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Ozenoxacin, a New Effective and Safe Topical Treatment for Impetigo in Children and Adolescents

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Keywords
Ozenoxacin · Impetigo, paediatric · Efficacy · Safety · Topical antibiotics

Abstract
Background: Ozenoxacin is a topical antibiotic approved in Europe to treat non-bullous impetigo in adults and children aged ≥6 months. This analysis evaluated the efficacy and safety of ozenoxacin in paediatric patients by age group. ***Methods:*** Pooled data for patients aged 6 months to <18 years who had participated in a phase I or in two phase III clinical trials of ozenoxacin 1% cream were analysed by age group: 0.5–<2, 2–<6, 6–<12, and 12–<18 years. ***Results:*** The combined population comprised 529 patients with non-bullous impetigo treated with ozenoxacin (n = 239), vehicle (n = 201), or retapamulin as internal validation control (n = 89). Studies were well matched for extent and severity of impetigo and therapeutic schedule (twice daily application for 5 days). The clinical success rate after 5 days' treatment (day 6–7, end of therapy), and microbiological success rates after 3–4 days' treatment and at the end of therapy, were significantly higher with ozenoxacin than vehicle ($p < 0.0001$ for all comparisons). Clinical and bacterial eradication rates were higher with ozenoxacin than vehicle in each age group. No safety concerns were identified with ozenoxacin. One (0.3%) of 327 plasma samples exceeded the lower limit of quantification for ozenoxacin, but the low concentration indicated negligible systemic absorption. ***Conclusion:*** This combined analysis supports the efficacy and safety of ozenoxacin administered twice daily for 5 days. Ozenoxacin 1% cream is a new option to consider for treatment of non-bullous impetigo in children aged 6 months to <18 years.

Introduction

Impetigo is a bacterial skin infection common in children, with an estimated global prevalence approximately 2.5-fold higher than that in adults [1]. The main types of impetigo are non-bullous (70% of cases) and bullous (30% of cases). Non-bullous impetigo, or impetigo contagiosa, is caused by *Staphylococcus aureus* or *Streptococcus pyogenes*. It is characterised by superficial honey-coloured crusted lesions on the face and extremities which

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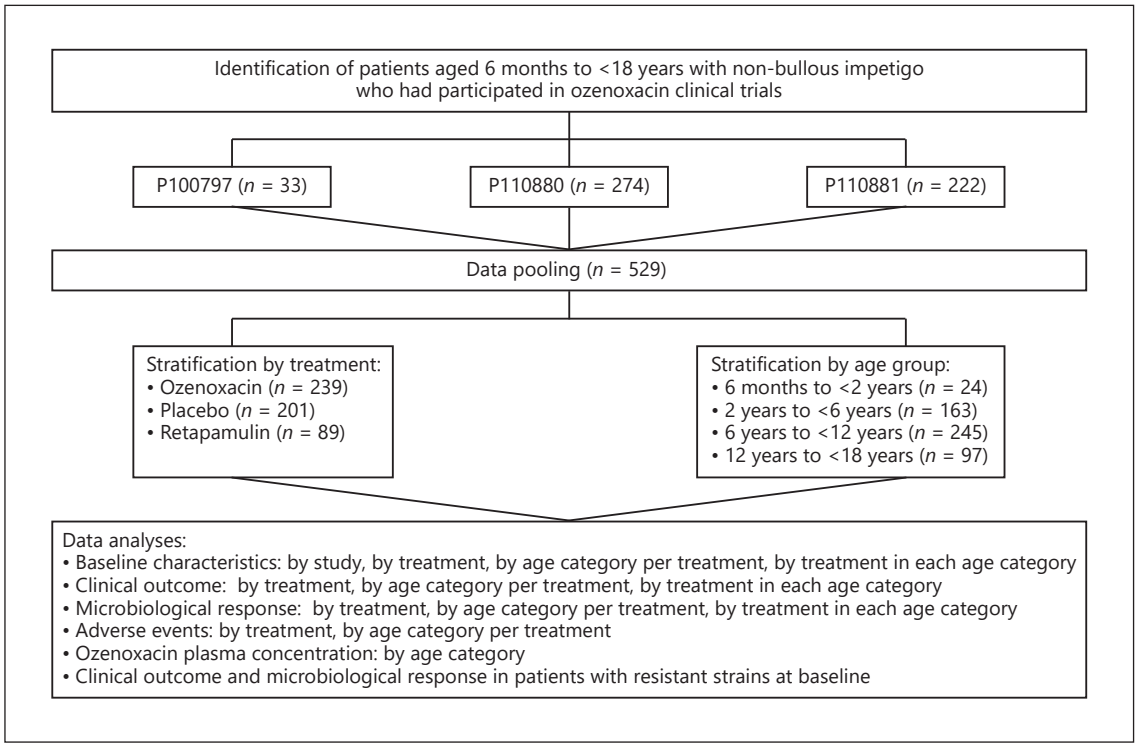

Fig. 1. Flowchart of Methods: overview of study procedures.

can spread to surrounding areas by auto-inoculation and transmit to close contacts [2–6]. Bullous impetigo is caused by toxin-producing *S. aureus* and is characterised by rapidly enlarging, flaccid bullae that can rupture and ooze, leaving a pathognomonic collarette of scales. Bullous impetigo tends to affect the trunk, extremities, and moist intertriginous areas such as the axillae, neck fold, and diaper area. Extensive lesions may be accompanied by systemic symptoms such as fever, diarrhoea, and weakness [2–6].

Factors associated with an increased risk of impetigo include residing in a tropical climate, crowded living conditions, poor hygiene, socio-economic deprivation, host immunity status and playing close-contact sports [1, 2, 5, 6]. As impetigo is highly contagious, it is a particular concern for schools and day care centres where the likelihood of transmission is increased [7]. Clinical practice guidelines recommend the use of topical antibacterial agents for small localised areas of lesions and recommend oral antibiotics for the treatment of numerous or more extensive lesions that are not responding to topical therapy, and for systemic infection [8].

Ozenoxacin is a novel non-fluorinated quinolone. As of May 2019, ozenoxacin 1% cream has been approved in 12 countries of the European Union (EU) for topical treatment of non-bullous impetigo in patients aged 6 months and older [9]. Although relatively few patients under 6 months of age and/or with bullous impetigo were enrolled in pivotal phase III clinical trials of ozenoxacin [10, 11], in the USA and Canada ozenoxacin 1% cream is indicated for topical treatment of non-bullous and bullous impetigo in patients aged 2 months and older [12, 13].

Comparative in vitro studies have shown that ozenoxacin has potent antimicrobial activity against staphylococci and streptococci, the major pathogens involved in impetigo. Ozenoxacin also has a broad range of activity against methicillin-, mupirocin-, and ciprofloxacin-resistant strains of *S. aureus* [14, 15]. Ozenoxacin's dual inhibitory activity against the bacterial replication enzymes, DNA gyrase and topoisomerase IV, protects it from development of resistance [16], and the absence of a fluorine atom in its molecular structure confers a better safety profile than that of fluorinated quinolones, including a lack of quinolone-induced chondrotoxicity [17]. Topical ozenoxacin is negligibly absorbed [18], and phase I studies showed excellent dermal tolerability [19]. Collectively, these properties suggest that ozenoxacin may be a valuable option for empirical therapy of localised impetigo.

Table 1. Demographic and baseline characteristics of the combined safety and efficacy population according to treatment

	Total (n = 529)	Ozenoxacin (n = 239)	Vehicle (n = 201)	Retapamulin (n = 89)
Study, *n* (%)				
Phase I [20]	33 (6.2)	33 (13.8)	0 (0.0)	0 (0.0)
Phase III [10]	274 (51.8)	94 (39.3)	91 (45.3)	89 (100.0)
Phase III [11]	222 (42.0)	112 (46.9)	110 (54.7)	0 (0.0)
Age range, *n* (%)				
≥6 months to <2 years	24 (4.5)	17 (7.1)	7 (3.5)	0 (0.0)
≥2 to <6 years	163 (30.8)	83 (34.7)	49 (24.4)	31 (34.8)
≥6 to <12 years	245 (46.3)	94 (39.3)	106 (52.7)	45 (50.6)
≥12 to <18 years	97 (18.3)	45 (18.8)	39 (19.4)	13 (14.6)
Gender, *n* (%)				
Female	226 (42.7)	107 (44.8)	87 (43.3)	32 (36.0)
Male	303 (57.3)	132 (55.2)	114 (56.7)	57 (64.0)
Race, *n* (%)				
Black	251 (47.4)	115 (48.1)	81 (40.3)	55 (61.8)
Caucasian/White	195 (36.9)	81 (33.9)	96 (47.8)	18 (20.2)
Mixed race/Multiracial	63 (11.9)	33 (13.8)	14 (7.0)	16 (18.0)
Asian	20 (3.8)	10 (4.2)	10 (5.0)	0 (0.0)
Affected areas (mean ± SD), *n*	3.1±3.2	3.1±2.6	2.8±2.8	3.8±4.9
Total affected area (mean ± SD), cm^2	7.2±10.8	7.3±10.2	7.8±11.3	5.7±11.3
Baseline Skin Infection Rating Scale total score (mean ± SD)	11.2±4.5	10.9±4.6	10.7±4.7	13.3±3.4
Microbiological susceptibility, *n* (%)				
Total	236	89	78	69
Resistant	10 (4.2)	5 (5.6)	3 (3.8)	2 (2.9)
Susceptible	226 (95.8)	84 (94.4)	75 (96.2)	67 (97.1)

Clinical studies of ozenoxacin 1% cream (twice daily for 5 days) demonstrated that it is effective and well tolerated in children and adults with impetigo [10, 11, 20]. To further ascertain the profile of ozenoxacin specifically in the paediatric population, we extracted and analysed data for children and adolescents aged 6 months to <18 years who had participated in ozenoxacin clinical trials.

Methods

For further details, see the supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000504536) (Fig. 1) [9–11, 20].

Results

Demographics and Baseline Clinical Characteristics

The pooled efficacy and safety population consisted of 529 patients aged ≥6 months to <18 years with non-bullous impetigo who were enrolled in phase I [20] or phase III [10, 11] clinical trials of ozenoxacin. Most patients were recruited in South Africa (n = 313), the USA (n = 79), or Germany (n = 60).

Demographic and baseline characteristics of the pooled efficacy and safety population are summarised in Table 1 according to treatment with ozenoxacin (n = 239), vehicle (n = 201), or retapamulin (n = 89). Demographic parameters and clinical characteristics were similar among treatment groups. Most patients were aged 6–<12 years (n = 245; 46.3%) or 2–<6 years (n = 163; 30.8%). There was a slight male preponderance (57.3%), and the most common ethnic groups were Black (47.4%) and Caucasian/White (36.9%). At baseline, patients had a mean Skin Infection Rating Scale total score of 11.2 ± 4.5, a mean of 3.1 ± 3.2 affected areas, and a mean total affected area of 7.2 ± 10.8 cm^2. Most patients (95.8%) had microbiological susceptibility at baseline.

Demographic and baseline characteristics of the pooled efficacy and safety population treated with ozenoxacin or vehicle and stratified by age group are shown in Table 2. The mean Skin Infection Rating Scale total score at baseline ranged from 10.0 ± 4.1 in the 6- to <12-

Table 2. Demographic and baseline characteristics of the combined safety and efficacy population according to treatment and age group

	Oxenoxacin				Vehicle			
	0.5–<2 years (*n* = 17)	2–<6 years (*n* = 83)	6–<12 years (*n* = 94)	12–<18 years (*n* = 45)	0.5–<2 years (*n* = 7)	2–<6 years (*n* = 49)	6–<12 years (*n* = 106)	12–<18 years (*n* = 39)
Study, *n* (%)								
Phase I [20]	11 (64.7)		4 (4.3)	9 (20.0)	–	–	–	–
Phase III [10]	0 (0.0)	40 (48.2)	36 (38.3)	18 (40.0)	0 (0.0)	22 (44.9)	52 (49.1)	17 (43.6)
Phase III [11]	6 (35.3)	34 (41.0)	54 (57.4)	18 (40.0)	7 (100.0)	27 (55.1)	54 (50.9)	22 (56.4)
Gender, *n* (%)								
Female	8 (47.1)	32 (38.6)	40 (42.6)	27 (60.0)	4 (57.1)	20 (40.8)	50 (47.2)	13 (33.3)
Male	9 (52.9)	51 (61.4)	54 (57.4)	18 (40.0)	3 (42.9)	29 (59.2)	56 (52.8)	26 (66.7)
Race, *n* (%)								
Black	9 (52.9)	46 (55.4)	45 (47.9)	15 (33.3)	5 (71.4)	19 (38.8)	43 (40.6)	29 (74.4)
Caucasian/White		22 (26.5)	35 (37.2)	21 (46.7)	2 (28.6)	25 (51.0)	48 (45.3)	6 (15.4)
Mixed race/Multiracial	4 (23.5)	13 (15.7)	8 (8.5)	8 (17.8)	0 (0.0)	5 (10.2)	6 (5.7)	3 (7.7)
Asian	1 (5.9)	2 (2.4)	6 (6.4)	1 (2.2)	0 (0.0)	0 (0.0)	9 (8.5)	1 (2.6)
Affected areas (mean ± SD), *n*	5.1±3.3	3.3±2.9	2.9±2.4	2.5±1.9	2.0±1.0	3.6±3.1	2.9±3.0	1.8±1.3
Total affected area (mean ± SD), cm^2	5.5±7.3	7.8±13.6	7.7±8.8	6.2±6.0	5.8±3.6	7.8±8.3	7.4±12.6	9.5±11.8
Baseline Skin Infection Rating Scale total score (mean ± SD)	11.2±3.6	10.9±4.5	10.0±4.1	12.7±5.4	9.1±3.6	10.8±4.7	10.7±4.6	10.9±5.5
Microbiological susceptibility, *n* (%)								
Total	1	42	33	13	0	21	48	9
Resistant	0 (0.0)	4 (9.5)	1 (3.0)	0 (0.0)	0 (0.0)	1 (4.8)	1 (2.1)	1 (11.1)
Susceptible	1 (100.0)	38 (90.5)	32 (97.0)	13 (100.0)	0 (0.0)	20 (95.2)	47 (97.9)	8 (88.9)

year age group to 12.7 ± 5.4 in the 12- to <18-year age group in patients treated with ozenoxacin, and from 9.1 ± 3.6 in the 0.5- to <2-year age group to 10.9 ± 5.5 in the 12- to <18-year age group in patients treated with vehicle. The mean number of affected areas at baseline ranged from 2.5 ± 1.9 in the 12- to <18-year age group to 5.1 ± 3.3 in the 0.5- to <2-year age group in patients treated with ozenoxacin, and from 1.8 ± 1.3 in the 12- to <18-year age group to 3.6 ± 3.1 in the 2- to <6-year age group in patients treated with vehicle. The mean total affected area at baseline ranged from 5.5 ± 7.3 cm^2 in the 0.5- to <2-year age group to 7.8 ± 13.6 cm^2 in the 2- to <6-year age group in patients treated with ozenoxacin, and from 5.8 ± 3.6 cm^2 in the 0.5- to <2-year age group to 9.5 ± 11.8 cm^2 in the 12- to <18-year age group in patients treated with vehicle.

Clinical Outcomes

The clinical success rate in the pooled paediatric population after 5 days' treatment was significantly higher with ozenoxacin than vehicle ($p < 0.0001$) (Fig. 2). In each of the four age groups ozenoxacin was associated with a higher clinical success rate compared with vehicle. Respective clinical success rates by age group for ozenoxacin versus vehicle were: 100 versus 57.1% for 0.5–<2 years; 88.0 versus 71.4% for 2–<6 years; 91.5 versus 77.4% for 6–<12 years; and 93.3 versus 79.5% for 12–<18 years. Results in the retapamulin control arm by age group were 93.5% for 2–<6 years, 71.1% for 6–<12 years, and 76.9% for 12–<18 years, respectively.

Microbiological Response

Microbiological response following ozenoxacin or vehicle treatment was evaluated at visit 2 (day 3–4 of treatment) and visit 3 (day 6–7, end of 5 days' therapy). In the pooled population, ozenoxacin was associated with significantly higher microbiological success rates than vehicle at visit 2 (Fig. 3) and visit 3 (Fig. 4) ($p < 0.0001$ at both time points). In each age group, ozenoxacin was associated with a higher microbiological success rate at both visits compared with vehicle. At visit 2, the respective microbiological success rates for ozenoxacin and vehicle were: 100 versus 60% for 0.5–<2 years; 81.8 versus 55.3% for 2–<6 years; 87.7 versus 59.8% for 6–<12 years; and 81.8 versus 42.3% for 12–<18 years (Fig. 3). At visit 3, the respective microbiological success rates for ozenoxacin and vehicle were: 100 versus 60% for 0.5–<2 years; 92.2 versus 70.3% for 2–<6 years; 97.2 versus 73.8% for 6–<12 years; and 90.5 versus 64.0% for 12–<18 years (Fig. 4).

Microbiological success rates in the retapamulin control arm by age group were 60% for 2–<6 years, 50% for 6–<12 years, and 46.2% for 12–<18 years, respectively, at visit 2, and 87.1% for 2–<6 years, 82.2% for 6–<12 years, and 84.6% for 12–<18 years, respectively, at visit 3.

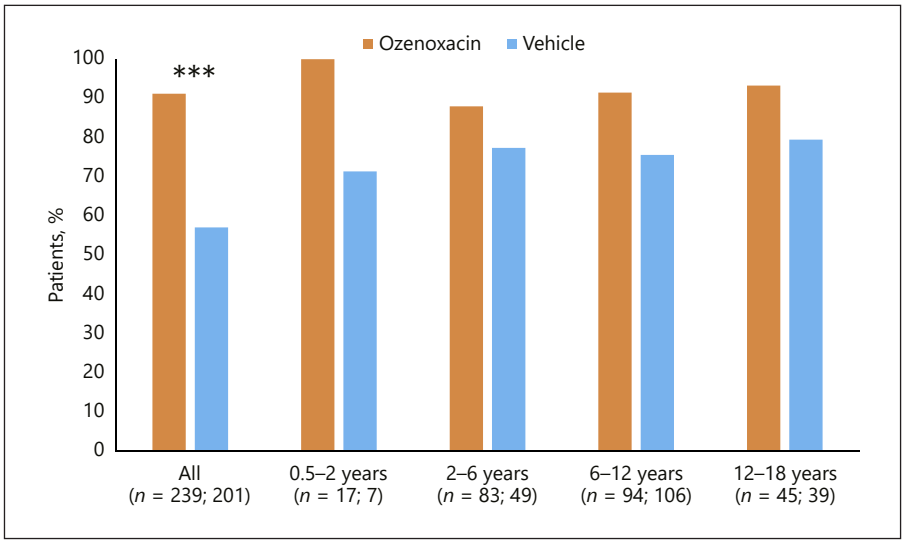

Fig. 2. Clinical success rates after 5 days' treatment (day 6–7; end of therapy) in ozenoxacin- and vehicle-treated paediatric patients stratified by age group. Clinical success was defined as cure or improvement according to predefined criteria. *** $p < 0.0001$.

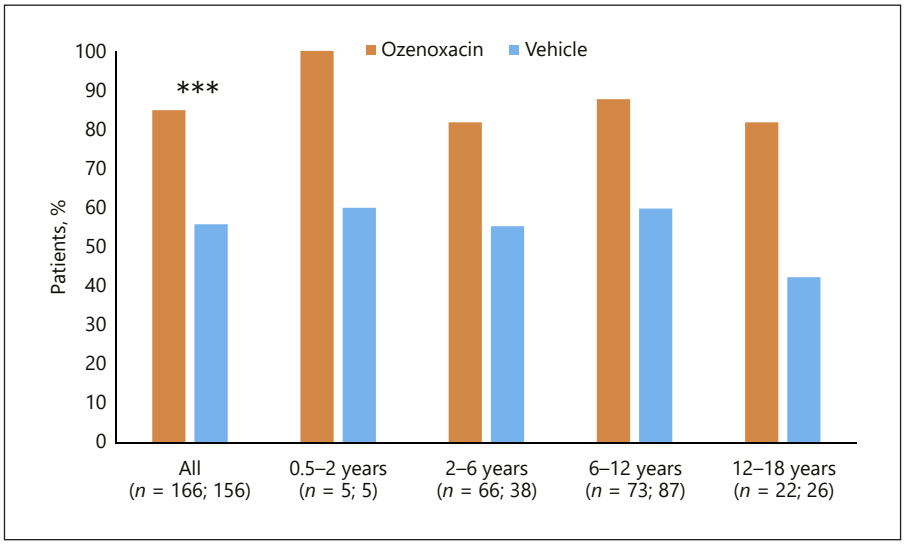

Fig. 3. Microbiological success rates at visit 2 (day 3–4 of treatment) in ozenoxacin- and vehicle-treated paediatric patients stratified by age group. Microbiological success was defined as the absence of original pathogen(s) in culture of the baseline specimen with/without the presence of new micro-organisms. *** $p < 0.0001$.

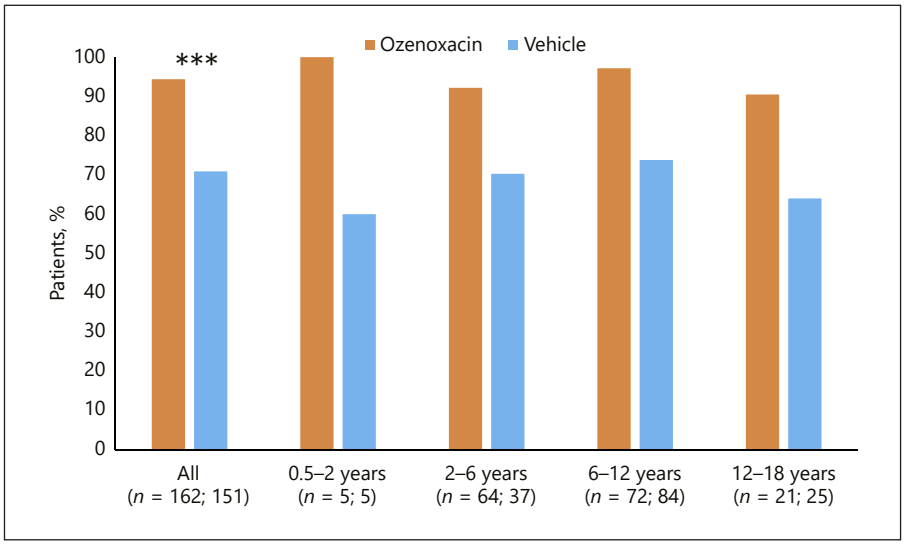

Fig. 4. Microbiological success rates at visit 3 (day 6–7, end of 5 days' therapy) in ozenoxacin- and vehicle-treated paediatric patients stratified by age group. Microbiological success was defined as the absence of original pathogen(s) in culture of the baseline specimen with/without the presence of new micro-organisms. *** $p < 0.0001$.

Table 3. Ozenoxacin plasma samples above the lower limit of quantification

	Patient groups				
	All (n = 33)	0.5–<2 years (n = 11)	2–<6 years (n = 9)	6–<12 years (n = 4)	12–<18 years (n = 9)
Samples, n	327	74	64	36	153
Samples above the LLQ, n (%)[1]	1 (0.3)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)

Data from Gropper et al. [20]. LLQ, lower limit of quantification: 0.489 ng/mL. [1] As a proportion of the number of samples.

Outcomes in Patients with Resistant Strains

At baseline, 10 patients had resistant bacterial strains, including 2 patients allocated to retapamulin. The clinical success rate (cure or improvement) after 5 days' treatment was 100% for 5 patients treated with ozenoxacin and 100% for 3 patients treated with vehicle. Ozenoxacin was superior to vehicle in terms of microbiological response. All 5 patients (100%) treated with ozenoxacin achieved microbiological eradication by visit 2 (day 3–4 of treatment) which was maintained at visit 3 (day 6–7, end of 5 days' therapy). One (33.3%) of 3 patients treated with vehicle achieved microbiological success at visit 2 and visit 3.

Safety

Across studies, there were 34 mild (n = 25) or moderate (n = 9) adverse events (AEs) reported in 28 (5.3%) patients during the course of treatment. No serious AEs were reported. A total of 15 AEs (12 mild, 3 moderate) were reported in 13 patients (5.4%) treated with ozenoxacin; 6 AEs (3 mild, 3 moderate) were reported in 6 patients (3.0%) treated with vehicle, and 13 AEs (9 mild, 4 moderate) were reported in 9 patients (10.1%) treated with retapamulin. No AE reported for ozenoxacin or vehicle was considered to be drug related. One AE reported with retapamulin, which occurred in the 6- to <12-year age group, was considered to be drug related.

Pharmacokinetic parameters were available for 33 paediatric patients treated with ozenoxacin in the phase I study (Table 3). A plasma concentration above the lower limit of quantification for ozenoxacin (0.489 ng/mL) was identified in a sample from a patient in the 2- to <6-year age group, representing 0.3% of 327 plasma samples tested. The measured concentration of 0.614 ng/mL indicated negligible systemic absorption.

Discussion

The efficacy and safety of ozenoxacin in the paediatric population with non-bullous impetigo were examined by pooling data for patients aged 6 months to <18 years of age who had participated in phase I [20] or phase III [10, 11] clinical trials. In the combined population, clinical and microbiological success rates with ozenoxacin were significantly superior to those with vehicle, confirming the results of the pivotal phase III trials. In analyses by age group, ozenoxacin demonstrated earlier and superior bacterial eradication compared with vehicle in all age groups. Clinical success rates after 5 days' treatment ranged from 88.0 to 100% with ozenoxacin, and from 57.1 to 79.5% with vehicle. Microbiological success rates with ozenoxacin ranged from 81.8 to 100% after 3–4 days of treatment, and from 90.5 to 100% after 5 days' treatment. Corresponding microbiological success rates were considerably lower with vehicle (42.3–60% and 60–73.8% at visit 2 and visit 3, respectively) and also in the retapamulin control arm (46.2–60% and 82.2–87.1% at visit 2 and visit 3, respectively). Due to the rapid bactericidal activity of ozenoxacin as indicated in this subanalysis, its early microbiological eradication activity may have critical importance in restricting the transmission of impetigo, a highly contagious condition.

There were no safety concerns among 239 paediatric patients treated with ozenoxacin across studies regardless of age; none of the 15 AEs reported with ozenoxacin was considered to be treatment related. The excellent dermal tolerability to topical ozenoxacin observed during clinical use aligns with phase I studies showing little to no tendency for single or repeated doses of ozenoxacin to cause irritation, sensitization, phototoxicity, or photoallergy [19]. Likewise, the virtual lack of systemic absorption after administration of topical ozenoxacin twice daily for 5 days is consistent with phase I studies showing no sys-

temic absorption after increasing single or multiple doses of ozenoxacin applied to intact or abraded skin [18].

National primary care treatment guidelines in European countries recommend fusidic acid, mupirocin, or retapamulin as topical treatments for impetigo [21]. However, the development and spread of staphylococcal strains resistant to these agents is a concern. Resistance to fusidic acid has been reported in Europe [22–26]. Fusidic acid resistance in strains of *S. aureus* causing impetigo is due to clonal expansion of the epidemic European fusidic acid-resistant impetigo clone (EEFIC) [23, 24, 27, 28], although EEFIC-related outbreaks have declined markedly since their peak in the early 2000s [29, 30]. Resistance to mupirocin has also been reported in Europe [31–33] and may be increasing. Investigators in Greece reported an increase from 4.2% in 2013 to 37.7% in 2016 in the rate of mupirocin-resistant *S. aureus* strains among community-associated staphylococcal infections, concurrent with increasing rates of resistance to fusidic acid [34].

Efforts to promote judicious use of antibiotics have centred mainly on oral and intravenous formulations; however, the consequences of drug resistance also extend to topical antibiotics [35]. Appropriate use of topical antibacterials in evidence-based indications provides important benefits. Delivering a high concentration of drug directly to infected areas of skin can overcome bacterial resistance, and minimal dermal absorption avoids potential systemic side effects associated with oral therapy [16].

Antibiotics with a rapid bactericidal effect are important for symptom resolution in a highly contagious disease such as impetigo. In susceptibility studies, ozenoxacin was shown to be bactericidal against methicillin-susceptible and methicillin-resistant *S. aureus*, methicillin-susceptible and methicillin-resistant *S. epidermidis* – including levofloxacin-susceptible and levofloxacin-resistant isolates – and against *S. pyogenes* and *S. agalactiae* [15]. Although the number of patients with resistant strains in the current analysis was limited, all 5 patients treated with ozenoxacin achieved bacterial eradication within 3 days of commencing treatment.

The main purpose of undertaking this analysis was to ascertain the efficacy and safety of topical ozenoxacin in the primary target population in the EU, namely paediatric patients aged 6 months or older with non-bullous impetigo. Study homogeneity with regard to inclusion/exclusion criteria and therapeutic schedule facilitated data pooling in order to evaluate outcomes in a larger patient population. The main limitation of the analysis is the few patients in the 0.5- to <2-year age category (ozenoxacin $n = 17$; vehicle $n = 7$), although this is consistent with the disease pattern, as non-bullous impetigo has a peak incidence in children aged 2–6 years [2]. Similar clinical and microbiological success rates and excellent tolerability to ozenoxacin observed across age groups support its EU indication to treat impetigo in children aged 6 months and older.

Conclusions

Although fusidic acid and mupirocin continue to be widely used in Europe to treat impetigo, resistance to these antibacterial agents is observed and may be increasing. Ozenoxacin, which has potent antibacterial activity against staphylococci and streptococci, a rapid bactericidal effect and low potential to select resistant mutants, appears to be a useful alternative to treat non-bullous impetigo in children and adolescents aged 6 months to 17 years.

Key Message

This pooled analysis confirmed the efficacy and safety of ozenoxacin in children with non-bullous impetigo.

Acknowledgements

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Statement of Ethics

All studies included in the pooled analyses were conducted in accordance with principles outlined in the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines.

Disclosure Statement

X.M. is an employee of SAIL. N.A.L. and I.Z. are employees of Ferrer Internacional. The remaining authors have no conflicts of interest to declare.

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Author Contributions

All authors contributed to the development of the trial protocol and were involved in drafting the manuscript or revising it critically for important intellectual content. N.A.L. and I.Z. participated in the conception and design of the study. Analysis and interpretation of the data were supported by A.T. and X.M. R.G. conducted a critical review of the manuscript, contributing important intellectual content. All authors gave final approval of the version for publication.

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