2. SYNOPSIS

Company name: ACRAF S.p.A.	**TABULAR FORMAT** **REFERRING TO**	(For National Authority Use Only)
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Title of the study: Clinical and microbiological assessment of prulifloxacin in patients with Acute Bacterial Rhinosinusitis.

[redacted]

Publication (reference): not applicable

Study period (years): 2012-2013	**Clinical Phase:** IV

Objectives: The primary study objective was to evaluate at the Test of Cure (TOC) Visit, the clinical efficacy of prulifloxacin in the treatment of patients with Acute Bacterial Rhinosinusitis (ABRS).
The secondary study objectives were:
i) to evaluate the microbiological efficacy of prulifloxacin in eradicating bacterial pathogens at the TOC Visit; ii) to compare the clinical and microbiological outcomes; iii) to compare the results of cultures obtained at the Screening Visit by Endoscopically Directed Middle Meatal (EDMM) sampling with those obtained by Maxillary Sinus Tap (MST) through the canine fossa; iv)to assess at the Late Post-Therapy (LPT) Visit the clinical efficacy of prulifloxacin; v) to evaluate the safety and tolerability of the investigational drug.

Methodology: open-label, single-arm, phase IV study in patients with ABRS. Five visits were scheduled for each patient: Screening (Visit 0, within 48h before Day 1), Baseline (Visit 1, Day 1), Intermediate (Visit 2, Day 5-7), TOC (Visit 3, Day 14-18) and LPT (Visit 4, Day 35-45).
At Screening: patient's information, written informed consent, eligibility (inclusion/exclusion criteria), overall severity indicated on a 10cm Visual Analogue Scale (VAS), clinical/endoscopic assessment, microbiological sampling, medical history, physical examination, vital signs, ECG, pregnancy test (when applicable), haematology, serum chemistry and urinalysis, concomitant treatments.
Subjects underwent to EDMM sampling from one nasal side. In a subgroup of consenting patients, secretions from the ipsilateral sinus were collected by MST through the canine fossa.

At Baseline: enrollment of eligible patients assigning a progressive number, investigational drug dispensing, questioning about concomitant treatments and adverse events (for the period starting from the informed consent signature).

At Intermediate: clinical and endoscopical assessment, microbiological results, questioning about concomitant treatments and adverse events.

At TOC: clinical and endoscopical assessment, EDMM sampling for microbiological assessment, drug accountability, physical examination, vital signs, pregnancy test (when applicable), questioning about concomitant treatments and adverse events, haematology, serum chemistry and urinalysis.

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Methodology:
At LPT: clinical and endoscopical assessment, physical examination, vital signs, pregnancy test (when applicable), questioning about concomitant treatments and adverse events.
In case of patient's withdrawal before the TOC, an Early Termination Visit (ETV) was performed, following the same procedures as reported for the TOC Visit.

Number of subjects: Recruitment of 40 clinically and microbiologically evaluable patients was planned. 52 patients (35 males and 17 females, age range 18 – 79 years) were evaluated for elegibility, randomised and received the study medication. No subjects discontinued intervention.

Diagnosis and inclusion criteria: Patients with ABRS. The inclusion criteria were:
i) male or female with no limitation of race, aged > 18 years; ii) ABRS as a superinfection of a pre-existing Acute Viral Rhinosinusitis characterized by persistent symptoms for 10 days or an increase of symptoms after 5 days, and with a duration lower than 12 weeks; iii) clinical diagnosis of ABRS as presence of 2 (including at least one between nasal blockage/congestion/obstruction or nalal discharge) or more of the following signs and symptoms: nasal blockage/congestion/obstruction, nasal discharge, anterior/post nasal drip, facial pain/pressure, reduction/loss of smell). The endoscopic confirmation of signs, namely anterior/posterior nasal discharge from the middle meatus and edema/mucosal congestion was required; iv) moderate to severe ABRS (VAS >3-10); v) a written informed consent to the trial signed and dated by the patient.

Test product, dose, mode of administration: Prulifloxacin 600 mg tablets, oral
Batches no. 236 (expired date October 31, 2012) and no. 279 (expired date December 31, 2013)

Duration of treatment: once daily for 10 days

Assessment criteria: The primary parameter to test the clinical efficacy of the study medication was the comparison of symptoms and signs scores reported at the TOC visit (4 to 8 days after the end of treatment) with those reported at the Screening.
The signs and symptoms such as nasal blockage/obstruction/congestion, nasal discharge (anterior/post nasal drip), facial pain/pressure, reduction/loss of smell were graded according to a four-point scale. The following definitions were used: cure (resolution of at least 1 of the acute pre-treatment signs and symptoms, with no worsening in the remaining signs and symptoms), failure (no resolution of acute pre-treatment signs and symptoms, or worsening at least 1 of the acute pre-treatment signs and symptoms, or treatment before the TOC visit with additional antibiotic therapy for ABRS) or indeterminate (presence of extenuating circumstances that precluded evaluation of the clinical response). Clinical cure was considered as a success for statistical purposes.

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Secondary parameters included microbiological efficacy and clinical efficacy at LPT visit. Patients cured at the TOC were followed-up and defined as sustained cure, LPT failure, or indeterminate. Microbiological assessments were performed on nasal sampling obtained at the TOC compared with those gained at the Screening. Sampling with EDMM represented the reference test. The following definitions were used: eradication (the causative organism detected at Screening was absent in the secretions culture at the TOC visit), presumed eradication (absence of appropriate culture material by EDMM at the TOC visit, i.e. no secretions from the middle meatus available, in presence of clinical cure), presumed persistence (absence of appropriate culture material by EDMM at the TOC visit, i.e. no secretions from the middle meatus available, in presence of clinical failure), persistence (the causative organism detected at Screening was still present in the secretions culture at the TOC visit, the identity of the organisms isolates at the two visits should have been confirmed by phenotypic and genotypic methods), superinfection/new colonization (a new pathogen was detected from the secretions culture at the TOC), indeterminate (bacteriological response not evaluable for any other reason). Eradication or presumend eradication were considered as bacteriological success for statistical purposes. The consistency and correlation of microbiological results obtained at Screening through EDMM and MST was also assessed. The correlation in the individual clinical and microbiological results obtained at the TOC visit was assessed. The following definitions were used "patient clinically cured with confirmed microbiological eradication" (patients with clinical cure at the TOC visit and with a negative culture), "patient clinically cured with presumed microbiological eradication" (patients with clinical cure at the TOC visit and without of appropriate culture material), "patient clinically cured with microbiological persistence" (patients with clinical cure at the TOC visit but with a positive culture showing the causative organism), "patient clinically cured with microbiological colonization" (patients with clinical cure at the TOC visit but with a positive culture showing a new pathogen), "patient with clinical failure and a microbiologically confirmed persistence" (patients with clinical failure at the TOC visit and with a positive culture showing the causative organism), "patient with clinical failure and a microbiologically confirmed superinfection" (patients with clinical failure at the TOC visit and with a positive culture showing a new pathogen) "patient with clinical failure and presumed microbiological persistence" (patients with clinical failure at the TOC visit and without an appropriate culture material) and "patient with non-microbiologically confirmed clinical failure" (patients with clinical failure at the TOC visit and with a negative culture).
Safety and tolerability were assessed by monitoring the occurrence of adverse events (AE). Primary variable was the frequency of adverse drug reactions (ADRs). Monitoring of vital signs and biological safety determined by means of haematology, clinical chemistry and urinalysis was also performed at the Screening and at the TOC (or ETV when applicable).

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Statistical methods: Three study populations were considered: Intention-To-Treat (ITT) population (defined as all patients who received at least one dose of the study medication, and having at least one efficacy evaluation following Baseline. Missing data for the efficacy analysis were replaced using the Last Observation Carried Forward [LOCF] method), Per-Protocol (PP) population (defined as all the efficacy and microbiologically evaluable patients showing a treatment compliance of at least 80% and with no major protocol deviations) and Safety Population (defined as all patients who received at least one dose of the study medication). The ITT population was considered as primary population for statistical analysis.
The primary efficacy endpoint was evaluated by calculating the percentage of clinical success and the relevant two-tailed 95% confidence interval (CI). The secondary efficacy endpoints were evaluated as follows: i) the microbiological parameter were evaluated by calculating the percentage of microbiological success and the relevant 95% CI, on the endoscopically collected samples at the TOC visit in comparison to the baseline. ii) The clinical and microbiological outcomes in terms of success and failures were compared by using the Cohen's K coefficient for agreement. iii) Calculation of correlative statistics in order to compare test procedure (EDMM) against the "gold standard" was performed using standard definitions for sensitivity, specificity and accuracy. iv) Clinical efficacy of prulifloxacin at the LPT was evaluated calculating the percentage of clinical success and the relevant two-tailed 95% CI. v) Safety and tolerability assessments consisted of the examination of ADRs incidence and the changes from Screening of laboratory variables. Laboratory values at each time point were compared with the relevant reference range and categorised as: low (below the lower limit of the reference range, normal (within the limits of the reference range) and high (above the upper limit of the reference range). Shift tables were used to present the change in category based on reference ranges from Screening/baseline to each post-baseline time point, as appropriate. Changes from Screening in physical examination and vital signs were summarized by descriptive statistics and evaluated by an analysis of variance in order to detect any significant changes.

SUMMARY – CONCLUSION

Efficacy results:

Fifthy two patients were included in the ITT population. The PP population consisted of 40 patients. Prulifloxacin 600 mg administered once daily for 10 days showed a clinical efficacy rate of 100% in both the ITT and PP population at the TOC visit. At the LPT visit the rate of patients with sustained cure was 100% considering both the efficacy populations. No late post-therapy failure was recorded.
At the Screening the EDMM sampling from the nasal cavity more affected was performed in all 52 subjects entered in the study. The MST was performed in 19 consenting patients ipsilateral to the side of EDMM. Globally, 141 isolates were found at the Screening in the ITT population: 102 using EDMM sampling and 39 using MST sampling. The final definition of commensals/contaminants and of putative causative agents was done retrospectively basing on the results of microscopy, culture and clinical and microbiological outcomes. Eighty out of 102 isolates at the Screening by EDMM (reference sampling method) were found in the PP (population for assessment of microbiological efficacy).

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SUMMARY – CONCLUSION

Efficacy results:

In the PP, 23 strains were recognized as commensals/contaminants and 57 strains as sinusal pathogens. Among sinusal pathogens, the species most frequently isolated was *S. constellatus* (19%), followed by *H. influenzae* (14%) *S. pneumoniae* (12%), *S. aureus* (10%) and *M. catarrhalis* (7%). *Streptococcus pyogenes*, Enterobacteriaceae, *Pseudomonas aeruginosa*, corynebacteria and anaerobic bacteria were also occasionally isolated. The minimum inhibitory concentration (MIC) values of ulifloxacin of the 57 sinusal pathogens were determined using the E-test strips in the local laboratory and the reference microdilution method in the reference laboratory.

Ulifloxacin MIC values were ≤1 µg /ml (local laboratory) and ≤ 1 µg/ml (reference laboratory) for all pathogens with the exception of one strain of a *Prevotella intermedia* with a MIC of 2 µg/ml in the reference laboratory.

Considering the PP population, at the TOC visit the rate of bacteriological success per patient was 90.0% (95%CI; 80.70-99.30) while the rate of bacteriological failure was 10% (95%CI; 0.70-19.30). The 90% of the clinically cured patients, was defined as bacteriological success due to microbiological eradication (85%) or presumed microbiological eradication (5%). The remaining 10% of the clinically cured patients was defined as bacteriological failure due to the persistence of the same pathogen in the posttreatment cultures (7.5%) or to the new colonization by a different strain (2.5%). The Cohen's K coefficient was not computed due to the absence of subjects in a category (all subjects clinically cured and not subjects clinically failure).

A correlative statistics was performed to evaluate the correlation between MST and EDMM culture. When putative causative agents and commensal/contaminants bacteria were considered, EDMM had an accuracy of 89.5% (95% CI; 66.9-98.7) when compared to the "gold standard" MST. If the analysis was restricted to the putative causative bacteria, the accuracy rate increased to 92.3 (95% CI; 64.0-99.8). In particular, the sensitivity of MST resulted higher than that of EDMM for anaerobes.

Safety results:

Fifthy two patients were included in the Safety population. Fifteen AEs were reported in 10 patients. No AE was judged as serious and all were mild-to-moderate in intensity. No deaths occurred during the study. The AEs involved principally the nervous system disorders (7 events) and the gastrointestinal disorders (5 events). Headache was the most frequent AE (5 events reported by 5 patients). Five patients reported 6 AEs (2 abdominal pain upper, 2 headache, 1 diarrhoea and 1 frequent bowel movements) judged as drug-related (i.e. highly probable, probable, possible) by the Investigators. When AEs were assessed on the basis of their expectedness, as listed in section 4.8 of the specific prulifloxacin Summary of Product Characteristics (SPC), 9 out 15 AEs resulted listed: 6 judged by the Investigator as treatment related and 3 as not treatment related.

The safety review of laboratory (blood and urine) analysis, vital signs and physical findings did not show any clinical effect of prulifloxacin on any of the parameters. Some clinically significant alterations were mainly related to the underling or concomitant diseases.

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Conclusion:

The present study was designed to comply with a specific request addressed by Italian Medicines Agency (AIFA) to ACRAF S.p.A. upon the completion of a Mutual Recognition Procedure resulting in the new prulifloxacin 600 mg indication for the treatment of patients with ABRS. The Company committed for submitting a clinical trial to be performed in a limited number of patients, including the microbiological assessment.

The aim of this trial was to confirm the clinical efficacy and microbiological activity of prulifloxacin in eradicating bacterial pathogens of patients with ABRS. Microbiology was assessed in cultures by EDMM sampling in all patients, and MST through the canine fossa as a "gold standard" method in a subset of patients. In the present study EDMM was used as reference method and the correlation between the two sampling procedures was investigated.

Prulifloxacin showed a clinical efficacy rate at the TOC visit of 100% in both efficacy populations.

At the TOC visit the rate of bacteriological success per patient was 90.0% (95%CI; 80.70-99.30) while the rate of bacteriological failure was 10% (95%CI; 0.70-19.30), in the PP population.

The small number representative of each species does not allow any definite consideration. The good activity of plurifloxacin against the most common bacteria in ABRS, such as *S. pneumoniae, H. influenzae* and *M. catarrhalis* was confirmed. Particularly, prulifloxacin eradicated all *S. pneumoniae*, *M. catharralis* and *S. aureus* and the majority of strains of other streptococcal species and anaerobic bacteria.

The 90% of the clinically cured patients, was defined as bacteriological success due to microbiological eradication (85%) or presumed microbiological eradication (5%). The remaining 10% of the clinically cured patients was defined as bacteriological failure due to the persistence of the same pathogen in the post-treatment cultures (7.5%) or to the new colonization by a different strain (2.5%).

The comparison between EDMM and the "gold standard" MST cultures obtained by 19 patients showed an accuracy between the two sampling methods of 89.5% (95% CI; 66.9-98.7) when putative causative agents and commensal/contaminant bacteria were considered. If the analysis was restricted to the putative causative bacteria, the accuracy rate increased to 92.3 (95% CI; 64.0-99.8). These results confirm EDMM as a viable culture method for determining antimicrobial efficacy and bacterial resistance patterns.

At the LPT visit the rate of patients with sustained cured was 100% considering the ITT and PP populations. No late post-therapy failure was recorded.

No deaths occurred during the study. Fifteen AEs were reported in 10 patients. No AE was judged as serious and all were mild-to-moderate in intensity.

The AEs involved principally the nervous system disorders (7 events) and the gastrointestinal disorders (5 events). Headache was the most frequent AE.

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SUMMARY – CONCLUSION

Five patients reported 6 AEs judged by the Investigators as drug-related (i.e. highly probable, probable, possible). When AEs were assessed on the basis of their expectedness, as listed in section 4.8 of the specific prulifloxacin SPC, 9 out 15 AEs resulted listed: 6 judged by the Investigator as treatment related and 3 as not treatment related.

The safety review of laboratory (blood and urine) analysis, vital signs and physical findings did not show a clinical effect of prulifloxacin on any of the parameters.

In conclusion, the results of this study confirmed the clinical efficacy and microbiological activity of 600 mg prulifloxacin administered once daily for 10 days in the treatment of patients with ABRS. No relapses were observed at the LPT visit endorsing the appropriateness of this therapeutic approach. The well-known positive safety profile of prulifloxacin was also confirmed.

Date of the Clinical Report: May 14th, 2014