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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NA
		Study Code:	L_8620
Generic drug name:	Lysine acetylsalicylate	**Date:**	21/Feb/2008

Title of the study:	A French, multicentre, placebo-controlled, randomised, double-blind, parallel group study to compare the efficacy and safety of lysine acetylsalicylate 1800 mg, administered either by oral route or by gargling then ingestion, in the treatment of pain due to acute tonsillitis of infectious origin in adults.		
Investigator(s):	Professor Christian DUBREUIL Centre Hospitalier Lyon Sud, 69495 PIERRE BENITE LYON cedex		
Study center(s):	Approximately 20 centres in France: General Practitioners		
Publications (reference):			
Study period: Date first patient enrolled: 03-dec-2004 Date last patient completed: 23-may-2005		**Phase of development:** IV	
Objectives:	**Primary objective:** • To demonstrate the efficacy of a dose of LAS 1800 mg by oral route (LAS 1800 mg > placebo) in the treatment of pain due to acute tonsillitis of infectious origin in adults. **Secondary objectives:** • To evaluate the efficacy of LAS 1800 mg by gargling then ingestion as compared to that of LAS 1800 mg by oral route (gargling then ingestion > oral route) in the treatment of tonsillitis pain in adults, over the first two days of treatment. • To evaluate the clinical safety of LAS 1800 mg by gargling then ingestion and LAS 1800 mg by oral route.		
Methodology:	A French, multicentre, placebo-controlled, randomised, double-blind, parallel group study.		
Number of patients:	Planned: 180	Randomized: 199	Treated: 198
Evaluated:	Efficacy/Pharmacodynamics: 183	Safety: 199	
Diagnosis and criteria for inclusion:	Outpatients. Male or female patients aged 18 to 65 years. • Erythematous or erythematous/blistering tonsillitis. • Tonsillitis score ≥ 4. • Pain when swallowing: recent onset (≤ 2 days) and with intensity ≥ 50 mm on a visual analog scale • First dose of treatment before 5 pm.		

Investigational product: **Dose:** **Administration:**	**LAS 1800 mg** packet containing 1800 mg of LAS = Aspegic® 1000 mg
Duration of treatment: 3 days	**Duration of observation: a maximum of 8 days**
Reference therapy: **Dose:** **Administration:**	**Placebo of LAS 1800 mg**
Criteria for evaluation:	
Efficacy:	**Primary efficacy endpoint** The primary endpoint of this trial was: **SPID: "SUM OF PAIN INTENSITY DIFFERENCES" = SUM OF PID**, pain intensity being evaluated using a VAS (0 mm: no pain; 100 mm: very intense paint) at D1 H0, 5', 15', 30', 45', H1, 1hr 30', 2hr, 3hr, 4hr, 6hr Calculated until D1H6 and D2H12, according to the following equation: $SPID = \sum PID_i \times [\Delta time_i]$ with $PID_i = P_i - P_0$ and $\Delta time_i$ = time (hours) elapsed since the previous measurement **Secondary efficacy endpoints** The following criteria were defined as secondary: • **Intensity of pain** (VAS): - PID (PID at D1T30min = main secondary endpoint), - PIDmax, - Responders (pain reduction ≥ 25% or 50%). • **Pain relief** assessed using a 5-point scale (0: none, 1: mild, 2: moderate, 3: severe, 4: total) at the same times: pain relief scores (PRS), PRSmax, sum of PRS = SPRS (area under the curve), • Overall assessment of **the efficacy of treatment** on **D1**H6, **D2** H12. • **Patient satisfaction:** (1: exceptionally satisfied, 2: very satisfied, 3: satisfied, 4: neither satisfied nor unsatisfied, 5: unsatisfied): **D1** H6, **J2**H12
Safety:	Collection of adverse events declared spontaneously by the patient

Statistical methods:	Statistical tests were interpreted with a bilateral α-risk of 5%. Descriptive statistics were produced based on the types of variables: – for quantitative variables: number of patients, means, standard deviations, minimum and maximum values, medians, quartiles and number of missing data were presented, – for qualitative variables: number of patients, percentages and number of missing data were presented, **Primary efficacy population:** "intention-to-treat" population (ITT population): patients who were randomized and exposed (having received at least one dose of treatment), with at least one evaluation of the primary endpoint after baseline. **Secondary efficacy population:** per-protocol population (PP population): ITT patients after exclusion of patients presenting with a major deviation from the protocol **Bilateral tests with** a **= 5%.** **Continuous variables:** ANOVA, Wilcoxon's test, covariance analysis, log-rank test. **Categorical variables:** CHI-2 or Fisher test. Last observation carried forward (LOCF). **Primary analysis:** SPID after correction of SED, in ITT, comparison of the groups using Wilcoxon's test. The following correction rules were applied to VAS of SED: • recalculation of data over theoretical times after verification of SEDs • application of LOCF technique for all missing data starting with H15; • calculation by linear graphic interpolation of missing data at T5 min (interpolation between T0 and T15 min values); • calculation of SPID impossible if T0 data missing; • no calculation of SPID if, between T0 and H6, two consecutive missing occur, or if 3 data or more are missing (LOCF technique not applied). VAS values measured at times not consistent with other times of SED were deleted and left missing. Only 6 patients presented with missing and/or aberrant data.

Summary:	
Efficacy results:	For analysis of the primary endpoint, it was not possible to apply the LOCF procedure for 6 patients (5 in the LAS "oral route" group and 1 patient in the "placebo" group). Analysis of the primary endpoint in ITT and in PP was performed on a reduced population after removal of 6 patients for whom missing data could not be corrected. **ITT (and PP) analysis shows a markedly significant SPID in favour of the LAS gargling group versus placebo, and a significant SPID versus placebo for LAS oral route.** **<u>Secondary efficacy endpoints</u>** **<u>Pain when swallowing (VAS):</u>** Patients in LAS "oral route" perceived a reduction in pain intensity that was statistically significant between T 30 min and the fourth hour, as compared to placebo. Patients in the LAS gargling group perceived a reduction in pain intensity that was statistically significant between the first evaluation (T 5min) and the fourth hour, as compared to placebo. The PIDs of patients in the "LAS gargling" group were greater than those of patients in the "LAS oral route" group at all of the study evaluation times, but were not significantly different. **PID at D1T90 min:** Analysis of the **main secondary endpoint** shows a significant difference between patients in the "LAS oral route" group and those in the placebo group, and a very significant difference between patients in the "LAS gargling" group and those in the placebo group. There was no statistically significant difference between the two treated groups. The results of analyses of SPID at D2 and D1+D2 show no statistically significant difference between the treatment groups. **25% responders:** A 25% reduction in pain at each interval. Starting with T 30 min, the number of responders in the "LAS oral route" group was significantly greater than in the placebo group. For the "LAS gargling" group, the difference was significant starting at T 15 min. There was no difference between the 2 groups treated with LAS.

	The maximum peak response was, at H2: **– 67.7% responders in the "LAS oral route" group** **– 69% responders in the "LAS gargling" group** **50% responders:** A 50% reduction in pain at each interval. At T 30 min and T 90 min, the number of responders in the "LAS oral route" group was significantly greater than in the placebo group. From T 30 min to H6, the number of responders in the "LAS gargling" group was significantly greater than in the placebo group. At H6, it was observed that the "LAS gargling" group was significantly higher than the "LAS oral route" group. **Maximum response peak:** **– At T 90 min: 33.9% responders in the "LAS oral route" group** **– At T2: 39.4% responders in the "LAS gargling" group** **Time until response:** The time until response (reduction in VAS score of ≥ 25%) over the 6 hours was significantly shorter in the "LAS oral route" (54.53 ± 58.53 min) and the "LAS gargling" (46.02 ± 51.84 min) groups than in the placebo group (82.75 ± 87.26 min) (LAS oral route-placebo: p=0.0109; LAS gargling-placebo: p=0.0100). The time until response (reduction in VAS score of ≥ 50%) over the 6 hours was significantly shorter in the "LAS oral route" (77.34 ± 76.33 min) and the "LAS gargling" (90.39 ± 89.64 min) groups than in the placebo group (141.10 ± 125.04 min) (LAS oral route-placebo: p=0.0289; LAS gargling-placebo: p=0.0018). **<u>Efficacy of treatment according to the patients:</u>** At D2H12, 46.5% of patients deemed the efficacy of "LAS gargling" treatment to be good, very good or excellent; this value was 66.0% at D2H12. In the "LAS oral route" group, these values were 41.5% at D1H6 and 63.2% at D2H12. These percentages at D1H6 were significantly higher than in the placebo group. At D1H6, 25.4% of patients deemed the efficacy of "LAS gargling" treatment to be good or excellent; this value was 43.7% at D2H12. This percentage was significantly higher than in the 2 other groups at D1H6. **<u>Patient satisfaction:</u>** The two groups of treated patients had similar levels of satisfaction, which were significantly higher than the placebo group.
Safety results:	A total of 18 patients reported 21 adverse events (AE) during the trial. One AE was declared to be serious (patient in, "LAS gargling" group, right tonsil phlegmon occurring after 2nd dose on D2). 3 patients ended the study following an AE. The vast majority of AEs were mild in intensity.
Date of report:	11-Apr-2007