A RANDOMIZED VEHICLE-CONTROLLED TRIAL TO ASSESS THE EFFICACY, SAFETY AND TOLERABILITY OF OZENOXACIN 1% CREAM IN 465 PATIENTS 2 YEARS AND OLDER WITH IMPETIGO

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ABSTRACT

Introduction
Ozenoxacin is a non-fluorinated quinolone antibiotic with potent activity against gram-positive bacteria, being developed as a 1% cream for the topical treatment of impetigo.

Objectives
The primary objective of the study was to compare the efficacy and evaluate the safety and tolerability of ozenoxacin 1% cream versus vehicle after 5 day BID topical applications (10 applications) in patients with impetigo. Retapamulin 1% ointment was included as an active control.

Methods
A Phase 3 multicenter, randomized, vehicle- and active-controlled, parallel, double-blind clinical trial in patients aged 2 years and older with impetigo. Patients were randomized in a 1:1:1 ratio to ozenoxacin, vehicle, or retapamulin. Efficacy was evaluated utilizing a clinical Skin Infection Rating Scale (SIRS) and microbiological culture. Safety and tolerability were also evaluated.

Results
After 5 days of therapy, ozenoxacin demonstrated clinical superiority to vehicle. Ozenoxacin also demonstrated superior microbiological success compared to vehicle as early as after 2 days of treatment. In addition, ozenoxacin demonstrated superior microbiological success to retapamulin after 2 days. Ozenoxacin was safe and well tolerated.

Conclusions
Ozenoxacin demonstrated superior clinical and microbiological response compared to vehicle and presented a favorable safety and tolerability profile. Ozenoxacin also demonstrated early microbiological superiority versus both vehicle and retapamulin. Ozenoxacin represents a novel topical therapeutic option being developed for the treatment of impetigo.

METHODS

- A total of 465 patients were enrolled into the study (3 sites in the USA, 4 sites in Germany, 2 sites in Romania, 5 sites in Ukraine, and 13 sites in South Africa).
- Eligible patients were randomized to receive ozenoxacin 1% cream (155 patients), vehicle (156 patients), or retapamulin 1% ointment (154 patients) applied topically BID for 5 days to all impetigo affected areas, with a maximum extension of 100 cm^2. The first application was done under the guidance of the delegated person appointed by the investigator. After randomization, patients returned at: Visit 2 (Day 3-4, on-therapy) and Visit 3 (during the following day after last application, Day 6-7, end of therapy). Patients returned for a Final Visit (Visit 4, Day 10-13). Additionally, a telephone contact on Day 2 (24-36 hours after baseline visit) was required to assess for any worsening of infection.
- The primary efficacy endpoint was clinical response (success or failure) at end of therapy (Visit 3) analyzed in the intent-to-treat clinical (ITTC) population.
- Success at Visit 3 was defined as SIRS score 0 for exudates/pus, crusting, tissue warmth and pain and no more than 1 each for erythema/inflammation, tissue oedema and itching and no additional antimicrobial therapy on the baseline affected area(s) necessary.
- Main secondary efficacy endpoints were clinical response at all visits in all study populations and microbiological response (success or failure) at all visits in the bacteriological population.
- The evaluation of safety was based on the assessment of adverse events (type, nature, incidence and outcome) and changes in clinical laboratory parameters (hematology, clinical chemistry, urinalysis), vital signs and physical examination.
- For all efficacy analyses, the primary treatment comparison of interest was ozenoxacin versus vehicle, to test the superiority of ozenoxacin versus vehicle. A secondary comparison (for internal validity) of retapamulin versus vehicle was done for the analysis of clinical response (clinical success or clinical failure) at the end of therapy visit (Visit 3) in the ITTC population.

RESULTS

Table 1. Primary Endpoint
Clinical response at end of therapy (Visit 3, Day 6-7) (ITTC population)

P880	Ozenoxacin	Placebo	Retapamulin
N	155	156	154
Clinical success	54 (34.8%)	30 (19.2%)	58 (37.7%)
Clinical failure	98 (63.2%)	120 (76.9%)	91 (59.1%)
Unable to determine	3 (1.9%)	6 (3.8%)	5 (3.2%)
p-value (vs placebo)	**0.003**		**<0.001**

Ozenoxacin demonstrated a statistically significant superior clinical response compared to vehicle at end of treatment. The results for retapamulin were also superior to vehicle and similar to ozenoxacin.

Table 2.
Combined Criteria of Clinical Success at end of therapy (Visit 3, Day 6-7) (Randomized patients)

P880	Ozenoxacin	Placebo	Retapamulin
N	155	156	154
Clinical success	132 (85.2%)	115 (73.7%)	128 (83.1%)
Clinical failure	21 (13.5%)	36 (23.1%)	24 (15.6%)
Unable to determine	2 (1.3%)	5 (3.2%)	2 (1.3%)
p-value (vs placebo)	**0.0276**		

The analysis of Combined Criteria of Clinical Success (posthoc) was defined as a total absence of the treated lesions (lesion extension=0) or the treated lesions became dry without crusts compared to baseline (SIRS=0 for exudate and for crusting), or improvement (defined as decline in the size of the affected area, number of lesions or both) such that no further antimicrobial therapy was necessary. This broader definition of clinical success includes improvement, and reflects the same criteria for clinical success as that used in pivotal Phase 3 clinical trials of other topical antibiotics approved for impetigo.

Overall, 7.5% of patients experienced at least 1 adverse event (AE) and the incidences were generally similar across treatment groups. Most AEs were of mild intensity and only 2 (application site pain and urticaria) both in the retapamulin group were considered to be possibly related to study medication. There were no clinically relevant changes in laboratory hematology, clinical chemistry or urinalysis, or in vital signs.

Table 3.
Microbiological response at Visit 2 (day 3-4) and at end of therapy (Visit 3, Day 6-7) (ITTB population)

P880	Ozenoxacin	Placebo	Retapamulin
Visit 2, Day 3-4			
N	154	152	153
Microbiological success	109 (70.8%)	58 (38.2%)	86 (56.2%)
Microbiological failure	37 (24.0%)	90 (59.2%)	60 (39.2%)
Unable to determine	8 (5.2%)	4 (2.6%)	7 (4.6%)
p-value (vs placebo)	**<0.0001**		
p-value (vs retapamulin)	**0.0087***		
Visit 3, Day 6-7			
N	154	152	153
Microbiological success	122 (79.2%)	86 (56.6%)	124 (81.0%)
Microbiological failure	16 (10.4%)	55 (36.2%)	18 (11.8%)
Unable to determine	16 (10.4%)	11 (7.2%)	11 (7.2%)
p-value (vs placebo)	**<0.0001**		

* Statistical significance confirmed post-hoc

Ozenoxacin demonstrated a statistically significant superior microbiological response compared to vehicle at Visit 2 (day 3-4) and at end of treatment (Visit 3). Ozenoxacin demonstrated superior microbiological success compared to retapamulin after 2 days.

CONCLUSION

In summary, in a randomized controlled trial of 465 patients that included adults and children ages 2 years and older with impetigo, ozenoxacin demonstrated superior clinical and microbiological response versus vehicle after 5 days of therapy, and was safe and well tolerated. Ozenoxacin also demonstrated microbiological superiority versus retapamulin after 2 days of treatment. Ozenoxacin represents a novel topical therapeutic option being developed for the treatment of impetigo.

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