Pierre Fabre Médicament
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1. TITLE PAGE

CLINICAL STUDY REPORT

STUDY OF EFFICACY AND SAFETY OF V0498 VERSUS PLACEBO IN ACUTE SORE THROAT PAIN

Investigational product:	V0498 ibuprofen / lozenge / 25 mg
Study Design:	Multicenter, randomized, placebo-control parallel group study
EudraCT number:	**2012-004423-20**
Protocol number:	V00498 TA 3 01
Phase of development:	Phase III
Date of first enrolment:	15 Feb 2013
Date of last completed:	25 Jun 2013
Coordinating Investigator:	Yves DONAZZOLO, MD, MSc Eurofins Optimed 1, Rue des Essarts, 38610 Gières Phone: + 33 (0)4 38 37 27 47
Sponsor Representative for study report:	Athmane BOUROUBI, MD, Head of Therapeutic Area Centre de Recherche et Développement 3, Avenue Hubert Curien, 31100 Toulouse Phone: +33 (0)5 34 50 63 45
Date of report:	**18 December 2013**

Study performed in compliance with Good Clinical Practice.

2. SYNOPSIS

Name of Company: Pierre Fabre Médicament	**Individual Study Table**	**(For National Authority Use Only)**
Name of finished product: V0498 lozenge	**Referring to Module 5 of the Dossier**	
Name of active substance *(or ingredient)*: Ibuprofen (as sodium dihydrate)	**Vol.: .....Page: .....**	

Title of study:	Study of Efficacy and Safety of V0498 versus Placebo in Acute Sore Throat Pain
Coordinating Investigator:	Yves DONAZZOLO, MD, MSc, France
Investigators:	France: 1 Principal Investigators (PI) + coordinating investigator (CI); Germany: 1 PI; UK: 2 PIs; Latvia: 13 PIs
Study center(s):	17 centers in 4 countries in Europe (France [1 center], Germany [1 center], UK [2 centers] and Latvia [13 centers; 3 of which did not recruit patients])
Publication (reference):	No publication based on this study has been written to date.

Studied period:		**Phase of development:**
Date of first enrolment:	15 Feb 2013	III
Date of last completed:	25 Jun 2013	

Objectives:

Primary:

<u>To compare the effect of V0498 lozenges to that of placebo</u>:

- **on the Total Pain Relief (TOTPAR)** assessed on a 7-point rating scale called **the Sore Throat Relief Scale (STRS) over 120 min** after the start of sucking of first study drug administered

Secondary:

<u>To compare the effect of V0498 ibuprofen lozenges versus placebo</u>:

- **on the TOTPAR** assessed on a 7-point rating scale called **the STRS** over 15, 30, 45, 60, and 90 min after the start of sucking of the first study drug administered.
- **on the TOTPAR 33% and TOTPAR 50%** (number of patients presenting respectively a pain relief ≥33% and a pain relief ≥50% of the percentage of maximum TOTPAR [MaxTOTPAR]) 15, 30, 45, 60, 90, and 120 min after the start of sucking of the first study drug administered.
- **on the STRS** 15, 30, 45, 60, 90, and 120 min after the start of sucking of the first study drug administered, on the evening of D1, and on D2, D3, and D4.
- **at the onset of meaningful pain relief** within 120 min after the start of sucking the first study drug administered.
- **on the normalized Sore Throat Pain Intensity Difference (PID) on swallowing** from baseline to 15, 30, 45, 60, 90, and 120 min after the start of sucking of the first study drug administered, on the evening of D1, and on D2, D3, and D4.
- **on the Sum of Pain Intensity Differences on swallowing ($SPID_{norm}$)** from baseline to 15, 30, 45, 60, 90, and 120 min after the start of sucking of the first study drug administered.
- **on the global efficacy rating by the patient** assessed on a 4-point rating scale 120 min after the start of sucking of the 1st study drug administered, on the evening of D1, and on D2, D3, and D4.
- **on the investigator's overall assessment** assessed on a 4-point rating scale (very good, good, moderate, poor) 120 min after the start of sucking of the first study drug administered and during the study-end visit (D5).

<u>To assess the **lozenge consumption**</u> (number of lozenges and the mean time between 2 lozenge intakes) by calendar day from D1 to D4 (from the first intake to the last intake of the day).

<u>To assess the **local and global tolerability**</u> of repeated administrations of V0498 lozenges versus placebo.

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Methodology:

This multinational, multicenter trial was conducted using a randomized, double-blind, placebo-controlled, 2-parallel group design, in 385 patients aged at least 18 years, suffering from acute sore throat pain.

At the screening/inclusion visit (D1), patients were randomized (in a 1:1 ratio) to one of the following 2 treatment groups:

- V0498 group: ibuprofen 25 mg lozenge
- Placebo group: lozenge matching the V0498 lozenge

All patients received repeat oromucosal administrations (up to a maximum of 6 lozenges per day) over 3 to 4 consecutive days, with a minimal interval between study drug intake of at least 2 hours.

The total study duration was 5 to 6 days with 2 phases:

- A 2.5 to 3-hour stationary phase (at D1), followed by
- An ambulatory phase from D1 (end of stationary phase) to D4 (end of study treatment).

A study-end visit was performed on D5 (or exceptionally postponed to D6 for patient/center convenience).

Number of patients (planned and analyzed):

A total of 382 patients were planned to be randomized: 191 patients per group; a total of 385 patients were analyzed (194 received V0498 lozenge and 191 received placebo)

	Placebo n=191		**V0498 lozenge n=194**		**Total n=385**	
Full Analysis [FAS]	191	(100.0%)	194	(100.0%)	385	(100.0%)
Per Protocol [PP]	190	(99.5%)	191	(98.5%)	381	(99.0%)

Diagnosis and main criteria for inclusion:

Patients aged at least 18 years, suffering from acute sore throat pain of recent onset (within the last 72 hours) and sore throat pain intensity scale (STPIS) score when swallowing ≥60 mm on a 100 mm visual analogue scale (VAS).

Test product,
Dose,
Mode of administration,
Batch number:

V0498 lozenge
25 mg, as ibuprofen sodium dihydrate 32.0 mg
Oromucosal, multiple dose
CL0021 (expiry date: 04/2013 extended: 10/2013)

Reference therapy
Dose,
Mode of administration,
Batch number:

Placebo matching V0498 lozenge
Not applicable
Oromucosal, multiple dose
CL0022 (expiry date: 04/2013 extended: 10/2013)

Duration of treatment:

3 to 4 days: all patients received repeat oromucosal administrations (up to a maximum of 6 lozenges per day) over 3 to 4 consecutive days, with a minimal interval between study drug intake of at least 2 hours

Other product

Not applicable

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Criteria for evaluation:

Efficacy:

Pain relief: Sore throat relief scale (STRS) rated on a 7-point rating scale of 0 (no relief) to 6 (complete relief)

Pain intensity: Sore throat pain intensity scale (STPIS) on swallowing rated on a 0-100 mm VAS

Other: Patients global efficacy (assessed on a 4-point rating scale: very good, good, moderate, poor, in response to the following question: "Globally since the study onset, how do you consider the effect of this study drug?"), investigator's overall assessment (assessed on a 4-point rating scale: very good, good, moderate, poor, in response to the following question: "How do you consider the effect of this study drug on your patient's disease?")

Investigational drug consumption

Safety:

General tolerability: Adverse events (AEs)

Other tolerability: local tolerability (extent of erythema, edema, petechiae, hemorrhages and ulceration), patient's overall tolerability

Statistical methods:

Data sets:

- The Full Analysis Set (FAS) was composed of all randomized patients who received at least one dose of the study treatment, and used to perform all analyses of efficacy and safety
- The Per Protocol (PP) Set which was a subset of the FAS composed of all patients without any major protocol deviation or other source of bias for primary criteria analyses and with at least one primary efficacy data available. This data set was used to perform supportive efficacy analyses of the main criterion.

Only the primary analysis of the primary efficacy endpoint, on which the sample size justification was based, could lead to a causal interpretation. All other statistical results are to be regarded in a descriptive perspective.

Prior to breaking the blind, centers having a too small number of patients in the FAS were pooled with other center(s) according to the rules decided during the validation committee meeting, in order to achieve a reliable treatment effect estimate. In all analyses, the center effect was replaced by the pooled center effect.

The global statistical significance level of the various 2-sided tests performed was 5%, using the fixed sequence testing procedure.

Primary efficacy endpoint: TOTPAR over 120min ($TOTPAR_{0-120}$) after the start of sucking of 1st study drug administered, which is calculated as the Area Under the Curve (AUC) between 0 and 120 min using the STRS values.

Primary Efficacy Analysis

The primary analysis was performed on the FAS after the worst case imputation of missing data, and used an analysis of variance (ANOVA) with treatment group and pooled center as fixed effects in order to compare the TOTPAR over 120min of V0498 lozenge versus placebo.

Adjusted means, standard error and corresponding 95% confidence interval (CI) were provided for each treatment group and for the difference between V0498 lozenge and placebo.

Supportive Analysis

The primary analysis of the main criterion was repeated on the PP Set.

Sensitivity Analyses

The primary analysis was performed without missing value extrapolation.

Because the normality of the variable $TOTPAR_{0-120}$ could be questioned, the primary efficacy endpoint was compared between treatment groups, on the FAS, using a Cochran-Mantel-Haenszel (CMH) test (row mean scores) stratified by pooled center, using modified ridit (modridit) scores.

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Statistical methods:

Secondary Efficacy Analysis

All the secondary efficacy criteria were described over time and analyzed to compare V0498 lozenge versus Placebo on the FAS. Additionally, the following analyses were performed:

- $TOTPAR_{0-15}$, $TOTPAR_{0-30}$, $TOTPAR_{0-45}$, $TOTPAR_{0-60}$, $TOTPAR_{0-90}$: same analysis as the primary analysis of the primary efficacy endpoint.
- TOTPAR 33% and TOTPAR 50%: CMH test stratified by pooled center after validation of the condition of Mantel and Fleiss.
- STRS values over time: at each time, CMH test (row mean scores) stratified by pooled center, using modridit scores.
- Onset of meaningful pain relief: survival curves according to Kaplan-Meier (KM) method and a Log-rank test were performed.
- PID over time: analysis of covariance (ANCOVA) with treatment group and pooled center as fixed effects and the baseline of STPIS score as covariate.
- SPIDnorm over 15, 30, 45, 60, 90 and 120 min: ANCOVA with treatment group and pooled center as fixed effects and the baseline of STPIS score as covariate.
- Patient's global efficacy rating, Investigator's overall assessment: at each time, CMH test (row mean scores) stratified by pooled center, using modridit scores.
- Daily number of lozenge intakes, daily mean time between 2 lozenge intakes by calendar day: only a descriptive analysis.

Safety Analysis

The safety analysis (extent of exposure, AEs, local and patients' overall tolerability, global physical examination and concomitant treatments) was presented on the FAS as treated, as descriptive summary statistics by treatment group.

Summary - Conclusions:

Study patients

Of 385 patients randomized, 194 received V0498 lozenge and 191 received placebo. A total of 12 patients (3.1%) were withdrawn from the study, one due to efficacy concerns (1 patient on placebo) and 11 due to other reasons (8 due to "study drug success" [5 on V0498 lozenge, 3 on placebo]; 373 patients (96.9%) completed the study.

A total of 4 patients (1.0%) had major protocol deviations and were excluded from the PP Set.

Demographic characteristics were very similar between treatment groups; overall 38.7% of patients were male and 61.3% were female; the mean (standard deviation [SD]) age was 35.1 (13.6) years. The tonsillo-pharyngitis assessment (TPA) scores at baseline were as expected for this population of patients with sore throat and were similar between treatment groups; mean (SD) total score was 8.1 (2.2) for the V0498 lozenge group and 8.1 (2.0) for the placebo group.

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Efficacy results

Pain Relief

The primary efficacy criterion, $TOTPAR_{0-120}$, showed statistical significance in favor of V0498 lozenge treatment: mean (SD) $TOTPAR_{0-120}$ was 3.244 (2.220) for the V0498 lozenge group and 2.777 (2.251) for the placebo group (p = 0.045); the adjusted mean difference (standard error [SE]) was 0.44 (0.22).

TOTPAR on the interval [0 min; 120 min] Worst case imputation, ANOVA [FAS]

	Placebo n=191	**V0498 lozenge n=194**
Missing	-	-
TOTPAR at Day 1 T120min		
Mean (SD)	2.777 (2.251)	3.244 (2.220)
Min/Median/Max	0.00 / 2.250 / 10.25	0.00 / 3.000 / 10.00
Analysis of variance model: TOTPAR = Treatment + Pooled Site		
Pooled Site effect: p-value <0.0001		
Treatment effect: p-value =0.045		
Adjusted mean		
LSMeans (SE)	3.14 (0.20)	3.58 (0.19)
[LSM 95%CI]	[2.76 ; 3.53]	[3.20 ; 3.96]
Adjusted mean difference vs Placebo		
LSMeans (SE)		0.44 (0.22)
[LSM 95%CI]		[0.01 ; 0.87]

The primary results were confirmed by the supportive analysis of $TOTPAR_{0-120}$ on the PP Set (p = 0.029). Over the two planned sensitivity analyses, the one on observed cases data for the FAS confirmed the results (p = 0.039), the one using a non parametric test was very close to the limit of significance (p = 0.053).

TOTPAR at all other timepoints on D1 showed statistical significance in favor of V0498 lozenge treatment: TOTPAR was consistently higher for patients receiving V0498 lozenge than those receiving placebo and the difference increased over time (adjusted mean difference [standard error] ranging from 0.07 [0.03] at 15 min to 0.40 [0.16] at 90 min).

TOTPAR 33% and 50% at 15, 30, and 45 min on D1 were higher for the V0498 lozenge group (30.1%-31.4% and 15.5%-17.0% of patients for TOTPAR 33% and 50%, respectively) than the placebo group (17.8%-18.8% and 6.8%-8.9% of patients for TOTPAR 33% and 50%, respectively) and the differences were statistically significant. From 60 to 120 min, the differences between treatments were smaller and were not statistically significant.

The mean STRS values, on which TOTPAR was calculated, reflected the same pattern. From the morning of D2 to the evening of D4 there were no statistically significant differences between treatments, however a slight trend in favor of V0498 was observed.

The time to onset of meaningful pain relief was slightly shorter in the V0498 lozenge group compared with placebo, however no statistically significant differences were observed.

Pain Intensity

In terms of the STPIS, and endpoints derived from the STPIS, there were no statistically significant differences observed.

Patient and Investigator Overall Assessments

The patient's global efficacy rating was statistically significant in favor of V0498 lozenge on D1 at 120 min and on the evening of D1. From D2 onwards, the percentage of patients reporting a high rating increased in both treatment groups, with a slight trend in favor of V0498, however no statistically significant differences were observed.

No statistically significant differences between treatment groups were observed for the investigator's overall assessment.

Investigational Drug Consumption

The mean (SD) daily number of lozenges consumed per day was similar between treatment groups, ranging from 3.5 (1.8) on D4 to 4.5 (1.4) on D2. Likewise, the mean (SD) daily time between 2 lozenge intakes was similar between treatment groups on each day, ranging from 3:37 (1:31) on D1 to 4:32 (2:19) on D4; mean time between 2 lozenge intakes increased between D1 and D4.

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Safety results

No patient receiving V0498 lozenges experienced either a serious adverse event (SAE) or a treatment-emergent adverse event (TEAE) leading to treatment withdrawal.

In the placebo group, one TEAE (bronchitis) leading to treatment discontinuation and one post-study SAE (limb crushing injury) were reported.

Overall, a slightly lower percentage of patients experienced TEAEs in the V0498 group than the placebo group: 14 patients (7.2%) receiving V0498 lozenge experienced a total of 21 TEAEs and 20 patients (10.5%) receiving placebo experienced a total of 26 TEAEs. The majority of TEAEs were mild or moderate in intensity.

The most frequently reported TEAE overall, and in each treatment group, was headache (5 patients [2.6%] in the V0498 group and 6 patients [3.1%] in the placebo group) followed by pyrexia (2 patients [1.0%] in the V0498 group and 3 patients [1.6%] in the placebo group) and diarrhea (2 patients [1.0%] in each group).

A slightly higher percentage of patients in the V0498 lozenge group (8 patients [4.1%]) experienced **TEAEs considered related to treatment** (12 events) than those in the placebo group (6 patients [3.1%] reported 6 events). This was largely due to patients receiving V0498 lozenge experiencing gastrointestinal disorders considered related to treatment such as abdominal pain, abdominal pain upper, eructation, flatulence, and nausea.

Local tolerability was satisfactory over time for patients in both treatment groups and there were no notable differences between treatments. Overall tolerability rated by the patient was generally good or very good throughout the study and there were no notable differences between treatments.

Conclusion

Overall, V0498 lozenge provided a more effective and rapid relief of sore throat pain in patients over the first 120 min after the start of sucking the first lozenge compared to placebo. From the morning of D2 to the evening of D4, a slight trend in favor of V0498 lozenge was observed, however there were no statistically significant differences between treatments**.** For the patients' overall rating of pain relief, the superior efficacy was noticed throughout the first day. V0498 lozenge was well-tolerated and the safety profile was as expected for a low dose ibuprofen product.

Date of report: 18 December 2013