were used to analyze the number of lozenges used during each treatment day and number of patients who discontinued treatment due to lack of efficacy.

Safety analyses were descriptive, based on the safety population (defined as randomized population who received at least one dose of IMP).

Summary: A total of 422 patients were screened in 11 centers in South Africa; 390 (92.4%) were randomized to 1 of 2 treatment groups (196 patients in ambroxol group and 194 patients in placebo group) and all of them were exposed to the study medication and included in the safety analysis. Among them 6 (1.5%) patients permanently discontinued from treatment (4 (2.0%) in ambroxol group and 2 (1.0%) in placebo group) due to adverse events, lack of efficacy and withdrawal by subject.

Population characteristics: Patients' demographics and characteristics at baseline were similar between the 2 treatment groups. The mean age of ITT population was 36.9 years old (37.1 in ambroxol and 36.7 in placebo group. All patients have scored 6 or greater on a 0-10 point pain intensity at pre-dose baseline. This measurement was missing in 2 patients in ambroxol group, who were excluded from the mITT population.

A relatively high proportion (9.7% patients in ambroxol group and 7.2% in placebo group) of patients took prohibited concomitant medication. The most frequently used prohibited medications were analgesics (12 (6.1%) patients versus 11 (5.7%) patients in ambroxol and placebo groups, respectively), other prohibited concomitant medications used were anti-inflammatory agents (8 (4.1%) patients versus 3 (1.5%) patients, respectively) and antihistamines (6 (3.1%) patients versus 4 (2.1%) patients, respectively).

Baseline Pain Intensity scores (mean ± standard deviation) in ambroxol and placebo groups were 7.09 ± 0.98 and 6.93 ± 0.92, respectively.

Exposure to ambroxol and placebo was similar (median exposure of 69.9 hours and 71.3 hours respectively).

Efficacy results:

The primary objective of the study was not met; superiority of ambroxol versus placebo was not demonstrated. The means (SD) for the primary endpoint ($SPID_{norm,0\text{-}3h}$) were -0.386 (0.259) in ambroxol group and -0.366 (0.243) in placebo group (p=0.443 for ambroxol versus placebo). Treatment groups were also comparable when subgroups of gender, tobacco smoking habit, alcohol habit, oral temperature at baseline, baseline redness of pharyngeal mucosa group and baseline pain intensity group were analyzed for the primary efficacy endpoint. All sensitivity analyses on the primary efficacy endpoint yielded results consistent with those of the primary analysis.

Comparable results between treatment groups were found for the secondary endpoints including $SPID_{norm,0\text{-}24h}$, and patient

assessment of efficacy at 3 and 24 hours after the first lozenge intake.

Comparable results between treatment groups were also found for exploratory endpoints including time course of PID from pre-dose baseline over the first 24 hours, time to perceptible pain relief after the first lozenge, time to the second lozenge intake after the first lozenge, number of lozenges taken during each treatment day, patient assessment of efficacy at the end of each treatment day and final investigator assessment, assessment of redness of pharyngeal mucosa, and number of patients who discontinued treatment due to lack of efficacy.

Safety results:

In this study, comparable incidences of TEAEs between the 2 treatment groups (23 (11.7%) patients in ambroxol group versus 18 (9.3%) patients in placebo group) were observed, and no AEs not likely covered by the medical concept of the listed adverse drug reactions for ambroxol or the underlying disease were reported. The most common TEAEs in ambroxol patients were headache (3.1%) and dizziness (2.6%).

No treatment-emergent SAEs occurred during the study.

No AESIs like pregnancy, symptomatic overdose, anaphylactic shock, increase of ALT or SCARs occurred during the study.

Incidence of the TEAEs leading to treatment discontinuation was greater in the ambroxol group versus placebo group (4 (2.0%) patients in ambroxol group [oropharyngeal pain, diarrhea, throat irritation and pharyngitis (aggravation)] versus 1 (0.5%) patient in placebo group [erythema]).

No deaths occurred during the study.

The percentage of patients and investigators who considered the IMP tolerability to be from good to excellent was comparable in both treatment groups.

Oral temperature decreased similarly and negligibly in both treatment groups.

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