

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208945Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Office of Clinical Pharmacology Review

NDA Number	208945
Link to EDR	\\CDSESUB1\evsprod\NDA208945\208945.enx
Submission Date	06/23/2016
Submission Type	NME; Standard
Brand Name	(b) (4)
Generic Name	Ozenoxacin cream, 1%
Dosage Form and Strength	Cream, 1% 10 mg ozenoxacin/1g of cream in 10-, 30- and 45-gram multiple use tubes, as well as a 3 gram physician's sample.
Route of Administration	Topical
Proposed Indication	Topical treatment of impetigo in adults and pediatric patients 2 months of age and older due to <i>Staphylococcus aureus</i> or <i>Streptococcus pyogenes</i>
Applicant	Ferrer International, SA., PA, 19087
Associated INDs	IND 105567
OCP Review Team	Xiaohui (Tracey) Wei, Ph.D.: Primary Reviewer Seong H. Jang, Ph.D.: Team Leader
OCP Final Signatory	John Lazor, Pharm.D.: Division of Clinical Pharmacology IV Director

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY	2
1.1 RECOMMENDATIONS	2
1.2 POST-MARKETING REQUIREMENTS AND COMMITMENTS	3
2 SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT	4
2.1 PHARMACOLOGY AND CLINICAL PHARMACOKINETICS	4
2.2 DOSING AND THERAPEUTIC INDIVIDUALIZATION	5
2.3 OUTSTANDING ISSUES	5
2.4 SUMMARY OF LABELING RECOMMENDATIONS	5
3 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW	6
3.1 OVERVIEW OF THE PRODUCT AND REGULATORY BACKGROUND	6
3.2 GENERAL PHARMACOLOGY AND PHARMACOKINETIC CHARACTERISTICS	6
3.3 CLINICAL PHARMACOLOGY REVIEW QUESTIONS	8
4 APPENDICES	11
4.1 LABELING RECOMMENDATIONS	11
4.2 SUMMARY OF BIOANALYTICAL METHOD VALIDATION	12
4.3 REVIEW OF INDIVIDUAL STUDY REPORTS	13

1 EXECUTIVE SUMMARY

Ozenoxacin is a quinolone antimicrobial drug presented in the pharmaceutical form of 10 mg/g (1%) cream for a short-term topical treatment of impetigo in adults and pediatric patients 2 months of age and older due to *Staphylococcus aureus* (methicillin-susceptible and methicillin-resistant isolates) or *Streptococcus pyogenes*. The Applicant's proposed dosing is to apply a thin layer of (b) (4) (Ozenoxacin 1% Cream) to the affected area twice daily for five days.

A 5-day, twice daily treatment regimen with the ozenoxacin 1% cream strength was selected from the Phase 2 dose-ranging study and demonstrated to be safe and effective in two pivotal Phase 3 clinical studies. Results of the Phase 3 studies, individually and collectively, showed that ozenoxacin 1% cream was superior to placebo cream for clinical success (difference in the success rates of 0.160, $p < 0.001$). Ozenoxacin 1% cream was well tolerated by healthy volunteers and patients.

As from the Applicant, ozenoxacin 1% cream demonstrated negligible systemic absorption following the topical application in healthy subjects and in patients with impetigo. The negligible systemic absorption of ozenoxacin following ozenoxacin 1% cream topical application supports its topical treatment of mild skin infections as impetigo. There are no major Clinical Pharmacology-related review issues. It was confirmed that there is no or negligible systemic absorption of ozenoxacin following topical administration. The appropriateness of the proposed dosing regimen for the adult and pediatric patients with impetigo was evaluated based on efficacy and safety data obtained from Phase 2 and Phase 3 studies.

1.1 Recommendations

The Clinical Pharmacology information provided by the Applicant in the NDA submission is acceptable.

The application is approvable from a clinical pharmacology perspective, provided that an agreement is reached between the Applicant and the Agency on the labeling recommendations. Key review issues with specific recommendations and comments are summarized below:

Table 1.1-1: Summary of OCP’s Recommendations & Comments on Key Review Issues

Review Issue	Recommendations and Comments
Supportive evidence of effectiveness	Two Phase 3 safety and efficacy studies in pediatric (2 months of age and older) and adult subjects with impetigo provided adequate data to support the effectiveness of ozenoxacin 1% cream in impetigo patients.
General dosing instructions	The Applicant proposed that a thin layer of (b) (4) should be applied to the affected area twice daily for 5 days. We recommend adding information regarding the application area based on the dosing regimen evaluated in pivotal Phase 3 studies: apply a thin layer of (b) (4) topically to the affected area twice daily for 5 days. The application area may be up to 100 cm ² in adult and pediatric patients 12 years of age and older or 2% total body surface area and not exceeding 100 cm ² in pediatric patients less than 12 years of age. .
Dosing in patient subgroups (intrinsic and extrinsic factors)	<p>The dose strength, dosing frequency and treatment duration of (b) (4) (Ozenoxacin 1% Cream) recommended for pediatric patients are the same as for adult patients. However, the application area for pediatric patients less than 12 years of age is different (see above).</p> <p>Since systemic absorption of ozenoxacin was negligible following topical application of ozenoxacin 1% cream in healthy volunteers and impetigo patients, no dose individualization is recommended based on intrinsic and extrinsic factors.</p>
Labeling	The Applicant’s proposed labeling is generally acceptable except for the aforementioned dosing instruction. In addition, the review team has specific content and formatting change recommendations.
Bridge between the to-be-marketed and clinical trial formulations	Not applicable.

1.2 Post-Marketing Requirements and Commitments

There are no post-marketing requirements and commitments being made.

2 Summary of Clinical Pharmacology Assessment

2.1 Pharmacology and Clinical Pharmacokinetics

Ozenoxacin is a quinolone antimicrobial drug. The molecular formula is $C_{21}H_{21}N_3O_3$ and the molecular weight is 363.41 Da.

Mechanism of Action: Ozenoxacin acts as an inhibitor of DNA replication with a dual target of action, blocking the bacterial DNA gyrase and the topoisomerase IV enzymes.

Ozenoxacin 1% cream demonstrated negligible systemic absorption following topical application in healthy subjects and in patients with impetigo. There was no systemic absorption of ozenoxacin following topical application of ozenoxacin 2% cream (twice the strength of the proposed to-be-marketed formulation) on intact or abraded skin in healthy volunteers. When testing the skin availability of ozenoxacin 2% cream formulation in healthy volunteers, concentrations of ozenoxacin in the stratum corneum and epidermis (upper skin layer) were high and increased with the number of administrations, whereas its concentrations in the dermis (lower skin layer) remained near the limit of quantitation (5.01 ng/mg). These results indicated that ozenoxacin does not easily penetrate into the lower skin layers and support the negligible systemic absorption of ozenoxacin observed in humans.

2.2 Dosing and Therapeutic Individualization

2.2.1 General Dosing

The Applicant proposed the following dose regimen of ozenoxacin 1% cream in adult and pediatric (2 months of age and older) patients with impetigo: Apply a thin layer of (b) (4) to the affected area twice daily for five days. We disagree with the Applicant's proposed dosing instructions and recommend including the following dosing instructions in the label: Apply a thin layer of (b) (4) topically to the affected area twice daily for 5 days. The application area may be up to 100 cm² in adult and pediatric patients 12 years of age and older or 2% total body surface area and not exceeding 100 cm² in pediatric patients less than 12 years of age.

The Applicant's proposed dosing is supported by the efficacy, safety and PK data from the clinical trials submitted in the NDA. Our recommendation to provide additional information regarding the application area is based on how (b) (4) was applied for adult and pediatric (2 months of age and older) patients with impetigo in pivotal Phase 3 studies.

2.2.2 Therapeutic Individualization

The dose regimen of (b) (4) for pediatric patients is the same as for adult patients except for the application area for pediatric patients less than 12 years of age (see section 2.2.1). This is supported by a similar or better clinical success rate of ozenoxacin 1% cream in pediatric patients compared to adult patients.

Since systemic absorption of ozenoxacin was negligible following topical application of ozenoxacin 1% cream to healthy subjects and to patients with impetigo, no dose individualization is recommended based on intrinsic and extrinsic factors.

2.3 Outstanding Issues

There are no outstanding issues.

2.4 Summary of Labeling Recommendations

In general, the proposed labeling related to Clinical Pharmacology is acceptable except for dosing instructions (see section 2.2.1). Additional minor labeling recommendations were made in the clinical pharmacology related sections of the labeling (see section 4.1).

3 Comprehensive Clinical Pharmacology Review

3.1 Overview of the Product and Regulatory Background

(b) (4) (Ozenoxacin 1% Cream) is a topical quinolone antimicrobial drug and has been developed for the short-term treatment of impetigo in patients aged 2 months and older. Ozenoxacin is chemically and clinically distinct from the orally administered (and hence systemically bioavailable) members of the related fluoroquinolones on the US market. The proposed dose regimen is to apply a thin layer of (b) (4) to the affected area twice daily for five days.

The clinical development of topical ozenoxacin included a total of 17 clinical trials conducted with ozenoxacin as an ointment or cream formulation with different strengths. Fifteen studies were conducted with the ozenoxacin cream formulation: 11 Phase 1 studies in healthy adult volunteers, one Phase 1 study in patients with impetigo, one Phase 2 study in patients with secondarily infected traumatic lesions (SITLs) and two Phase 3 studies in adult and pediatric patients with impetigo. An ointment formulation was used in the first two Phase 1 PK studies in healthy volunteers, whereas the cream formulation was used in the rest of Phase 1 and Phase 2/3 studies at different strengths.

The Applicant has requested a waiver for the conduct of clinical studies in the pediatric age group aged 0 to 2 months because necessary studies are impossible or highly impractical. This waiver request was granted by the Division of Anti-infective Products.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Mechanism of Action

Ozenoxacin acts as an inhibitor of DNA replication enzymes, DNA gyrase and the topoisomerase IV. This effect is mediated by the ability of quinolones to stabilize complexes of DNA and both DNA gyrase and topoisomerase IV, thus blocking progression of the replication fork. Ozenoxacin has been shown to be bactericidal against *Staphylococcus aureus* (MRSA, MSSA, VISA) and *Streptococcus pyogenes* (EryR and EryS) organisms that are involved in skin infections.

Pharmacodynamics

Cardiac Electrophysiology:

Ozenoxacin inhibited hERG current by $16.8 \pm 0.9\%$ (Mean \pm SEM; N = 3) at 17 μ M (the highest feasible formulation concentration based on solubility testing) versus $0.8 \pm 0.4\%$ (N = 4) in control. No prolongation in QT and QTc interval was observed at relatively high doses of ozenoxacin in dogs (up to oral administration of 500 mg/kg) and guinea pigs (up to intravenous administration of 30 mg/kg). Due to the negligible systemic exposure of ozenoxacin following topical application, there is no concern for QT prolongation in patients.

Pharmacodynamic Drug Interactions:

Potential antibacterial interactions of ozenoxacin was tested *in vitro* with 17 other commonly used anti-infective agents (cefepime, imipenem, aztreonam, azithromycin, amikacin, tetracycline, rifampin, linezolid, ciprofloxacin, piperacillin, tazobactam, trimethoprim, sulphamethoxazole, daptomycin, mupirocin, fusidic acid and retapamulin) against different organisms of *S. aureus*, *S. epidermidis*, *S. pyogenes* and *S. pneumoniae*. From a total of 630 combination experiments with other antimicrobial agents, 4 antagonism interactions with ozenoxacin were observed: with ciprofloxacin against *S. aureus* and with aztreonam, rifampicin and retapamulin against

S. epidermidis. In addition, 26 combinations with ozenoxacin demonstrated a partial synergy/addition. However, the low incidence suggests that this is not likely to be clinically significant.

Pharmacokinetics

Absorption:

An *in vitro* topical absorption study through excised human skin (with 1% ointment and with 1% or 2% creams) showed low skin penetration of ozenoxacin and thus, a likely limited topical absorption.

Four clinical pharmacokinetic studies were conducted in 110 patients utilizing varying strengths of ozenoxacin cream, up to 2% (twice the concentration of the marketed formulation). Three of these studies assessed systemic absorption in healthy subjects and in patients with impetigo. These studies were conducted with either single or repeated application of up to 1 g ozenoxacin cream to intact or abraded skin (up to 200 cm² surface area). No systemic absorption was observed in 84 of 86 subjects, and negligible systemic absorption was observed near the level of the detection limit (0.489 ng/mL) in 2 subjects (see sections 4.5.1, 4.5.2, 4.5.4).

Following topical application of ozenoxacin 2% cream formulation to healthy subjects, ozenoxacin appears to remain in the upper skin layers (stratum corneum & epidermis) and does not easily penetrate to the lower skin layers (dermis) (see section 4.5.3).

Distribution:

Plasma protein binding of [¹⁴C]-ozenoxacin was moderate (~80 to 85%) and did not appear to be dependent on concentration. Since negligible systemic absorption was observed in clinical studies, tissue distribution has not been investigated in humans.

Metabolism:

Ozenoxacin was not metabolized in the presence of fresh human skin discs and was minimally metabolized in human hepatocytes (<2%).

In vitro, ozenoxacin caused mild inhibition of CYP3A4 and CYP2C9 at high concentrations (≥100 μM). No significant inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2D6 or CYP2E1 activity by ozenoxacin in human liver microsomes was observed. Ozenoxacin does not induce cytochrome P450 enzymes *in vitro* in human hepatocytes.

No study was conducted to evaluate the potential interactions between ozenoxacin and transporters.

Excretion:

Studies have not been investigated in humans due to the negligible systemic absorption observed in clinical studies.

3.3 Clinical Pharmacology Review Questions

3.3.1 Was ozenoxacin systemically absorbed following the topical administration of ozenoxacin 1% cream in human subjects?

The systemic absorption of ozenoxacin following the topical application of ozenoxacin 1% cream was negligible in healthy subjects and in patients with impetigo.

Four clinical pharmacokinetic studies were performed in a total of 110 subjects following single or repeated application of the topical formulation to intact or abraded skin (up to 200 cm² surface area) in strengths up to 2%, twice the to-be-marketed formulation. Three of these studies assessed systemic absorption in a total of 86 subjects. Among them, 38 pediatric patients of 2 months to less than 18 years of age were included in one clinical pharmacokinetic study. No systemic absorption was observed in 84 of 86 subjects, and very low plasma concentrations of ozenoxacin (ranged from 0.539 to 0.681 ng/mL, with a lower limit of quantitation level of 0.489 ng/mL) were observed in 2 pediatric subjects (see sections 4.5.1, 4.5.2, and 4.5.4).

When testing the skin availability of ozenoxacin 2% cream formulation in healthy volunteers, concentrations of ozenoxacin in the stratum corneum and epidermis (upper skin layer) was high and increased with the number of administrations, whereas its concentrations in the dermis (lower skin layer) remained near the limit of quantitation (5.01 ng/mg). These results indicated that ozenoxacin does not easily penetrate into the lower skin layers and support the negligible systemic absorption of ozenoxacin observed in humans (see section 4.5.3).

3.3.2 Is the proposed dosing regimen appropriate for the adult and pediatric patients with impetigo?

The proposed dose strength, dosing frequency and treatment duration are appropriate for adult and pediatric patients with impetigo. However, in pivotal Phase 3 studies, the application area of (b) (4) was limited to no greater than 100 cm² in adult and pediatric patients 12 years of age and older or 2% total body surface area and not exceeding 100 cm² in pediatric patients less than 12 years of age. Thus, we recommend the Applicant provide this information in the labeling (see section 2.2.1).

A Phase 2 dose-ranging study (Study P-080623-01) evaluated the effectiveness of ozenoxacin cream at concentrations of 0.25%, 1%, and 2% in adult subjects with secondarily-infected traumatic lesions (SITL). Since both SITL and impetigo are caused mainly by the same pathogens (*S. aureus* and *S. pyogenes*) in both adult and pediatric subjects, results from this Phase 2 dose-ranging study were considered to be indicative of the selection of ozenoxacin dose strength for the Phase 3 clinical studies. In this study, the efficacy, safety, and tolerability of 3 concentrations of ozenoxacin cream (0.25%, 1%, and 2%) were compared to placebo cream when applied twice daily for 7 days in adults with SITL. A follow-up visit was also included at Day 14. The evaluation of efficacy was based on the following parameters: clinical assessment by the investigator, skin infection rating scale (SIRS), and the microbiological response. The primary efficacy endpoint was the clinical response (success or failure) at the final study visit (Day 14) in the intent-to-treat clinical (ITTC) population. A clinical success was defined to be resolution of all entry clinical signs and symptoms and no additional antibiotic therapy was necessary. Results from this study showed that no significant differences in clinical response between placebo cream and any of the ozenoxacin cream strengths were observed on Day 14. However, at the end of the treatment on Day 7 (a secondary efficacy endpoint), ozenoxacin 1% cream group showed both a

significantly greater clinical response ($p = 0.042$; ITTC population) and a significantly greater microbiological response ($p = 0.001$; intent-to-treat bacteriological (ITTb) population) relative to placebo cream (Table 3.3.2-1). The clinical and microbiological response rates in the 2% ozenoxacin cream group were numerically lower than those in the 1% ozenoxacin group. Meanwhile, the improvement in clinical response and microbiological response did not achieve statistical significance in both 0.25% and 2% ozenoxacin cream groups as compared to the placebo cream group at the end of treatment. Although the reason for the lower response rates in the 2% ozenoxacin cream group compared with the 1% ozenoxacin group was not known, the results indirectly indicate that the increase of ozenoxacin dose from 1% to 2% may not provide additional benefit in terms of efficacy. The 1% formulation was selected for further Phase 3 development. The treatment duration was 5 days based on the *in vitro* activity of ozenoxacin against the pathogens causing impetigo. No PK samples were collected in this Phase 2 dose-ranging study. Other clinical studies evaluating the PK of ozenoxacin cream indicate a negligible systemic absorption in healthy subjects and in impetigo patients. Therefore, exposure-response analysis was not performed to inform the dose selection of ozenoxacin cream in patients with impetigo.

Table 3.3.2-1 Clinical Response of Ozenoxacin Cream at Concentrations of 0.25%, 1%, and 2% from Phase 2 Dose Range Study in Patients with SITL

Clinical response	Placebo	GF-001001-00		
		0.25%	1%	2%
ITTC population	(N=48)	(N=49)	(N=49)	(N=51)
Success [n (%)]	13 (27.1)	19 (38.8)	23 (46.9)	16 (31.4)
Failure [n (%)]	35 (72.9)	30 (61.2)	26 (53.1)	35 (68.6)
Comparison with placebo				
Odds Ratio		1.710	2.477	1.306
95% CI		0.707, 4.134	1.033, 5.943	0.534, 3.194
Wald Chi Square		1.418	4.130	0.343
p-value		0.23	0.042	0.56
<hr/>				
Microbiological response	Placebo	GF-001001-00		
		0.25%	1%	2%
	(N=42)	(N=39)	(N=43)	(N=44)
Visit 3 (Day 7)				
Success [n (%)]	10 (23.8)	16 (41.0)	25 (58.1)	18 (40.9)
Failure [n (%)]	31 (73.8)	23 (59.0)	17 (39.5)	26 (59.1)
Comparison with placebo				
Odds Ratio		2.462	5.420	2.696
95% CI		0.874, 6.934	1.957, 15.010	0.985, 7.384
Wald Chi Square		2.907	10.576	3.723
p-value		0.088	0.001	0.054

Clinical success: resolution of all entry clinical signs and symptoms and no additional antibiotic therapy was necessary. Improvement, relapse and failure were all considered to be clinical failure. The lack of improvement (unable to determine improvement) was categorized as failure as well.

Microbiological success: absence of the original pathogen from the post-treatment culture of specimen obtained from the original site of infection, or complete resolution of signs and symptoms associated with absence of culturable material.

SITL: secondarily-infected traumatic lesions; ITTC: intent-to-treat clinical; CI: confidence interval

Two pivotal Phase 3 studies (Studies P-110880-01 and P-110881-01) were conducted in subjects with nonbullous or bullous impetigo with similar study design. Study P-110880-01 included subjects who were ≥ 2 years of age, while Study P-110881-01 included subjects who were ≥ 2 months of age. In these two Phase 3 studies, the same dose regimen of ozenoxacin 1% cream twice daily topical application for 5 days (10 applications) was tested in both adult and pediatric patients with impetigo. However, the application area was limited to no greater than 100 cm² in

adult and pediatric patients 12 years of age and older or 2% total body surface area and not exceeding 100 cm² in pediatric patients less than 12 years of age. The clinical success rates at the end of therapy (Visit 3, Day 6-7) in the ozenoxacin 1% cream group were 34.8% and 55.2% in Studies P-110880-01 and P-110881-01, respectively, and were significantly higher than the placebo groups (19.2 % and 39.2% in Studies P-110880-01 and P-110881-01, respectively). The clinical success rate at the end of therapy (Visit 3, Day 6-7) for the integrated analysis of the two Phase 3 studies was 46.8% in the ozenoxacin 1% cream group and 30.8% in the placebo cream group. The difference in the success rates (16.0%) was statistically significant ($p < 0.001$). In addition, greater clinical success rates were observed in subjects receiving ozenoxacin 1% cream than that in subjects receiving placebo cream for both adults and pediatric patients regardless of age category.

3.3.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic factors?

Since the systemic absorption of ozenoxacin was negligible following topical application of ozenoxacin 1% cream in healthy volunteers and impetigo patients, dose individualization is not necessary based on intrinsic and extrinsic factors.

The dose strength, dosing frequency and treatment duration of (b) (4) for pediatric patients are the same as for adult patients except application area in pediatric patients less than 12 years of age (see section 2.2.1). This is supported by a similar or better clinical success rate of ozenoxacin 1% cream in pediatric patients compared to adult patients when the dose regimen was used in the adult and pediatric patients with impetigo. In Phase 3 studies, the difference in the clinical success rate between the active and placebo groups was greater in pediatric patients (2 months to < 12 years of age, 22.7 %) than in the whole evaluable patient population (16.0%).

4. Appendices

4.1 Labeling Recommendations

The Office of Clinical Pharmacology recommends the following edits be included in the labeling:

- Under DOSAGE AND ADMINISTRATION of HIGHLIGHTS OF PRESCRIBING INFORMATION section, replace “Apply a thin layer of (b) (4) to the affected areatwice daily for 5 days” with the following wording:
“Apply a thin layer of (b) (4) topically to the affected area twice daily for 5 days. (b) (4) area may be up to 100 cm² in adult and pediatric patients 12 years of age and older or 2% total body surface area and not exceeding 100 cm² in pediatric patients less than 12 years of age.”
- Under section 2 DOSAGE AND ADMINISTRATION, replace “Apply a thin layer of (b) (4) to the affected area) twice daily for 5 days” with the following wording:
“Apply a thin layer of (b) (4) topically to the affected area) twice daily for 5 days. (b) (4) area may be up to 100 cm² in adult and pediatric patients 12 years of age and older or 2% total body surface area and not exceeding 100 cm² in pediatric patients less than 12 years of age
 - Wash hands after applying (b) (4) cream
 - (b) (4) cream is for topical use only
 - Not for oral, ophthalmic, intranasal, or intravaginal use.”
- Under section 12.3 Pharmacokinetics, replace the statement of (b) (4) (b) (4) with “Ozenoxacin was not metabolized in the presence of fresh human skin discs and was minimally metabolized in human hepatocytes.”

4.2 Summary of Bioanalytical Method Validation

Ozenoxacin plasma concentrations were measured by Liquid Chromatography-Tandem Mass Spectrometry (LC/MS/MS). The analytical methods used to measure concentrations of ozenoxacin in human plasma were validated in two reports (P-050373-01, P-110884-01) and found acceptable to support the individual study reports for PK studies in healthy subjects (P-080582-01, P-090778-01) and PK study in patients with impetigo (P-100797-01). The limit of detection of this LC/MS/MS method was 0.5 ng/mL. The assays showed acceptable linearity, good inter-batch and intra-batch accuracy and precision, a good stability of solutions in human plasma when stored at room temperature for 5 hours, 3 freeze thaw cycles, and stored frozen in the range of -25°C to -15°C and -75°C to -65°C for up to 24 weeks. The relevant validation parameters are summarized in Table 4.2-1.

Table 4.2-1. Validation Parameters of Ozenoxacin in Human Plasma Determined by High Performance Liquid Chromatography/Mass spectrometry Assay

Report Parameters	P-050373-01	P-110884-01
Linearity	$r^2 \geq 0.9899$	$r^2 \geq 0.9931$
Nominal calibration range (ng/mL)	0.5 - 500	0.5 - 500
Lower limit of quantitation (LLOQ) (ng/mL)	0.5	0.5
Intra-batch accuracy (%)	92.8 -106.8	92.2 – 109.9
Intra-batch precision (%)	≤ 3.7	≤ 7.9
Inter-batch accuracy (%)	99.8 -110.3	89.5 – 104
Inter-batch precision (%)	≤ 6.4	≤ 9.3
Accuracy at LLOQ (%)	92.8 – 110.2	
Precision at LLOQ (%)	≤ 6.4	
% Recovery of ozenoxacin QC (mean \pm SD)		53.0 \pm 6.3
% Recovery of lomefloxacin (internal standard) QC (mean \pm SD)		72.3 \pm 5.2

The Applicant did not provide validation results for the assay used to measure the concentration of ozenoxacin in skin tissues (stratum corneum, epidermis and dermis, Study P-090745-01). Results from skin tissue availability study showed that ozenoxacin remained in the upper skin layers (stratum corneum & epidermis) and did not easily penetrate to the lower skin layers (dermis) following topical application of ozenoxacin 2% cream formulation to healthy subjects. Therefore, the reviewer considers that the qualitative skin tissue penetration data of ozenoxacin support the conclusion of negligible systemic absorption of ozenoxacin in humans. ^{(b) (4)}

4.3 Review of Individual Study Reports

The following individual studies were reviewed.

Study No.	Study information
P-080582-01	Systemic bioavailability; healthy subjects
P-090778-01	Systemic bioavailability; intact and abraded skin; healthy subjects
P-090745-01	Skin tissue exposure; healthy subjects
P-100797-01	Systemic bioavailability; patients with impetigo

4.3.1 Study P-080582-01 Systemic Bioavailability in Healthy Subjects

1. Title

GF-001001-00 2% cream formulation. A Phase 1, double blind, 2-way crossover, placebo controlled, multiple dose study to examine the systemic bioavailability and safety of topical applications in healthy volunteers

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted by Ferrer Internacional S.A. from November 27, 2008 to February 13, 2009 with the final report date - September 9, 2010.

3. Objectives

The primary objective was to assess the systemic absorption following repeated topical applications of ozenoxacin 2% cream by analyzing the pharmacokinetic parameters derived from plasma ozenoxacin concentrations.

The secondary objectives were to assess the safety and tolerability after repeated topical applications of ozenoxacin 2% cream.

4. Trial Design

This was a multiple-dose, double blind, randomized, placebo controlled and 2-way crossover clinical trial. Twenty healthy subjects were included. Each subject received 3 applications of 0.5 g ozenoxacin 2% cream each day for 6 days and 1 single application of 0.5 g ozenoxacin 2% cream on Day 7 or 3 applications of placebo for 6 days and 1 single application of placebo on Day 7 at each period according to a randomization code.

The individual doses for each treatment were:

Administration A = 0.5 g ozenoxacin 2% cream for topical application.

Administration B = 0.5 g placebo cream for topical application.

Each subject received a total of 19 applications during each period (3 applications per day for 6 days and 1 single application in the morning on Day 7). Treatments were administered on the back over an area of 90 cm² (9.5 cm x 9.5 cm). The acceptable dosing range is 0.4 g to 0.6 g. Following application, the application area was covered immediately using semioclusive dressing until next application. There was at least a 14-day wash-out period between the Day 7 dosing in Period 1 and the first dose of Day 1 in Period 2 for each subject. Each study period was of 10 days duration.

5. Excluded Medications, Restrictions

- Subject had taken antibiotics within two weeks prior to dosing.
- Regularly prescribed and over the counter drugs 2 weeks before the study start and throughout the duration of the study dosing periods.
- A history of previous allergy / sensitivity to ozenoxacin or other quinolone antibiotics
- A history of drug or alcohol abuse.

6. Rationale for Doses Used in the Trial

The strength selected was the highest intended strength for further clinical development. This strength was applied to a skin surface of 90 cm² resulting in a total dose of 10 mg ozenoxacin.

7. Drugs Used in the Trial

The study medication consisted of ozenoxacin 2% cream and matching placebo cream for topical application.

The documentation supplied with the study medication made it possible to retrace the composition and pharmaceutical quality of the product.

8. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Blood samples for plasma ozenoxacin concentration measurements were collected Pre the 1st and the 2nd applications on Day 1, pre the 2nd applications on Day 2, Pre the 1st and 3rd applications on Day 3 and Day 4, pre each application on Day 5 and Day 6, pre application on Day 7 and at 0.5, 1, 2, 4, 8, 12, 24, 48 and 72 hours after the Day 7 application.

Bioanalytical method

Ozenoxacin plasma levels were measured using a validated Liquid Chromatography-Tandem Mass Spectrometry (LC/MS/MS) method at [REDACTED] ^{(b) (4)} (validation reports P-050373-01 and P-110884-01). A bioanalytical report associated with this study was not submitted.

9. Results

9.1 Subject Demographics and Disposition

Twenty subjects received study medication. All twenty subjects completed the study successfully as per protocol.

9.2 Pharmacokinetic and Statistical Analysis

The plasma ozenoxacin concentrations were below the lower limit of quantitation (LLOQ) after administrations of both drug and placebo (LLOQ = 0.493 ng/mL) for all subjects. This indicated that no detectable systemic absorption in plasma was observed following multiple topical applications of 0.5 g ozenoxacin 2% cream. Therefore, no pharmacokinetic parameters were derived from plasma ozenoxacin concentrations.

9.3 Safety Analysis

No clinically significant abnormal vital sign results were reported during the study. No clinically significant abnormal ECGs were recorded. No clinically significant abnormal biochemistry, hematology or urinalysis results were recorded during the study.

One-hundred eighty-three AEs were recorded. Eighty-two AEs were recorded by all 20 subjects following the administration of active drug. One-hundred one adverse events were recorded by all 20 subjects following the administration of placebo.

There were no clinically significant differences in local tolerability results between the active drug and placebo.

The most commonly recorded adverse events following both multiple topical applications of ozenoxacin 2% cream and placebo cream were marginal erythema due to adhesive dressing, application site erythema and application site pruritus. There were no serious AEs reported. Repeated topical applications of ozenoxacin 2% cream have been well tolerated.

10. Sponsor's Conclusions

All plasma ozenoxacin concentrations were below the limit of quantitation. No systemic absorption of ozenoxacin was observed in healthy subjects. Repeated topical applications of ozenoxacin 2% cream (twice the strength of the proposed to-be-marketed formulation) have been well tolerated in healthy subjects.

11. Reviewer's Assessment

The P-080582-01 trial evaluated the systemic bioavailability of topical applications of ozenoxacin 2% cream (twice the strength of the proposed to-be-market formulation) in healthy volunteers. The Applicant concluded that no detectable systemic absorption in plasma was observed following multiple topical applications of 0.5 g ozenoxacin 2% cream, however, a bioanalytical report associated with this study was not submitted. The Phase 1 PK study in patients (Study P-100797-01) that had the bioanalytical report (P-110898-01) is the pivotal study that can be used to conclude that absorption was negligible.

The results from the study support the proposed label claim – “*negligible systemic absorption was observed in clinical studies.*”

4.3.2 Study P-090778-01 Systemic Bioavailability on Intact and Abraded Skin in Healthy Volunteers

1. Title

GF-001001-00: A Phase 1, crossover, randomised study to examine the systemic bioavailability and safety of topical applications of ozenoxacin 2% cream on intact and abraded skin in healthy volunteers.

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted by Ferrer Internacional S.A. from April 12, 2010 to May 22, 2010, with the final report date – November 22, 2010.

3. Objectives

The primary objective was to compare the systemic absorption following repeated topical applications of ozenoxacin 2% cream on intact and abraded skin by analyzing the pharmacokinetic parameters derived from plasma ozenoxacin concentrations.

The secondary objectives were to assess the safety and tolerability after repeated topical applications of ozenoxacin 2% cream on intact and abraded skin.

4. Trial Design

This was a multiple-dose, open-label, crossover, randomized, clinical trial. Twenty healthy subjects were included. The subjects received 2 dose applications of 1 g ozenoxacin 2% cream in 200 cm² of intact skin each day for 7 days and 1 single dose application of 1 g ozenoxacin 2% cream on Day 8 (treatment A) and 2 dose applications of 1 g ozenoxacin 2% cream on 200 cm² of abraded skin each day for 7 days and 1 single dose application of 1 g ozenoxacin 2% cream on Day 8 after 2 weeks wash out period (treatment B) or vice versa. Study medication was administered on two sites on the back (the first treatment period on the left scapula area, second treatment period on the right scapula area). AB and BA sequences were assigned to patients according to a randomization code.

The individual doses for each treatment were:

- Treatment A = 1 g ozenoxacin 2% cream for topical application (intact skin)
- Treatment B = 1 g ozenoxacin 2% cream for topical application (abraded skin)

Each subject received a total of 15 applications during each treatment period (2 applications per day for 7 days and 1 single application in the morning on Day 8). Treatments were administered on the back over an area of 200 cm² (20 cm x 10 cm). The acceptable dose weighing range was 0.9 g to 1.1 g. Study medication was administered on two sites on the back (the first treatment period on the left scapula area, second treatment period on the right scapula area). Study medication was applied on the abraded skin by the clinic staff 10 minutes after completion of the tape-stripping or 10 minutes after evaluation and cleaning of intact skin. Following application, the application area was covered immediately with a semiocclusive dressing until next application.

5. Excluded Medications, Restrictions

- Subject had a known sensitivity to any components of the test materials.
- Subject had taken antibiotics within 14 days prior to dosing.
- Regularly prescribed and over the counter drugs 2 weeks before the study start and throughout the duration of the study dosing periods.
- Evidence of renal, hepatic, central nervous system, respiratory, cardiovascular, haematological or metabolic dysfunction.
- A clinically significant history of previous allergy / sensitivity to ozenoxacin or other quinolone antibiotics.
- A clinically significant history of drug or alcohol abuse.
- A clinically significant history of photosensitivity and photoallergy.

6. Rationale for Doses Used in the Trial

The strength selected (2%) was the highest intended strength for further clinical development. This strength was applied to a skin surface of 200 cm² resulting in a total dose < 1.5 g ozenoxacin 2% cream per treatment period. This dose was considered enough to cover a skin surface of 200 cm² while applying the same quantity of ozenoxacin per cm² as in other ongoing studies.

7. Drugs Used in the Trial

The investigational medicinal product (IMP) was ozenoxacin 2% cream for topical application. The documentation supplied with the IMP made it possible to retrace the composition and pharmaceutical quality of the product.

8. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

Blood samples for plasma ozenoxacin concentration measurements were collected pre the 1st dose on Day 1 and at 0.5, 1, 2, 4, 8, 12 hours after the Day 1 morning dose, pre the morning dose on Day 2, Day 3, Day 4, Day 5, Day 6 and Day 7, pre dose on Day 8 and at 0.5, 1, 2, 4, 8, 12, 24, 48 and 72 hours after the Day 8 dosing.

Bioanalytical methods

Ozenoxacin plasma levels were measured using a validated Liquid Chromatography-Tandem Mass Spectrometry (LC/MS/MS) method at [REDACTED] (b) (4) (validation reports P-050373-01 and P-110884-01). A bioanalytical report associated with this study was not submitted.

9. Results

9.1 Subject Demographics and Disposition

Twenty subjects received study medication. Eighteen subjects completed the study successfully. One subject (Subject 5) was withdrawn at the investigator's request due to the adverse event of syncope (vasovagal). The event resolved on the same day and was considered unlikely to be related to the study medication. Subject 5 completed Period 1 following application of ozenoxacin on intact skin and was withdrawn prior to starting Period 2 on abraded skin. One

subject (Subject 14) withdrew for personal reasons. Subject 14 completed Period 1 following application of ozenoxacin on abraded skin and withdrew Day 3 of Period 2 on intact skin.

9.2 PK Results

All ozenoxacin concentrations were below the limit of quantification after administration of drug to both intact and abraded skin (lower limit of quantitation, LLOQ = 0.485 ng/mL). No pharmacokinetic parameters were derived from plasma ozenoxacin concentrations.

9.3 Safety Results

There were no clinically significant physical examination, vital sign, ECG, biochemistry, hematology or urinalysis results recorded during the study. There were no clinically significant differences in the local tolerability or AE profile following application of ozenoxacin cream to intact or abraded skin.

One-hundred seventeen AEs were recorded following application of ozenoxacin, 49 on intact and 68 on abraded skin. The majority were considered mild and not related to the application of ozenoxacin, the most common being erythema (74 events) attributed to the adhesive dressing. There were no clinically significant differences in the local tolerability or AE profile following application of ozenoxacin to intact or abraded skin. One severe AE was reported. This was considered unlikely to be related to the study medication.

In conclusion, repeated topical applications of ozenoxacin cream to intact or abraded skin are safe and well tolerated.

10. Sponsor's Conclusions

There was no systemic absorption of ozenoxacin following application of ozenoxacin 2% cream on intact or abraded skin. Ozenoxacin was safe and well tolerated with similar local tolerability and safety profiles following repeated topical applications to intact or abraded skin.

11. Reviewer's Assessment

The P-080582-01 trial evaluated the systemic bioavailability of topical applications of ozenoxacin 2% cream (twice the strength of the proposed to-be-market formulation) on intact and abraded skin in healthy volunteers. The Applicant concluded that no detectable systemic absorption in plasma was observed following multiple topical applications of ozenoxacin 2% cream on intact or abraded skin, however, a bioanalytical report associated with this study was not submitted. The Phase 1 PK study in patients (Study P-100797-01) that had the bioanalytical report (P-110898-01) is the pivotal study that can be used to conclude that absorption was negligible.

The results from the study support the proposed label claim – “*negligible systemic absorption was observed in clinical studies.*”

4.3.3 Study P-090745-01 Skin Tissues Exposure in Healthy Subjects

1. Title

GF-001001-00: A single-center, Phase 1, open label, parallel cohorts, multiple dose study to compare the skin tissues exposure of once versus twice a day topical applications of 2 % cream formulation.

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted by Ferrer Internacional S.A from December 7, 2009 to January 29, 2010 with the final report date – November 22, 2010.

3. Objectives

The primary objective was to assess and compare the skin exposure of ozenoxacin 2% cream following multiple topical applications on the upper back of healthy volunteers in once daily and twice daily administration regimen.

The secondary objectives were to assess the safety and tolerability after repeated topical applications of ozenoxacin 2% cream.

4. Trial Design

This was a multiple-dose, open label, parallel, non-therapeutic clinical trial. Twenty-four healthy male subjects were included. Twelve subjects in Group 1 received 1 dose per day of 0.2 g ozenoxacin 2% cream on different treatment areas on the upper back for three consecutive days. Twelve subjects in Group 2 received 2 doses per day (12 hours apart) of 0.2 g ozenoxacin 2% cream on different treatment areas on the upper back for three consecutive days.

Each subject in Group 1 received a total of 3 applications during the treatment period (1 application per day for 3 days). Each subject in Group 2 received a total of 6 applications during the treatment period (2 applications per day 12 hours apart for 3 days).

0.2 g of the study medication was applied to three distinct dosing areas (Areas 1-3):

Day 1: the study drug was applied on Area 1, Area 2 and Area 3 (once daily for Group 1 and twice daily for Group 2)

Day 2: biopsy was taken from Area 1. The study drug was applied on Area 2 and Area 3 evenly (once daily for Group 1 and twice daily for Group 2)

Day 3: biopsy was taken from Area 2. The study drug was applied on Area 3 evenly (once daily for Group 1 and twice daily for Group 2)

Day 4: biopsy was taken from Area 3.

Day 5: volunteers were discharged the morning following the last biopsy

Each application site measured 7 cm × 7 cm. Following application the treatment areas were not covered for 30 minutes (the subjects were told not to lay down on their backs or cover the treatment area with any clothing) and then covered with loose fitting clothing.

5. Excluded Medications, Restrictions

- Subject had taken antibiotics within two weeks prior to dosing.
- Subjects who had been exposed to UV radiation and/or tanning beds within two weeks of Day 1.
- Regularly prescribed and over the counter drugs 2 weeks before the study start and throughout the duration of the study dosing periods.
- Evidence of renal, hepatic, central nervous system, respiratory, cardiovascular or metabolic dysfunction.
- A clinically significant history of previous allergy / sensitivity to ozenoxacin or other quinolone antibiotics.
- A known sensitivity to local anaesthetics (i.e. Lidocaine).
- A history of keloid scars.
- A clinically significant history of drug or alcohol abuse.
- Subjects who smoked more than 5 cigarettes per day.
- Subjects who had consumed more than 2 units of alcohol per day from seven (7) days prior to the first dose or had consumed any alcohol within the 48 hour period prior to the first dose.

6. Rationale for Doses Used in the Trial

The strength selected was the highest intended for further clinical development. This strength was applied to a skin surface of 49 cm² resulting in total dose of approximately 1.2 g ozenoxacin 2% cream for Group 1 and 2.4 g ozenoxacin 2% cream for Group 2.

Previous clinical experience of ozenoxacin ointment at a different strength (1%) exists (Study P-050374-03). This strength was applied to various skin areas (up to 5% of body surface area equivalent to approximately 900 cm²) ensuring application of a very high dose of ozenoxacin (50 mg) which was higher than the maximum dose that was applied in this study (24 mg).

7. Drugs Used in the Trial

The study medication consisted of ozenoxacin 2% cream for topical application. The documentation supplied with the study medication made it possible to retrace the composition and pharmaceutical quality of the product.

8. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

Tape stripping and skin biopsies were performed at the following times:

- Day 1: Pre-dose from untreated area
- Day 2: 24 hours post-first dose
- Day 3: 24 hours post Day 2 morning dose
- Day 4: 24 hours post Day 3 morning dose

Study drug tissue concentration was analyzed from the stratum corneum and from the epidermis and dermis. At each biopsy point approximately 12 tapes were numbered and analyzed in 3 groups (group 1: tapes 1-4, group 2: tapes 5-8, group 3: tapes 9-12) for stratum corneum drug concentration. The biopsies were analyzed for epidermis and dermis drug concentration. Each

biopsy was cut in parallel to the skin surface through the dermis into an upper (superficial) and lower (deeper) half of roughly similar size.

Bioanalytical methods

Bioanalysis of tape and tissue samples were performed using Liquid Chromatography-Tandem Mass Spectrometry (LC/MS/MS) method at (b) (4). The Applicant did not submit the validation and performance reports for the assay used to measure the concentration of ozenoxacin in skin tissues.

Pharmacokinetic Assessments

Tissue concentrations were listed and summarized by treatment, with n, mean, standard deviation, median, minimum and maximum as appropriate.

9. Results

9.1 Subject Demographics and Disposition

All 24 subjects completed the study and had sufficient samples to obtain skin and tape drug concentration samples, and were therefore included in the pharmacokinetic population.

9.2 Pharmacokinetic Analysis

The summary of ozenoxacin concentration in the epidermis (upper skin layer) and dermis (lower skin layer) for once a day and twice a day dosing is presented in Table 1.

Table 1: Ozenoxacin Concentrations in Epidermis (Upper Skin) and Dermis (Lower Skin) Following Once versus Twice a Day Topical Application (ng/mg) in P-090745-01

			N	Mean	Std Dev	CV	Min	Median	Max
Dose	Day	Position							
Ozenoxacin 2% cream once a day	Day 1	Upper	12	0.000	0.000	-	0.00	0.00	0.00
		Lower	12	0.000	0.000	-	0.00	0.00	0.00
	Day 2	Upper	12	3.171	3.608	113.772	0.00	2.56	12.48
		Lower	12	0.000	0.000	-	0.00	0.00	0.00
	Day 3	Upper	12	3.829	3.683	96.195	0.00	3.51	13.77
		Lower	12	2.368	8.204	346.410	0.00	0.00	28.42
	Day 4	Upper	12	5.452	5.471	100.346	0.00	4.30	15.87
		Lower	12	0.000	0.000	-	0.00	0.00	0.00
Ozenoxacin 2% cream twice a day	Day 1	Upper	12	0.000	0.000	-	0.00	0.00	0.00
		Lower	12	0.000	0.000	-	0.00	0.00	0.00
	Day 2	Upper	12	3.710	3.440	92.734	0.00	3.45	10.04
		Lower	12	0.000	0.000	-	0.00	0.00	0.00
	Day 3	Upper	12	5.804	5.665	97.595	0.00	4.19	16.71
		Lower	12	0.000	0.000	-	0.00	0.00	0.00
	Day 4	Upper	12	7.112	5.539	77.885	0.00	7.61	15.40
		Lower	12	0.634	1.488	234.699	0.00	0.00	4.15

A graphical representation of the mean (\pm SD) ozenoxacin concentrations in epidermis for once a day and twice a day dosing is shown in Figure 1. There is no graphical representation of the ozenoxacin in the dermis due to the low number of data points for both once a day and twice a day dosing.

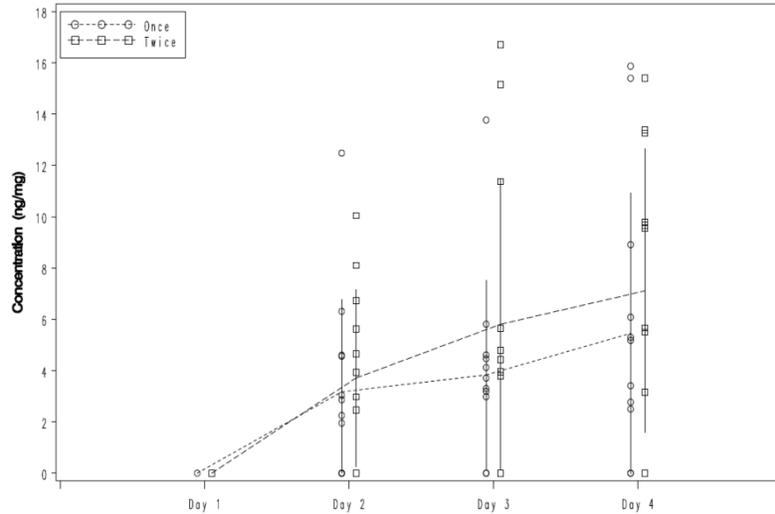


Figure 1: Mean (\pm SD) Ozenoxacin Concentrations in Human Skin (Epidermis) (ng/mg) in Study P-090745-01

Table 2 shows the measured concentrations of the stratum corneum samples (skin stripping tape).

Table 2: Summary of Ozenoxacin Concentration in Human Skin Stripping Tape (ng/mg) in Study P-090745-01

		N	Mean	Std Dev	CV	Min	Median	Max
Ozenoxacin 2% cream once a day	Day 1	12	7.681	26.606	346.410	0.00	0.00	92.17
	Day 2	12	4398.503	4065.510	92.429	1156.94	2367.97	13233.68
	Day 3	12	10104.598	8301.653	82.157	1255.09	7137.64	23946.55
	Day 4	12	6112.811	5431.203	88.850	542.74	5405.25	16135.61
Ozenoxacin 2% cream twice a day	Day 1	12	129.853	449.824	346.410	0.00	0.00	1558.24
	Day 2	12	8141.072	5076.293	62.354	1954.32	6983.07	19309.50
	Day 3	12	21956.226	15300.047	69.684	4047.50	17507.51	52290.95
	Day 4	12	10404.052	8144.992	78.287	2125.53	8870.10	27414.30

A graphical representation of the mean (\pm SD) ozenoxacin concentrations of the stratum corneum tapes (skin stripping samples) for once a day and twice a day dosing is shown in Figure 2.

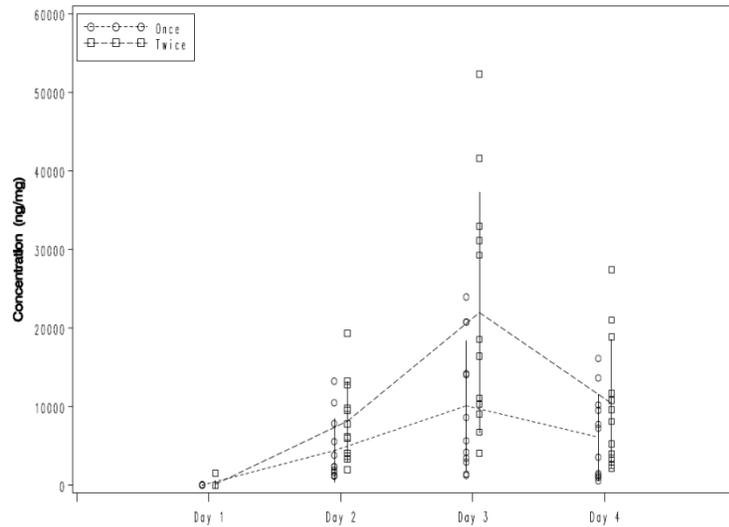


Figure 2: Mean (\pm SD) Ozenoxacin Concentrations in Human Skin Stripping Tape (ng/mg) in Study P-090745-01

The summary of the number of subjects (frequency) in each ozenoxacin concentration range from human skin stripping tape (stratum corneum) is presented in Table 3.

Table 3: Number of Subjects (Frequency) in Each Ozenoxacin Concentration Range from Human Skin Stripping Tape Following Once versus Twice a Day Topical Application in Study P-090745-01

		< 1000 (ng/ml)	1000-4999 (ng/ml)	5000-10000 (ng/ml)	> 10000 (ng/ml)
Dose	Day				
Ozenoxacin 2% cream once a day	Day 1	12 (100.0)	0	0	0
	Day 2	0	8 (66.7)	2 (16.7)	2 (16.7)
	Day 3	0	5 (41.7)	2 (16.7)	5 (41.7)
	Day 4	2 (16.7)	4 (33.3)	3 (25.0)	3 (25.0)
Ozenoxacin 2% cream twice a day	Day 1	11 (91.7)	1 (8.3)	0	0
	Day 2	0	4 (33.3)	5 (41.7)	3 (25.0)
	Day 3	0	1 (8.3)	2 (16.7)	9 (75.0)
	Day 4	0	4 (33.3)	3 (25.0)	5 (41.7)

There were high concentrations of ozenoxacin in all stratum corneum tapes after 24 hours of treatment. Ozenoxacin concentrations in stratum corneum (skin surface) increased from Day 1 to Day 3 for both once a day and twice a day administrations. The stratum corneum concentration on Day 4 was lower than on Day 3 for both once a day and twice a day administrations. This may

suggest that by Day 3 equilibrium (ie, steady-state) had been reached and concentrations did not increase further. There was a linear response in the exposure in stratum corneum between 1 and 2 applications in all days of sampling.

Ozenoxacin concentrations from epidermis (upper skin) increased from Day 1 to Day 4 for both once a day and twice a day administrations. The drug concentrations in the epidermis (upper skin) for the twice a day administration were higher than in the once a day administration on all days. Ozenoxacin level in dermis (lower skin) was mainly below the level of quantitation (5.01 ng/mg). This indicated that ozenoxacin does not easily penetrate into the lower skin layers and therefore was not detected in the systemic circulation.

9.3 Safety Analysis

No clinically significant physical examination results were recorded during the study; no clinically significant abnormal vital sign results were reported during the study; no clinically significant abnormal ECGs were recorded. There were no reports of erythema, edema, itching or other dermatological signs of irritation, and any clinically significant abnormal biochemistry, hematology or urinalysis results were recorded during the study. All adverse events that were reported during the study were considered unrelated to the tested drug.

10. Sponsor's Conclusions

The study demonstrated that ozenoxacin appears to remain in the upper skin layers (stratum corneum & epidermis) and does not easily penetrate to the lower skin layers (dermis). The repeated topical applications of ozenoxacin 2% cream (twice the strength of the proposed to-be-marketed formulation) were well tolerated in healthy subjects.

11. Reviewer's Assessment

The P-090745-01 trial assessed the skin tissues exposure of once versus twice a day topical applications of 2 % cream formulation in healthy subjects. We concur with the Applicant's conclusion: ozenoxacin appears to remain in the upper skin layers (stratum corneum & epidermis) and does not easily penetrate to the lower skin layers (dermis) following topical applications of ozenoxacin 2% cream. The Applicant did not submit the validation and performance reports for the assay used to measure the concentration of ozenoxacin in skin tissues. (b) (4)

The results from the study support the proposed label claim – “negligible systemic absorption was observed in clinical studies.”

4.3.4 Study P-100797-01 Systemic Bioavailability in Patients with Impetigo

1. Title

A Phase 1 open-label multiple dose study to examine the systemic bioavailability and safety of twice daily topical applications of ozenoxacin 1 % cream formulation in patients with impetigo.

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted by Ferrer Internacional SA from February 6, 2012 to June 4, 2012 with the final report date - December 12, 2012.

3. Objectives

The primary objective of the study was:

- To assess the systemic absorption of ozenoxacin 1 % cream following repeated topical applications by analyzing plasma ozenoxacin concentrations in patients with impetigo.

The secondary objectives of the study were:

- To assess the safety and tolerability of ozenoxacin 1 % cream after repeated topical applications in patients with impetigo.
- To evaluate the clinical response at the end of therapy.

4. Trial Design

This was a multiple dose, open-label study to assess the systemic absorption following repeated topical applications of ozenoxacin 1% cream in patients with impetigo.

Patients (≥ 2 months to 65 years) were stratified by the following age subsets:

- Group 1: 18 years to 65 years (8 patients)
- Group 2: 12 years to <18 years (9 patients)
- Group 3: 2 years to <12 years (9 patients)
- Group 4: 2 months to < 2 years (20 patients), with the following subsets:
 - 12 months to < 2 years: 8 patients
 - 6 months to < 12 months: 6 patients
 - 2 months to < 6 months: 6 patients

Ozenoxacin 1% cream formulation, was applied by the patient or their caretakers topically as a thin layer to the same baseline identified impetigo affected area(s) (maximum area 100 cm²), 2 times a day, in the morning and in the evening, 12 hours apart for 5 days. The application area for pediatric patients <12 years old was limited to 2% of body surface and not exceeding 100 cm². The drug treatment included a single dose on Day 1 followed by twice daily (12-hourly) dosing for 4 days, followed by a single dose on Day 6 (10 applications in total). Approximately 0.5 g of cream was sufficient to properly cover the maximum extension of 100 cm². For children < 12 years old, after each application, the treated area had to be covered with a fresh standard dressing (non-adherent dressing for at least 4 hours).

5. Excluded Medications, Restrictions

- A history of hypersensitivity to the investigated medical product (IMP) or any of the excipients or to medicinal products with similar chemical structures (especially significant allergies to antibiotics).
- Treatment with any other IMP in the last 12 weeks before administration of the first dose in this clinical study.
- Pregnant or lactating women.
- Received systemic or topical skin treatment with immunosuppressive agents within 21 days before dosing with the investigational medicinal product (IMP, inhaled or intranasal steroids for asthma or rhinitis could be used).
- A history of, or known current problems with, drug or alcohol abuse. Positive drug or alcohol test at Visit 1 (which could not had been explained by the use of chronic medication) judged by the investigator as clinically significant (alcohol use >21 units of alcohol per week for males and >14 units of alcohol per week for females and/or regular exposure to other substances of abuse within the past year).
- Planned treatment with antibacterial medication (other than the IMP) during the study.

6. Rationale for Doses Used in the Trial

Results from the dose finding Phase 2 study where the compound was administered twice daily for 7 days in secondarily infected traumatic lesions (SITLs), showed a statistically significant superiority of ozenoxacin 1 % cream vs. placebo cream at the end of treatment. The strengths tested (0.25%, 1% and 2%) were safe and well tolerated in this study (P-080623-01). Since both indications, SITLs and Impetigo are caused mainly by the same pathogens (*Staphylococcus aureus* and *Streptococcus pyogenes*) in both adult and pediatric populations, it is considered that the 1% dose and the twice daily posology are adequate for the development of ozenoxacin cream in impetigo patients. Regarding the duration of treatment, considering the potent in vitro activity of ozenoxacin against the pathogens causing impetigo (*Staphylococcus aureus* and *Streptococcus pyogenes*) a 5-day treatment period was considered justifiable.

7. Drugs Used in the Trial

Ozenoxacin 1% cream formulation, ^{(b) (4)} - Batch Number(s): 1303E0101A (Manufactured by Ferrer Internacional SA (FISA))

8. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

For Group 1 (18 years to 65 years) and Group 2 (12 years to < 18 years), blood samples for ozenoxacin concentration measurements were drawn on Day 1 (15 minutes before investigational medicine product (IMP) application), on Day 2 (15 minutes before IMP morning application, 1 h, 4 h and 12 h after IMP application), on Day 4 (15 minutes before IMP morning application, 1 h, 4 h and 12 h after IMP application), on Day 6 (15 minutes before IMP morning application, 0.5 h, 1 h, 2 h, 4 h, 8 h and 12 h after IMP application) and on Day 7 (24 h after last IMP application).

For Group 3 (2 years to < 12 years), blood samples for ozenoxacin concentration measurements were drawn on Day 1 (15 minutes before IMP application), on Day 2 (15 minutes before IMP morning application, 1 h after IMP application), on Day 4 (15 minutes before IMP morning

application, 1 h after IMP application) and on Day 6 (15 minutes before IMP morning application, 1 h, 4 h, 12 h after IMP application)

For Group 4 (2 months to < 2 years), blood samples for ozenoxacin concentration measurements were drawn on Day 1 (15 minutes before IMP application), on Day 2 (15 minutes before IMP morning application, 1 h after IMP application), on Day 4 (15 minutes before IMP morning application, 1 h after IMP application) and on Day 6 (15 minutes before IMP application, 1 h after IMP application)

For Groups 3 and 4 the time point for the blood samples after IMP application could have been adjusted after evaluation of PK profile of Groups 1 and 2.

The study schedule for all patients except pediatric patients of 2 months to < 6 months of Group 4 is shown in Table 1:

Table 1: Schematic Study Design P-100797-01 for Subjects ≥ 6 Months

Procedures	Study design for Groups 1,2,3 and 4 ¹							
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Days 10-13
	Visit 1	Visit 2		Visit 3		Visit 4	Visit 5 ²	Visit 6
IMP administration	x	x	x	x	x	x		
Plasma IMP concentration assessment	x	x		x		x	x	
Clinical assessment	x	x		x		x	x	x
Safety assessments ³	x	x		x		x	x	x
Clinical chemistry and hematology	x			x				

IMP= investigational medicinal product.

¹ Group 4, subset 12 months to < 2 years and subset 6 months to < 12 months.

² Only Groups 1 and 2.

³ Vital signs, physical examination and recording of adverse events.

Pediatric patients of 2 months to < 6 months of Group 4 followed a schedule with a slightly reduced number of assessments (Table 2).

Table 2: Schematic Study Design for P-100797-01 Group 4 Subset Subjects 2 Months to < 6 Months

Procedures	Study design for Groups 4 ¹							
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Days 10-13
	Visit 1	Visit 2		Visit 3		Visit 4	Visit 5	Visit 6
IMP administration	x	x	x	x	x	x		
Plasma IMP concentration assessment	x	x		x		x		
Clinical assessment	x	x		x		x		x
Safety assessments ²	x	x		x		x		x
Clinical chemistry and hematology	x			x				

IMP= investigational medicinal product.

¹ Group 4 included subset 2 months to > 6 months.

² Vital signs, physical examination and recording of adverse events.

Bioanalytical method

Ozenoxacin plasma levels were measured using a validated Liquid Chromatography-Tandem Mass Spectrometry (LC/MS/MS) method at (b) (4) (validation reports P-050373-01 and P-110884-01; bioanalytical report P-110898-01). Results of the assay performance reported in the bioanalytical report associated with this study are acceptable.

9. Results

9.1 Subject Demographics and Disposition

In this Phase 1 open-label, multiple dose study, 46 patients received ozenoxacin 1 % cream formulation 2 times a day, in the morning and in the evening, 12 hours apart for 5 days. Forty-four patients completed all study procedures, 2 patients were excluded due to insufficient blood sampling and protocol non-compliance.

9.2 Pharmacokinetic Analysis

No systemic absorption was observed in 44/46 patients following repeated topical applications of ozenoxacin 1% cream in adult and pediatric patients with impetigo. Four PK samples showed concentrations slightly above the lower limit of quantification (LLOQ = 0.5 ng/ml) in 2 pediatric patients, ranged from 0.539 to 0.681 ng/mL. No further PK analyses were performed and no pharmacokinetic parameters could be calculated.

9.3 Safety Analysis

Except for one adverse event, dermatitis, which was assessed as unlikely related to ozenoxacin, all adverse events recorded in the study were assessed as not related to ozenoxacin and were mild and moderate in intensity.

10. Sponsor's Conclusions

Plasma concentrations of ozenoxacin were below the limit of quantification (with an exception of 4 plasma samples that had concentrations slightly above the limit of quantification) following repeated topical applications of ozenoxacin 1% cream in adult and pediatric patients with impetigo. Ozenoxacin 1% cream was well tolerated and safe in the four groups, including the pediatric subset of 2 months to < 2 years, exposed to treatment.

11. Reviewer's Assessment

The P-100797-01 trial assessed the systemic bioavailability of twice daily topical applications of ozenoxacin 1 % cream formulation in patients with impetigo. We concur with the Applicant's conclusion: plasma concentrations of ozenoxacin were below the limit of quantification (LLOQ = 0.5 ng/ml , with an exception of 4 plasma samples that had concentrations slightly above the limit of quantification) following repeated topical applications of ozenoxacin 1% cream in adult and pediatric patients with impetigo.

The results from the study support the proposed label claim – “*negligible systemic absorption was observed in clinical studies.*”

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

XIAOHUI WEI
03/31/2017

SEONG H JANG
03/31/2017

JOHN A LAZOR
03/31/2017