2. SYNOPSIS

Company name: ACRAF S.p.A	Tabular format referring to	(For National Authority Use Only)
Name of the finished product: Tantum Verde	Volume:	
Name of the active substance: benzydamine	Page:	

Title of the study: Efficacy and safety of an alcohol-free formulation of 0.15% benzydamine spray in children with sore throat. Randomized, double blind, placebo-controlled study

[redacted]

Study centre(s): Multicenter clinical trial

Publication (reference): not applicable

Study period (years): 2010-2011 | **Clinical Phase**: III/IV

Objectives:

Primary: evaluation of the analgesic activity of 0.15% benzydamine spray in single administration compared to placebo.

Secondary: evaluation of the 0.15% benzydamine spray tolerability and safety in single administration compared to placebo; evaluation of the 0.15% benzydamine spray tolerability and safety after a 3-day administration period.

Methodology: This was an international, randomized, multicenter, parallel group, placebo-controlled, single dose study, followed by a 3-day treatment period with benzydamine in open conditions. For each patient 3 Visits were scheduled (V0 and V1 at Day 1, and V2 at Day 4).

Number of subjects (total and per treatment): 201 patients (99 benzydamine, 102 placebo, age range 5-12 years) were enrolled and treated with the study medications.

Diagnosis and inclusion criteria: male and female outpatients with sore throat diagnosis (Tonsillo-Pharyngitis Scale > 6 points); onset of sore throat symptoms within 7 days; moderate-to-severe sore throat (Children's Sore Throat Pain Thermometer > 120mm); willingness of the parents/legally authorized representative/child to comply with the requirement of the study protocol; written informed consent to the trial signed and dated by the parents or legal representative according to the local regulations.

Test product 1, dose, mode of administration, batch no.:

Double-blind period: benzydamine 0.15% spray (manufacturer batch no. 000000031), a single application (4 nebulizations).

Open period: benzydamine 0.15% spray (manufacturer batch no. 000000031), a single application (4 nebulizations) up to 6 times daily, for a duration of 3 days.

Duration of treatment: up to 3 days.

Reference therapy, dose, mode of administration, batch no.:

Double-blind period: placebo spray (manufacturer batches no. 00266IP01 and 00266IP10), a single application (4 nebulizations).

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Assessment criteria:

Efficacy: the following scales were used to assess pain and pain relief: the Children's Sore Throat Pain Thermometer (filled in by patients), the Children's Sore Throat Pain Intensity (filled in by investigators and parents), and the Children's Sore Throat Relief (filled in by patients).

Safety: adverse events monitoring, physical examination, and global tolerability rating. Immediately after the first administration, the Investigator asked the patient the taste of the administered formulation, in terms of fresh (yes/no), sweet (yes/no), bitter (yes/no), and expressed a global assessment in terms of good or bad.

Statistical methods:

Efficacy analyses were performed on two patient populations: Intention To Treat population (ITT) defined as all randomised patients who have at least two post basal evaluations and received the study drug (missing values were replaced by the Last Observation Carried Forward - LOCF), and Per Protocol population (PP) defined as all randomised patients who met eligibility criteria, received the study drug and completed all post-baseline evaluations.

Description of the investigational population was performed for all the parameters recorded at baseline. Changes from baseline values, measured by the Children's Sore throat Pain Thermometer and Children's Sore throat Pain Intensity, were evaluated as the Sum of Pain Intensity Difference Score (SPID), estimated as the area under the pain intensity differences versus time curve. Children's Sore throat Relief was estimated as the area under the pain relief versus time curve (TOTPAR). SPID and TOTPAR were analyzed by an analysis of variance (ANOVA). Analysis of variance was also applied to compare TPS scores at V2 with respect to baseline.

Randomized patients who took the study drug were included in the safety analysis. Fisher's exact test was used for comparisons between treatment groups in the incidence of adverse events. Patients who showed at the final visit a significant change in physical examination with respect to baseline were presented. Tolerability rating was analyzed with the Cochran-Mantel-Haenzel test. Taste evaluation was analyzed with the Cochran-Mantel-Haenzel test.

SUMMARY – CONCLUSION

Efficacy results:

The ITT population included all randomized patients, while the PP population excluded 40 patients (18 in the benzydamine group, and 22 in the placebo group) under concomitant treatment with analgesic or anti-inflammatory drugs during the observation period at Day 1.

Changes from baseline in efficacy parameters calculated as the area under the curve versus time, in terms of SPID and TOTPAR, are reported in the following table (ITT population; mean and SD).

	Benzydamine (n=99)	Placebo (n=102)
Children's Sore Throat Pain Thermometer - SPID	-3919.1 (2629.7)	-4127.7 (2495.6)
Children's Sore Throat Pain Intensity (parents) - SPID	-1830.7 (1202.5)	-1922.9 (1387.1)
Children's Sore Throat Pain Intensity (investigators) - SPID	-1902.5 (1012.1)	-1895.7 (1176.8)
Children's Sore Throat Relief - TOTPAR	214.1 (65.1) [$]	217.3 (65.6) [$$]

[$] n=97 [$$] n=100

No statistically significant differences were found. All the efficacy parameters consistently showed an improvement with respect to baseline in both the ITT and PP populations. During the 90 minutes of observation following the first administration, children treated with placebo had a continuous and

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unexpected improvement over the time of sore throat symptoms, confirmed by either parents and investigators.

After the 3-day benzydamine treatment period the TPS was very low, demonstrating the resolution of sore throat.

Safety results:

No serious or severe AEs occurred during the study.

During the double-blind part of the study, 15 AEs and 13 AEs occurred in 12 patients of the benzydamine group and 13 patients of the placebo group, respectively. The most frequent AE was pyrexia in both treatment groups (7 benzydamine, 7 placebo). The majority of AEs were most probably related to the underlying disease and were similarly distributed between treatment groups. One mild nausea judged as treatment-related occurred in both groups.

Other 23 AEs occurred in 19 patients treated with benzydamine in open conditions. The most frequent AE was pyrexia in both treatment groups (6 reports) followed by headache (3 reports). Only one AE (moderate vomiting) were judged as treatment-related, while others were most probably related to the underlying disease. All the investigators' judgements in the Tolerability rating were good or very good. No statistically significant differences between groups were detected (p=0.3173). After the first administration in double-blind conditions, the main part of children judged both the study medications as fresh and having a good taste.

Conclusion:

This study did not show statistically significant differences in efficacy between active treatment and placebo in the treatment of children with sore throat. The performance in efficacy of the placebo group was higher than previously observed in a double-blind placebo-controlled trial performed with benzydamine mouthwash in children with sore throat, using similar efficacy parameters. The very good safety profile of benzydamine was confirmed.

Date of report: March 7th, 2013