Pierre Fabre Médicament
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1. TITLE PAGE

CLINICAL STUDY REPORT

Analgesic profile of 3 new Ibuprofen lozenges (V0498TA01A 15 mg, 25 mg, 35 mg) after single administration in acute sore throat pain.

Investigational product:	V0498TA01A
Study Design:	Multicentre, randomized, parallel groups study: 3 tested dosages of V0498TA01A and placebo in double blind, positive control in single blind administration.
EudraCT number:	2011-005848-10
Protocol number:	V00498 TA 2 01
Phase of development:	Phase II
Date of first enrolment:	15 February 2012
Date of last completed:	02 November 2012
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 – BP 13562, 31035 Toulouse Phone: +33 (0)5 34 50 63 45
Date of report:	**29 October 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: V0498TA01A	**Referring to Module 5 of the Dossier**	
Name of active substance *(or ingredient)***:** Ibuprofen	**Vol.: .....Page: .....**	

Title of study:	Analgesic profile of 3 new Ibuprofen lozenges (V0498TA01A 15 mg, 25 mg, 35 mg) after single administration in acute sore throat pain.
Coordinating Investigator:	Yves DONAZZOLO, MD, MSc
Study centres:	This multinational, multicentre study was conducted in 4 centres: • Two centres in France, under the responsibility of Doctor Yves Donazzolo, Eurofins Optimed (1 rue des Essarts - 38610 Gières) and Eurofins Optimed Lyon (Pavillon 4N 4O – Centre hospitalier Lyon - 69310 Pierre Bénite). • One centre in Germany, under the responsibility of Doctor Juliane Körner (SocraTec R&D GmbH, Mainzerhofplatz 14, 99084 Erfurt, Germany) • One centre in UK, under the responsibility of Doctor Suhair Jawad (Common Cold Centre & Healthcare Clinical Trials, Cardiff School of Biosciences, Cardiff University, Museum Avenue, Cardiff, CF10 3AX, United Kingdom) The last 2 centres (in Germany and UK) were added in amendment PA02 dated 15 June 2012.
Publication (reference):	No publication based on this study has been written to date.
Studied period:	**Phase of development: II**
Date of first enrolment	15 February 2012
Date of last completed	02 November 2012
Objectives:	**Primary:** To compare the analgesic effect of Ibuprofen lozenges (V0498TA01A 15 mg, 25 mg, 35 mg) to placebo at 60 min after the start of sucking of study drug administered in single dose. **Secondary:** – To compare the analgesic effect of Ibuprofen lozenges (V0498TA01A 15 mg, 25 mg, 35mg) to placebo at 30 min, 90 min, 120 min, 180 min, 240 min, 300 min and 360 min after the start of sucking of study drug administered in single dose, – To describe the analgesic effect of the positive control: Strefen® at 30 min, 60 min, 90 min, 120 min, 180 min, 240 min, 300 min and 360 min after the start of sucking of study drug administered in single dose, – To describe the safety of Ibuprofen lozenges (V0498TA01A 15 mg, 25 mg, 35 mg), placebo and positive control.
Methodology:	Multicentre, randomized, parallel groups study: 3 tested dosages of Ibuprofen lozenges (V0498TA01A 15 mg, 25 mg, 35 mg) and placebo in double blind, positive control (Strefen®) in single blind administration. The single dose of tested products (V0498TA01A 15 mg, 25 mg, 35 mg, placebo and positive control) was administered by authorized investigational site persons. The patient had to suck actively one lozenge in the mouth about 10 minutes until its complete dissolution, at distance of any drink or food intake. During the first 2 hours following the study drug administration, the patient stayed quietly seated and had to have nothing else in his/her mouth. The clinical evaluations of efficacy and safety parameters were done every 30 minutes up to 120 minutes after the start of sucking of study drug, then every 60 minutes up to 360 minutes. The discharge of patients was 6 hours after drug intake, once all efficacy and safety parameters were completed. Patients received a phone call, the day after the study visit, to collect any adverse events for the documentation of the safety of tested products. The study duration was 2 days: Study visit on Day 1 and Phone Call on Day 2.

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Number of patients:	185 patients were planned; 186 were randomised and completed the study.
Diagnosis and main criteria for inclusion:	– Patients having signed a written informed consent, – Male or female patients 18 years and older. – Patients with a sore throat associated or not with an Upper Tract Respiratory Infection (URTI) $\geq$ 24 hours and $\leq$ 5 days duration, in the absence of Streptococcus group A as confirmed by a swab test before randomisation. – Patients with tonsillopharyngitis $\geq$ 6 on 21-point Tonsillo Pharyngitis Assessment (TPA) scale. – Patients with a Sore Throat Pain Intensity Scale assessed by Visual Analogue Scale (VAS) more than or equal to 60 mm. – For female patients of child-bearing potential: · Negative urinary pregnancy test. · Use of an effective contraceptive method (oral contraception, surgical method, intra-uterine device or diaphragm) during the study and at least one week after the study end visit or · Agreement to have her male partner(s) use a condom during each sexual intercourse during the study and at least one week after the study end visit. – Patients able to understand and to comply with all study procedures (e.g., such as those who could understand correctly the use of the pain rating scales). – Patients having signed a written informed consent. – Patients affiliated to a social security system or are beneficiaries.
Test products, Doses, **Mode of administration,** **Batch numbers:**	V0498TA01A: Ibuprofen Lozenge (15 mg, 25 mg, 35 mg) Single oromucosal administration One lozenge sucked actively until complete dissolution (about 10 minutes), at distance of any drink or food intake. Lozenge had not to be crunched or swallowed. V0498TA01A 15 mg: SB0875, expiry date 10/2012, extended 04/2013 V0498TA01A 25 mg: SB0876, expiry date 10/2012, extended 04/2013 V0498TA01A 35 mg: SB0877, expiry date 10/2012, extended 04/2013
Reference therapy, Dose, **Mode of administration,** **Batch number:**	Placebo matching V0498TA01A lozenges Single oromucosal administration The placebo was administered in the same conditions as the test products. SB0874, expiry date 10/2012, extended 04/2013
Duration of treatment:	A single administration
Other product, Dose, **Mode of administration,** **Batch numbers:**	Positive control: Strefen®: flurbiprofen Lozenge 8.75 mg Single oromucosal administration The positive control was administered in the same conditions as the test product. 6KK, expiry date 07/2013 and AD235, expiry date 03/2014

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Criteria for evaluation:

- The pain intensity was assessed by a Sore Throat Pain Intensity Scale (STPIS) and a Verbal Rating Scale (VRS).

These two scales were assessed in the investigational centre at baseline and, 30 min, 60 min, 90 min,120 min 180 min, 240 min, 300 min and 360 min after the start of sucking of the study drug administered.

* Sore Throat Pain Intensity Scale (STPIS), assessed on a 0-100 mm Visual Analogue Scale. The patient rated his(her) average level of pain on swallowing by making a vertical line on the line between 0 meaning "no pain" and 100 meaning "extreme pain".
* Verbal Rating Scale (VRS) according to a 6 points scale (from 0 meaning "no pain" to 5 meaning "very severe pain").

- The pain relief was assessed on the Sore Throat Relief Scale (STRS) according to a 7 points scale (from 1 meaning "no relief" to 7 meaning "complete relief").

The STRS was assessed in the investigational centre at 30 min, 60 min, 90 min, 120 min, 180 min, 240 min, 300 min and 360 min after the start of sucking of the study drug administered

- General tolerability (adverse events all along the study).

- Local tolerability: mouth examination (including extent of erythema, oedema, petechial haemorrhages, ulceration, all according to a 4 points scale (from 0 meaning "none" to 3 meaning "severe") on Day 1 at T0 and T360 minutes.

Statistical methods:

Data sets:

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

Primary efficacy endpoint: change from baseline of the Sore Throat Pain Intensity Scale (Pain Intensity assessed by VAS) to 60 min

Primary analysis of the primary efficacy endpoint:

On the Full Analysis data Set (FAS) composed of all patients having received the single treatment administration, analysis of covariance of the change from baseline to 60 min with treatment and centre effects *(considered as fixed effects)* and the baseline as covariate were performed to compare each dose group of V0498TA01A versus Placebo (using the fixed-sequence procedure).

Adjusted means and corresponding 95% confidence interval (CI) were provided for each treatment group.

Note: The Last observation Carried Forward (LOCF) principle was applied on the Sore Throat Pain Intensity Scale at 60 min to impute missing values.

Analysis was done according to a fixed-sequence testing procedure which involved a pre-specified ordering of the test:

(V0498TA01A 35 mg versus Placebo) then (V0498TA01A 25 mg versus Placebo) then (V0498TA01A 15 mg versus Placebo). If one test was non-significant, the following test was not performed.

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Statistical methods:

Supportive analysis:

Same analysis as the primary analysis of the primary efficacy criterion was performed on the Per Protocol Set (PP).

Sensitivity analysis:

- An analysis of variance with treatment group and centre as fixed effects using the fixed-sequence procedure was performed on the FAS (without baseline covariate).
- An analysis of covariance with treatment and centre effects *(considered as fixed effects)* and the baseline as covariate was performed on the FAS, without missing data extrapolation.
- A descriptive analysis (mean, standard deviation, and 95% confidence interval of the difference) was provided between Positive control and Placebo, using the analysis of covariance issued from primary analysis.

Additional analyses:

- Dose effect relationship analysis, using appropriate contrasts both with and without the placebo group in an analysis of covariance with treatment group and centre as fixed effect and baseline as covariate. Graphs with doses on the abscissa and adjusted mean change from baseline to 60 min issued from the analysis of covariance on the ordinate were provided

Treatment by baseline covariate interaction was explored using an analysis of covariance with treatment group and centre as fixed effects, baseline as covariate and treatment by baseline covariate interaction.

Secondary efficacy endpoints

- Change from baseline of the Sore Throat Pain Intensity Scale according to VAS to 30, 90, 120, 180, 240, 300 and 360 min: same analysis as the primary analysis of the primary efficacy endpoint.
- $TOTPAR_{0-30}$, $TOTPAR_{0-60}$, $TOTPAR_{0-90}$, $TOTPAR_{0-120}$, $TOTPAR_{0-180}$, $TOTPAR_{0-240}$, $TOTPAR_{0-300}$ and $TOTPAR_{0-360}$ [calculated as Area Under the Curve (AUC) of the Total Pain Relief (TOTPAR) according to STRS]: An analysis of variance (ANOVA) was performed including treatment group and centre as fixed effects.
- SPID norm $_{0-30}$, SPID norm $_{0-60}$, SPID $norm_{0-90}$, SPID $norm_{0-120}$, SPID $norm_{0-180}$, SPID $norm_{0-240}$, SPID $norm_{0-300}$ and SPID $norm_{0-360}$ according to VRS (representing the time-weighted average pain intensity difference over the selected period): An analysis of covariance was performed including treatment group and centre as fixed effects and Pain intensity at baseline as covariate.

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Statistical methods:

Exploratory criteria

- The Area Under the Curve (AUC) of the Sum of Pain Intensity Difference ($SPID_{AUCVAS}$) was presented on 8 interval times (0–30 min, 0–60 min, 0–90 min, 0–120 min, 0–180 min, 0–240 min, 0–300 min, 0–360 min: An ANCOVA with treatment group and centre as fixed effects and pain intensity at baseline as covariate was performed to compare the mean of $SPID_{AUCVAS}$ between each dose group of V0498TA01A versus Placebo, using the fixed sequence testing procedure.
- The Normalised Sum of Pain Intensity Difference according to VAS (SPIDnormVAS) assessed on 8 interval times: SPIDnorm 0-xx (representing the time-weighted average pain intensity difference over the selected period; xx was successively 30, 60, 90, 120, 180, 240, 300 and 360): An analysis of covariance (ANCOVA) was performed including treatment group and centre as fixed effects and Pain intensity at baseline as covariate was performed to compare the mean of SPIDnormVAS between each dose group of V0498TA01A versus Placebo, using the fixed sequence testing procedure.
- Analysis of Pain Responders rates: defined as the reduction of 30% or 50% of baseline score on the STPIS were calculated at each time point after the start of sucking of the 1st study drug administered. A Cochran Mantel Haenszel (CMH) test stratified by centre was performed to compare the rates of pain responders between each dose of V0498TA01A versus Placebo, using the fixed sequence testing procedure.

Safety analysis

On all patients having received the single treatment administration, descriptive statistics of the local tolerability, summarizing adverse events and concomitant treatments were performed by treatment group.

Summary - Conclusions:

Study Patients

All the 186 randomised patients (37 in the placebo group, 36 in the Positive control (Strefen®) group and 39, 37 and 37 in the V0498TA01 A groups, 35 mg, 25 mg and 15 mg respectively) were treated and completed the study.

Overall, the age of subjects was 32.8 (SD: 13.6) years on average and ranged between 18 and 70 years; the sex ratio was ~2/1 (68.8% of females and 31.2% of males), the Body Mass Index (BMI) was 24.8 Kg/m² (SD: 4.9) on average and ranged between 15.2 and 43.3 Kg/m².

The 186 randomised patients composed the FAS population, among them 184 composed the PP as 2 patients, in the V0498TA01A 15 mg group, had one major deviation each and were excluded from the PP population.

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Summary - Conclusions:

Efficacy results:

Analysis of the primary efficacy endpoint, change from baseline to 60 minutes after treatment intake in the Sore Throat Pain Intensity Scale (STPIS) performed on the FAS (and confirmed on the PP), did not show any clinically or statistically significant difference between the V0498TA01A groups and placebo. Similar findings were observed with Strefen®, thus bringing into question the overall sensitivity of the study to determine differences in efficacy.

No clinically or statistically significant difference was detected in the STPIS between placebo and V0498TA01A 35 mg at 60 minutes ($p = 0.610$) which prevents any further statistical analysis, as per protocol.

For the secondary criteria based on pain intensity, $SPID_{norm}$ and $SPID_{AUC}$, no statistically significant effect was observed.

Although 20.5% to 22.2% of patients in the V0498TA01A groups presented a 30% reduction in pain at T30 min compared to 13.5% in the placebo group, and nearly 50% of patients in the V0498TA01A groups at T120 min, compared to 30% of patients in the placebo group, this effect observed on pain responders was not statistically significant.

Concerning the pain relief assessment, the analysis of Total Pain Relief (TOTPAR), assessed by Sore Throat Relief Scale (STRS) on the FAS, showed a statistically significant difference between placebo and V0498TA01A from 30 min (first evaluation) to 360 min for the 25 mg and 35 mg doses. For the 15 mg dose, a statistically significant difference was shown only from 90 to 360 min. For this parameter, the 25 mg and 35 mg doses induced a similar rapidity of response compared to placebo, the difference between 25 mg and placebo being more pronounced: at T60 min a mean difference of 0.85 was calculated for 25 mg ($p = 0.003$) versus 0.58 ($p = 0.036$) for 35 mg.

Table: Summary of TOTPAR results (ANOVA) – FAS

	Placebo (N=37)	**V0498TA01A - 35 mg (N=39)**	**V0498TA01A - 25 mg (N=37)**	**V0498TA01A - 15 mg (N=37)**
[0-30 min]	1.05 (0.12)**	1.35 (0.11)** 0.30 (0.15)* p = 0.044	1.45 (0.12)** 0.40 (0.15)* p = 0.009	1.28 (0.12)** 0.24 (0.15)* p = 0.124
[0-60 min]	2.23 (0.22)**	2.80 (0.21)** 0.58 (0.27)* p = 0.036	3.08 (0.22)** 0.85 (0.28)* p = 0.003	2.76 (0.22)** 0.53 (0.28)* p = 0.058
[0-90 min]	3.52 (0.32)**	4.31 (0.31)** 0.79 (0.40)* p = 0.049	4.78 (0.32)** 1.26 (0.40)* p = 0.002	4.41 (0.32)** 0.89 (0.41)* p = 0.030
[0-120 min]	4.87 (0.42)**	5.99 (0.41)** 1.12 (0.53)* p = 0.036	6.54 (0.42)** 1.67 (0.54)* p = 0.002	6.16 (0.42)** 1.29 (0.54)* p = 0.018
[0-180 min]	7.54 (0.62)**	9.55 (0.60)** 2.02 (0.78)* p = 0.011	9.90 (0.62)** 2.37 (0.79)* p = 0.003	9.92 (0.62)** 2.38 (0.80)* p = 0.003
[0-240 min]	10.23 (0.86)**	12.96 (0.83)** 2.73 (1.08)* p = 0.013	13.26 (0.86)** 3.03 (1.10)* p = 0.007	13.59 (0.86)** 3.36 (1.11)* p = 0.003
[0-300 min]	13.01 (1.09)**	16.20 (1.06)** 3.19 (1.37)* p = 0.022	16.73 (1.09)** 3.72 (1.39)* p = 0.008	17.21 (1.10)** 4.20 (1.40)* p = 0.003
[0-360 min]	15.95 (1.33)**	19.33 (1.29)** 3.38 (1.67)* p = 0.045	20.28 (1.33)** 4.33(1.70)* p = 0.012	20.67 (1.34)** 4.72 (1.71)* p = 0.006

** Adjusted mean difference (V0498TA01A-Placebo) (SE) ** Adjusted mean (SE)*

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Summary - Conclusions:

Safety results:

Neither SAEs, nor premature withdrawal, nor AEs severe in intensity were reported during the study course.

Overall 3 adverse events were reported by 3 patients during the study, all occurred after treatment initiation, were reported in V0498TA01A groups and were resolved before the end of the study. One patient of V0498TA01A 35 mg group, experienced a "feeling of tingling of the throat" (reported term), 20 minutes after treatment administration which lasted 1 hour and 40 minutes, mild in intensity, and judged related to study drug (suspected relationship by the investigator). Two patients of V0498TA01A 25 mg group experienced 2 headache, moderate in intensity, judged not related to study drug administration in the investigator's opinion.

There were no AEs in the V0498TA01A 15 mg, placebo and Strefen® groups.

Mouth examination showed a relevant improvement for extent of erythema on palate, in all groups, more pronounced in patients having severe erythema at baseline with V0498TA01A groups.

As expected, a good safety profile of the 3 V0498TA01A lozenges (containing 15 mg, 25 mg, or 35 mg ibuprofen) was observed.

Conclusion:

In these study conditions, the efficacy of V0498TA01A at the 3 tested doses could not be demonstrated. However, no definitive conclusion could be drawn as there was no difference in pain intensity between the positive control (Strefen®) and placebo, thus bringing into question the sensitivity of the study, which can be qualified as unconclusive.

However, a rapid pain relief was observed on secondary criteria (TOTPAR) with the 25 and 35 mg (less rapid for the 15 mg) ibuprofen lozenges compared to placebo. All 3 lozenges presented a good safety profile.

Date of report: 29 October 2013