2. SYNOPSIS

Company name: ACRAF S.p.A.	**TABULAR FORMAT REFERRING TO**	(For National Authority Use Only)
Name of the finished product: Unidrox®	Volume:	
Name of the active substance: Prulifloxacin	Page:	

Title of the study: A pilot study of prulifloxacin vs. levofloxacin in prevention of post-operative urinary bacterial infections in patients undergoing TURP.

[redacted]

Study centre(s): Multicentre

Publication (reference): not applicable

Study period (years): October 2, 2008 – April 29, 2011	**Clinical Phase:** II, pilot

Objectives:
The primary study objective was to assess the microbiological efficacy in the prevention of post-operative urinary bacterial infections of prulifloxacin 600 mg in comparison with levofloxacin 500 mg, both administered once daily for three days in patients undergoing Transurethral Resection of Prostate (TURP).
The secondary study objectives were:

- to assess at V4 the clinical parameters in patients undergoing TURP,
- to assess at V5 the comparative microbiological and clinical efficacy in patients undergoing TURP,
- to assess the comparative safety and tolerability in patients undergoing TURP.

Methodology: pilot phase II, multicenter, randomized, levoflaxacin-controlled, parallel groups study in patients candidate to TURP. Five visits were scheduled for each patient: V1 (baseline, from 1 to 10 days before surgery), V2 (day of surgery), V3 (catheter removal, 1-3 days after surgery), V4 (final, 7-10 days after surgery) and V5 (follow-up, 28-32 days after surgery).

Number of subjects (total and per treatment):
Recruitment of 100 evaluable patients (50 per treatment group) was planned. The enrolment was stopped at 68 patients since the study was closed prematurely due to the low rate of enrolment.

Diagnosis and inclusion criteria: Patients candidate to TURP. The inclusion criteria were:
1) male with no limitation of race, aged between 40 and 80 years;
2) patients requiring TURP due to BPH according to the Investigator's opinion;
3) pre-operative sterile urine (uropathogen < 104 cfu/ml in midstream-urine)
4) a written informed consent to the trial signed and dated by the patient was available.

Test product, dose, mode of administration: Prulifloxacin 600 mg, oral
Batches no. 111 (expired date June 2009), no. 149 (expired date July 2010).

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Reference therapy, dose, mode of administration: levofloxacin 500 mg (Levoxacin® GSK S.p.A.) oral.
Batches no. Z018 (expired date April 2009), no. 9014 (expired date February 2012).

Duration of treatment: one table once a day for 3 days

Assessment criteria:
Primary endpoint: the assessment of the prophylactic effect of the two treatments in preventing urinary bacterial infections in patients undergoing TURP.
Secondary endpoints: the assessment of the microbiological efficacy and clinical evaluation (including incidence and intensity of the following signs and symptoms: leucocytosis, dysuria, nocturia, haematuria, urgency, frequency and fever) of the two treatments at V4; the clinical evaluation (including incidence and intensity of the following signs and symptoms: leucocytosis, dysuria, nocturia, haematuria, urgency, frequency and fever) of two treatments at V5, the assessment of the safety and tolerability of the two treatments.
Efficacy variables: Efficacy was assessed by microbiological and clinical examinations. The microbiological efficacy of prulifloxacin in comparison to the reference compound to maintain the patient free of bacteriuria (uropathogen < 10^4 cfu/ml in midstream urine) was evaluated at V4 and V5.
The following definitions were used for the microbiological assessment at V4: success (patient with a negative [< 10^4 cfu/ml)] post-surgery urine culture; failure (patient with bacteriuria ≥10^4 cfu/ml in the urine sample collected post-surgery) and indeterminate (no post-operative urine culture results available). The following definitions were used for the microbiological assessment at V5: success (patient with a negative [< 10^4 cfu/ml] urine culture collected at follow-up visit; late failure (patient with bacteriuria ≥10^4 cfu/ml in the urine sample collected at follow-up visit); indeterminate (no post-operative urine culture results available at follow-up visit).
Clinical endpoints were evaluated by the assessment of the incidence and intensity of the following signs and symptoms: dysuria, nocturia, urgency, frequency, haematuria, leukocytosis and fever (graded according to predefined scales).
Criteria of safety and tolerability: Safety was assessed by monitoring the frequency of adverse events in each treatment group. In addition, changes from baseline in physical examination, vital signs, laboratory analyses and ECG were assessed.

Statistical methods: A description of the treated population was planned for all the parameters recorded at baseline in all patients. Efficacy assessment was based on the evaluable patients at V4 or ETV, defined as all randomised patients who received at least one dose of the study drug, who provided complete baseline data (pre-operative sterile urine) and had a microbiological observation available at V4 or ETV, without protocol deviations judged to interfere with the efficacy assessment of the study medications. The efficacy variables were mainly descriptive and no formal test of hypothesis was carried out. Microbiological outcome was analyzed assessing the infection rates for each group considered at V4 and V5.

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Statistical methods:
The planned analysis of primary and secondary endpoints was descriptive or focused on the confidence interval. In addition the 95% confidence interval of the infection rates of prulifloxacin and levofloxacin was calculated.
Clinical outcomes were evaluated by calculating the number and percentage of the signs and symptoms at Visit 4 and Visit 5. Safety and tolerability assessments were planned for the treated population. A description of laboratory test, vital signs, ECG was performed for all the parameters recorded. Laboratory parameters were evaluated on the basis of the Investigator's judgement. AEs, reported by body system, severity and correlation to the test medication, were tabulated by treatment groups. The number of subjects reporting AEs within each treatment group, together with the relevant 95% confidence interval, were reported globally and by AE. Global Tolerability Rating was recorded as frequency distribution.

SUMMARY – CONCLUSION
Efficacy results:
The clinical part of the study lasted from October 2nd, 2008 (first patient-in) to April 29th, 2011 (last patient out). Due to the low rate of enrolment, the study was closed on March 31st, 2011. No safety reasons were implicated in the premature termination of the study. A total of 68 out of 100 planned patients has been enrolled in the study. Fifthy randomised patients (24 in the prulifloxacin group and 26 in the levofloxacin group) who received at least one dose of the study drug, who provide complete baseline data (pre-operative sterile urine) and had a microbiological observation available at V4 or ETV without protocol deviations judged to interfere with the efficacy assessment of the study medications were included in the efficacy analysis.
Twenty three out of 24 patients treated with prulifloxacin 600 mg (once daily for 3 days) and 24 out of 26 patients treated with levofloxacin 500 mg (once daily for 3 days), presented sterile urine at V4 or ETV and were considered as microbiological success. The rate of microbiological failure was 4.17 % (95%CI; -3.83; 12.16) in the prulifloxacin group and 7.69 % (95%CI; -2.55; 17.93) in the levofloxacin group.
Microbiological assessment performed at V5 on patients that presented sterile urine at V4, confirmed the efficacy of the two treatments to maintain the patient free of bacteriuria. At V5, the rate of microbiological success was 100.00% both in prulifloxacin and in levofloxacin and more than 50% of patients in each treatment group was free of signs and symptoms.
Safety results:
Prulifloxacin was well tolerated in patients undergoing TURP. No deaths occurred during the study.

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Safety results:
Fourty eight AEs were reported in 29 patients during the study treatment, 21 AEs in 14 prulifloxacin-treated patients and 27 AEs in 15 levofloxacin-treated patients. Sixteen out of 48 AEs were judged as serious: 7 SAEs were reported in the prulifloxacin group and 9 in the levofloxacin group.
Qualitative analysis of AEs and SAEs did not reveal major differences between treatment groups in the total number and, for the AEs only, in the distribution of events across systems. SAEs occurred during the study were clearly not related with the administration of the investigational medications.
The safety review of vital signs, physical findings and ECG and laboratory examinations urinalysis did not show a clinical effect of both products on any of the parameters. The analysis of the available data confirms that findings on drug safety are consistent with the information reported in the reference document and confirms the positive risk/benefit ratio for prulifloxacin.
Overall, the analysis of the safety parameters was not suggestive of any major risks. The well-know favourable safety profile of both investigational medications is confirmed in this study.

Conclusion:
The small number of patients and the descriptive statistical analysis performed do not allow the drawing of definitive conclusions. However, results of this study suggest a possible use of prulifloxacin in prevention of post-operative urinary bacterial infections in patients undergoing TURP. Confirmatory studies in a larger population are needed.

Date of the Clinical Report: December 7th, 2016