# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 208945Orig1s000

# CLINICAL REVIEW(S)

# Deputy Office Director Decisional Memo

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| **Date** | (electronic stamp) |
| **From** | John Farley, MD, MPH |
| **Subject** | Deputy Office Director Decisional Memo |
| **NDA#** | NDA 208945 |
| **Applicant Name** | Ferrer Internacional, S.A. |
| **Date of Submission** | June 23, 2016 |
| **PDUFA Goal Date** | June 22, 2017 |
| **Proprietary Name / Established (USAN) Name** | Xepi/Ozenoxacin cream, 1% |
| **Dosage Forms / Strength** | Topical cream; 10 mg/g |
| **Applicant Proposed Indication(s)/Populations** | Topical treatment of impetigo in adults, adolescents, (b) (4) and children 2 months and older |
| **Action:** | ***Complete Response*** |

| **Material Reviewed/Consulted** OND Action Package, including: | **Names of discipline reviewers** |
|---|---|
| Medical Officer Review | Nicholas Rister MD |
| Statistical Review | Christopher Kadoorie PhD |
| Pharmacology Toxicology Review | Tessie Alapatt PhD |
| OPQ Review | Dorota Matecka PhD* |
| Microbiology Review | Avery Goodwin PhD |
| Clinical Pharmacology Review | Xiaohui (Tracey) Wei PhD |
| OPDP | Puja Shah, PharmD, RAC |
| OSI | Sharon Gershon PharmD |
| OSE/DMEPA | Deborah Myers, RPh, MBA |
| OSE/DRISK | Till Olickal, PhD, PharmD |
| CDTL Review | Thomas Smith MD |
| Division Director | Sumathi Nambiar, MD, MPH |

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
*Application Technical Lead

# 1. Benefit-Risk Assessment

**Benefit-Risk Summary and Assessment**

I concur with the Benefit-Risk Assessment written by the Division Director and include it here with my additional summary comments.

The Applicant Ferrer Internacional, S.A. has demonstrated the safety and efficacy of ozenoxacin cream, 1%, (Xepi) in two adequate and well-controlled superiority trials for the topical treatment of impetigo due to *Staphylococcus aureus* or *Streptococcus pyogenes* in patients two months of age and older. The NDA cannot be approved during this review cycle due to outstanding issues regarding manufacturing facilities. The NDA will receive a Complete Response letter. Satisfactory resolution of these issues will be needed before the NDA can be approved.

Impetigo is a common, generally self-limited, superficial bacterial skin infection caused by *S. aureus* and *S. pyogenes*. Impetigo may be treated with topical or systemic antibacterial drugs. Systemic (oral) therapy is recommended for patients with multiple lesions or during outbreaks. There are FDA-approved topical therapies for impetigo including mupirocin ointment, retapamulin ointment, and gentamicin sulfate cream and ointment. FDA-approved oral therapies for impetigo and uncomplicated skin and skin structure infections (includes impetigo) include anti-staphylococcal penicillins, cephalosporins, clindamycin, and fluoroquinolones.

Study P-110880-01 (Trial 880) was a three-arm trial comparing ozenoxacin cream with placebo; a third arm, retapamulin 1% ointment, was included to test internal validity; all treatments were administered twice daily for 5 days. Clinical response rates (success/cure) at the end of therapy were 34.8% for ozenoxacin, 19.2% for placebo, and 37.7% for retapamulin. The treatment difference was 15.6% (95% confidence intervals (CI), 5.8, 25.3, p = 0.002). Study P-110881-01 (Trial 881) was a two-arm trial comparing ozenoxacin cream with placebo; treatments were twice daily for 5 days. Clinical response rates (success/cure) at the end of therapy were 54.4% for ozenoxacin and 37.9% for placebo. The treatment difference was 16.5% (95% CI, 6.9, 25.8), p <0.001). In Trial 881, the response rates in both arms were approximately 20% higher than that seen in Trial 880. In these trials, different versions of the response rating instrument were used and the definition of the primary endpoint of success also differed with regard to some of the specific components of the endpoint. The treatment difference for ozenoxacin over placebo was consistent across trials. Also, the response rate of the oxenoxacin group in Trial 880 was similar to that of the retapamulin group in that trial. Subgroup analyses suggest the treatment benefit may be limited for patients over 12 years of age and for patients with bullous impetigo.

No significant safety concerns were identified in the clinical program. No serious adverse reactions were observed. (b) (4) (b) (4).

The Office of Pharmaceutical Quality review team concluded that the NDA did not provide sufficient CMC information to assure the identity,

strength, purity, and quality of the proposed drug product and recommended issuance of a Complete Response letter. A Warning Letter has been issued for the drug substance manufacturing site. Satisfactory resolution of the observations at his facility will be need before the NDA can be approved.

I agree with the recommendations provided by the review team, the CDTL, and the Division Director. The applicant will receive a Complete Response Letter at this time and will need to resolve the outstanding issues with the manufacturing facility before the NDA can be approved.

The following table has been adapted from the reviews by Dr. Rister (Medical Officer) and Dr. Smith (CDTL).

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| **Analysis of Condition** | Impetigo is a common bacterial skin infection that is more common in the pediatric population. The disease manifests as thin walled vesicles or bullae that rupture resulting in superficial erosions which crust over and heal without scarring. The disease is generally self-limiting and resolves without complication in the vast majority of cases over the course of 2-3 weeks; progression to more severe soft tissue or systemic infection is rare. The most common etiologic agents are *S. aureus* and *S. pyogenes*. | Impetigo is a superficial skin infection that is generally self-limited and does not progress to more severe skin infections. |
| **Current Treatment Options** | Retapamulin and mupirocin are FDA-approved for the treatment of impetigo. The IDSA treatment guidelines[1], recommend the use of topical agents for treatment and oral antibacterial drugs when there are numerous lesions or in outbreaks affecting several people to help decrease transmission of infection. | Currently available treatment options including systemic therapy are generally efficacious in the treatment of impetigo. The availability of additional treatment options, especially topical therapies is always beneficial. |
| **Benefit** | The efficacy of ozenoxacin 1% cream was demonstrated in two adequate and well-controlled Phase 3 trials. In both trials, the primary endpoint was clinical response at end of therapy. In Trial 880, ozenoxacin cream 1% was compared to placebo cream. A 1% retapamulin ointment arm was included for internal validity. In Trial 881, ozenoxacin cream 1% was compared to placebo cream. In both trials, ozenoxacin was superior | Ozeonaxcin was superior to placebo in two adequate and well-controlled trials. While the cure rates were low in the ozenoxacin arm, they were similar to that seen with retapamulin, an agent approved for the treatment of impetigo. Although, the overall success rates were |

[1] Stevens DL, Bisno AL, Chambers HF et al. Infectious Diseases Society of America Practice Guidelines for Skin and Soft Tissue Infections. *Clin Infect Dis.*2014;59(2)147-59.

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | to placebo. While the treatment difference between ozenoxacin and placebo were similar in the two trials, the success rates were higher in both arms of Trial 881. In these trials, different versions of the response rating instrument were used and the definition of the primary endpoint of success also differed with regard to some of the specific components of the endpoint. Success at the end of therapy was largely consistent across various subgroups of interest. Cure rates appear to be lower in patients > 12 years of age. | different in the two trials, the treatment difference between ozenoxacin and placebo was consistent across the two trials. |
| **Risk** | The ozenoxacin clinical program included 17 clinical studies: 14 Phase 1 studies, one Phase 2 trial, and two Phase 3 trials. A total of 1354 subjects were exposed to single or repeated doses of ozenoxacin at concentrations of 0.25% to 2% as cream or ointment formulations. No significant safety concerns were identified in the clinical program. No serious adverse reactions were observed. | There were no major safety concerns noted with the use of this topical product. |
| **Risk Management** | In the Phase 2 trial, application site irritation and application site pruritus were the most frequently reported adverse events, and one patient receiving oxenoxacin 2% cream in the Phase 2 trial withdrew due to application site irritation. | These risks can be adequately described in labeling. No additional risk mitigation strategies are anticipated based on this review. |

# 2. Further discussion to support regulatory action

**Background**

Ferrer Internacional, S.A. has submitted this NDA for ozenoxacin cream, 1%, a non-fluorinated quinolone antibacterial drug, for the topical treatment of impetigo due to *S. aureus* or *S. pyogenes* in patients two months of age and older. Ozenoxacin cream is not approved in any country. Ozenoxacin lotion, 2%, (Zebiax) is approved in Japan for the treatment of superficial skin infections and acne (accompanied by purulent inflammation).

**Product Quality**

The Office of Pharmaceutical Quality review team concluded that the NDA did not provide sufficient information to assure the identity, strength, purity, and quality of the proposed drug product and recommended issuance of a Complete Response letter, pending resolution of the issues with the drug substance manufacturing facility. I concur with this conclusion.

Multiple cGMP deficiencies were identified at the drug substance manufacturing site, (b) (4) during the most recent inspection in (b) (4). A Warning Letter was issued for this facility in (b) (4). The overall recommendation from the Office of Process and Facilities for this NDA is "Withhold".

The drug product specifications were found to be acceptable as were the product microbiology data. There were changes in manufacturing sites between Phase 1 and 2 and Phase 3 batches and the proposed to be marketed product. The Biopharmaceutics reviewer concluded that in vitro release data were adequate to support bridging as well as the proposed change in manufacturing site.

**Nonclinical Pharmacology/Toxicology**

The Pharmacology Toxicology reviewer did not identify any Pharmacology Toxicology issues that would preclude approval, and I concur with this assessment.

Ozenoxacin 1% had a low potential for dermal irritation in rats, rabbits, and minipigs after repeated application. There was minimal systemic exposure when applied topically to intact and abraded skin in minipigs. With oral exposure, ozenoxacin did exhibit developmental toxicity: significant delays in ossification of rib pairs in rats, significant alteration in the number of thoracic and lumbar vertebrae and low fetal weight in rats and rabbits. The reviewer noted that findings in these studies are of limited relevance to the toxicity of ozenoxacin administered topically with minimal systemic exposure.

**Clinical Pharmacology**

The Clinical Pharmacology reviewer concluded that the Clinical Pharmacology information provided by the applicant was acceptable. I concur that there are no Clinical Pharmacology issues precluding approval.

Ozenoxacin 1% cream demonstrated negligible systemic absorption following topical application in healthy subjects and patients with impetigo. Labeling recommendations were made regarding limiting the topical application area to 100 $cm^2$.

**Clinical Microbiology**

The Clinical Microbiology reviewer did not identify Clinical Microbiology issues precluding approval, and I concur with this assessment.

In-vitro studies were adequate to characterize antibacterial activity. In the pooled Phase 3 trials, the most common isolates were *Staph. aureus, Strep. pyogenes, and Staph. epidermidis.* The number of methicillin-resistant *Staph. aureus* isolates was limited.

**Clinical/Statistical – Efficacy**

The Statistical and Clinical reviewers, the CDTL, and the Division Director all concluded that evidence of the efficacy of ozenoxacin cream 1% for the treatment of impetigo has been demonstrated in two adequate and well-controlled trials, and I concur with this assessment.

Trial 880 was a multicenter, three-arm (ozenoxacin, placebo, retapamulin assigned 1:1:1), investigator blind trial that compared the efficacy and safety of ozenoxacin cream with placebo in the treatment of impetigo; a retapamulin arm was included to test internal validity. This trial enrolled patients 2 years of age and older.

Trial 881 was a multicenter, randomized, double-blind trial that compared the safety and efficacy of ozenoxacin cream with placebo (assigned 1:1) in the treatment of impetigo. This trial enrolled patients 2 months of age and older.

Both trials used age group (< 12 years, 12 to < 18 years, ≥ 18 years) as a stratifying factor at randomization. For all patients, treatment was applied topically b.i.d. for 5 days to all impetigo affected areas. Study visits occurred on Day 3-4 (Visit 2 - on therapy), Day 6-7 (Visit 3 - end of therapy), and Day 10-13 (Visit 4 - final study visit).

Both trials used the Skin Infection Rating Scale (SIRS) as part of enrollment criteria as well as the primary endpoint definition. However, the two trials used different versions of the rating scale. In Trial 880, total SIRS scores were calculated using a rating scale of 0 to 6 (0 = absent, 2 = mild, 4 = moderate, 6 = severe) for 7 signs or symptoms (exudate/pus, crusting, erythema/inflammation, tissue warmth, tissue edema, itching, and pain); the maximum score is 42. In Trial 881, total SIRS scores were calculated using a rating scale of 0 to 3 (0 = absent, 1

= mild, 2 = moderate, 3 = severe) for 5 signs or symptoms (exudate/pus, crusting, erythema/inflammation, blistering, and itching/pain); the maximum score is 15.

In both trials, the primary efficacy endpoint was clinical success or cure at end of therapy (Visit 3, Day 6-7) in the ITT population. In Trial 880, patients classified as 'Cure' by Visit 3 had to have a SIRS score of 0 for exudates/pus, crusting, tissue warmth and pain and a score of 0 or 1 for all other signs/symptoms (i.e. erythema/inflammation, tissue edema and itching). In Trial 881, patients classified as 'Cure' by Visit 3 had to have a SIRS score of 0 for blistering, exudates/pus, crusting, itching/pain and a score of 0 or 1 for all other signs/symptoms (i.e. erythema/inflammation)[2]. In both trials, clinical cure rates were significantly higher in the ozenoxacin versus the placebo group. In Trial 880 rates were 54/155 (34.8%) vs. 30/156 (19.2%), a treatment difference of 15.6% (95% CI: 5.8%, 25.3%), p-value=0.002. In Trial 881, rates were 112/206 (54.4%) vs. 78/206 (37.9%), a difference of 16.0% (95% CI: 6.9%, 25.8%), p-value < 0.001.

In Trial 880, the clinical cure rate for the retapamulin arm was 58/154 (37.7%). The difference in success rate vs. placebo was statistically significant and the retapamulin cure rate was numerically similar to the cure rate for ozenoxacin, providing evidence of internal validity for the Trial 880 findings. Sensitivity analyses conducted for both trials showed that the treatment benefit of ozenoxacin was generally robust to various assumptions made regarding the analysis population, the timing of the visit and missing data. Analyses in selected secondary endpoints including changes in the size of baseline lesions, absence of baseline lesions, Total SIRS scores and the use of concomitant antimicrobial therapy were also supportive of primary analysis findings. While the treatment difference was consistent between the two trials, the cure rates for both ozenoxacin and placebo differed. The review team attributed this to different primary endpoint definitions and other trial design differences. There were limitations of note in a few subgroups such as patients between the ages of 2 months to less than 2 years of age (limited number of patients, n=28), older patients 12 years and older (lower cure rates compared with younger patients), and patients with bullous impetigo (success rate similar to placebo, 29.3% vs. 29.4%).

**Safety**

The Clinical Reviewer, CDTL, and Division Director each concluded that there were no safety issues that would preclude approval, and I concur.

Across all studies, 1354 subjects were exposed to single or repeated doses of ozenoxacin at concentrations of 0.25% to 2%, with 802 subjects/patients exposed to the 1% cream. There were no deaths and no SAEs related to study drug in the development program. Phase 1 studies evaluated dermal tolerability of ozenoxacin 1% and 2% creams and showed low potential for irritation, photo-irritation, photoallergy, and dermal sensitization. In Trials 880 and 881, adverse events were reported in 4.4% of patients who received ozenoxacin and 4.7%

[2] The endpoint definition in Trial 881was consistent with the recommendations included in the FDA *Draft Guidance on Mupirocin*, released by the Office of Generic Drugs in 2010. Available at: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm217138.pdf

of patients who received placebo. The only adverse events reported in at least two patients who received ozenoxacin were nasopharyngitis (4 patients) and diarrhea (2 patients).

In the Phase 2 trial, application site irritation and application site pruritus were the most frequently reported adverse events, and one patient receiving ozenoxacin 2% cream in the Phase 2 trial withdrew due to application site irritation. I concur with the review team that this risk can be adequately addressed in labeling and do not anticipate additional risk mitigation strategies will be needed.

**Advisory Committee Meeting**

An Advisory Committee was not convened as there were no issues raised in the course of NDA review that would benefit from an Advisory Committee discussion.

**Pediatrics**

The applicant requested a partial waiver of pediatric studies in children less than 2 months of age because studies are impossible or highly impracticable in this age group. The Division of Anti-Infective Products (DAIP) presented the partial waiver request and the pediatric assessment to the Pediatric Review Committee (PeRC) on May 17, 2017, and PeRC concurred with the granting of a partial waiver.

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JOHN J FARLEY
06/22/2017

# Cross-Discipline Team Leader Review

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| **Date** | June 14, 2017 |
| **From** | Thomas Smith, M.D. |
| **Subject** | Cross-Discipline Team Leader Review |
| **NDA/BLA # Supplement#** | NDA 208945 |
| **Applicant** | Ferrer Internacional, S.A. |
| **Date of Submission** | June 23, 2016 |
| **PDUFA Goal Date** | June 22, 2017 |
| **Proprietary Name / Non-Proprietary Name** | Xepi/Ozenoxacin cream, 1% |
| **Dosage form(s) / Strength(s)** | Topical cream; 10 mg/g |
| **Applicant Proposed Indication(s)/Population(s)** | Impetigo in adults, adolescents, (b) (4), and children 2 months and older |
| **Recommendation on Regulatory Action** | Complete Response |
| **Recommended Indication(s)/Population(s)** (if applicable) | |

## 1. Benefit-Risk Assessment

**Benefit-Risk Summary and Assessment**

Ozenoxacin cream, 1%, (Xepi) is a non-fluorinated quinolone antibacterial developed by Ferrer Internacional, S.A., for the topical treatment of impetigo due to *Staphylococcus aureus* or *Streptococcus pyogenes* in patients two months of age and older. Outstanding CMC issues preclude approval of this application during this review cycle, and the regulatory recommendation is issuance of a Complete Response letter. Satisfactory resolution of these issues is required before this application may be approved.

Impetigo is a common, superficial bacterial skin infection caused by *S. aureus* and *S. pyogenes*. Two forms are recognized, nonbullous and bullous. Both forms occur most commonly in young children. Impetigo is generally mild and self-limited with a low risk of complications. Impetigo may be treated with topical or systemic oral antimicrobial therapy, with oral therapy recommended for patients with multiple lesions or in outbreaks. FDA-approved topical therapies for impetigo include mupirocin ointment, retapamulin ointment, and gentamicin sulfate cream and

ointment. Topical therapies are well-tolerated, with most adverse reactions due to local effects. FDA-approved oral therapies for impetigo and uncomplicated skin and skin structure infections include anti-staphylococcal penicillins, cephalosporins, clindamycin, and fluoroquinolones. Oral therapies have a greater risk of adverse reactions because of systemic exposure.

The applicant conducted two pivotal trials of ozenoxacin 1% cream in the treatment of impetigo. Study P-110880-01 was a three-arm trial comparing ozenoxacin cream with placebo; a third arm, retapamulin 1% ointment, was included to test internal validity; all treatments were twice daily for 5 days. Clinical response rates (success/cure) at the end of therapy were 34.8% for ozenoxacin, 19.2% for placebo, and 37.7% for retapamulin. The treatment difference of 15.6% for ozenoxacin over placebo was statistically significant. Study P-110881-01 was a two-arm trial comparing ozenoxacin cream with placebo; treatments were twice daily for 5 days. Clinical response rates (success/cure) at the end of therapy were 54.4% for ozenoxacin and 37.9% for placebo. The treatment difference of 16.5% for ozenoxacin over placebo was statistically significant. The response rates were approximately 20% higher in Study P-110881-01, which used a different version of the response rating instrument and a different primary endpoint definition. The treatment difference for ozenoxacin over placebo was consistent across trials. In addition, the point estimate for the response rate of the oxenoxacin group in Study P-110880-01 was similar to that of the retapamulin group. The number needed to treat (the number of patients that need to be treated for one to benefit compared with control) is between 6 and 7. Subgroup analyses suggest the treatment benefit may be limited for patients over 12 years of age and for patients with bullous impetigo.

The Office of Pharmaceutical Quality review team concluded that the NDA did not provide sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product and recommended issuance of a Complete Response letter. No significant safety concerns were identified in the clinical program. No serious adverse reactions were observed. (b) (4)

Outstanding CMC issues preclude approval of this application during this review cycle, and the regulatory recommendation is issuance of a Complete Response letter. Satisfactory resolution of these issues is required before this application may be approved.

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • Impetigo is a common, superficial bacterial skin infection caused by *Staphylococcus aureus* and *Streptococcus pyogenes*. Two forms are recognized, nonbullous and bullous. The more common form, nonbullous impetigo, is characterized by erythematous papules and vesicles that rupture and result in the formation of honey-colored crusts. Lesions typically develop on exposed areas at sites of minor trauma to the skin. This form is observed most often in the summer and is classically associated with *S. pyogenes* infection. In recent years, *S. aureus* has become the most common pathogen; frequently, | Impetigo is a common, superficial bacterial skin infection that is most common in young children. It is generally mild and self-limited with a low risk of complications. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | both organisms are isolated. Bullous impetigo is characterized by flaccid, generally painless bullae that rupture easily, leaving moist, erythematous erosions that dry to a thin brown crust. This form is caused almost exclusively by *S. aureus*. Both forms occur most commonly in young children.<br>• Impetigo is generally mild and self-limited with a low risk of complications. | |
| **Current Treatment Options** | • Impetigo may be treated with topical or systemic oral antimicrobial therapy, with oral therapy recommended for patients with multiple lesions or in outbreaks.<br>• FDA-approved topical therapies for impetigo include mupirocin ointment, retapamulin ointment, and gentamicin sulfate cream and ointment. Topical therapies are well-tolerated, with most adverse reactions due to local effects.<br>• FDA-approved oral therapies for impetigo and uncomplicated skin and skin structure infections include anti-staphylococcal penicillins, cephalosporins, clindamycin, and fluoroquinolones. Oral therapies have a greater risk of adverse reactions because of systemic exposure. | There are many topical and oral antimicrobial therapies available for impetigo. Topical therapies are well-tolerated. Oral therapies are recommended in certain situations and have a greater risk of adverse reactions. |
| **Benefit** | • The applicant conducted two pivotal trials of ozenoxacin 1% cream for the treatment of impetigo.<br>○ Study P-110880-01 was a three-arm trial comparing ozenoxacin cream with placebo; a third arm, retapamulin 1% ointment, was included to test internal validity; all treatments were twice daily for 5 days. A total of 465 patients two years of age and older were randomized. The primary endpoint was clinical response at the end of therapy; clinical evaluations were performed using a Skin Infection Rating Scale (SIRS). Clinical response rates (success/cure) at the end of therapy were 34.8% for ozenoxacin, 19.2% for placebo, and 37.7% for retapamulin. The treatment difference of 15.6% for ozenoxacin over placebo was statistically significant.<br>○ Study P-110881-01 was a two-arm trial comparing | The data submitted meet the evidentiary standard for approval of ozenoxacin 1% cream for the treatment of impetigo in patients two months of age and older. The clinical benefit of a 15% to 16% improvement over placebo is limited; approximately 6 to 7 patients would need to be treated for one to benefit. Ozenoxacin would provide another option for the treatment of impetigo. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | ozenoxacin cream with placebo; treatments were twice daily for 5 days. A total of 412 patients two months of age and older were randomized. The primary endpoint was clinical response at the end of therapy; clinical evaluations were performed using a different version of the SIRS. Clinical response rates (success/cure) at the end of therapy were 54.4% for ozenoxacin and 37.9% for placebo. The treatment difference of 16.5% for ozenoxacin over placebo was statistically significant.<br>• Skin Infection Rating Scales have been used in the past for endpoint assessment in trials for impetigo. Scores are calculated based on numerical ratings for signs and symptoms associated with impetigo.<br>• The response rates based on SIRS scores were approximately 20% higher in Study P-110881-01, which used a different version of the SIRS and a different primary endpoint definition. The treatment difference for ozenoxacin over placebo was consistent across trials. In addition, the point estimate for the response rate of the oxenoxacin group in Study P-110880-01 was similar to that of the retapamulin group. The number needed to treat (the number of patients that need to be treated for one to benefit compared with control) is between 6 and 7.<br>• Subgroup analyses suggest the treatment benefit may be limited for patients over 12 years of age and for patients with bullous impetigo. | |
| Risk | • The Office of Pharmaceutical Quality review team concluded that the NDA did not provide sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product and recommended issuance of a Complete Response letter.<br>• The ozenoxacin clinical program included 17 clinical studies: 14 phase 1 studies, one phase 2 trial, and two phase 3 trials. Across all studies, 1354 subjects were exposed to single or repeated doses of ozenoxacin at concentrations of 0.25% to 2%: 0.25% cream (n = 50), 1% cream (n = 802), 2% cream (n = 459), and 1% ointment (n = 43).<br>• No significant safety concerns were identified in the clinical program. | The outstanding CMC issues preclude approval of this application during this review cycle.<br><br>No significant safety concerns were identified in the clinical program. No serious adverse reactions were observed. (b) (4) |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | No serious adverse reactions were observed<br>(b) (4) | |
| Risk Management | • Risks can be managed adequately through product labeling.<br>• Routine postmarketing safety monitoring is sufficient. | Risks can be managed adequately through product labeling. Routine postmarketing safety monitoring is sufficient. |

# 2. Background

Ozenoxacin cream, 1%, (Xepi) is a non-fluorinated quinolone antibacterial developed by Ferrer Internacional, S.A., for the topical treatment of impetigo due to *Staphylococcus aureus* or *Streptococcus pyogenes* in patients two months of age and older. The proposed dosage and administration is a thin layer of cream applied to the affected area twice daily for five days.

Impetigo

Impetigo is a common, superficial bacterial skin infection caused by *S. aureus* and *S. pyogenes*[1]. Two forms are recognized, nonbullous and bullous. The more common form, nonbullous impetigo, is characterized by erythematous papules and vesicles that rupture and result in the formation of honey-colored crusts. Lesions typically develop on exposed areas at sites of minor trauma to the skin. This form is observed most often in the summer and is classically associated with *S. pyogenes* infection. In recent years, *S. aureus* has become the most common pathogen; frequently, both organisms are isolated. Bullous impetigo is characterized by flaccid, generally painless bullae that rupture easily, leaving moist, erythematous erosions that dry to a thin brown crust. This form is caused almost exclusively by *S. aureus*. Both forms most commonly occur in young children. Impetigo may be treated with topical or systemic oral antimicrobial therapy, with oral therapy recommended for patients with multiple lesions or in outbreaks[2]. FDA-approved topical therapies for impetigo include mupirocin ointment, retapamulin ointment, and gentamicin sulfate cream and ointment. FDA-approved oral therapies include anti-staphylococcal penicillins, cephalosporins, clindamycin, and fluoroquinolones; the approved indication for the oral therapies is generally skin and skin structure infections or uncomplicated skin and skin structure infections, which include impetigo.

Regulatory history

A pre-IND meeting was held with Ferrer Internacional on September 28, 2009. The sponsor's (b) (4) plan was to develop ozenoxacin for the treatment of (b) (4) (b) (4) impetigo. Ferrer submitted IND 105567 on February 23, 2010. The phase 3 clinical development plan was discussed at an end-of-phase 2 meeting on June 10, 2011. The general design of two superiority trials for the impetigo indication was discussed, and DAIP recommended that the primary endpoint evaluation be based on a skin infection rating scale (SIRS). (b) (4) A pre-NDA meeting was held January 13, 2016, and NDA 208945 was submitted June 23, 2016.

The clinical program included 14 phase 1 studies, one phase 2 trial, and two phase 3 trials.

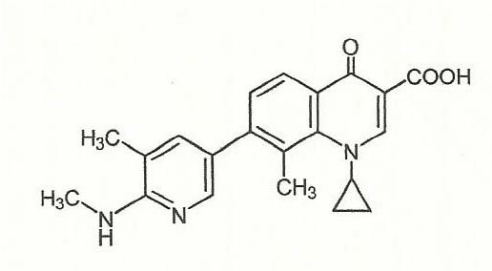
[1] Jackson MA. Bacterial skin infections. In: Feigin RD, Cherry JD, Demmler-Harrison GJ, Kaplan SL (eds). Feigin & Cherry's Textbook of Pediatric Infectious Diseases. Philadelphia, Saunders Elsevier, 2009.
[2] Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis 2014;59:e10-52.

Ozenoxacin lotion, 2%, (Zebiax) was approved in Japan in 2015 for the treatment of superficial skin infections and acne (accompanied by purulent inflammation). Ozenoxacin 1% cream is not approved in any country.

## 3. Product Quality

Dorota Matecka, Ph.D., was the application technical lead for the product quality assessment team. The team's findings are summarized below.

Ozenoxacin (1-cyclopropyl-8-methyl-7-[5-methyl-6-methylamino-pyridin-3-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid) is a white to pale yellow crystalline solid with a molecular formula of $C_{21}H_{21}N_3O_3$, a molecular weight of 363.41, and the following structural formula:




Ozenoxacin drug substance is [redacted](b) (4), as described in DMF [redacted](b) (4). The drug substance specifications include tests and acceptance criteria for appearance, identification, clarity of solution, water, residue on ignition, heavy metals, related substances, assay, residual solvents, and particle size, and were considered adequate. Stability data support a retest period of [redacted](b) (4) months.

The drug product manufacturer for the phase 3 trials was Ferrer Internacional, S.A., Spain; the proposed commercial manufacturer is Teligent Pharma, Inc., U.S. The drug product, ozenoxacin cream, 1%, is a pale yellow cream supplied in 10-, 30-, and 45-gram aluminum tubes. The drug substance is [redacted](b) (4). Inactive ingredients include octyldodecanol, peglicol 5 oleate, pegoxol 7 stearate, propylene glycol, stearyl alcohol, purified water, and benzoic acid [redacted](b) (4). The drug product specifications include tests and acceptance criteria for appearance, identification, pH, viscosity, particle size distribution, ozenoxacin assay, degradation products, benzoic acid assay, tube content uniformity, weight loss, package integrity, and microbial limits, and were considered acceptable. Stability data support expiration dating for the drug product of 36 months when stored at room temperature.

The drug manufacturing process review found [redacted](b) (4) that maximum processing and hold times during manufacturing were not established. These issues were resolved during the review cycle.

The product quality microbiology review found deficiencies regarding microbial limits, (b) (4) and stability testing, which did not include assessment for *Burkholderia cepacia* complex. These issues were resolved during the review cycle, and the product quality microbiology reviewer, Alifiya Ghadiali, Ph.D., recommended approval.

The biopharmaceutics review found that the in vitro release test method and in vitro drug release data were adequate to support the proposed change in manufacturing site from Ferrer to Teligent.

Multiple cGMP deficiencies were identified at the drug substance manufacturing site, (b) (4) during the most recent inspection in (b) (4). Deficiencies included (b) (4) A warning letter was issued for this facility in (b) (4) The drug product manufacturing and testing facilities were acceptable. The facilities reviewer, David Anderson, Ph.D., recommended withholding approval until re-inspection of the drug substance manufacturing site confirms that corrective actions were taken and data integrity is verified.

The Office of Pharmaceutical Quality review team concluded that the NDA did not provide sufficient CMC information to assure the identity, strength, purity, and quality of the proposed drug product and recommended issuance of a Complete Response letter. The specific deficiencies are listed below:

Facilities (*conveyed via the Mid-Cycle Communication*):

> During a recent inspection of the (b) (4) manufacturing facility for this ANDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this application may be approved.

# 4. Nonclinical Pharmacology/Toxicology

Tessie Alapatt, Ph.D., was the pharmacology/toxicology reviewer for this application. Her findings are summarized below.

Ozenoxacin 1% showed low potential for dermal irritation after repeated application to rats, rabbits, and minipigs. It was well-tolerated when administered to intact and abraded skin in a 4-week repeat-dose study in minipigs. Ozenoxacin plasma concentrations were below the lower limit of quantitation when ozenoxacin 1% cream was applied topically to intact and abraded skin in minipigs. No target organs were identified in the tissues evaluated. Ozenoxacin cream and its vehicle did not demonstrate potential for contact sensitization in a murine local lymph node assay.

Safety pharmacology studies using an oral form of ozenoxacin revealed no effects on the cardiovascular system of dogs or the respiratory and central nervous systems of rats. Ozenoxacin

did not affect fertility or reproduction in male and female rats. Delays in ossification of rib pairs and alterations in the numbers of thoracic and lumbar vertebrae were observed in rats, and low fetal weights were observed in rats and rabbits. Dr. Alapatt noted that rabbits are more sensitive to the developmental effects of many antimicrobials because of alterations in maternal gut flora, with subsequent adverse effects in the offspring. She considered the safety pharmacology and reproductive and developmental toxicity findings to be of limited relevance for a topically administered drug with minimal systemic exposure.

Long-term studies in animals to evaluate carcinogenic potential have not been conducted. Ozenoxacin demonstrated no genotoxicity when evaluated in vitro for gene mutation and/or chromosomal effects in the Ames test, mouse lymphoma cell assay, or when evaluated in vivo in a rat micronucleus test with demonstrated systemic exposure.

Dr. Alapatt concluded that the nonclinical studies supported the approval of ozenoxacin 1% cream for the topical treatment of impetigo in patients two months of age and older. Labeling recommendations to the applicant included changes to Section 8.1 (Pregnancy) (b) (4) to modify the risk summary statement and to Section 8.2 (Lactation) to modify the risk summary statement. (b) (4)

## 5. Clinical Pharmacology

Ozenoxacin cream, 1%, is to be applied topically as a thin layer to the affected area twice daily for 5 days. The affected area may be up to 100 $cm^2$ in adult and pediatric patients 12 years of age and older or 2% of the total body surface area and not exceeding 100 $cm^2$ in pediatric patients less than 12 years of age. The concentration was selected following the phase 2 dose-ranging study described briefly in Section 5 of this review.

Xiaohui (Tracey) Wei, Ph.D., was the clinical pharmacology reviewer for this application. Her findings are summarized below.

In healthy subjects administered ozenoxacin 2% cream, ozenoxacin concentrations were high in the stratum corneum and epidermis and near the lower limit of quantitation (5.01 ng/mg) in the dermis, indicating that ozenoxacin penetrates poorly into deeper layers of the skin.

Three pharmacokinetic studies evaluated systemic absorption of ozenoxacin in healthy subjects and in patients with impetigo, with single or repeated application of up to 1 g to intact or abraded skin (up to 200 $cm^2$ surface area). Plasma ozenoxacin concentrations were below the lower limit of quantitation (approximately 0.5 ng/mL) for 84 of 86 subjects. Negligible absorption was observed in two pediatric patients, with levels ranging from 0.539 to 0.681 ng/mL, slightly above the lower limit of quantitation.

Because of the negligible systemic absorption, tissue distribution and excretion have not been evaluated in humans. Ozenoxacin was not metabolized in the presence of fresh human skin discs and was minimally metabolized in human hepatocytes.

Dr. Wei concluded that the proposed dosing of ozenoxacin was supported by efficacy, safety, and pharmacokinetic data from the clinical trials and that the information provided in the application is acceptable. She recommended minor modifications to the draft labeling. The application is approvable from the clinical pharmacology perspective pending agreement on labeling.

## 6. Clinical Microbiology

Avery Goodwin, Ph.D., was the clinical microbiology reviewer for this application. His findings are summarized below.

Ozenoxacin is a non-fluorinated quinolone antimicrobial drug with a mechanism of action that involves the inhibition of bacterial DNA replication enzymes, DNA gyrase A and topoisomerase IV. It has been shown to be bactericidal against *S. aureus* and *S. pyogenes*, with MBC/MIC ratios $\leq$4. Quinolone resistance can arise through mutations of one or more of the genes that encode DNA gyrase or topoisomerase IV. The frequency of resistant mutants selected by ozenoxacin is $\leq 10^{-10}$.

The in vitro activity of ozenoxacin was evaluated against gram-positive isolates from multiple sources, including skin, wounds, abscesses, tissue, and blood, collected from centers in the U.S. and worldwide. The $MIC_{90}$ against 2398 *S. aureus* isolates was 0.25 mg/L and against 657 *S. pyogenes* isolates was 0.015 mg/L.

Ozenoxacin has been tested in combination with 17 other commonly used antimicrobial agents against *S. aureus* and *S.pyogenes*. Antagonistic interactions with ozenoxacin were observed with ciprofloxacin against *S. aureus*. The clinical significance of this finding is unknown.

The clinical microbiology findings in the phase 3 trials are summarized in Section 5.

Dr. Goodwin concluded that this application was approvable from the clinical microbiology perspective pending agreement on labeling. He recommended modifications to Section 12.4 (Microbiology) of draft labeling, including limiting the listed organisms to *S. aureus* and *S. pyogenes*, to be consistent with the indication, (b) (4)

## 7. Clinical/Statistical- Efficacy

Nicholas Rister, M.D., was the clinical reviewer, and Christopher Kadoorie, Ph.D., was the statistical reviewer for this application. The clinical program included a phase 2 trial in SITL and two phase 3 trials in impetigo.

The phase 2 trial was a four-arm placebo-controlled trial that evaluated three concentrations of ozenoxacin cream, 0.25%, 1%, and 2%, in the treatment of adult patients with SITL; 199 patients were treated. At the end of the seven-day treatment course, clinical responses were observed to be greater in the 1% arm compared with placebo; the 0.25% and 2% arms did not demonstrate significant improvement over placebo. The 1% concentration was therefore chosen for study in phase 3.

Impetigo trials

Study P-110880-01 (Study 880) was a multicenter, three-arm, investigator blind trial that compared the efficacy and safety of ozenoxacin cream with placebo in the treatment of impetigo; a third arm, retapamulin, which is approved for treatment of impetigo, was included to test internal validity. This trial enrolled patients 2 years of age and above and was conducted at sites in the U.S., Europe, and South Africa from 2012 to 2013. Study P-110881-01 (Study 881) was a multicenter, randomized, double-blind trial that compared the efficacy of ozenoxacin cream with placebo in the treatment of impetigo. This trial enrolled patients 2 months of age and above and was conducted at sites in the U.S., Puerto Rico, Europe, and South Africa from 2014 to 2015.

The clinical evaluation of impetigo in these trials was based on two versions of a Skin Infection Rating Scale. In Study 880, total SIRS scores were calculated using a rating scale of 0 to 6 (0 = absent, 2 = mild, 4 = moderate, 6 = severe) for 7 signs or symptoms (exudate/pus, crusting, erythema/inflammation, tissue warmth, tissue edema, itching, and pain); the maximum score is 42. In Study 881, total SIRS scores were calculated using a rating scale of 0 to 3 (0 = absent, 1 = mild, 2 = moderate, 3 = severe) for 5 signs or symptoms (exudate/pus, crusting, erythema/inflammation, blistering, and itching/pain); the maximum score is 15. The reference for the scale used in Study 881 is FDA's Office of Generic Drugs Draft Guidance on Mupirocin[3].

In Study 880, patients 2 years and above with a clinical diagnosis of bullous or non-bullous impetigo with an affected area of 1-100 $cm^2$ and a total SIRS score of at least 8, including a pus/exudate score of at least 1, were eligible for enrollment. In Study 881, patients 2 months and above with a clinical diagnosis of bullous or non-bullous impetigo with an affected area of 2-100 $cm^2$ and a total SIRS score of at least 3, including a pus/exudate score of at least 1, were eligible for enrollment. In both trials, surrounding erythema could not extend for more than 2 cm from the edge of any affected area, and, for patients under 12 years of age, the total affected area could not exceed 2% of body surface area. Patients were excluded if they had an underlying skin disease with evidence of a secondary infection, a bacterial infection that could not be treated appropriately with a topical antimicrobial, or signs or symptoms of a systemic infection. In addition, patients could not have been treated with on oral antimicrobial within the previous 7 days, a topical antimicrobial within 5 cm of the edge of the affected area within the previous 7 days, or a long-acting injectable antimicrobial within the previous 30 days. Any topical therapeutic agent could not have applied to the affected area within the previous 24 hours. Samples from the affected area were to be collected for culture at baseline and at subsequent visits if culturable material was present and could be collected.

[3] FDA Draft Guidance on Mupirocin (June, 2010)

In Study 880, patients were randomly assigned (1:1:1) to receive oxenoxacin 1% cream, a matching placebo cream, or retapamulin 1% ointment. In Study 881, patients were randomly assigned (1:1) to receive oxenoxacin 1% cream or a matching placebo cream. Randomization was stratified by age (<12 years, 12-<18 years, ≥18 years). All treatments were twice daily for 5 days. Patients returned for follow-up on day 3-4 (on-therapy), day 6-7 (end-of-therapy), and day 10-13 (final visit).

The primary efficacy endpoint for both studies was clinical response (success or failure) at the end of therapy visit on day 6-7. In Study 880, success at this visit was defined as SIRS score of 0 for exudate/pus, crusting, tissue warmth and pain, and no more than 1 each for erythema/inflammation, tissue edema, and itching. In Study 881, success at this visit was defined as SIRS score of 0 for blistering, exudate/pus, crusting, itching/pain, and no more than 1 for erythema/inflammation. In both trials, for success, the clinical response had to be such that no additional antimicrobial therapy for the affected area was necessary.

The primary analysis population was the intent-to-treat clinical (ITTC) population, which was all patients who were randomized. Secondary endpoint analyses were performed in the intent-to-treat bacteriological (ITTB) population, which was all patients in the ITT population who had a baseline pathogen identified; in Study 881, this pathogen had to be *S. aureus* or *S. pyogenes*. These are the only bacteria that will be discussed in the remainder of this review. Secondary analyses were also performed in the per protocol clinical (PPC) population, which was the subset of ITTC patients without protocol deviations, and the per protocol bacteriological (PPB) population, which was the subset of PPC patients with a baseline pathogen identified.

Both trials tested the superiority of ozenoxacin over placebo for clinical response at the end of therapy visit in the ITTC population. For Study 880, using a 2-group $\chi^2$ test with a 5% 2-sided significance level, the applicant calculated that a sample size of 465 patients (155 per group) had 90% power to detect a 20% difference in proportions, assuming a clinical cure rate of 70% in the ozenoxacin group and a dropout rate of 20%. This trial was to include at least 258 patients from 2 years to <12 years of age and at least 24 patients from 12 to 18 years of age. For Study 881, using a 2-group $\chi^2$ test with a 5% 2-sided significance level, the applicant calculated that a sample size of 412 patients (206 per group) had 90% power to detect a 15% difference in proportions, assuming a clinical cure rate of 35% in the ozenoxacin group and a dropout rate of 10%. This trial was to include at least 226 patients from 2 months to <12 years of age and at least 20 patients from 12 to 18 years of age.

In Study 880, 465 patients were randomized, 155 to ozenoxacin, 156 to placebo, and 154 to retapamulin. The median age was 9 years; 283 (61%) patients were 2 years to <12 years of age, and 52 (11%) were 12 to ≤18 years of age. Approximately 60% of patients were male, and 50% were black. Most patients (67%) were from South Africa; 6% were from the U.S. Approximately 80% of patients had non-bullous impetigo, and 20% had bullous impetigo. *S. aureus* was isolated from 61% of patients and *S. pyogenes* from 46%. Approximately 50% of patients had a single affected area. The mean SIRS score was 14.7.

In Study 881, 412 patients were randomized, 206 to ozenoxacin and 206 to placebo. The median age was 10 years; 28 (7%) patients were 2 months to <2 years of age, 199 (48.3%) were 2 years

to <12 years of age, and 46 (11%) were 12 to ≤18 years of age. Approximately 50% of patients were male, and 64% were white. European sites enrolled 36% of patients; 34% were from the U.S., and 11% were from Puerto Rico. Approximately 86% of patients had non-bullous impetigo, and 14% had bullous impetigo. *S. aureus* was isolated from 54% of patients and *S. pyogenes* from 9%. Approximately 40% of patients had a single affected area. The mean SIRS score was 7.6.

Table 1 shows clinical response rates at the end of therapy in Study 880. The FDA primary analyses consider all patients with missing or indeterminate outcomes as failures. Success rates at the end of therapy were significantly greater for both ozenoxacin and retapamulin compared with placebo. The finding for retapamulin supports the internal validity of the trial.

Table 1: Study 880: Clinical Response at End of Therapy (ITTC Population)

| | **Ozenoxacin (N=155)** | | **Retapamulin (N=154)** | | **Placebo (N=156)** | |
|---|---|---|---|---|---|---|
| **Clinical Outcome** | **n** | **(%)** | **n** | **(%)** | **n** | **(%)** |
| Clinical Success/Cure | 54 | (34.8) | 58 | (37.7) | 30 | (19.2) |
| Clinical Failure/ | 101 | (65.2) | 96 | (62.3) | 126 | (80.8) |
| Improvement | 97 | (62.6) | 90 | (58.4) | 119 | (76.3) |
| Failure | 1 | (0.6) | 1 | (0.7) | 1 | (0.6) |
| Unable to Determine | 3 | (1.9) | 5 | (3.2) | 6 | (3.8) |
| Difference in success rate vs. placebo (95% CI), p-value | 15.6 (5.8, 25.3) p = 0.002 | | 18.4 (8.5, 28.2) p < 0.001 | | | |

Adapted from FDA Statistical Review, Table 10

Clinical success rates at the follow-up visit on day 10-13 were also significantly greater for ozenoxacin and retapamulin compared with placebo. For nonbullous impetigo, clinical success rates were 49/122 (40.2%) in the ozenoxacin group and 22/122 (18.0%) in the placebo group. In contrast, for bullous impetigo, success rates were 5/33 (15.2%) and 8/34 (23.5%), respectively.

Table 2 shows clinical response rates at the end of therapy in Study 881. Again, the FDA primary analyses consider all patients with missing or indeterminate outcomes as failures. Success rates at the end of therapy were significantly greater for ozenoxacin over placebo. Success rates in this trial were approximately 20% greater in both the ozenoxacin and placebo arms, but the treatment difference is consistent across trials, with differences in success rates of 15.6% and 16.5% in favor of ozenoxacin. The trials used different SIRS versions and different primary endpoint definitions.

Table 2: Study 881: Clinical Response at End of Therapy (ITTC Population)

| | **Ozenoxacin (N=206)** | | **Placebo (N=206)** | |
|---|---|---|---|---|
| **Clinical Outcome** | **n** | **(%)** | **n** | **(%)** |
| Clinical Success/Cure | 112 | (54.4) | 78 | (37.9) |
| Clinical Failure/ | 94 | (45.6) | 128 | (62.1) |
| Improvement | 84 | (40.8) | 105 | (51.0) |
| Failure | 7 | (3.4) | 16 | (7.8) |
| Unable to Determine | 3 | (1.5) | 7 | (3.4) |
| Difference in success rate vs. placebo (95% CI), p-value | 16.5 (6.9, 25.8) p < 0.001 | | | |

Adapted from FDA Statistical Review, Table 11

Clinical success rates at the follow-up visit on day 10-13 were also significantly greater for ozenoxacin compared with placebo. For nonbullous impetigo, clinical success rates were 100/182 (55.3%) in the ozenoxacin group and 66/172 (38.4%) in the placebo group. For bullous impetigo, success rates were 12/25 (48.0%) and 12/34 (35.3%), respectively.

In both trials, additional analyses performed by Dr. Kadoorie of changes in SIRS scores, reduction in size of the affected area, and complete resolution of lesions supported the primary analyses.

Table 3 shows clinical success rates at the end of therapy for patients who had *S. aureus* or *S. pyogenes* at baseline. In each trial, for both pathogens, cure rates were greater for ozenoxacin than for placebo.

Table 3: Clinical Success at End of Therapy by Pathogen (ITTB Population)

| | **Study 880** | | | | **Study 881** | | | |
|---|---|---|---|---|---|---|---|---|
| | **Ozenoxacin** | | **Placebo** | | **Ozenoxacin** | | **Placebo** | |
| **Pathogen** | **n/N** | **(%)** | **n/N** | **(%)** | **n/N** | **(%)** | **n/N** | **(%)** |
| *S. aureus* | 35/93 | (37.6) | 16/98 | (16.3) | 66/115 | (57.4) | 36/108 | (33.3) |
| *S. pyogenes* | 29/73 | (39.7) | 7/67 | (10.4) | 15/19 | (78.9) | 8/20 | (40.0) |

Adapted from FDA Statistical Review, Tables 16 and 22 and draft label

The differences in study populations, SIRS versions, and clinical response definitions in the trials preclude pooling across trials for subgroup analyses of efficacy. In general, subgroup analyses by age, race, sex, and geographic region favored ozenoxacin. The treatment benefit appeared to be somewhat less in patients ≥12 years of age in both trials.

Conclusions

Drs. Rister and Kadoorie concluded that there was adequate evidence to demonstrate the efficacy of ozenoxacin for the treatment of impetigo in patients two months of age and older. Dr. Kadoorie noted no major statistical issues with this application and found that both trials demonstrated superiority of ozenoxacin to placebo. Primary efficacy findings were limited for older patients (≥12 years of age) and for patients with bullous impetigo. I concur that the phase 3 trials have provided substantial evidence of effectiveness to support approval for this indication.

# 8. Safety

Nicholas Rister, M.D., reviewed the safety data for this application.

The ozenoxacin clinical program included 17 clinical studies: 14 phase 1 studies, one phase 2 trial, and two phase 3 trials. Across all studies, 1354 subjects were exposed to single or repeated doses of ozenoxacin at concentrations of 0.25% to 2%: 0.25% cream (n = 50), 1% cream (n = 802), 2% cream (n = 459), and 1% ointment (n = 43).

There were no deaths and a single serious adverse event reported in the clinical program. One

patient in a dermal sensitization study had a serious adverse event of upper limb fracture, which was unrelated to study drug.

Eight phase 1 studies evaluated dermal tolerability of ozenoxacin 1% and 2% creams and showed low potential for irritation, photo-irritation, photoallergy, and dermal sensitization. The most commonly reported adverse events in these studies were nasopharyngitis and headache. The most commonly reported adverse events in the six phase 1 systemic absorption and skin exposure studies were erythema associated with the adhesive dressing, application site erythema, and application site pruritus.

In the phase 2 SITL trial in adults, the most frequently reported adverse events were application site irritation and application site pruritus. There were three adverse events leading to withdrawal from the trial: worsening skin laceration in a patient receiving placebo, diabetic nephropathy in a patient receiving ozenoxacin 1% cream, and application site irritation in a patient receiving ozenoxacin 2% cream.

In the pooled phase 3 trials, adverse events were reported in 16 of 352 (4.4%) patients who received ozenoxacin and in 17 of 361 (4.7%) patients who received placebo. The most commonly reported adverse events were nasopharyngitis, diarrhea, eosinophilia, and rhinitis. The only adverse events reported in at least two patients who received ozenoxacin were nasopharyngitis (4 patients) and diarrhea (2 patients). A single patient receiving ozenoxacin had two adverse events, rosacea and seborrheic dermatitis, considered to be drug-related.

Dr. Rister concluded that there were no significant safety concerns regarding ozenoxacin 1% cream. I concur with his assessment. (b) (4)

## 9. Advisory Committee Meeting

Not applicable.

## 10. Pediatrics

The applicant requested a partial waiver of pediatric studies in children less than 2 months of age because studies are impossible or highly impracticable in this age group. The Division of Anti-Infective Products (DAIP) presented the partial waiver request and the pediatric assessment to the Pediatric Review Committee (PeRC) on May 17, 2017, and PeRC concurred with DAIP's plan to grant the partial waiver.

## 11. Other Relevant Regulatory Issues

The Office of Scientific Investigations conducted inspections of three clinical investigator sites from the phase 3 trials and concluded that the data from the trials may be considered reliable. Ferrer stated there were no clinical investigators who had disclosable financial interests or arrangements.

# 12. Labeling

The Division of Medication Error Prevention and Analysis (DMEPA) of the Office of Surveillance and Epidemiology determined that the proprietary name, Xepi, was acceptable. DMEPA and the Office of Prescription Drug Promotion provided recommendations to be incorporated into final labeling.

Although the recommended regulatory action is a complete response letter because of CMC issues, DAIP negotiated labeling with the applicant in anticipation of approval following resolution of those issues.

# 13. Postmarketing Recommendations

Routine postmarketing safety monitoring will be sufficient. There are no recommended postmarketing requirements or commitments.

# 14. Recommended Comments to the Applicant

During a recent inspection of the (b) (4) manufacturing facility for this ANDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this application may be approved.

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/s/

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THOMAS D SMITH
06/14/2017

# CLINICAL REVIEW

| | |
|---|---|
| **Application Type** | Original NDA |
| **Application Number(s)** | 208945 |
| **Priority or Standard** | Standard |
| **Submit Date(s)** | June 23, 2016 |
| **Received Date(s)** | June 23, 2016 |
| **PDUFA Goal Date** | June 22, 2017 |
| **Division/Office** | CDER/OND/OAP/DAIP |
| **Reviewer Name(s)** | Nicholas Rister, M.D. |
| **Review Completion Date** | March 23, 2017 |
| **Established Name** | 1% ozenoxacin cream |
| **(Proposed) Trade Name** | Pending |
| **Applicant** | Ferrer Internacional, S.A. |
| **Formulation** | Topical cream<br>1% (10 mg/g) |
| **Dosing Regimen** | Applied as a thin layer of cream to the affected area twice daily for 5 days |
| **Indication** | Topical treatment of impetigo |
| **Intended Populations** | Adults, adolescents, (b) (4) and children 2 months and older |

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## Glossary

| | |
|---|---|
| AE | adverse event |
| BID | Twice daily |
| BRF | Benefit Risk Framework |
| BSA | Body surface area |
| CDER | Center for Drug Evaluation and Research |
| CFR | Code of Federal Regulations |
| CMC | chemistry, manufacturing, and controls |
| CRF | case report form |
| eCTD | electronic common technical document |
| eCRF | electronic case report form |
| EOP | End of Phase |
| FDA | Food and Drug Administration |
| GCP | good clinical practice |
| ICH | International Conference on Harmonization |
| IND | investigational New Drug |
| IRB | institutional review board |
| ISE | integrated summary of effectiveness |
| ISS | integrated summary of safety |
| ITT | intent to treat |
| ITTB | intent to treat bacteriological |
| ITTC | intent to treat clinical |
| IWRS | Interactive Web Response System |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NDA | new drug application |
| NME | new molecular entity |
| OCS | Office of Computational Science |
| OPQ | Office of Pharmaceutical Quality |
| OSE | Office of Surveillance and Epidemiology |
| OSI | Office of Scientific Investigation |
| PD | pharmacodynamics |
| PeRC | Pediatric Review Committee |
| PK | pharmacokinetics |
| PMC | postmarketing commitment |
| PMR | postmarketing requirement |
| PP | per protocol |
| PPB | per protocol bacteriological |

| | |
|---|---|
| PPC | per protocol clinical |
| pvl | Panton Valentine leukocidin |
| REMS | risk evaluation and mitigation strategy |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SIRS | Skin infection rating scale |
| SITL | Secondarily infected traumatic lesions |
| SOP | standards of practice |
| TEAE | treatment emergent adverse event |

# 1 Executive Summary

## 1.1. Product Introduction

Ozenoxacin (1-cyclopropyl-8-methyl-7-[5-methyl-6-methylamino-pyridin-3-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid) is an antibacterial agent that has been developed into a cream for short term topical use in the treatment of impetigo. Ozenoxacin is a new molecular entity (NME) and is not currently marketed or available in any formulation in the U.S. or internationally.

Ozenoxacin is pharmacologically classified as a non-fluorinated quinolone antibacterial and is a member of the pharmacotherapeutic group of J01M-quinolone antibacterials. Ozenoxacin acts as a selective inhibitor of DNA replication with a dual target of action, blocking the bacterial DNA gyrase and the topisomerase IV enzymes.

Ozenoxacin 1% cream is intended for short term topical use in adults and children aged 2 months and older, to be applied as a thin layer of cream to the affected area twice daily for 5 days.

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

According to my review of the clinical data, I recommend that ozenoxacin 1% cream be approved for the treatment of adult and pediatric patients with impetigo. Data from two independent, adequate, and well-controlled Phase 3 studies support the efficacy of ozenoxacin 1% for the proposed indication. Both Phase 3 studies demonstrated that treatment with ozenoxacin 1% was superior to placebo when given twice daily for five days.

## 1.3. Benefit-Risk Assessment

## Benefit-Risk Summary and Assessment

Ozenoxacin 1% cream is an antibacterial agent proposed for the short term topical treatment of impetigo in adults and children >2 months of age. The drug is proposed to provide a more rapid resolution of symptoms then occurs with the natural course of the disease. According to my review of the clinical data, I recommend that ozenoxacin 1% cream be approved for the treatment of adult and pediatric patients >2 month of age with impetigo.

Impetigo is a non-serious medical condition which causes mild symptoms and clinical manifestations, is generally self-limiting and rarely progresses to more serious infections or conditions. Patients commonly experience symptoms of mild inflammation including erythema, edema, itching, pain, and localized warmth, but rarely more systemic signs of infection including fever. The standard of care for impetigo is the use of topical antibiotics including FDA-approved agents (including mupirocin and retapamulin) which lead to a more rapid resolution of symptoms when compared to placebo or the natural course of the disease. Additionally, while topical antibiotics have been found to be effective in the majority of impetigo cases, systemic antibiotics are used for infections that involve large areas or have not adequately responded to topical treatment. The currently available treatments provide good options for the majority of impetigo patients.

The submitted efficacy data for ozenoxacin 1% cream demonstrates that patients treated with the agent experience increased resolution of symptoms after a 5 day course relative to those treated with placebo. While the difference is small, this does translate into less discomfort and more rapid healing for a very common condition. While there were large variations between studies in the absolute rate of cure of impetigo at the primary endpoint, the difference in these rates between ozenoxacin and placebo groups was consistently 15-20% across both trials and evaluated subgroups and was similar in effect to an internal comparator, retapamulin, in one trial. This consistency provides substantial evidence for the effectiveness of ozenoxacin 1% cream in the treatment of impetigo. The limited microbiologic evidence suggests earlier eradication of causative organisms including *Staphylococcus aureus* and *Streptococcus pyogenes*. The clinical response for patients with *S. aureus* and *S. pyogenes* impetigo infections demonstrated the increased resolution of symptoms noted in the entire treatment population. Currently available topical antibiotics provide similar efficacy for the treatment of impetigo caused by *S. aureus* and *S.* pyogenes. While there is no identified advantage for ozenoxacin cream, it provides an alternative for patients unable to tolerate other topical preparations due to rare complications of allergy or irritation.

There is no evidence for any significant safety concerns regarding ozenoxacin 1% cream from a detailed review of the available safety database.

Clinical Review
Nicholas Rister, M.D.
NDA 208945
Ozenoxacin cream 1%

Ozenoxacin 1% cream shows efficacy in the resolution of impetigo when compared to placebo cream for a 5 day treatment course while having no significant safety concerns. While the difference in efficacy is small for a condition that generally self-resolves, the effect is comparable to similarly available products and there are no safety concerns.

In conclusion, the available evidence shows a small but significant benefit for the use of ozenoxacin 1% cream for the topical treatment of impetigo in patients >2 months caused by *S. aureus* or *S. pyogenes* while demonstrating no significant risks. I recommend approval for this indication

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • Impetigo is a common, highly contagious, superficial bacterial skin infection that is most prevalent in the pediatric population. The disease manifests with the development of thin walled vesicles or bullae that rupture and leave behind superficial erosions which crust over and heal without scarring. Some patients report pain and swollen lymph nodes near sites of involvement, but systemic complaints of fever, malaise, and anorexia are atypical.<br>• While robust data on the severity and natural course of impetigo are lacking, expert consensus suggests the disease is generally self-limiting and resolves without complication in the vast majority of cases over the course of 2-3 weeks. Based on expert opinion and limited reports in the literature, progression to more severe soft tissue or systemic infection is rare.<br>• Worldwide, *Staphylococcus aureus* and *Streptococcus pyogenes* cause the majority of impetigo infections, but specific rates vary over time and geographic region often with limited evidence. | • Impetigo is a non-serious medical condition which causes mild clinical manifestations, is self-limiting, and rarely progresses to more serious conditions.<br>• The lack of robust evidence on the natural course of the disease and the exact rate of spontaneous resolution creates challenges for quantifying treatment benefits. |
| Current Treatment Options | • Topical antibiotics, including retapamulin and mupirocin, are FDA-approved for the treatment of impetigo and have widespread use. They are recommended in recent IDSA guidelines.<br>• Topical agents have a minimal side effect profile and are well tolerated.<br>• Oral antibiotics including erythromycin, cephalexin, clindamycin, and dicloxacillin have indications for soft tissue infections and are used in cases of impetigo when there are numerous lesions or lesions do not appear to be responding to topical | • The currently available treatment options for impetigo adequately provide coverage for the needs of the patient population.<br>• The currently available treatment options for impetigo are safe and tolerable for the vast majority of patients. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | treatments.<br>• There has been growing concern for antibiotic resistant organisms including MRSA as etiologies for skin and soft tissue infections. | |
| Benefit | • The efficacy of ozenoxacin 1% cream was evaluated in two pivotal Phase 3 trials:<br>o Study P-110880-01 compared 1% ozenoxacin cream (n = 155) to placebo cream (n = 156) with a primary endpoint of clinical response at end of therapy. A 1% retapamulin ointment arm (n = 154) was included for internal validity. A difference in success rates between ozenoxacin and placebo of 0.155 was calculated and was statistically significant.<br>o Study P-110881-01 compared 1% ozenoxacin cream (n = 203) to placebo cream (n = 199) with the same primary endpoint as the prior pivotal study. A difference in success rates of 0.160 was calculated and was statistically significant.<br>• While there was a clear statistical significant trend towards improved clinical response in both studies in the ozenoxacin group vs placebo, there was only an increase of ≈16% in clinical success (the primary endpoint) in the ozenoxacin groups over the placebo treated groups. Additionally, the overall clinical success rates were low in both arms 46.8% and 30.8% (ozenoxacin and placebo, respectively).<br>• The definitions of clinical success were based on a subjective scale designed to evaluate severity of impetigo infection based on a number of signs/symptoms (the SIRS score).<br>• Numerous secondary endpoints were studied (see relevant sections later in this report). Of note, the microbiological response of subjects with *S. aureus* or *S. pyogenes* infections did show evidence of early eradication of organisms.<br>• The trend towards improved clinical success at end of therapy was largely consistent across evaluated subgroups, the exceptions being age and bullous impetigo. There was evidence of higher efficacy in younger patients. Additionally, there was no evidence for a difference in the primary outcome for bullous impetigo patients although the sample size was insufficient to draw statistical conclusions. | • The submitted evidence meets evidentiary standards to show ozenoxacin 1% cream provides efficacy in the treatment of impetigo for adults and children >2 months in the treatment of impetigo caused by *S. aureus* and *S. pyogenes*.<br>• While the difference is small, more patients treated with ozenoxacin had resolution of symptoms at end therapy than those treated with placebo. For patients, this translates to less discomfort and rapid resolution of lesions for a common condition.<br>• There is no evidence to suggest the efficacy of ozenoxacin in the treatment of bullous impetigo. Sample size was a concern with a relatively small number of patients having bullous impetigo. This may also represent difficulty in the SIRS scale and study definition in accounting for characteristics of bullous impetigo, which is much less common than the non-bullous form. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Risk | • 1917 subjects were included in the topical ozenoxacin safety database across 17 trials including 14 Phase 1 trials, 1 Phase 2 dosing study, and 2 pivotal Phase 3 studies. This safety database and case reports were reviewed and felt to be extensive and complete. The database addresses relevant drug doses and formulations, duration of treatment, patient demographics, and disease severity.<br>• No safety concerns were identified during the review of the safety database.<br>• The safety database included a range of ozenoxacin strengths (0.25 to 2%) and durations (single dose to multi-dose regiments for 21 days).<br>• There was negligible evidence of systemic absorption for topical ozenoxacin across various studies including a range of concentrations and regimens. | • There is no evidence for any significant safety concerns regarding ozenoxacin topical cream from the available safety database which is adequate.<br>• In post-market use, it can be expected that ozenoxacin 1% cream will be utilized for longer durations and increased frequency then studied in the pivotal trials (BID x 5 days). Studies from the safety database in higher concentrations and longer durations of ozenoxacin in damaged skin did not reveal any additional safety concerns. |
| Risk Management | • Minimal risks were observed during the clinical trials for ozenoxacin 1% cream. As noted above, there were no specific safety concerns. | • Routine post marketing monitoring is considered sufficient for ozenoxacin 1% cream. |

# 2 Therapeutic Context

## 2.1. Analysis of Condition

Impetigo or impetigo contagiosum is a common, superficial bacterial skin infection that is most prevalent in the pediatric population.

The disease can be categorized as primary (direct bacterial invasion of previously healthy skin) or secondary (bacterial superinfection of disrupted skin barrier due to previous dermatologic condition such as eczema or scabies). Additionally, impetigo can be designated as bullous or non-bullous based on the presence or absence of bullae (blisters) on physical exam.

The usual natural history of non-bullous impetigo begins with the development of thin-walled vesicles that rapidly rupture leaving behind superficial erosions with yellowish-brown or honey-colored crusts. Crusted skin lesions then dry and separate leaving behind red marks which subsequently heal without scarring. Non-bullous lesions are most commonly found on the limbs and face. Bullous impetigo has a similar course except that larger bullae develop initially and remain for a few days before rupturing and are more commonly found on the trunk. Some patients report pain at the site of infection and swollen lymph nodes at sites of lymphatic drainage are common. Systemic symptoms such as fever, malaise, and anorexia are atypical and suggestive of a more severe infection. It is commonly believed that the majority of impetigo cases spontaneously resolve in 2-3 weeks; however there are no robust data on the natural history of impetigo[1]. Reported cure rates with placebo creams vary from 8% to 42% at 7 to 10 days[2] [3].

*Staphylococcus aureus* and *Streptococcus pyogenes* are considered to be the main bacterial causes of impetigo. *S. aureus* is more common in moderate climates while *S. pyogenes* appears to be more prevalent in warmer, humid regions. There has also been variation over time with *S. aureus* impetigo becoming more prevalent in the United States during the past two decades[4]. *S. aureus* is always the etiology of bullous impetigo and more common in secondary cases.

While the majority of cases resolve without complications, there remains a risk for local and systemic spread of the infection including cases of cellulitis, lymphangitis, and septicemia. Also, infections due to *S. pyogenes* have been associated with guttate psoriasis, scarlet fever, and glomerulonephritis.

While the exact incidence and prevalence of impetigo is unknown, rates of presentation to general practitioners for the condition in patients aged 1-18 years are reported between 1-3% depending on location[5]. Impetigo is considered the third most common dermatologic condition

in children after eczema and viral warts[6] and the most common skin infection in children ages 0 to 4[7].

## 2.2. Analysis of Current Treatment Options

There have been a variety of approaches to the management of impetigo with the aim reducing the soreness caused by lesions and the disease's unsightly appearance, and to decrease recurrence and spread of disease. The approaches have included no pharmacological treatment with natural resolution, topical disinfectants (e.g., saline, hexachlorophene, povidone iodine, and chlorhexidine), topical antibiotics (e.g., neomycin, bacitracin, polymyxin B, gentamicin, fusidic acid, mupirocin, retapamulin), and systemic antibiotics (e.g., penicillin, cloxacillin, amoxicillin/clavulanic acid, erythromycin, and cephalexin)[1].

Multiple topical antibiotics have been approved for the indication of impetigo (see Table 2.1). These include mupirocin ointment, topical gentamicin sulfate, and retapamulin (Altabax ointment). The reported clinical efficacy rate of Bactroban was 95% while Altabax reported an efficacy rate of 85.6%; however there is great variability in how clinical success was defined relative to this review of ozenoxacin cream (see Section 7.3). Impetigo is considered an uncomplicated skin and skin structure infection and multiple drugs have been approved for this indication including: fluoroquinolones (levofloxacin, moxifloxacin, ofloxacin), cephalosporins (cefuroxime, cefdinir, cefprozil, cefpodoxime, cefditoren, cefadroxil), macrolides (clarithromycin, azithromycin), and linezolid.

**Table 2.1 Summary of FDA Approved Treatments for Impetigo**

| Drug Name | Indication |
|---|---|
| mupirocin ointment | Impetigo due to susceptible isolates of *Staphylococcus aureus* and *Streptococcus pyogenes* |
| retapamulin ointment | Impetigo due to *Staphylococcus aureus* (methicillin-susceptible isolates only) or *Streptococcus pyogenes* in patients aged 9 months or older |
| gentamicin sulfate cream; ointment | Primary skin infections: Impetigo contagiosa, superficial folliculitis, ecthyma, furunculosis, sycosis barbae, and pyoderma gangrenosum. Secondary skin infections: Infectious eczematoid dermatitis, pustular acne, pustular psoriasis, infected seborrheic dermatitis (including poison ivy), infected excoriations, and bacterial superinfections of fungal or viral infections |
| levofloxacin (in 0.9% sodium chloride) injection; tablets; oral solution | Uncomplicated skin and skin structure infections (mild or moderate) including abscesses, cellulitis, furuncles, impetigo, pyoderma, wound infections, due to *Staphylococcus aureus* or *Streptococcus pyogenes* |

The Infectious Diseases Society of America (IDSA) 2014 practice guidelines[8] for the diagnosis and management of skin and soft-tissue infections recommends that bullous and nonbullous impetigo can be treated with oral or topical antimicrobials, but oral therapy is recommended for patients with numerous lesions or in outbreaks affecting several people to help decrease transmission of infection with the following details:

- Treatment of bullous and nonbullous impetigo should be with topical mupirocin or

retapamulin twice daily (bid) for 5 days.

- Oral therapy for impetigo should be a 7-day regimen with an agent active against *S. aureus* unless cultures yield streptococci alone (when oral penicillin is the recommended agent. Because *S. aureus* isolates from impetigo are usually methicillin susceptible, dicloxacillin or cephalexin is recommended. When MRSA is suspected or confirmed, doxycycline, clindamycin, or sulfamethoxazole-trimethoprim (SMX-TMP) is recommended.
- Systemic antimicrobials should be used for infections during outbreaks of poststreptococcal glomerulonephritis to help eliminate nephritogenic strains of *S. pyogenes* from the community.

The goals with any treatment for impetigo are to be effective while remaining inexpensive and minimizing side effects. This is especially important given the high suspected rates of natural resolution[9] [10]. Topical cleansing used to be advised in the 1970s as an alternative for antibiotic treatment, but this was later found to be no more effective than placebo[11]. Topical agents have the benefit of being applied directly to affected areas and generally having fewer side effects (most commonly gastrointestinal disturbances with systemic antibiotics). Older generations of topical antibiotics, including neomycin and gentamicin, are more likely to be related to skin sensitization and allergic reactions [12]. Additionally, topical agents that are not used systemically are preferred to reduce the spread of resistance that has been increasing with erythromycin and penicillin in recent decades[11]. There are limited data on the comparable effectiveness of systemic vs. topical antibiotics in widespread or severe impetigo, but current practice guidelines recommend systemic antibiotics in these cases for ease of administration and reduction in spread of disease (both within a particular individual and between individuals).

# 3 Regulatory Background

## 3.1. U.S. Regulatory Actions and Marketing History

Ozenoxacin is a new molecular entity and is not currently marketed in the U.S. or any other country and thus has no prior regulatory or marketing history.

## 3.2. Summary of Presubmission/Submission Regulatory Activity

A pre-investigational new drug (IND) meeting was held on September 28, 2009, regarding the use of ozenoxacin cream for the treatment of (b) (4) impetigo in patients aged 2 years and older. The FDA noted that a 4 week dermal toxicology study and irritation, photo-irritation, sensitization, and photo-allergenicity studies would be required prior to Phase 3 studies. It was agreed that carcinogenicity studies would not be required. The FDA recommended the use of a superiority trial for (b) (4) impetigo given the

difficulty in establishing non-inferiority margins in infections with high rates of spontaneous resolution. There was agreement on the use of an active comparator to establish internal validity. The FDA noted that 2 trials with identical regimens of drug would be required to support a single indication approval for (b) (4) impetigo (b) (4) A Pediatric Plan was discussed and the FDA noted that the inclusion of patients >2 months would be required to support an indication for impetigo (b) (4).

An End of Phase 2 (EOP2) meeting was held on June 10, 2011. The sponsor had completed all agreed upon dermal toxicology and irritation studies in preparation for Phase 3. The FDA confirmed that the primary endpoint evaluation was based on the results of the skin infection rating scale (SIRS) score for the two planned pivotal studies (P-110880-01 and P-110881-01) (b) (4) (b) (4) (b) (4) A pharmacokinetic (PK) study in adults and children with impetigo (P-100797-01) was the basis for not requiring studies in QT prolongation. The FDA agreed that the planned clinical studies (P-110880-01, P-110881-01, and P-100797-01) would be sufficient to support the safety and efficacy of ozenoxacin cream for the impetigo indication. The FDA recommended that study P-100797-01 include 16-20 patients aged 2 months to 2 years stratified by age. Satisfactory results would provide the basis for including patients >2 months in one of the Phase 3 studies and fulfill requirements for pediatric studies. The Agency agreed on a plan to waive studies for patients <2 months of age.

A pre-NDA meeting was held on January 13, 2016. The Agency and sponsor agreed on formats, components, and analyses to be included in the NDA submission. A pooled Integrated Summary of Efficacy and Safety combining results from the two Phase 3 studies (P-110880-01 and P-110881-01) was requested by the FDA along with study data from individual Phase 1 and 2 studies.

### 3.3. Foreign Regulatory Actions and Marketing History

Ozenoxacin has no foreign regulatory or marketing history at the time of this review.

## 4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

### 4.1. Office of Scientific Investigations (OSI)

Two foreign (Germany and South Africa) and one domestic (California) clinical investigator sites were inspected in support of NDA 208945. An inspection of the sponsor, Ferrer Internacional, in

Barcelona, Spain was also conducted. Based on the results of these inspections the data submitted by the sponsor in support of the pending application for these sites are acceptable and the studies were conducted adequately. For further details, please refer to the full clinical inspection summary by the OSI reviewer, Sharon Gershon, Pharm.D.

### 4.2. Product Quality

During an inspection of the (b) (4) manufacturing facility for NDA 208945, the field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Issues have been identified related to the equipment compatibility and proposed holding times in the manufacturing process and product quality microbiology controls. These concerns will need to be resolved prior to approval of the NDA from a Product Quality perspective.

### 4.3. Clinical Microbiology

Ozenoxacin 1% cream demonstrated microbiological efficacy in children and adults with impetigo. The microbiological response rates against *S. aureus* and *S. pyogenes* were equally effective for ozenoxacin and retapamulin at the end of therapy. Please see the full clinical microbiology review by Avery Goodwin, Ph.D. for the complete discussion.

### 4.4. Nonclinical Pharmacology/Toxicology

From a Pharmacology/Toxicology perspective, there is no objection to the approval of Ozenoxacin (1% cream) for dermal application in the treatment of impetigo in adults and children aged 2 months and older. Ozenoxacin 1% had a low potential for dermal irritation and contact sensitization potential, no systemic target organ toxicity, and minimal systemic exposure with plasma concentrations less than the lowest level of quantitation when applied topically in studied animal models. Please see the full Nonclinical Pharmacology/Toxicology Review by Tessie Alapatt, Ph.D. for the complete discussion.

### 4.5. Clinical Pharmacology

No substantive review issues have been raised regarding the Clinical Pharmacology review including mechanism of action, pharmacodynamics and pharmacokinetics. Please refer to the full review by Xiaohui Wei, Ph.D. which is pending at the time of this submission.

### 4.6. Devices and Companion Diagnostic Issues

Not applicable.

### 4.7. **Consumer Study Reviews**

Not applicable.

## 5 Sources of Clinical Data and Review Strategy

### 5.1. **Table of Clinical Studies**

Table 5.1. Major Clinical Trials Relevant to this NDA

| **Study Identity** | **Study Objective** | **Study Design** | **Test Products, Regimen, Route** | **No. of Centers and Countries** | **Treatment Duration** | **No. of patients enrolled** | **Study Population/ Number of Pediatric Patients** | **Study Endpoints** |
|---|---|---|---|---|---|---|---|---|
| P-110880-01 (Phase 3) | To evaluate efficacy, safety, and tolerability of ozenoxacin 1% cream compared with placebo and retapamulin | Multicenter, randomized, placebo-controlled, parallel, blinded, and compared with retapamulin 1% ointment[a] | Approximately 0.5 g of: ozenoxacin 1% cream, placebo cream, or retapamulin 1% ointment, twice daily, topical | 27 (US, Germany, Romania, Ukraine, and South Africa) | 5 days | 465/464[b] (ozenoxacin: n = 156; retapamulin: n = 152; placebo n = 156) | 2 years of age and older with nonbullous and bullous impetigo<br><br>335 pediatric patients (283 age 2 - <12 years; 52 age 12 - <18 years) | *Primary endpoint:* Clinical response (success or failure) at end of therapy (Visit 3, Day 6-7) in the ITTC population<br><br>*Secondary endpoints*[c]<br><br>*Safety variables:* AEs, clinical laboratory[d] parameters, vital signs, physical exam, treatment compliance |
| P-110881-01 (Phase 3) | To evaluate efficacy, safety, and tolerability of ozenoxacin 1% cream compared with placebo | Multicenter, randomized, placebo-controlled, parallel, double-blinded clinical study | Ozenoxacin 1% cream or placebo cream, twice daily, topical | 36 (US including Puerto Rico, Germany, Spain, Romania, Russia, and South Africa | 5 days | 412/411[e] (ozenoxacin: n = 206; placebo: n = 205) | 2 months of age and older with nonbullous and bullous impetigo<br><br>272 pediatric patients (226 age >2 mo - <12 years, 46 age 12 - <18 years) | *Primary endpoint:* Clinical response (clinical success or clinical failure) at end of therapy (Visit 3) in the ITTC population<br><br>*Secondary endpoints* [cf] |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | *Safety variables:* AEs, vital signs, physical exam, treatment compliance |
| P-080623-01 (Phase 2) | To evaluate efficacy, safety, and tolerability of 3 doses of ozenoxacin (0.25%, 1%, and 2%) cream compared with placebo | Multicenter, double-blind, randomized, placebo-controlled study | Ozenoxacin (0.25%, 1%, or 2%) cream or placebo cream, twice daily, topical | 16 (Germany, France, Italy, Spain, the Czech Republic, and South Africa) | 7 days | 202/199d (0.25%: n = 50, 1%: n = 50; 2%: n = 51; placebo: n = 48) | Adult subjects with SITL | *Primary endpoint:* Clinical response (success or failure) at the Final Visit (Day 14) in the ITTC population<br><br>*Secondary endpoints*[g]<br><br>*Safety variables:* AEs, clinical laboratory parameters[d], vital signs, physical examination, exposure to treatment and treatment compliance |

[a] Double-blind for ozenoxacin 1% cream versus placebo cream and investigator-blinded for retapamulin 1% ointment versus placebo cream. An active comparator was included in the study design for internal validity.

[b] 465 subjects were randomized, but 1 subject randomized to the retapamulin 1% ointment group did not receive study drug; therefore, the total number of treated subjects was 464.

[c] Clinical response (clinical success or clinical failure) at end of therapy (Visit 3) in the PPC, PPB, and ITTB populations; Clinical response (clinical improvement, no clinical improvement) at Visit 2 in the ITTC, PPC, ITTB, and PPB populations; Clinical response (clinical success, clinical unchanged, clinical relapse) at Visit 4 in the ITTC, PPC, ITTB, and PPB population; The difference from baseline (Visit I) in SIRS scores at Visit 2, Visit 3 and Visit 4 in the ITTC, PPC, ITTB, and PPB populations; Size of the affected area at Visit 2, Visit 3 and Visit 4 as a ratio of baseline (Visit I) in the ITTC, PPC, ITTB, and PPB populations; Microbiological

response (microbiological success or microbiological failure) at Visit 2 and Visit 3 in the ITTB, and PPB population; Microbiological response (microbiological recurrence or microbiological reinfection) at Visit 4 in the ITTB and PPB population; Clinical and Microbiological response at Visit 2, Visit 3 and Visit 4 by microbiological susceptibility profile of pathogens identified at Visit I to methicillin; ciprofloxacin, retapamulin, mupirocin and fusidic acid and the presence of pvl gene in the ITTB and PPB populations; Therapeutic response (combined clinical and microbiological response-success or failure) at Visit 3 in the ITTB and PPB populations; Time to clinical response; Time to bacterial eradication

[d] hematology, clinical chemistry, urinalysis

[e] 412 subjects were randomized, but 1 pediatric subject randomized to placebo cream did not receive study drug; therefore, the total number of treated subjects was 411.

[f] Clinical response (clinical success or clinical failure) at end of therapy visit (Visit 3) in the ITTC, PPC, PPB, and ITTB populations with a combined criteria of clinical success (including SIRS and size/extension of lesion). According to these criteria clinical success was defined as follows: 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; Therapeutic response (combined microbiological and clinical response, success or failure) at Visit 3 in the ITTB and PPB populations; Clinical and microbiological response at Visits 2-4 by presence of psm gene in the ITTB and PPB populations; Clinical and microbiological response at Visit 2, Visit 3 and Visit 4 in patients with *S. aureus* and *S. pyogenes* co-infection in the ITTB and PPB populations; Use of additional antimicrobial therapy at Visit 2 and Visit 3 in the ITTC, PPC, ITTB, and PPB populations; Number of new lesions and area of new lesions at Visit 2 and Visit 3 in the ITTC, PPC, ITTB, and PPB populations; Patient satisfaction with treatment in the ITTC, PPC, ITTB, and PPB populations.

[g] Clinical response (success or failure) at the Final Visit (Day 14) in the PPC, PPB, and ITTB populations; Clinical response (success or failure) at Visit 21(Day 5) and Visit 3 (Day 7) in the ITTC, PPC, ITTB, and PPB populations; Difference from baseline in SIRS score at Visit 2 (Day 5), Visit 3 (Day 7) and Final Visit (Day 14) in the ITTC, PPC, ITTB, and PPB populations; Microbiological response (success or failure) at Visit 2 (Day 5), Visit 3 (Day 7) and Final Visit (Day 14) in the ITTB, and PPB populations

### 5.2. **Review Strategy**

The submitted clinical protocols, study reports, and relevant literature were reviewed. The clinical review of efficacy and safety focuses on the two pivotal Phase 3 studies, P-110880-01 and P-110881-01. These randomized, controlled, blinded, multicenter trials provide the strongest data for ozenoxacin efficacy and safety. Section 6.1 and 6.2 will review each study individually. Given similar study design and scope, the two pivotal studies were combined appropriately in the applicant's submitted integrated summary of efficacy and integrated summary of safety. The combined analysis for efficacy will be reviewed in Section 7. This section will briefly discuss two smaller trials, P-080623-01 and Phase 1 P-100797-01. P-080623-01 is mentioned for its contribution to the applicant's choice of medication dose and P-100797-01 is regarding the inclusion of pediatric patients.

The clinical efficacy and safety review was performed by a single reviewer in collaboration with the review team. Of note, the review is performed as a review and commentary on the applicant's submitted analysis. When necessary, primary analysis was performed by the clinical reviewer utilizing JReview 9.2.6 Software for clarification and/or additional understanding.

## 6 Review of Relevant Individual Trials Used to Support Efficacy

### 6.1. **Study P-110880-01**

#### 6.1.1. **Study Design**

##### **6.1.1.1. Overview and Objective**

*A Phase III, 3 Arms, Multicenter, Randomized, Investigator-blind Study to Assess the Efficacy and Safety of Ozenoxacin 1% Cream Applied Twice Daily for 5 Days Versus Placebo in the Treatment of Patients with Impetigo*

The primary objective of Study P-110880-01 was to compare the efficacy of twice daily topical application for 5 days (10 total doses) of ozenoxacin 1% cream versus placebo cream in patients with impetigo. As a secondary objective the study sought to evaluate the efficacy of a comparable course (twice daily, topical, 10 doses) of retapamulin 1% ointment versus placebo cream in patients with impetigo to assess internal validity.

##### **6.1.1.2. Trial Design**

This study was a phase 3, multicenter, randomized, placebo-controlled, parallel, blinded (double-blind for ozenoxacin versus placebo comparison and investigator blinded for

retapamulin versus placebo comparison), superiority clinical study comparing ozenoxacin cream versus placebo cream and retapamulin ointment vs placebo cream in patients with a clinical diagnosis of non-bullous or bullous impetigo. Retapamulin was included in the study design for internal validity. Retapamulin 1% ointment has been established as effective for the indication of impetigo in the United States by the FDA. The study treatment was selected based on results of prior Phase 1/2 trials which showed potential effectiveness and safety for 1% ozenoxacin cream when utilized for a course of 5 days (BID dosing) in the treatment of impetigo.

**Enrollment**

The study planned to include 465 patients with impetigo, including at least 258 patients from 2 to <12 years and at least 24 patients from 12 to <18 years. In total, 41 study sites in 5 countries were initiated, and 27 study sites recruited patients. Patients were enrolled in 3 sites in the US, 4 sites in Germany, 2 sites in Romania, 5 sites in Ukraine, and 13 sites in South Africa. First enrollment began March 27, 2012, and last patient visits occurred in January 3, 2013 (study duration of approximately 9 months). Table 6.1 details the inclusion and exclusion criteria for the study.

The predominance of international patients (in particular, South African subjects) raises concerns for applicability of study results for patients in the United States. However, common microbiological etiologies of impetigo would be expected to be similar and were monitored during the trial. To further address these concerns, the second pivotal trial (P-118801-01) included a larger portion of subjects from the United States.

**Table 6.1 Criteria for Enrollment**

| Important Inclusion Criteria |
|---|
| 1. Male and female patients at least 2 years of age.<br>2. Clinical diagnosis of bullous or non-bullous impetigo. The patient was required to have a total affected area comprised between 1 to 100 $cm^2$ with surrounding erythema not extending more than 2 cm from the edge of any affected area. In case of multiple affected areas, the total area was the sum of each affected area and was not to exceed 100 $cm^2$. Additionally, for patients less than 12 years, the total area was not to exceed a maximum of 2% of the body surface area.<br>3. Total Skin Infection Rating Scale (SIRS) score of at least 8, including pus/exudate score of at least 1. |
| **Important Exclusion Criteria** |
| 1. Had an underlying skin disease, such as pre-existing eczematous dermatitis, with clinical evidence of secondary infection.<br>2. Had a bacterial infection, which in the opinion of the investigator, could not be appropriately treated by a topical antibiotic.<br>3. Had systemic signs and symptoms of infection (e.g. a fever; defined as an axillary temperature over 37.2°C (99.0°F).<br>4. Documented or suspected bacteremia.<br>5. Treatment with the following anti-infective agents prior to study medication administration: oral antibiotic within 7 days; topical antibiotic (at the investigational area(s) or within 5 cm from the edge of the investigational area(s)), within 7 days; a long-acting injectable antibiotic within 30 days. |

6. Had applied any topical therapeutic agent (including, but not limited to, glucocorticoid steroids) directly to the impetigo lesions within 24 hours before entry into the study.
7. Had applied any topical (at the investigational area(s) or within 5 cm from the edge of the investigational area(s)) treatment with antiseptics (e.g., alcohol, chlorhexidine, hydrogen peroxide or iodine) or other treatment that in the investigator's opinion could confound the evaluation of the treatment effect on the investigational area(s) within 8 hours before study start or planned treatment during the study.
8. Had taken any systemic or topical (at the investigational area(s) or within 5 cm from the edge of the investigational area(s)) treatment with analgesics, anti-inflammatory or antihistaminic within 8 hours before entry into the study.
9. Daily dose of >15 mg of systemic prednisone or equivalent for >10 days within the period starting 14 days prior to study medication administration or anticipated through the study period.

The inclusion/exclusion criteria target a select population with uncomplicated impetigo in patients >2 years of age. However, the selection criteria limit the inclusion of immunocompromised patients and those with prior disorders of the integumentary system, thereby limiting the ability to generalize results to these populations.

**Randomization**
Patients were allocated a unique identification number based on chronological enrollment. Patients were randomized in a 1:1:1 ratio to receive ozenoxacin, placebo, or retapamulin during the treatment period at Visit 1. Randomization list generation and maintenance was performed by (b) (4). Central randomization via an Interactive Web Response System (IWRS) was used to allocate patients to treatment groups. The IWRS provided the randomization assignment for dispensing study medication.

**Blinding**
The study was double-blinded for comparison of ozenoxacin and placebo and investigator/evaluator-blinded for comparison of retapamulin and placebo. The placebo cream appears appropriate for its role in allowing for double blinding. Of note, the study was designed with retapamulin ointment vs. placebo as a test for internal validity only. While some comparisons between the study drug (ozenoxacin) and retapamulin can be considered during the review, the differing appearance of retapamulin ointment and the placebo cream prevented proper double blinding. Treatment application instructions were provided by a delegate of the investigator to ensure that the investigator remained blinded. Study medications were provided in identical opaque boxes. All subjects were instructed to wash hands completely before and after applying product. The delegate of the investigator was responsible for dispensing, retrieving, and keeping account of study medications to maintain blinding.

**Treatment Administration and Dosing**
Patients in the treatment arm received ozenoxacin 1% cream twice daily for 5 days (total of 10 doses). This dose and regimen was selected based on findings from a Phase 2 study (P-080623-01) where ozenoxacin was administered twice daily for 7 days in SITLs and showed a statistically

significant superiority of ozenoxacin 1% cream versus placebo cream at the end of therapy. The strengths tested (0.25%, 1%, and 2%) were all safe and well tolerated. While study P-080623-01 focused on SITLs, the causative organism (*S. aureus* and *S. pyogenes*) are the same as impetigo. The duration of 5 days was based on the potent *in vitro* activity of impetigo against these same organisms in Phase 1 studies.

Affected skin area was calculated based on a specific lesions greatest length and width (vesicle/crusting edge to vesicle/crusting edge) multiplied for a calculated square centimeter area. Multiple areas were then summated for patients with multiple lesions. Body surface area (BSA) was calculated using the Mosteller formula.

Ozenoxacin, placebo, and retapamulin were applied topically as a thin layer twice daily for 5 days to all impetigo affected areas beginning on day 1 after randomization. Standardized cream application and lesion care techniques were taught to each patient prior to first dosing. A fingertip unit (approximately 0.5 g) was to be applied uniformly over the lesion. One tube of medication was provided to patients and their caretakers with instructions to continue study medication for 5 days (10 applications) without missing a dose regardless of lesion resolution. Any additional affected areas appearing during the treatment period were treated twice daily for remaining treatment days with study medication but were not considered as part of the clinical or microbiological assessments. Table 6.2 details the timing and schedule of events for each visit of the study and is referred to throughout this review.

**Table 6.2 Schedule of Time and Events**

| **Visit** | **Visit 1** | **Telephone call** | **Visit 2** | **Visit 3** | **Visit 4** | **Early Termination Visit** |
|---|---|---|---|---|---|---|
| Day | Day 1 | Day 2 | Day 3-4 | Day 6-7 | Day 10-13 | |
| Activity | Screening/ Randomization/ Baseline/ Treatment start | 24 to 36 hours after baseline visit [a] | On-therapy | End of therapy | Final visit | |
| Patient information/ informed consent | X | | | | | |
| Inclusion/exclusion criteria | X | | | | | |
| Medical history | X | | | | | |
| Demographic data | X | | | | | |
| Randomization | X | | | | | |
| Prior/Concomitant medication | X | | X | X | X | X |
| Drug dispensing | X | | | | | |
| Study medication | X | X | X | X | | |
| Dispensing of patient diary | X | | | | | |
| Review of patient diary | | | X | X | | |
| Compliance Check | | X | X | X | | X |
| Drug accountability | | | | X | | X |
| Clinical assessment by investigator | X | X | X | X | X | X |
| SIRS evaluation | X | | X | X | X | X |
| Microbiological samples | X | | X | X | X | X |
| Physical exam | X | | X | X | X | X |
| Vital Signs | X | | X | X | X | X |
| AEs/SAEs | X | X | X | X | X | X |
| Blood Sampling | X | | | X | X[c] | X |
| Urine Sampling | X | | | X | X[c] | X |
| Pregnancy Test[b] | X | | | | X | X |

*Table adapted from NDA 208945 Section 5.3.5.1 P-110880-01 Study Report Table 2*

[a] *The telephone contact took place 24 to 36 hours after the baseline visit by the investigator or an appropriately qualified designee. Patients who were deemed a clinical failure completed the end of therapy visit assessments and were withdrawn from study.*

[b] *Only for female patients of childbearing potential.*

[c] *Only in case any result at Visit 3 was abnormal.*

**Concomitant Medications**

The medical history including information on prior medication use was obtained and documented at Visit 1. All medications continued by the patient on enrollment and all medications given in addition to the study medications during the study were regarded as concomitant medications and documented. All changes in doses or formulations of these medications were also recorded. The following medications were prohibited during the study and drug and dose documented if reported:

- Systemic antibiotics including oral, parenteral or long-acting injectable antibiotics
- Topical therapeutic agents including glucocorticoid steroids, antibacterials or antifungals, applied directly to the treated lesion(s)
- Antibacterial soaps, antibacterial lotions and antibacterial wipes were prohibited for use on the infected lesion(s) during the course of the study
- Topical treatment with antiseptics (e.g. alcohol, chlorhexidine, hydrogen peroxide or iodine) or other treatment that in the investigator's opinion could confound the evaluation of the treatment effect applied directly to the treated lesion(s)
- > 15 mg of systemic prednisone or equivalent

**Treatment Compliance**

Treatment compliance was monitored via a combination of a drug inventory/dispensing record maintained by authorized personnel for all drugs provided and dispensed at each study, number and condition of dispensed/returned tubes at end of the study, and patient reported data from treatment diaries. Please refer to Table 6.1 regarding key exclusion criteria. Table 6.3 details indications for removal of patients from therapy and removal from the study

**Table 6.3 Withdrawal of Subjects or Study Medications**

| Reasons for removal of Patients from Therapy or Assessment |
|---|
| 1. Pregnancy<br>2. Development of study-related AEs that affected the patient's participation in the study.<br>3. Lack of response to randomized study medication that, at the discretion of the investigator, needed an alternative therapy, e.g. patients having been confirmed as clinical failure during the early visit triggered by the Day 2 telephone contact<br>4. The patient or his/her parent/legal guardian withdrew consent, i.e. did not wish to continue, irrespective of the reason.<br>5. The investigator/study physician felt it was medically in the best interest of the patient to discontinue the study medication. |

| Reasons for removal of Patients from Study |
|---|
| 1. Voluntary discontinuation by the patient, who was at any time free to discontinue his/her participation in the study, without prejudice to further treatment/medical care (incapacitated patients could be withdrawn from the study by their legally authorized representative and pediatric patients could be withdrawn from the study by their parents or legal guardians).<br>2. Development of an intercurrent illness, condition, or procedural complication, which would interfere with the patient's participation in the study.<br>3. Patient lost to follow up. |

In the case of discontinuation of study medication, patients were followed up as noted in Table 6.2 and any AE leading to discontinuation was followed. If a patient was removed from the study, every effort was made to perform the evaluations scheduled for the Final Visit (Visit 4) and the reason for removal documented. Patients were not replaced.

#### 6.1.1.3. Study Endpoints

The primary efficacy endpoint was a clinical response (success or failure) at end of therapy (Visit 3, Day 6-7) in the intent-to-treat clinical (ITTC) population.

Additionally, the study had many secondary efficacy endpoints:

- Clinical response (clinical success or clinical failure) at end of therapy (Visit 3) in the per-protocol (PPC), per-protocol bacteriological (PPB), and intent-to-treat bacteriological (ITTB) populations
- Clinical response (clinical improvement, no clinical improvement) at Visit 2 in the ITTC, PPC, ITTB, and PPB populations
- Clinical response (clinical success, clinical unchange, clinical relapse) at Visit 4 in the ITTC, PPC, ITTB, and PPB population
- The difference from baseline (Visit 1) in SIRS scores at Visit 2, Visit 3 and Visit 4 in the ITTC, PPC, ITTB, and PPB populations
- Size of the affected area at Visit 2, Visit 3 and Visit 4 as a ratio of baseline (Visit 1) in the ITTC, PPC, ITTB, and PPB populations
- Microbiological response (microbiological success or microbiological failure) at Visit 2 and Visit 3 in the ITTB, and PPB population
- Microbiological response (microbiological recurrence or microbiological reinfection) at Visit 4 in the ITTB, and PPB population
- Clinical and Microbiological response at Visit 2, Visit 3 and Visit 4 by microbiological susceptibility profile of pathogens identified at Visit 1 to methicillin, ciprofloxacin, retapamulin, mupirocin and fusidic acid and the presence of Panton Valentine leukocidin (pvl) gene in the ITTB and PPB populations
- Therapeutic response (combined clinical and microbiological response-success or failure) at Visit 3 in the ITTB and PPB populations
- Time to clinical response
- Time to bacterial eradication

The study includes a large number of secondary endpoints that were discussed with the FDA prior to final submission. The primary endpoint is largely of interest in considering approval for the intended indication, but additional endpoints are discussed briefly throughout the review.

Evaluation of efficacy was based on the following: clinical assessment by investigator, SIRS, microbiological response. Please refer to Table 6.2 regarding the timing of assessments. Throughout Study P-110880-01 and the related Study P-110881-01, there is use of the Skin Infection Rating Scale (SIRS) to assess the clinical severity of a case of impetigo. This definition was used to define clinical response and change during the studies.

The SIRS score is calculated from combining scores for 7 signs and symptoms: (1) Exudate/pus, (2) Crusting, (3) Erythema/inflammation, (4) Tissue Warmth, (5) Tissue edema, (6) Itching, and (7) Pain. Each sign/symptom is rated on a numerical scale from 0-6 using whole integers as defined below:

**Table 6.4 SIRS Criteria (Study P-1108801-01)**

| Score | Description | Definition |
|---|---|---|
| 0 | Absent | No evidence of signs/symptoms |
| 1 | | |
| 2 | Mild | Signs/symptoms are present but not intense |
| 3 | | |
| 4 | Moderate | Signs/symptoms are clearly evident and are somewhat bothersome to the subject |
| 5 | | |
| 6 | Severe | Signs/symptoms are clearly evident, intense, and extremely bothersome to the subject |

If the baseline affected area was the sum of multiple affected areas, then the highest score for a particular sign/symptom was applied.

It is important to note the SIRS utilized in the two pivotal studies (P-110880-01 and P-110881-01) differ. In particular, categories of tissue edema and tissue warmth are included explicitly in the SIRS for P-110880-01 but not in P-110881-01. The opposite is true for the category of blistering included only in P-110881-01. While these two scales would be expected to overlap greatly in their trends to assess impetigo severity, some difference would be expected and difficult to predict.

The following (Table 6.5 through Table 6.7) detail the definitions for clinical assessments utilized throughout the study. The clinical assessment definitions are central to this review. In particular, Visit 3 definitions are used in the primary endpoint assessment. Please see the addendum Section 13.3 for detailed definitions for microbiological assessments utilized in secondary endpoints.

**Table 6.5 Clinical Assessment at Visit 2**

| Classification / Category | Definition |
|---|---|
| Improvement / Clinical improvement | Some degree of improvement defined as:<br>• Total SIRS score decreased >10% compared to baseline (Visit 1).<br>The patient continued treatment with study medication. |
| No improvement / No clinical improvement | • No change in total SIRS score, OR<br>• Total SIRS score increased compared to baseline (Visit 1), OR<br>• Total SIRS score decreased ≤10% compared to baseline (Visit 1).<br>The patient could continue treatment with study medication or other antimicrobial therapy at the discretion of the investigator. |

*Table adapted from NDA 208945 Section 5.3.5.1 P-110880-01 Study Report Table 3*

**Table 6.6 Clinical Assessment at Visit 3 (End of Therapy)**

| Classification / Category | Definition |
|---|---|
| Cure / Clinical success | SIRS score 0 for exudates/pus, crusting, tissue warmth and pain and no more than 1 each for erythema/inflammation, tissue edema and itching.<br>No additional antimicrobial therapy of the baseline affected area(s) necessary. |
| Improvement / Clinical failure | Some degree of improvement defined as:<br>• Total SIRS score decreased >10% compared to baseline (Visit 1) not fulfilling the criteria of individual SIRS scores for cure.<br>The patient could continue treatment with another antimicrobial therapy at the discretion of the investigator. |
| Failure/ Clinical failure | • No change in total SIRS score, OR<br>• Total SIRS score increased compared to baseline (Visit 1), OR<br>• Total SIRS score decreased ≤10% compared to baseline (Visit 1).<br>Additional antimicrobial therapy of the baseline affected area(s) necessary. |

*Table adapted from NDA 208945 Section 5.3.5.1 P-110880-01 Study Report Table 4*

**Table 6.7 Clinical Assessment at Visit 4**

| Classification / Category | Definition |
|---|---|
| **Patients Classified as Cure at Visit 3** | |
| Cure / Clinical success | Total SIRS score = 0.<br>No further antimicrobial therapy of the baseline affected area(s) necessary. |
| Unchange / Clinical unchange | Total SIRS >0 and individual SIRS score 0 for exudates/pus, crusting, tissue warmth and pain and no more than 1 each for erythema/ inflammation, tissue edema and itching.<br>No additional antimicrobial therapy of the baseline affected area(s) necessary. |
| Relapse / Clinical relapse | Total SIRS score >0 not fulfilling the criteria of individual SIRS scores for unchange.<br>The patient could continue treatment with another antimicrobial therapy at the discretion of the investigator. |
| **Patients Classified as Improvement or Failure at Visit 3** | |
| Post-therapy cure / Clinical post-therapy cure | Patients classified as improvement at Visit 3 who, at the discretion of the investigator did not receive any further antimicrobial therapy, and with total SIRS = 0 at Visit 4. |
| Failure / Clinical failure | Patients classified as improvement at Visit 3 who did not receive any further antimicrobial therapy, and with total SIRS score >0 at Visit 4, OR<br>Patients classified as improvement at Visit 3 who received another antimicrobial therapy, OR Patients classified as failure at Visit 3 |

*Table adapted from NDA 208945 Section 5.3.5.1 P-110880-01 Study Report Table 5*

Microbiological samples were obtained at all visits if there was culturable material present (i.e., SIRS score for pus/exudate >0) and/or at the discretion of the investigator. If multiple body areas were involved, then the most severe area affected was selected as the primary location for microbiological sampling purposes and samples preferentially collected from this primary location. In the case of bullous lesions, the samples were collected by aseptic needle aspiration or by swabbing of the bullae exudates. In patients with non-bullous lesions, a bacterial culture of fresh exudates was obtained by swabbing. If lesions crusted, the honey colored crust was cleansed then scab uplifted and fresh exudate beneath scab was swabbed.

Since *S. aureus* and *S. pyogenes* alone or in combination were the cause of nearly all cases of impetigo, other microorganisms were considered as pathogens only in cases where none of these pathogens were identified at Visit 1.

#### 6.1.1.4. Statistical Analysis Plan

There were five analysis populations defined for the study analysis:

- Intent-to-treat Clinical Population (ITTC) – defined as all randomized patients
- Per Protocol Clinical Population (PPC) – defined as all patients in the ITTC population who did not deviate from the protocol
- Intent-to-treat Bacteriological Population (ITTB) – defined as all randomized patients who had a pathogen identified at study entry
- Per Protocol Bacteriological Population (PPB) – defined as all patients in the ITTB population who did not deviate from the protocol
- Safety Population – defined as all patients who had at least one application of study drug (discussed in detail in the safety analysis in Section 8)

The primary efficacy analysis was based on the ITTC population and specific secondary analyses utilized the PPC, ITTB, and PPB populations. The main analysis of the secondary endpoints (with the exception of microbiological response) was based upon the ITTC population, with sensitivity analyses based on the PPC, ITTB, and PPB populations. For microbiological response the main analysis was based on the ITTB population, with sensitivity analysis that was based on the PPB population.

Summary statistics were presented for continuous variables; by way of number of patients with an observation (n), mean, standard deviation (SD), median, minimum and maximum, and by way of group frequencies and percentages for categories of categorical variables. All data were summarized for each treatment (ozenoxacin and placebo) using descriptive statistics. All statistical tests were two-sided and were performed using a 5% significance level and 95% confidence intervals (CI) were provided.

If clinical responses were missing then values were imputed as unable to determine. A review of missing clinical response data was made prior to breaking study blinding and any decisions regarding the handling of this data was documented prior to unblinding.

**Sample Size Determination**

A 2-group $\chi^2$ test with a 5% 2-sided significance level had 90% power to detect a difference of 20% in proportions at Visit 3, with the assumption that the clinical cure rate in the ozenoxacin group was 70% when the sample size was 124 for each group. Under the assumptions of a 20% dropout rate 155 patients for each group were required to achieve 90% power at 5% 2-sided significance level. A total of 465 patients were planned to be enrolled to ensure 90% power for the primary objective.

**Primary Analysis**

Clinical response classification (clinical success, clinical failure) at end of therapy (Visit 3) was summarized by treatment for the ITTC population by comparing ozenoxacin cream versus placebo cream. The same analysis was performed to compare retapamulin ointment versus placebo cream. These analyses were performed to test the superiority of ozenoxacin versus placebo and to estimate the effect of retapamulin compared to placebo (for internal validity).

For each treatment, the number and percentages of clinical success, clinical failure, and unable to determine were presented.

Further analyses (sensitivity analyses) similar to those above were performed using the ITTC population on the endpoint clinical response (success or failure) at end of therapy visit (Visit 3), to evaluate the sensitivity of the results to missing data. In a first sensitivity analysis missing responses (unable to determine) were imputed using a worst case approach (i.e., imputed as failures). A second sensitivity analysis was performed where missing responses were imputed by using the Markov Chain Monte Carlo (MCMC) method.

The worst case scenarios in the first sensitivity analysis differ between the two Phase 3 studies. P-110880-01 replaces both placebo and treatment with failures for missing responses; however, P-110881-01 replaces placebo with success and treatment with failure when responses are missing. The second study's sensitivity analysis therefore utilizes a worst case scenario less likely to suggest a difference in favor of the study drug. Please refer to the statistical review for additional information regarding study analysis.

**Secondary Analysis**

The study pursued multiple secondary endpoints as detailed previously in this section. Clinical response and clinical response categorization (clinical success, clinical failure, and unable to determine) for visits 2, 3, and 4 were analyzed in a manner similar to the primary analysis regarding the ITTC, PPC, ITTB, and PPB populations.

Microbiological response and response classification was summarized at Visits 2, 3, and 4 for the ITTB and PPB populations.

Clinical and microbiological responses at Visits 2-4 were analyzed by microbiological susceptibility (sensitive or resistant) of pathogens (*S. aureus* or *S. pyogenes*) identified at Visit 1 to methicillin, ciprofloxacin, retapamulin, mupirocin, and fusidic acid for the ITTB and PPB populations. These data allowed for the calculation of the clinical response at Visits 2-4 for specific pathogens.

SIRS scores were analyzed for all visits (1-4) in the ITTC, PPC, IITB, and PPB populations. The total and single item scores were summarized by treatment group.

For ITTC, PPC, ITTB, and PPB populations, a summary table (frequencies with respective percentages and descriptive statistics, where applicable) was provided for baseline affected area identification for: type of impetigo, number of affected areas, affected area(s) location, total affected area, and percent of affected BSA.

**Exploratory Analysis**

The derived clinical response (clinical success or clinical failure) at Visit 3 (primary efficacy endpoint) was analyzed for the ITTC population, stratified for the following parameters:

- Clinical diagnosis of impetigo (bullous, non-bullous)
- Number of affected areas (1, 2- 4, 5-10, >10)
- Baseline total affected area (0-2 $cm^2$, 2-10 $cm^2$, 10-50 $cm^2$, 50-100 $cm^2$)
- Baseline SIRS total score (<15, 15-28, 29-42)
- Treatment compliance (<80%, 80-120%, >120%)

For each treatment, the numbers and percentages of clinical success, clinical failure and unable to determine were presented. The p-value of the chi-square test (without continuity correction) and corresponding 95% asymptotic (Wald) CI for the difference in success rates were provided. Please refer to the statistical review for additional detail on the provided data analysis.

#### 6.1.1.5. Protocol Amendments

The protocol underwent amendments on November 3, 2011, and October 23, 2012. The first amendment removed the phrase "Total SIRS score decreased >10% compared to baseline" from the definition of cure at end of therapy. Additionally, this amendment removed the wording that the Visit 4 "clinical failures" would be evaluated only for safety. The second amendment added the following secondary endpoints: therapeutic response, time to clinical response, time to bacterial eradication.

The first amendment was made to incorporate comments from the Food and Drug Administration. The second amendment was introduced to comply with the Pediatric Investigational Plan agreed with the European Medicines Agency Pediatric Committee.

#### 6.1.1.6. Data Quality and Integrity: Sponsor's Assurance

The sponsor reported that study procedures followed the clinical study protocol and (b) (4) Standards of Practice (SOPs) which are based on current regulatory and ethical requirements. Additional methods or data assurance included: (1) a study-specific monitoring guideline, (2) a data validation plan, (3) a statistical analysis plan (SAP), (4) use of trained clinical monitors from (b) (4) (5) training of study personnel at site initiation visits, (6) an eCRF with data validated per the data validation plan, (7) audits of both sites and data entry per (b) (4)

The applicant's stated data quality assurance methods appear appropriate and consistent with expected standards. Additionally, the applicant provided audit certificates for all audits performed during the study. These included audits of multiple sites as well as the central laboratory along with its standardization methods.

### 6.1.2. Study Results

#### 6.1.2.1. Compliance with Good Clinical Practices

The applicant reports this study was conducted in accordance with International Conference on Harmonization (ICH) of Good Clinical Practice (GCP), the principles of the Declaration of Helsinki (Helsinki, 1964), all applicable amendments laid down by the World Medical Assemblies, and all other local and national laws and regulations. At each study center, the protocol and informed consent form were reviewed and approved by a duly constituted Institutional Review Board (IRB). A list of all IRBs and consulted ethics committees was provided with the application.

#### 6.1.2.2. Financial Disclosure

Ferrer Internacional, S.A. has determined there were no financial interests or arrangements to disclose from the investigators in Study P-110880-01. Please see Section 13.4 for Clinical Investigator Financial Disclosure

#### 6.1.2.3. Patient Disposition

**Table 6.8 Patient Disposition (Study P-110880-01)**

| | Ozenoxacin N (%) | Placebo N (%) | Retapamulin N (%) | Overall N (%) |
|---|---|---|---|---|
| **Randomized** | 155 | 156 | 154 | 465 |
| **Safety population** | 156 (100.6%) | 156 (100%) | 152 (98.7%) | 464 (99.8%) |
| **ITTC population** | 155 (100%) | 156 (100%) | 154 (100%) | 465 (100%) |
| **PPC population** | 134 (86.5%) | 132 (84.6%) | 138 (89.6%) | 404 (86.9%) |
| **ITTB population** | 154 (99.4%) | 152 (97.4%) | 153 (99.4%) | 459 (98.7%) |
| **PPB population** | 133 (85.8%) | 128 (82.1%) | 138 (89.6%) | 399 (85.8%) |
| **Completed the Study** | | | | |
| Yes | 153 (98.7%) | 150 (96.2%) | 152 (98.7%) | 455 (97.8%) |
| No | 2 (1.3%) | 6 (3.8%) | 2 (1.3%) | 10 (2.2%) |
| **Reason for early Discontinuation from Study Post-Randomization** | | | | |
| Withdrew Consent | 2 (100%) | 1 (16.7%) | 0 | 3 (30.0%) |
| Lost to follow-up | 0 | 2 (33.3%) | 1 (50.0%) | 3 (30.0%) |
| Worsening condition | 0 | 3 (50.0%) | 0 | 3 (30.0%) |
| Not treated | 0 | 0 | 1 (50.0%) | 1 (10.0%) |
| **Excluded from Per Protocol populations** | | | | |
| Yes | 21 (13.5%) | 24 (15.4%) | 16 (10.4%) | 61 (13.1%) |
| No | 134 (86.5%) | 132 (84.6%) | 138 (89.6%) | 404 (86.9%) |
| **Reason for exclusion from Per Protocol** | | | | |
| Inclusion/exclusion criteria | 13 (61.9%) | 12 (50.0%) | 9 (56.3%) | 34 (55.7%) |
| Visit schedule not according to protocol | 10 (47.6%) | 11 (45.8%) | 5 (31.3%) | 26 (42.6%) |
| Disallowed medications | 0 | 0 | 3 (18.8%) | 3 (4.9%) |
| Study medication administration/study treatment | 1 (4.8%) | 1 (4.2%) | 1 (6.3%) | 3 (4.9%) |
| Study blind broken | 0 | 1 (4.2%) | 1 (6.3%) | 2 (3.3%) |

*Table adapted from NDA 208945 Section 5.3.5.1 P-110880-01 Study Report Table 15*

The study met the goal subject numbers based on the statistical analysis plan. A relatively small number of subjects were either discontinued from the study or were excluded from the per protocol analysis – reasons for these exclusions and violations are discussed in Section 6.1.2.4. Numbers of subjects excluded/discontinued were similar in different treatment arms and are not expected to skew analysis.

#### 6.1.2.4. Protocol Violations/Deviations

As noted in Table 6.8, 61 patients were excluded from the PPB and PPC populations due to protocol deviations (representing 13.1% of the total randomized patient population). The most common reasons for exclusion were non-compliance with inclusion/exclusion criteria and visit schedule not according to the protocol. The most common inclusion/exclusion criterion deviation was total baseline of affected area too small (30 of the 34 deviations in this category).

The major deviations in the inclusion/exclusion criteria and visits schedule appear to be equally distributed between treatment arms and sites suggesting consistent adherence to protocol between sites. I do not expect that these exclusions lead to significant impact on the study results/outcomes. Additional types of deviation were rare and unlikely to have significant impact on the study analysis. Specific cases are detailed below.

- One patient randomized to the retapamulin group was not treated. This patient was excluded from all populations except the ITTC population.

- One patient was randomized to the retapamulin group but received ozenoxacin during the study and was included in the ozenoxacin group in the safety population and the retapamulin group in the ITTC and ITTB populations. This patient was excluded from the PPB and PPC populations.

- Three patients were excluded for taking disallowed medications (2 used additional antibiotics and 1 utilized an antihistamine) and were excluded from PPB and PPC populations.

- Two patients took <10 doses of the study medication and were excluded from PPB and PPC populations.

- Two patients were excluded from PPB and PPC for breaking blinding by returning unboxed study medication and revealing study drug color in a phone call to investigators.

#### 6.1.2.5. Demographic Characteristics

**Table 6.9 Demographic Characteristics P-110880-01 Safety Population**

| | Ozenoxacin (N = 156) | Placebo (N = 156) | Retapamulin (N = 152) | Overall (N = 464) |
|---|---|---|---|---|
| **Age (years)** | | | | |
| Mean (SD) | 16.1 (17.71) | 17.3 (17.18) | 15.0 (14.97) | 16.1 (16.66) |
| Min, Max | 2, 76 | 3, 83 | 2, 71 | 2, 83 |
| **Age group, N (%)** | | | | |
| <2 years | 0 | 0 | 0 | 0 |
| 2 - <12 years | 95 (60.9%) | 94 (60.3%) | 94 (61.8%) | 283 (61.0%) |
| 12 - <18 years | 19 (12.2%) | 18 (11.5%) | 15 (9.9%) | 52 (11.2%) |
| 18 - <65 years | 36 (23.1%) | 40 (25.6%) | 40 (26.3%) | 116 (25.0%) |
| ≥65 years | 6 (3.8%) | 4 (2.6%) | 3 (2.0%) | 13 (2.8%) |
| **Gender, N (%)** | | | | |
| Male | 100 (64.1%) | 96 (61.5%) | 90 (59.2%) | 286 (61.6%) |
| Female | 56 (35.9%) | 60 (38.5%) | 62 (40.8%) | 178 (38.4%) |

| | | | | |
|---|---|---|---|---|
| **Predominant Race, N (%)** | | | | |
| Black or African American | 78 (50.0%) | 77 (49.4%) | 78 (51.3%) | 233 (50.2%) |
| White | 58 (37.2%) | 62 (39.7%) | 50 (32.9%) | 170 (36.6%) |
| Mixed Race | 19 (12.2%) | 15 (9.6%) | 22 (14.5%) | 56 (12.1%) |
| Asian | 1 (0.6%) | 0 | 2 (1.3%) | 3 (0.6%) |
| American Indian or Alaska Native | 0 | 2 (1.3%) | 0 | 2 (0.4%) |
| **Geographic Location, N (%)** | | | | |
| Germany | 31 (19.9%) | 33 (21.2%) | 24 (15.8%) | 88 (19.0%) |
| Romania | 4 (2.6%) | 4 (2.6%) | 3 (2.0%) | 11 (2.4%) |
| Ukraine | 10 (6.4%) | 10 (6.4%) | 7 (4.6%) | 27 (5.8%) |
| United States | 4 (2.6%) | 11 (7.1%) | 11 (7.2%) | 26 (5.6%) |
| South Africa | 107 (68.6%) | 98 (62.8%) | 108 (71.1%) | 313 (67.5%) |
| **Height (cm)** | | | | |
| Mean (SD) | 132.38 (32.16) | 139.04 (28.18) | 132.10 (30.14) | 134.53 (30.31) |
| Min, Max | 78.0, 194.0 | 85.8, 190.0 | 77.0, 203.5 | 77.0, 203.5 |
| **Weight (kg)** | | | | |
| Mean (SD) | 38.85 (26.38) | 41.50 (25.86) | 37.29 (24.74) | 39.23 (25.68) |
| Min, Max | 9.0, 103.0 | 12.3, 139.0 | 10.0, 105.0 | 9.0, 139.0 |
| **Body Surface Area ($m^2$)** | | | | |
| Mean (SD) | 1.17 (0.53) | 1.24 (0.50) | 1.14 (0.50) | 1.18 (0.51) |
| Min, Max | 0.44, 2.30 | 0.56, 2.45 | 0.46, 2.42 | 0.44, 2.45 |

*Table modified from NDA 208945 Section 5.3.5.1 P-110880-01 Study Report Table 16*

The documented characteristics are evenly distributed among the three study arms suggesting proper randomization and assignment of patients during the study. Of note, the population is skewed towards the younger age ranges (i.e. 2 - <12 years old) paralleling the ages typically afflicted with impetigo. There are no patients in the <2 years age range because the study intentionally did not recruit this age group (the related pivotal study P-110881-01 includes ages 2 months to <2 years old).

A review of the geographic location demographics reveals a predominance of international patients in the study and a low number of patients from the United States. South Africa, in particular, has the majority of patients and sites in the study. These findings raise concerns for the applicability of the study conclusions to patient populations in the United States. This leads to racial demographics that are far different in the study than in the US, although impetigo is not generally considered to differ clinically based on patient racial background. These concerns regarding a large international patient population were discussed with the applicant following study completion and a larger cohort of USA patients was included in the pivotal study P-110881 which followed).

#### 6.1.2.6. Other Baseline Characteristics

**Table 6.10 Disease Characteristics at Baseline (P-110880-01 Safety Population)**

| | Ozenoxacin (N = 156) | Placebo (N = 156) | Retapamulin (N = 152) | Overall (N = 464) |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| **Type of Impetigo, N (%)** | | | | |
| Bullous | 34 (21.8%) | 34 (21.8%) | 28 (18.4%) | 96 (20.7%) |
| Non-bullous | 122 (78.2%) | 122 (78.2%) | 124 (81.6%) | 368 (79.3%) |
| **Number of Affected Areas** | | | | |
| Mean (SD) | 3.0 (3.70) | 2.8 (3.44) | 3.4 (4.31) | 3.1 (3.83) |
| Min, Max | 1, 29 | 1, 29 | 1, 24 | 1, 29 |
| 1 | 72 (46.2%) | 78 (50.0%) | 76 (50.0%) | 226 (48.7%) |
| 2 – 4 | 59 (37.8%) | 54 (34.6%) | 44 (28.9%) | 157 (33.8%) |
| 5 – 10 | 18 (11.5%) | 18 (11.5%) | 24 (15.8%) | 60 (12.9%) |
| >10 | 7 (4.5%) | 6 (3.8%) | 8 (5.3%) | 21 (4.5%) |
| **Location, N (%)** | | | | |
| Face | 80 (51.3%) | 68 (43.6%) | 73 (48.0%) | 221 (47.6%) |
| Upper trunk | 5 (3.2%) | 3 (1.9%) | 7 (4.6%) | 15 (3.2%) |
| Lower trunk | 12 (7.7%) | 10 (6.4%) | 8 (5.3%) | 30 (6.5%) |
| Right arm | 24 (15.4%) | 22 (14.1%) | 18 (11.8%) | 64 (13.8%) |
| Left arm | 26 (16.7%) | 21 (13.5%) | 18 (11.8%) | 65 (14.0%) |
| Right leg | 30 (19.2%) | 37 (23.7%) | 41 (27.0%) | 108 (23.3%) |
| Left leg | 47 (30.1%) | 47 (30.1%) | 40 (26.3%) | 134 (28.9%) |
| **Total Affected Area ($cm^2$)** | | | | |
| Mean (SD) | 9.34 (16.73) | 12.85 (21.40) | 12.12 (22.51) | 11.43 (20.36) |
| Min, Max | 0.48, 94.62 | 0.36, 98.31 | 0.40, 99.00 | 0.36, 99.00 |
| 0 – 2 $cm^2$ | 46 (29.5%) | 34 (21.8%) | 42 (27.6%) | 122 (26.3%) |
| 2 – 10 $cm^2$ | 74 (47.4%) | 80 (51.3%) | 75 (49.3%) | 229 (49.4%) |
| 10 – 50 $cm^2$ | 28 (17.9%) | 30 (19.2%) | 23 (15.1%) | 81 (17.5%) |
| 50 – 100 $cm^2$ | 8 (5.1%) | 12 (7.7%) | 12 (7.9%) | 32 (6.9%) |
| % of BSA Mean (SD) | 0.084 (0.127) | 0.098 (0.1404) | 0.096 (0.1493) | 0.093 (0.1389) |
| % of BSA Median | 0.040 | 0.050 | 0.040 | 0.040 |
| % of BSA Min, Max | 0, 1.06 | 0, 0.78 | 0, 1.02 | 0, 1.06 |
| **SIRS Total Score** | | | | |
| Mean (SD) | 15.1 (4.48) | 15.0 (4.00) | 14.0 (4.07) | 14.7 (4.21) |
| Min, Max | 8, 29 | 8, 27 | 8, 31 | 8, 31 |
| <15 | 80 (51.3%) | 78 (50.0%) | 97 (63.8%) | 255 (55.0%) |
| 15 – 28 | 75 (48.1%) | 78 (50.0%) | 54 (35.5%) | 207 (44.6%) |
| 29 – 42 | 1 (0.6%) | 0 | 1 (0.7%) | 2 (0.4%) |
| **Number of Pathogens** | **N = 143** | **N = 146** | **N = 140** | **N = 429** |
| Mean (SD) | 2.2 (0.98) | 2.3 (1.04) | 2.2 (0.98) | 2.2 (1.00) |
| Min, Max | 1, 5 | 1, 6 | 1, 6 | 1, 6 |
| *Staphylococcus aureus* | 93 (65.0%) | 98 (67.1%) | 94 (67.1%) | 285 (66.4%) |
| *Streptococcus pyogenes* | 73 (51.0%) | 67 (45.9%) | 74 (52.9%) | 214 (49.9%) |
| *Staphylococcus epidermidis* | 31 (21.7%) | 25 (17.1%f) | 24 (17.1%) | 80 (18.6%) |
| Others | 51 (35.7%) | 58 (39.7%) | 57 (40.7%) | 166 (38.7%) |

*Table modified from NDA 208945 Section 5.3.5.1 P-110880-01 Study Report Table 16*

The three treatment arms had similar lesion characteristics including type, size, number, and location. The tendency of the study lesions to be relatively small (<10 $cm^2$) and fewer in number (<4) is consistent with the planned treatment population that would receive a topical agent only for impetigo. It should be noted that the types of pathogens documented area similar as well; however, the validity of *Staphylococcus epidermidis* as a true pathogen is doubtful. This

organism along with additional organisms in the "others" category are typically considered contaminants in an otherwise healthy patient population.

#### 6.1.2.7. Treatment Compliance, Concomitant Medications, and Rescue Medication Use

**Table 6.11 Treatment Compliance P-110880-01 Safety Population**

| | Ozenoxacin (N – 156) | Placebo (N = 156) | Retapamulin (N = 152) |
|---|---|---|---|
| **Mean (SD)** | 99.6 (7.19) | 97.9 (14.31) | 100.5 (2.52) |
| **Min, Max** | 33, 120 | 10, 120 | 100, 120 |
| **<80%, n (%)** | 2 (1.3%) | 6 (3.8%) | 0 |
| **80% – 120%, n (%)** | 154 (98.7%) | 150 (96.2%) | 152 (100%) |
| **>120%, n (%)** | 0 | 0 | 0 |

*Table adapted from NDA 208945 Section 5.3.5.1 P-110880-01 Study Report Table 18*

There was good treatment compliance documented throughout the study in all arms of treatment. This likely reflects the short duration and ease of use of a topical agent for impetigo. The mean treatment compliances were similar in all treatment arms and differences are unlikely to influence trial outcomes. Poor compliers were included in all ITT populations for primary endpoint analysis.

**Table 6.12 Concomitant Medications P-110880-01 Safety Population**

| ATC Level 2 Preferred Term, N (%) | Ozenoxacin (N = 156) | Placebo (N = 156) | Retapamulin (N = 152) | Overall (N = 464) |
|---|---|---|---|---|
| **Patients with at least 1 concomitant medication** | 33 (21.2%) | 43 (27.6%) | 37 (24.3%) | 113 (24.4%) |
| Antibiotics and chemotherapeutics for dermatologic | 14 (9.0%) | 25 (16.0%) | 16 (10.5%) | 55 (11.9%) |
| Mupirocin | 14 (9.0%) | 24 (15.4%) | 16 (10.5%) | 54 (11.6%) |
| Sex hormones and modulators of the genital system | 5 (3.2%) | 6 (3.8%) | 7 (4.6%) | 18 (3.9%) |
| Antibacterial for systemic use | 5 (3.2%) | 8 (5.1%) | 4 (2.6%) | 17 (3.7%) |
| Analgesics | 2 (1.3%) | 6 (3.8%) | 1 (0.7%) | 9 (1.9%) |
| Beta blocking agents | 4 (2.6%) | 3 (1.9%) | 2 (1.3%) | 9 (1.9%) |
| Antihistamines for systemic use | 0 | 0 | 3 (2.0%) | 3 (0.6%) |

*Table modified from NDA 208945 Section 5.3.5.1 P-110880-01 Study Report Table 17*

Around ¼ of patients in all treatment arms took at least 1 concomitant medication. There were an increased number of patients in the placebo arm that utilized topical mupirocin and systemic antibiotics which may reflect a decreased efficacy of placebo and decision to provide additional treatment. These patients were appropriately considered treatment failures by the study criteria.

#### 6.1.2.8. Efficacy Results – Primary Endpoint

**Table 6.13 Primary Efficacy Endpoint: Clinical Response at Visit 3 (P-110880-01) - ITTC Population**

| | Ozenoxacin (N = 155) | Placebo (N = 156) | Retapamulin (N = 154) |
|---|---|---|---|
| **Clinical Success, N (%)** | 54 (34.8%) | 30 (19.2%) | 58 (37.7%) |
| **Clinical Failure, N (%)** | 98 (63.2%) | 120 (76.9%) | 91 (59.1%) |
| **Unable to determine, N (%)** | 3 (1.9%) | 6 (3.8%) | 5 (3.2%) |
| **Difference in success rates** | 0.155 | | 0.189 |
| **95% CI** | 0.056-0.255 | | 0.088 – 0.290 |
| **p-value** | 0.003 | | <0.001 |

*Table adapted from NDA 208945 Section 5.3.5.1 P-110880-01 Study Report Table 19*

The primary efficacy result shows greater clinical success at end of therapy visit 3 in the treatment arm versus placebo. The absolute value of the difference is relatively small (0.155) but is felt to be clinically significant. Additionally, while the clinical success rate of ozenoxacin was low, it was comparable to retapamulin (34.8% vs. 37.7%, respectively), a previously approved topical medication for impetigo included for internal validity.

#### 6.1.2.9. Data Quality and Integrity – Reviewer's Assessment

A random selection of 10% of the case report forms was requested from the sponsor and provided to the FDA. A review of these case report forms was consistent with prior information provided in the electronic submission of the application and documented elsewhere throughout this review.

#### 6.1.2.10. Efficacy Results – Secondary and other relevant endpoints

**Table 6.14 Clinical Response at Visit 3 (P-110880-01) by Pathogen - ITTB Population**

| | ***Staphylococcus aureus*** | | ***Streptococcus pyogenes*** | |
|---|---|---|---|---|
| | **Ozenoxacin (N=93)** | **Placebo (N=94)** | **Ozenoxacin (N=72)** | **Placebo (N=66)** |
| **Cure, N (%)** | 35 (37.6%) | 16 (17.0%) | 29 (40.3%) | 7 (10.6%) |
| **Improvement, N (%)** | 57 (61.3%) | 72 (76.65) | 42 (58.3%) | 54 (81.8%) |
| **Failure, N (%)** | 1 (1.1%) | 1 (1.1%) | 1 (1.4%) | 1 (1.5%) |
| **Unable to determine, N (%)** | 0 | 5 (5.3%) | 0 | 4 (6.0%) |

Within the ITTB population at Visit 3, the ozenoxacin treatment group had greater rates of cure relative to the placebo groups for both *S. aureus* and *S. pyogenes*, the two primary bacterial etiologies for impetigo. The placebo groups were associated with an increased rate of patients categorized as "unable to determine" at Visit 3, but even when these patients are considered cures (worst case analysis), the ozenoxacin group achieved cure rates about 1.5 times to 2.5 times those for placebo for *S. aureus* and *S. pyogenes*, respectively.. The overall patient population with culture confirmed *S. aureus* and *S. pyogenes* is small, but the available data

suggests ozenoxacin is associated with clinically significant increased rates of cure over placebo in these patients.

**Table 6.15 Secondary Efficacy Endpoint: Clinical Response at Visit 3 (End of Therapy) - PPC Population**

| | Ozenoxacin (N = 134) | Placebo (N = 132) |
|---|---|---|
| **Clinical Success, N (%)** | 46 (34.3%) | 22 (16.7%) |
| **Clinical Failure, N (%)** | 88 (65.7%) | 109 (82.6%) |
| **Unable to determine, N (%)** | 0 | 1 (0.8%) |
| **Difference in success rates** | 0.175 | |
| **95% CI** | 0.073 – 0.278 | |
| **p-value** | 0.001 | |

*Table adapted from NDA 208945 Section 14 Table 14.2.2.1.2*

The clinical response at end of therapy in the per-protocol population is similar in direction and magnitude to the primary clinical endpoint in the intention-to-treat population. The larger difference in success rates is due to a reduced efficacy of the placebo arm in this analysis.

**Table 6.16 Derived Clinical Response at Visit 4 (Post-Therapy) -- ITTC Population**

| | Ozenoxacin (N = 155) | Placebo (N = 156) |
|---|---|---|
| **Clinical Success, N (%)** | 48 (31.0%) | 26 (16.7%) |
| **Clinical Post-Therapy Cure, N (%)** | 34 (21.9%) | 37 (23.7%) |
| **Clinical Unchanged, N (%)** | 3 (1.9%) | 2 (1.3%) |
| **Clinical Relapse, N (%)** | 1 (0.6%) | 2 (1.3%) |
| **Clinical Failure, N (%)** | 64 (41.3%) | 82 (52.6%) |
| **Unable to determine, N (%)** | 5 (3.2%) | 7 (4.5%) |
| **Clinical Cumulative Success[1], N (%)** | 82 (52.9%) | 63 (40.4%) |
| **No Clinical Cumulative Success[1], N (%)** | 73 (47.1%) | 93 (59.6%) |
| **Difference in success rates** | 0.125 | |
| **95% CI** | 0.015 – 0.235 | |
| **p-value** | 0.027 | |

*Table adapted from NDA 208945 Section 5.3.5.1 P-110880-01 Study Report Table 22*
[1]Only cumulative success and no clinical cumulative success were used for difference in success rates, confidence intervals and p-value calculations. Clinical cumulative success = "Clinical success" or "Clinical post-therapy cure."

When looking at subjects at visit 4 (post-therapy visit occurring 5-8 days after completion of treatment), the difference between the placebo and treatment arms continues to favor a successful clinical response in the ozenoxacin group, but the absolute value of the difference declines and is no longer statistically significant. This trend likely reflects the self-limiting nature of impetigo.

**Table 6.17 Derived Clinical Response at Visit 2 -- ITTC Population**

| | Ozenoxacin (N = 155) | Placebo (N = 156) |
|---|---|---|
| **Clinical Improvement, N (%)** | 147 (94.8%) | 146 (93.6%) |
| **No Clinical Improvement, N (%)** | 5 (3.2%) | 7 (4.5%) |
| **Unable to determine, N (%)** | 3 (1.9%) | 3 (1.9%) |
| **Difference in success rates** | 0.013 | |
| **95% CI** | -0.031 – 0.056 | |
| **p-value** | 0.564 | |

*Table adapted from NDA 208945 Section 5.3.5.1 P-110880-01 Study Report Table 21*

There appears to be no statistically or clinically relevant difference in treatment response by the time of the second visit in the study (day 3-4 on therapy) based on the criteria outline previously. The majority of patients in both arms (94.2%) showed improvement suggesting the natural course of impetigo is improvement over this time period independent of treatment with ozenoxacin.

**Dose/Dose Response**

Not-applicable

**Durability of Response**

Not-applicable

**Persistence of Effect**

Not-applicable

**Additional Analyses Conducted on the Individual Trial**

Not-applicable

## 6.2. Study P-110881-01

### 6.2.1. Study Design

#### 6.2.1.1. Overview and Objective

*A Phase 3, 2 Arms, Multicenter, Randomized, Double-Blind Study to Assess the Efficacy and Safety of Ozenoxacin 1% cream Applied Twice Daily for 5 Days versus Placebo in the Treatment of Patients with Impetigo*

The primary objective of Study P-110881-01 was to compare the efficacy of a twice daily topical application for 5 days (10 total doses) of an ozenoxacin 1% cream versus placebo in patients

with impetigo. The results of this study are analyzed together with a comparable study (P-110880-01) discussed in Section 6.1. Please see Section 7 regarding the integrated analysis of efficacy.

#### 6.2.1.2. Trial Design

This study was a global Phase 3, multicenter, randomized, placebo-controlled, parallel, double-blind, clinical study to compare efficacy and safety of ozenoxacin cream versus placebo in patients with a clinical diagnosis of non-bullous and bullous impetigo. Unlike study P-110880-01, this study did not include a third treatment arm for retapamulin 1% ointment as an internal validity assessment.

The study planned to include 412 patients with impetigo, including at least 226 patients from 2 months to <12 years and at least 20 patients from 12 to <18 years. In total, 44 sites in 6 countries were initiated and 34 sites recruited patients. Patients were enrolled at sites in Germany, USA (including sites in Puerto Rico), Romania, Russia, South Africa, and Spain. First enrollment began June 2, 2014, and last patient visits occurred on May 30, 2015 (study duration of approximately 12 months).

The inclusion and exclusion criteria for study P-110881-01 are identical to those listed in Section 6.1.1.2 for its sister pivotal study with two exceptions. First, a patient in P-110881-01 required a SIRS score of at least 3 rather than 8 in the previous study. This difference is based on changes to the SIRS criteria definition documented in Table 6.18. Second, the affected area calculated was required to be between 2-100 $cm^2$ (changed from 1-100 $cm^2$ in P-110880-01).

The two pivotal studies of ozenoxacin 1% cream utilized near-identical study design regarding randomization, treatment administration and dosing, concomitant medications, compliance, and blinding. Please see Section 6.1.1.2 for a detailed explanation with the following differences in study P-110881-01:

- With only two treatment arms instead of three, patients were randomized 1:1 between ozenoxacin and placebo with double-blinding (patient and investigator) for both arms.
- The schedule of events and timing for assessments is described in Table 6.2. However, study P-110880-01 did not collect blood or urine samples from patients as part of the study (except for pregnancy testing).
- Treatment with analgesics, anti-inflammatory, antihistaminic or other treatment that in the Investigator's opinion could confound the evaluation of the SIRS symptoms was added as an explicit prohibited concomitant medication.

The two pivotal studies utilize the same criteria for patient withdrawal from study or discontinuation of study treatments (see Section 6.1.1.2).

#### 6.2.1.3. Study Endpoints

As with Study P-110880-01, the primary efficacy endpoint was a clinical response (success or failure) at end of therapy (Visit 3) in the intent-to-treat clinical (ITTC) population.

The secondary endpoints of studies P-110880-01 and P-110881-01 are largely identical (see Section 6.1.1.3) except for some additional new endpoints including:

- Clinical response (clinical success or clinical failure) at Visit 3 in the ITTC, PPC, PPB, and ITTB populations with a combined criterion of clinical success: 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.
- Clinical and microbiological response at Visits 2-4 in patients with *Staphylococcus aureus* and *Streptococcus pyogenes* co-infection in the ITTB and PPB populations.
- Use of additional antimicrobial therapy at Visits 2 and 3 in the ITTC, PPC, ITTB, and PPB populations.
- Number of new lesions and area of new lesions at Visit 2 and 3 in the ITTC, PPC, ITTB, and PPB populations.

Throughout Study P-110881-01 and the related pivotal Study P-110880-01, there is use of the Skin Infection Rating Scale (SIRS) to assess the clinical severity of a case of impetigo. This definition was used to define clinical response and change during the studies. The scale utilizes five (or seven in the prior study) signs or symptoms to define a numerical rating scale as shown in
Table 6.4 and Table 6.18.

**Table 6.18 Skin Infection Rating Scale (Study P-110881-01)**

| Signs/Symptom | Score | Definition |
|---|---|---|
| Blistering | 0 = Absent | No evidence of blisters |
| | 1= Mild | Few raised vesicles present on close evaluation |
| | 2 = Moderate | Fluid filled vesicles are obvious and are bothersome to the patient |
| | 3 = Severe | Extensive area covered with many vesicles which may include large bullous vesicles |
| Exudate/Pus | 0 = Absent | No evidence of exudates or pus |
| | 1 = Mild | Small amounts of fluid/pus coming from the lesions |
| | 2 = Moderate | Exudate/pus infected area is moderate |
| | 3 = Severe | Extensive areas infected and there is draining exudates |
| Crusting | 0 = Absent | No evidence of crusting |
| | 1 = Mild | A few areas have some evidence of crusting lesions |
| | 2 = Moderate | Crusting is present throughout the infected area |

| | | |
|---|---|---|
| | 3 = Severe | Thick crusting appears over the entire impetiginous area |
| Erythema/Inflammation | 0 = Absent | Skin tone and color are normal; no signs of erythema or inflammation |
| | 1 = Mild | Skin is pink with minimal signs of inflammation |
| | 2 = Moderate | Skin is red with definite sings of inflammation |
| | 3 = Severe | Skin is red and severe inflammation is present |
| Itching/Pain<br>(Adult patients and pediatric patients able to self-report) | 0 = Absent | No signs of itching or indication of pain |
| | 1 = Mild | Some evidence of scratching or rubbing the area is evident and patient reports minor discomfort |
| | 2 = Moderate | Evidence of scratching and patient reports bothersome<br><br>painful lesions |
| | 3 = Severe | Evidence of extensive scratching and patient reports pain that interferes with daily activities or sleep |
| Itching/Pain<br>(Pediatric Patients not able to self-report) | 0 = Absent | No signs of itching or indication of pain; Normal behavior |
| | 1 = Mild | Some evidence of scratching and the patient is crying more than usual with no effect on normal activity/behavior |
| | 2 = Moderate | Evidence of scratching and the patient is crying more than usual and interference with normal activity/behavior |
| | 3 = Severe | Evidence of extensive scratching and the patient is crying and cannot be comforted and prevents normal activity/behavior and/or sleep |

*Table adapted from NDA 208945 Section 9.5.3.4 P-110881-01 Study Report*

The SIRSs utilized in the two pivotal studies (P-110880-01 and P-110881-01) differ. In particular, categories of tissue edema and tissue warmth are included explicitly in the SIRS for P-110880-01 but not in P-110881-01. The opposite is true for the category of blistering included only in P-110881-01. While these two scales would be expected to overlap greatly in their trends to assess impetigo severity, some difference would be expected and difficult to predict.

The following Table 6.19 through Table 6.21 discuss the definitions for clinical assessments for study P-110881-01 which differ slightly from those utilized in P-110880-01 (see Table 6.5. through Table 6.7). Please see Section 13.3 for microbiological assessment definitions which remained consistent between the two studies.

**Table 6.19 Clinical Assessment at Visit 2 – Definitions (P-110881-01)**

| Classification / Category | Definition |
|---|---|
| Early Cure | Sufficient improvement defined as:<br>• Total SIRS score decreased >10% compared to Baseline (Visit 1)<br>This was such that according to the Investigator criteria no further antimicrobial therapy could be necessary.<br>The patient continued treatment with study drug. |
| Improvement | Some degree of improvement defined as:<br>• Total SIRS score decreased >10% compared to Baseline (Visit 1)<br>The patient continued treatment with study drug. |

| | |
|---|---|
| No Improvement | • No change in total SIRS score<br>OR<br>• Total SIRS score increased compared to Baseline (Visit 1)<br>OR<br>• Totals SIRS score decreased ≤10% compared to Baseline.<br>The patient could continue treatment with study drug or other antimicrobial therapy at the discretion of the Investigator. |

*Table adapted from NDA 208945 Section 5.5.3.2 P-110881-01 Study Report*

**Table 6.20 Clinical Assessment at Visit 3 – Definitions (P-110881-01)**

| Classification / Category | Definition |
|---|---|
| Cure / Clinical Success | • SIRS score 0 for blistering, exudates/pus, crusting, itching/pain and no more than 1 for erythema/inflammation<br>This was such that no additional antimicrobial therapy in the Baseline (Visit 1) affected area was necessary. |
| Improvement / Clinical Failure | Some degree of improvement defined as:<br>• Total SIRS score decreased >10% compared to Baseline (Visit 1) not fulfilling the criteria of individual SIRS scores for cure.<br>The patient could continue treatment with another antimicrobial therapy at the discretion of the Investigator. |
| Failure / Clinical Failure | • No change in total SIRS score<br>OR<br>• Total SIRS score increased compared to Baseline (Visit 1)<br>OR<br>• Total SIRS score decreased ≤10% compared to Baseline (Visit 1).<br>This was such that additional antimicrobial therapy in the Baseline (Visit 1) affected area was necessary. |

*Table adapted from NDA 208945 Section 5.5.3.2 P-110881-01 Study Report*

**Table 6.21 Clinical Assessment at Visit 4 – Definitions (P-110881-01)**

| Classification / Category | Definition |
|---|---|
| **Patients Classified as Cure at Visit 3** | |
| Cure / Cumulative Cure | • Total SIRS score = 0 |
| Unchange / Cumulative Cure | • Total SIRS >0 and individual SIRS score 0 for blistering, exudates/pus, crusting and itching/pain and no more than 1 for erythema/inflammation<br>This was such that no additional antimicrobial therapy in the Baseline (Visit 1) affected area was necessary |
| Relapse | • Total SIRS score >0 not fulfilling the criteria of individual SIRS scores for unchange |
| **Patients Classified as Improvement or Failure at Visit 3** | |
| Post Therapy Cure / Cumulative Cure | Patients classified as improvement at Visit 3 who, at the discretion of the Investigatory did not receive any further antimicrobial therapy, and with total SIRS = 0 at Visit 4. |
| Failure | Patients who received another antimicrobial therapy<br>OR<br>With total SIRS score >0. |

*Table adapted from NDA 208945 Section 5.5.3.2 P-110881-01 Study Report*

The most notable differences to the clinical assessment criteria between the two Phase 2 studies revolve around the change in SIRS criteria. The maximum score in Study P-110881-01 is 15 while it was 42 in Study P-110880-01. Additionally, Study P-110881-01 adds an early cure category at Visit 2 not present in the prior pivotal study.

Microbiological samples were obtained utilizing the same methods as Study P-110880-01 as described in Section 6.1.1.2. Only *S. aureus* and *S. pyogenes* alone or in combination were considered pathogens. If neither pathogen was identified at Visit 1 then the microbiological response assessment was unable to determine.

#### 6.2.1.4. Statistical Analysis Plan

There were five analysis populations defined for the study analysis:

- Intent-to-treat Clinical Population (ITTC) – defined as all randomized patients
- Per Protocol Clinical Population (PPC) – defined as all patients in the ITTC population who did not deviate from the protocol
- Intent-to-treat Bacteriological Population (ITTB) – defined as all randomized patients who had a pathogen (*S. aureus* or *S. pyogenes*) identified at study entry
- Per Protocol Bacteriological Population (PPB) – defined as all patients in the ITTB population who did not deviate from the protocol
- Safety Population – defined as all patients who had at least one application of study drug (discussed in detail in the safety analysis in Section 8)

As with the prior pivotal study (P-1108801-01) the primary efficacy analysis was based on the ITTC population and secondary analyses were performed based upon the PPC, ITTB, and PPB populations to assess the sensitivity of the analysis to the choice of analysis population. The main analysis of the secondary endpoints (with the exception of microbiological response) was based upon the ITTC population, with sensitivity analyses based on the PPC, ITTB, and PPB populations. For microbiological response the main analysis was based on the ITTB population, with sensitivity analysis that was based on the PPB population.

Summary statistics were presented for continuous variables; by way of number of patients with an observation (n), mean, standard deviation (SD), median, minimum and maximum, and by way of group frequencies and percentages for categories of categorical variables. All data were summarized for each treatment (ozenoxacin and placebo) using descriptive statistics. All statistical tests were two-sided and were performed using a 5% significance level and 95% confidence intervals (CI) were provided.

**Sample Size Determination**

A 2-group $\chi^2$ test with a 5% 2-sided significance level had 90% power to detect a difference of

15% in proportions at Visit 3 with the assumption that the clinical success rate in the ozenoxacin group was 35% when the sample size was 185 for each group. Under the assumption of a 10% dropout rate, 206 patients for each group were required to achieve 90% power at 5% 2-sided significance level. A total of 412 patients were to be enrolled to ensure 90% power to reject the null hypothesis of no difference.

**Primary Analysis**

Clinical response classification (clinical success, clinical failure, and unable to determine) at end of therapy (Visit 3) was summarized by treatment for the ITTC population.

When an early termination visit was performed instead of Visit 3 and this early termination visit was performed after the telephone call then the results collected at the early termination visit were used for the analysis.

The treatment comparisons were done using the outcomes of clinical success and clinical failure. The p-value of the chi-square test (without continuity correction) and corresponding 95% asymptotic (Wald) CI for the difference in success rates for the ozenoxacin versus placebo were provided. The analysis was performed to test the superiority of ozenoxacin versus placebo.

Sensitivity analyses were performed using the ITTC population on the endpoint of clinical response at the end of therapy visit (Visit 3) and these analyses evaluated the sensitivity of the results to missing data. In a first sensitivity analysis, missing responses (Unable to determine) were imputed as clinical failures. A second sensitivity analysis was performed where missing responses were imputed by using the Monotone Logistic Regression (MLR) method. A third sensitivity analysis was performed where missing responses (unable to determine) were imputed using the worst case approach (i.e., ozenoxacin as clinical failure and placebo as clinical success). Please refer to the statistical review for additional details.

**Secondary Analysis**

The study pursued multiple secondary endpoints as detailed previously. The majority of these secondary endpoints are identical to those detailed in Section 6.1.1.3 for study P-110880-01 with changes/additions as previously noted.

**Exploratory Analysis**

The primary endpoint of clinical response at end of therapy visit (Visit 3) was summarized for the ITTC population by category levels for each of the following covariates: clinical diagnosis of impetigo (bullous, non-bullous), number of affected areas (1 area, 2–4 areas, 5-10 areas, >10

areas), total area (≥2 $cm^2$ to <10 $cm^2$, ≥10 $cm^2$ to <50 $cm^2$ and, ≥50 $cm^2$ to 100 $cm^2$), Baseline SIRS total score (3-9, 10-15), age (≥2 months to <12 years old, ≥12 years to <18 years old, ≥18 years old), race (Caucasian, Black, Asian, Native American, Pacific Islander, Mixed Race, Other), country (per country), and treatment compliance (<80%, 80%-120%, >120%). The difference in success rates between the ozenoxacin and placebo groups, together with the corresponding 95% CI, was reported for each category level for each Baseline characteristic. Please refer to the statistical review for additional details.

#### 6.2.1.5. Protocol Amendments

There were 3 local protocol amendments to the final protocol. Two of the amendments addressed age-based inclusion criteria: the inclusion age of patients in Germany was amended to be ≥10 years of age and the inclusion age of patients in South Africa was amended to be ≥6 months of age. The last amendment included HIV testing for patients recruited in South Africa and the exclusion of patients with positive testing.

Additional modifications of importance to the original study protocol include: addition of an "early cure" category to Visit 2 along with its analysis, "clinical failure" category added to clinical response at Visits 3 and 4 to perform treatment comparison, and the number of new lesions and area of these new lesions at Visits 2 and 3 was replaced by the number of patient with new lesions when performing analysis of treatment groups.

The amendments/modifications to the study protocol and statistical plan are not felt to have a significant impact on the integrity of the trial or interpretation of the results.

#### 6.2.1.6. Data Quality and Integrity: Sponsor's Assurance

The following steps, visits, and procedures were conducted by the sponsor to ensure accurate, consistent and complete data collection and quality assurance: (1) site selection visits, (2) standardized study procedures based on the clinical study protocol and statistical analysis plan, (3) trained clinical monitors provided instructions to study site participants during a study initiation visit, (4) clinical monitors had access to all source documents and independent clinical quality assurance audits available at any time, (5) a central laboratory was utilized geographic area, (6)electronic case report forms (eCRF) utilized for consistent data collection, (7) quality control and data validation procedures applied to the clinical database.

The applicant's stated data quality assurance methods appear appropriate and consistent with expected standards. Additionally, the applicant provided audit certificates for all audits performed during the study.

### 6.2.2. Study Results

#### 6.2.2.1. Compliance with Good Clinical Practices

The applicant reports this study was conducted in accordance with International Conference on Harmonization (ICH) of Good Clinical Practice (GCP), the principles of the Declaration of Helsinki (Helsinki, 1964), all applicable amendments laid down by the World Medical Assemblies, and all other local and national laws and regulations.

Written consent was a mandatory condition to participate in the study and was obtained from patients, parents, or legal guardians prior to any study-specific procedure. Sample consent forms where included in the application.

#### 6.2.2.2. Financial Disclosure

Ferrer Internacional, S.A. has determined there were no financial interests or arrangements to disclose from the investigators in clinical study P-110881-01. Please see Section 0 for Clinical Investigator Financial Disclosures.

#### 6.2.2.3. Patient Disposition

**Table 6.22 Patient Disposition (P-110881-01)**

| | **Ozenoxacin N (%)** | **Placebo N (%)** | **Overall N (%)** |
|---|---|---|---|
| **Screened** | | | 420 |
| **Randomized** | 206 | 206 | 412 |
| **Safety Population** | 206 (100.0%) | 205 (99.5%) | 411 (99.8%) |
| **ITTC Population** | 206 (100.0%) | 206 (100.0%) | 412 (100.0%) |
| **PPC Population** | 195 (94.7%) | 195 (94.7%) | 390 (94.7%) |
| **ITTB Population** | 125 (60.7%) | 119 (57.8%) | 244 (59.2%) |
| **PPB Population** | 119 (57.8%) | 112 (54.4%) | 231 (56.1%) |
| **Prematurely Discontinued Study Treatment** | | | |
| Yes | 4 (1.9%) | 20 (9.7%) | 24 (5.8%) |
| No | 202 (98.1%) | 186 (90.3%) | 388 (94.2%) |
| **Reason for Discontinuation of Study Treatment** | | | |
| Pregnancy | 0 | 0 | 0 |
| Study Related AE | 1 (25.0%) | 1 (5.0%) | 2 (8.3%) |
| Lack of Response | 0 | 10 (50.0%) | 10 (41.7%) |
| Withdrawal of Consent | 2 (50.0%) | 1 (5.0%) | 3 (12.5%) |
| Development of Intercurrent Illness, Condition or Procedural Complication | 0 | 2 (10.0%) | 2 (8.3%) |
| Medically Best Interest of the Patient in the Opinion of the Investigator | 0 | 4 (20.0%) | 4 (16.7%) |
| Lost to follow-up | 1 (25.0%) | 2 (10.0%) | 3 (12.5%) |

| | | | |
|---|---|---|---|
| **Completed the Study** | | | |
| Yes | 200 (97.1%) | 186 (90.3%) | 386 (93.7%) |
| No | 6 (2.9%) | 20 (9.7%) | 26 (6.3%) |
| **Reason for Early Discontinuation from Study Post-randomization** | | | |
| Adverse Event | 1 (16.7%) | 3 (15.0%) | 4 (15.4%) |
| Lost to Follow-Up | 2 (33.3%) | 2 (10.0%) | 4 (15.4%) |
| Withdrawal of Consent | 2 (33.3%) | 1 (5.0%) | 3 (11.5%) |
| Worsening Patient Condition | 0 | 13 (65.0%) | 13 (50.0%) |
| Death | 0 | 0 | 0 |
| Screening Failure | 0 | 0 | 0 |
| Trouble Making Appointments | 1 (16.7%) | 0 | 1 (3.8%) |
| No improvement | 0 | 1 (5.0%) | 1 (3.8%) |
| **Excluded from Per Protocol Populations** | | | |
| Yes | 11 | 11 | 22 |
| No | 195 | 194 | 189 |
| **Reason for Exclusion from Per Protocol** | | | |
| Deviation from visit schedule | 5 (45.5%) | 5[ab] (45.5%) | 10[ab] (45.5%) |
| Prohibited medication | 5 (45.5%) | 4[b] (45.5%) | 9[b] (40.9%) |
| Violation of lesion size inclusion criteria | 1 (9.0%) | 1 (9.0%) | 2 (9.1%) |
| Concurrent Illness | 0 | 1[a] (9.0%) | 1[a] (4.5%) |
| Improper Storage | 0 | 1 (9.0%) | 1 (4.5%) |
| Withdrawal of Consent | 0 | 1 (9.0%) | 1 (4.5%) |

*Table adapted from NDA 208945 Section 5.3.5.1 P-110881-01 Study Report Table 10-1*
[a] single patient excluded for both concurrent illness and deviation from visit schedule
[b] single patient excluded for both prohibited medication and deviation from visit schedule

The study met the goal subject numbers based on the statistical analysis plan. A relatively small number of subjects were either discontinued from the study or were excluded from the per protocol analysis – reasons for these exclusions and violations are discussed in Section 6.2.2.4. Numbers of subjects excluded/discontinued were similar in different treatment arms and are not expected to skew analysis.

#### 6.2.2.4. Protocol Violations/Deviations

As noted in Table 6.22, 26 patients did not complete the study and ultimately 22 were excluded from the PPB and PPC populations due to protocol deviations (representing 5.3% of the total randomized patient population). All protocol violations were reviewed during the Blinded Data Review Meeting and decisions made for exclusion before unblinding.

- The most common reason for exclusion from the per-protocol analysis was a delay in Visit 3 by >1 day which may have impacted the primary efficacy endpoint (10 patients).

- Nine patients took medications on the prohibited medication lists. Of these, four were started on additional antibiotics per the discretion of the investigator: ciprofloxacin for worsening impetigo (ozenoxacin arm), bacitracin for worsening impetigo (placebo arm),

clindamycin for worsening impetigo (placebo arm), and azithromycin for pneumonia (ozenoxacin arm). Five patients received prohibited medications (loratadine, cetirizine, doxepine, Nyquil™, diphenhydramine).

- One patient from each arm had a single case where lesions were measured as an overall involved area and not calculated per protocol leading to areas >100cm$^2$ and were excluded from PPB and PPC populations.

- One patient withdrew consent prior to receiving any study medications on day 1 of the study and was excluded from PPC and PPB populations.

- One patient was given a tube of placebo cream that was stored improperly (temperature range of refrigerator too wide) and was excluded from PPC and PPB populations.

The major deviations in the visit schedule and prohibited medications appear to be equally distributed between treatment arms and sites and are sufficiently rare to be unlikely to affect outcomes. Since impetigo is often self-limiting, excluding patients that were late to assessments by >1 day is reasonable to avoid a bias towards better clinical outcomes for all treatment arms. Additional types of deviation were rare and unlikely to have significant impact on the study analysis.

#### 6.2.2.5. Demographic Characteristics

**Table 6.23 Demographics (P-110881-01)**

| | **Ozenoxacin (N = 206)** | **Placebo (N = 205)** | **Overall (N = 411)** |
|---|---|---|---|
| **Age (years)** | | | |
| Mean (SD) | 18.71 (18.139) | 18.54 (18.628) | 18.63 (18.362) |
| Min, Max | 0.3, 79.6 | 0.2, 80.0 | 0.2, 80.0 |
| **Age group, N (%)** | | | |
| ≥2 months to <12 years | 114 (55.3%) | 112 (54.6%) | 226 (55.0%) |
| 12 to <18 years | 23 (11.2%) | 23 (11.2%) | 46 (11.2%) |
| ≥18 years | 69 (33.5%) | 70 (34.1%) | 139 (33.8%) |
| **Gender, N (%)** | | | |
| Male | 112 (54.4%) | 98 (47.8%) | 210 (51.1%) |
| Female | 94 (45.6%) | 107 (52.2%) | 201 (48.9%) |
| **Predominant Race, N (%)** | | | |
| Caucasian | 122 (59.2%) | 139 (67.8%) | 261 (63.5%) |
| Black | 53 (25.7%) | 38 (18.5%) | 91 (22.1%) |
| Asian | 16 (7.8%) | 15 (7.3%) | 31 (7.5%) |
| Mixed Race | 15 (7.3%) | 13 (6.3%) | 28 (6.8%) |
| **Geographic Location, N (%)** | | | |
| USA | 65 (31.6%) | 74 (36.1%) | 149 (36.3%) |
| South Africa | 43 (20.9%) | 34 (16.6%) | 77 (18.7%) |

| | | | |
|---|---|---|---|
| Russia | 27 (13.1%) | 30 (14.6%) | 57 (13.9%) |
| Romania | 26 (12.6%) | 26 (12.7%) | 52 (12.7%) |
| Puerto Rico | 23 (11.2%) | 23 (11.2%) | 46 (11.2%) |
| Germany | 21 (10.2%) | 16 (7.8%) | 37 (9.0%) |
| Spain | 1 (0.5%) | 2 (1.0%) | 3 (0.7%) |
| **Ethnicity, N (%)** | | | |
| Hispanic or Latino | 57 (27.7%) | 62 (30.2%) | 119 (29.0%) |
| Not Hispanic or Latino | 148 (71.8%) | 142 (69.3%) | 290 (70.6%) |
| Other | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| **Weight (kg)** | | | |
| Mean (SD) | 47.31 (28.86) | 45.59 (28.07) | 46.45 (28.49) |
| **Body Surface Area ($m^2$)** | | | |
| Mean (SD) | 1.32 (0.57) | 1.29 (0.53) | 1.30 (0.55) |

*Table adapted from NDA 208945 Section 5.3.5.1 P-110881-01 Study Report Table 10-2*

The documented characteristics are generally evenly distributed between the two study arms suggestive of proper randomization and assignment of patients during the study. The population is skewed towards the younger age ranges (i.e., >2 months - <12 years old) paralleling the ages typically afflicted with impetigo. The study includes patients >2 months - <2 years of age unlike the other pivotal study, P-110880-01. P-110880-01 also had concerns for lack of domestic patient enrollment, and the increased number of United States and Puerto Rican patients in P-110881-01 reflects discussions with the FDA to improve the ability of the study results to generalize to a US domestic population. The overall racial and ethnic distribution is likely a closer approximation of the United States population than prior studies as a result. However, it should be noted that South Africa continues to be a large contributor in both pivotal studies.

#### 6.2.2.6. Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

**Table 6.24 Baseline Characteristics (P-110881-01)**

| | Ozenoxacin (N = 206) | Placebo (N = 205) | Overall (N = 411) |
|---|---|---|---|
| **Type of Impetigo, N (%)** | | | |
| Bullous | 25 (12.1%) | 33 (16.1%) | 58 (14.1%) |
| Non-bullous | 181 (87.9%) | 172 (83.9%) | 353 (85.9%) |
| **Number of Affected Areas** | | | |
| Mean (SD) | 2.6 (2.2) | 2.5 (2.2) | 2.5 (2.2) |
| Min, Max | 1, 19 | 1, 16 | 1, 19 |
| 1 | 78 (37.9%) | 89 (43.4%) | 167 (40.6%) |
| 2 – 4 | 104 (50.5%) | 85 (41.5%) | 189 (46.0%) |
| 5 – 10 | 21 (10.2%) | 27 (13.2%) | 48 (11.7%) |
| >10 | 2 (1.0%) | 3 (1.5%) | 5 (1.2%) |
| Missing | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| **Location, N (%)** | | | |
| Face | 113 (54.9%) | 104 (50.7%) | 217 (52.8%) |

| | | | |
|---|---|---|---|
| Upper Trunk | 27 (13.1%) | 20 (9.8%) | 47 (11.4%) |
| Lower Trunk | 19 (9.2%) | 26 (12.7%) | 45 (10.9%) |
| Right Arm | 33 (16.0%) | 39 (19.0%) | 72 (17.5%) |
| Left Arm | 23 (11.2%) | 21 (10.2%) | 44 (10.7%) |
| Right Leg | 28 (13.6%) | 32 (15.6%) | 60 (14.6%) |
| Left Leg | 27 (13.1%) | 31 (15.1%) | 58 (14.1%) |
| **Total Affected Area ($cm^2$)** | | | |
| Mean (SD) | 10.29 (13.04) | 8.84 (8.12) | 9.56 (10.88) |
| Min, Max | 2.0, 96.0 | 2.0, 48.0 | 2.0, 96.0 |
| ≥2 $cm^2$ to <10 $cm^2$ | 141 (68.4%) | 144 (70.2%) | 285 (69.3%) |
| ≥10 $cm^2$ to <50 $cm^2$ | 58 (28.2%) | 60 (29.3%) | 118 (28.7%) |
| ≥50 $cm^2$ to <100 $cm^2$ | 6 (2.9%) | 0 | 6 (1.5%) |
| Missing | 1 (0.5%) | 1 (0.5%) | 2 (0.5%) |
| % of BSA Mean (SD) | 0.095 (0.148) | 0.074 (0.062) | 0.084 (0.114) |
| **SIRS Total Score** | | | |
| Mean (SD) | 7.6 (2.2) | 7.6 (2.3) | 7.6 (2.3) |
| Min, Max | 4, 14 | 3, 15 | 3, 15 |
| **Pathogens Isolated, N (%)** | | | |
| *Staphylococcus aureus* | 115 (55.8%) | 108 (52.7%) | 223 (54.3%) |
| *Streptococcus pyogenes* | 19 (9.2%) | 20 (9.8%) | 39 (9.5%) |
| Other Pathogens | 79 (38.3%) | 68 (33.2%) | 147 (35.8%) |

*Table adapted from NDA 208945 Section 5.3.5.1 P-110881-01 Study Report Table 10-3*

The two treatment arms had similar lesion characteristics including type, size, number, and location. The tendency of the study lesions to be relatively small (<10 $cm^2$) and fewer in number (<4) is consistent with the planned treatment population that would receive a topical agent only for impetigo. About a third of the isolated "pathogens" were categorized as "other pathogens" including Staphylococcus epidermidis and are likely contaminants and not true pathogens in this otherwise healthy patient population.

#### 6.2.2.7. Treatment Compliance, Concomitant Medications, and Rescue Medication Use

**Table 6.25 Treatment Compliance (P-110881-01) Safety Population**

| | **Ozenoxacin (N = 206)** | **Placebo (N = 205)** |
|---|---|---|
| **Mean (SD)** | 99.9 (11.9) | 95.6 (17.4) |
| **Min, Max** | 10, 120 | 10, 120 |
| **<80%** | 4 (1.9%) | 18 (8.8%) |
| **80 – 120%** | 202 (98.1%) | 187 (91.2%) |
| **>120%** | 0 | 0 |

*Table adapted from NDA 208945 Section 14.1 Table 14.1.6*

There was good treatment compliance documented throughout the study in both arms of treatment. This likely reflects the short duration and ease of use of a topical agent for impetigo.

However, it should be noted that treatment compliance was lower in placebo arm. Poor compliers were included in all intentional to treat populations for primary endpoint analysis.

**Table 6.26 Concomitant Medications (P-110881-01) Safety Population**

| ATC Level 2<br>Preferred Term, N (%) | Ozenoxacin<br>(N = 206) | Placebo<br>(N = 205) | Overall<br>(N = 411) |
|---|---|---|---|
| **Patients with at least 1 concomitant medication** | 55 (26.7%) | 73 (35.6%) | 128 (31.1%) |
| Antibiotics and chemotherapeutics for dermatologic | 17 (8.3%) | 35 (17.1%) | 52 (12.7%) |
| Mupirocin | 9 (4.4%) | 17 (8.3%) | 26 (6.3%) |
| Fusidic Acid | 4 (1.9%) | 12 (5.9%) | 16 (3.9%) |
| Chloramphenicol | 2 (1.0%) | 3 (1.5%) | 5 (1.2%) |
| Nebacetin/Neomycin/Bacitracin | 2 (1.0%) | 2 (1.0%) | 4 (1.0%) |
| Sex hormones and modulators of the genital system | 7 (3.4%) | 12 (5.9%) | 19 (4.6%) |
| Antibacterial for systemic use | 10 (4.9%) | 22 (10.7%) | 32 (7.8%) |
| Topical corticosteroids | 4 (1.9%) | 6 (2.9%) | 10 (2.4%) |
| Analgesics | 4 (1.9%) | 0 | 4 (1.0%) |
| Beta blocking agents | 4 (1.9%) | 0 | 4 (1.0%) |
| Antihistamines for systemic use | 2 (1.0%) | 3 (1.5%) | 5 (1.2%) |

*Table adapted from NDA 208945 Section 14.1 Table 14.1.5.2*

Around 1/3 of patients took at least 1 concomitant medication. There were an increased number of patients in the placebo arm that utilized topical mupirocin, topical fusidic acid, and systemic antibiotics which may reflect a decreased efficacy of placebo and decision to provide additional treatment. These patients were appropriately categorized as treatment failures based on study clinical definitions.

#### 6.2.2.8. Efficacy Results - Primary Endpoint

**Table 6.27 Primary Efficacy Endpoint: Clinical Response at Visit 3 (P-110881-01) - ITTC Population**

| | Ozenoxacin<br>(N = 203[a]) | Placebo<br>(N = 199[a]) |
|---|---|---|
| **Clinical Success, N (%)** | 112 (55.2%) | 78 (39.2%) |
| **Clinical Failure, N (%)** | 91 (44.8%) | 121 (60.8%) |
| **Difference In Success Rates (Ozenoxacin – Placebo)** | 0.160 | |
| **95% CI** | 0.063 – 0.256 | |
| **p-value** | 0.001 | |

*Table adapted from NDA 208945 Section 5.3.5.1 P-110881-01 Study Report Table 11-2*

[a] The treatment comparison was done using only clinical success and clinical failure outcomes. 3 patients in the ozenoxacin arm and 7 patients in the placebo arm had an outcome of unable to determine and were relabeled as clinical failures above (see commentary below).

The primary efficacy result shows greater clinical success at end of therapy (Visit 3) in the treatment arm versus placebo. The absolute value of the difference is relatively small (0.16) but is felt to be clinically significant. Of note, the primary efficacy results had a sensitivity analysis performed to address the patients that were in the unable to determine category at Visit 3. When such patients in the ozenoxacin group were treated as clinical failures and such patients in the placebo group were treated as clinical successes, the trend for statistical significance of the results persisted with a difference in success rate of 0.131. This suggests that these patients are not expected to change the primary endpoint results.

Additionally, while the values for difference in success rates are similar between studies P-110880-01 and P-110881-01 (0.155 and 0.16, respectively) the overall rate of clinical success was about 20% higher in all treatment arms for P-110880-01. Given the differences in the ratings scales utilized to grade impetigo and thus determine patient clinical outcomes (noted in detail in

Table *6.4* and Table 6.18), there would be expected differences in these absolute values. It is reassuring that the differences in the success rates persist between treatment vs. placebo arm in both studies, suggesting a true drug efficacy rate.

#### 6.2.2.9. Data Quality and Integrity – Reviewer's Assessment

A random selection of 10% of the case report forms was requested from the sponsor and provided to the FDA. A review of these case report forms was consistent with prior information provided in the electronic submission of the application and documented elsewhere throughout this review.

#### 6.2.2.10. Efficacy Results - Secondary and other relevant endpoints

**Table 6.28 Clinical Response at Visit 3 (P-110881-01) by Pathogen - ITTB Population**

| | ***Staphylococcus aureus*** | | ***Streptococcus pyogenes*** | |
|---|---|---|---|---|
| | **Ozenoxacin (N=108)** | **Placebo (N=100)** | **Ozenoxacin (N=18)** | **Placebo (N=14)** |
| **Cure, N (%)** | 60 (55.6%) | 35 (35.0%) | 14 (77.8%) | 8 (57.1%) |
| **Improvement, N (%)** | 46 (42.6%) | 52 (52.0%) | 3 (16.7%) | 3 (21.4%) |
| **Failure, N (%)** | 2 (1.9%) | 9 (9.0%) | 1 (5.6%) | 2 (14.3%) |
| **Unable to determine, N (%)** | 0 | 4 (4.0%) | 0 | 1 (7.1%) |

Within the ITTB population at Visit 3, the ozenoxacin treatment group had greater rates of cure relative to the placebo groups for both *S. aureus* and *S. pyogenes*, the two primary bacterial etiologies for impetigo. The placebo groups were associated with an increased rate of patients categorized as "unable to determine" at Visit 3, but even when these patients are considered cures (worst case analysis), the ozenoxacin group achieved cure rates about 1.2 times to 1.5 times those for placebo for *S. aureus* and *S. pyogenes*, respectively. The overall patient

population with culture confirmed *S. aureus* and *S. pyogenes* is small, but the available data suggests ozenoxacin is associated with clinically significant increased rates of cure over placebo in these patients.

**Table 6.29 Clinical Response Classification at Visits 2, 3 and 4 -- ITTC Population**

| | Ozenoxacin (N = 206) | Placebo (N = 206) |
|---|---|---|
| **Visit 2** | | |
| **Early Cure, N (%)** | 26 (12.6%) | 21 (10.2%) |
| **Improvement, N (%)** | 166 (80.6%) | 152 (73.8%) |
| **No Improvement, N (%)** | 9 (4.4%) | 17 (8.3%) |
| **Unable to Determine, N (%)** | 5 (2.4%) | 16 (7.8%) |
| **Visit 3** | | |
| **Cure, N (%)** | 112 (54.4%) | 78 (37.9%) |
| **Improvement, N (%)** | 84 (40.8%) | 105 (51.0%) |
| **Failure, N (%)** | 7 (3.4%) | 16 (7.8%) |
| **Unable to Determine, N (%)** | 3 (1.5%) | 7 (3.4%) |
| **Visit 4** | | |
| **Cure, N (%)** | 104 (50.5%) | 72 (35.0%) |
| **Unchange, N (%)** | 4 (1.9%) | 3 (1.5%) |
| **Relapse, N (%)** | 3 (1.5%) | 3 (1.5%) |
| **Post-Therapy Cure, N (%)** | 51 (24.8%) | 51 (24.8%) |
| **Failure, N (%)** | 38 (18.4%) | 54 (26.2%) |
| **Unable to Determine, N (%)** | 6 (2.9%) | 23 (11.2%) |

*Table adapted from NDA 208945 Section 5.3.5.1 P-110881-01 Study Report Table 11-3*

There appears to be no statistically or clinically relevant difference in treatment response by the time of the second visit in the study (day 3-4 on therapy) based on the criteria outlined previously. The majority of patients in both arms (93.2% vs 84.0%) showed improvement or early cure suggesting the natural course of impetigo is improvement over this time period independent of treatment with ozenoxacin.

When looking at subjects at visit 4 (post-therapy visit occurring 5-8 days after completion of treatment), the difference between the placebo and treatment arms continues to favor a successful clinical response in the ozenoxacin group. However, both arms have equal rates of post-therapy cures suggesting no persistent effect of therapy after completion and reflecting the natural history of impetigo to improve spontaneously over time.

**Dose/Dose Response**

Not-applicable

**Durability of Response**

Not-applicable

**Persistence of Effect**

Not-applicable

**Additional Analyses Conducted on the Individual Trial**

Not-applicable

# 7 Integrated Review of Effectiveness

## 7.1. Assessment of Efficacy across Trials

### 7.1.1. **Primary Endpoints**

The integrated review of efficacy is performed as a direct comparison of results between the studies P-110880-01 and P-1108881-01. The primary endpoint analysis for the two pivotal studies was not pooled for this review due to significant difference in rates of clinical success between the two studies. Specific secondary endpoints are reviewed and pooled when appropriate with discussion. Both of these trials have been discussed in detail previously in Sections 6.1and 6.2. Both studies utilized the clinical response (success or failure) at end of therapy (Visit 3, day 6-7) as the primary endpoint.

In both Phase 3 studies, in order for the patient to have clinical success, the patient must have had a combination of certain clinical signs/symptoms with scores 0 or ≤1 (as specified in each study). Both studies required SIRS scores of 0 for exudates/pus and crusting, and a SIRS score of ≤1 for erythema/inflammation. Although both studies evaluated itching and pain, Study P-110880-01 required the subject to have a SIRS score of 0 for pain and a SIRS score of ≤1 for itching, whereas Study P-110881-01 required the subject to have a SIRS score of 0 for itching/pain. Finally, tissue warmth and tissue edema were evaluated only in Study P-110880-01, while blistering was evaluated in only in Study P-110881-01. The inclusion and exclusion of specific clinical signs and symptoms are summarized below in Table 7.1 Signs and Symptoms Utilized in Skin Infection Rating Scale (SIRS). See
Table 6.4 and Table 6.18 for detailed descriptions of the SIRS scale for each individual study.

**Table 7.1 Signs and Symptoms Utilized in Skin Infection Rating Scale (SIRS)**

| Sign/Symptom | Study P-110880-01 | Study P-110881-01 |
|---|---|---|
| Exudate/Pus | + | + |
| Crusting | + | + |
| Erythema/Inflammation | + | + |
| Itching | + | + (Combined) |
| Pain | + | |

| | | |
|---|---|---|
| Tissue Warmth | + | - |
| Tissue Edema | + | - |
| Blistering | - | + |

Table 7.2 provides a direct comparison of the primary endpoints for the two pivotal studies. The primary endpoint chosen, clinical improvement at 5-7 days after start of therapy is clinically relevant because a large number of cases of impetigo would be expected to improve naturally or develop complications over this time period after initial presentation. However, the natural trend of impetigo to improve in many cases without treatment is reflected in the 19.2% and 37.9% of placebo cases which were classified in the clinical success category in the two studies. Despite the self-limiting nature of many cases of impetigo, a difference in success rates of 0.160 between the treatment arms is expected to be clinically significant for patients and representative of a trend towards earlier improvement in signs/symptoms.

**Table 7.2 Clinical Response at Visit 3 (Integrated Analysis) - Primary Efficacy Endpoint (ITTC Population)**

| | **P-110880-01** | | **P-110881-01** | |
|---|---|---|---|---|
| | **Ozenoxacin 1%** | **Placebo** | **Ozenoxacin 1%** | **Placebo** |
| **N** | 155 | 156 | 206 | 206 |
| **Clinical Success, N (%)** | 54 (34.8%) | 30 (19.2%) | 112 (54.4%) | 78 (37.9%) |
| **Clinical Failure, N (%)** | 101 (65.2%) | 126 (80.8%) | 94 (45.6%) | 128 (62.1%) |
| **Difference in success rates (ozenoxacin – placebo)** | 0.156 | | 0.165 | |
| **95% CI** | 0.059 – 0.253 | | 0.070 - 0.260 | |
| **p-value** | 0.002 | | <0.001 | |

The signs/symptoms chosen to be included in both versions of the SIRS scores (see Table 7.1) provide an adequate clinical interpretation for the severity of impetigo. The differences between the two scores, notably the removal of tissue edema and tissue warmth from study P-110881-01 suggest a reason why this trial had larger absolute values for the percent of patients achieving clinical success at the primary endpoint relative to the previous trial (54.4% vs. 34.8%). The large difference the absolute value inhibits the ability to pool data effectively and requires that the study results are compared, but not combined for the primary endpoint.

However, the similar difference in success rates between ozenoxacin and placebo for both studies suggests a consistent effectiveness for ozenoxacin despite differences in how effectiveness was measured. It is suspected that by utilizing 5-6 different signs/symptoms of cellulitis for each study, a more consistent clinical trend was adequately measured. Of note, when patients were categorized as unable to determine, they were included as treatment failures in the above analysis (see Section 6.1.2.8 and Section 6.2.2.8 for more detail on the sensitivity analysis for the studies) and did not significantly affect the results.

### 7.1.2. **Secondary and Other Endpoints**

**Table 7.3 Clinical Response at Visit 3 (Pooled Analysis) by Pathogen - ITTB Population**

| | *Staphylococcus aureus* | | *Streptococcus pyogenes* | |
|---|---|---|---|---|
| | Ozenoxacin (N=201) | Placebo (N=194) | Ozenoxacin (N=90) | Placebo (N=80) |
| Cure, N (%) | 95 (47.3%) | 51 (26.3%) | 43 (47.8%) | 15 (18.8%) |
| Improvement, N (%) | 103 (51.2%) | 124 (63.9%) | 45 (50%) | 57 (71.3%) |
| Failure, N (%) | 3 (1.5%) | 10 (5.2%) | 2 (2.2%) | 3 (3.8%) |
| Unable to Determine, N (%) | 0 | 9 (4.6%) | 0 | 5 (6.3%) |

The bacteriological data was pooled in this analysis to provide improved sample sizes and is displayed in Table 7.3 based on pathogens of interest. *S. aureus* and *S. pyogenes* are the only organisms from the pivotal studies felt to represent true pathogens in impetigo present in sufficient numbers for analysis. Please refer to sections 6.1.2.10 and 6.2.2.10 for detailed discussions on individual study results.

Both *S. aureus* and *S. pyogenes* groups treated with ozenoxacin showed clear trend towards clinical improvement at Visit 3 relative to placebo (cure rates of 47.3% vs. 26.3% and 47.8% vs. 18.8%, respectively). These results mirror the clinical response seen in the overall ITTC population. It is important to recognize that the overall numbers of subjects with culture results is small (especially in the *S. pyogenes*), but the consistent trend provides evidence for effectiveness in patients affected by impetigo caused by these organisms.

**Table 7.4 Pooled Phase 3 Studies: Microbiological Response by Pathogen at Visit 2, 3 and 4 (ITTB Population)**

| | ***S. aureus*** | | ***S. pyogenes*** | |
|---|---|---|---|---|
| | **Ozenoxacin 1% Cream (N = 208)** | **Placebo Cream (N = 205)** | **Ozenoxacin 1% Cream** | **Placebo Cream** |
| **Visit 2** | | | | |
| **Eradication** | 96 (46.2%) | 33 (16.2%) | 57 (62.6%) | 24 (27.9%) |
| **Presumed Eradication** | 84 (40.4%) | 69 (33.8%) | 12 (13.2%) | 10 (11.6%) |
| **Persistence** | 24 (11.5%) | 89 (43.6%) | 22 (24.2%) | 51 (59.3%) |
| **Presumed Persistence** | 0 | 0 | 0 | 0 |
| **Superinfection** | 3 (1.4%) | 0 | 0 | 1 (1.2%) |
| **Unable to Determine** | 0 | 12 (5.9%) | 0 | 0 |
| **Visit 3** | | | | |
| **Eradication** | 89 (42.8%) | 55 (26.8%) | 64 (70.3%) | 39 (45.3%) |
| **Presumed Eradication** | 105 (50.5%) | 80 (39.2%) | 16 (17.6%) | 13 (15.1%) |
| **Persistence** | 10 (4.8%) | 53 (26.0%) | 9 (9.9%) | 29 (33.7%) |
| **Presumed Persistence** | 0 | 0 | 0 | 0 |
| **Reinfection** | 1 (0.5%) | 1 (0.5%) | 1 (1.1%) | 1 (1.2%) |
| **Presumed Reinfection** | 0 | 0 | 0 | 0 |
| **Unable to Determine** | 2 (1.0%) | 16 (7.8%) | 1 (1.1%) | 4 (4.7%) |
| **Visit 4** | | | | |

| | | | | |
|---|---|---|---|---|
| **Eradication** | 88 (42.3%) | 68 (33.2%) | 70 (76.9%) | 54 (62.8%) |
| **Presumed Eradication** | 94 (45.2%) | 59 (28.9%) | 15 (16.5%) | 12 (14.0%) |
| **Persistence** | 2 (1.0%) | 18 (8.8%) | 1 (1.1%) | 8 (9.3%) |
| **Presumed Persistence** | 0 | 0 | 0 | 0 |
| **Reinfection** | 0 | 0 | 0 | 0 |
| **Presumed Reinfection** | 0 | 0 | 0 | 0 |
| **Recurrence** | 0 | 2 (1.0%) | 0 | 0 |
| **Presumed Recurrence** | 1 (0.5%) | 0 | 0 | 0 |
| **Unable to Determine** | 22 (10.6%) | 58 (28.4%) | 5 (5.5%) | 12 (14.0%) |

*Table adapted from NDA 208945 Section 5.3.5.3 ISE Table 3-6 and 3-7*

Subjects within the intention-to-treat bacteriological populations for the two pivotal studies were pooled using the same criteria for both studies (described in Section 6). Notably, while the eradication category is based on culture proven eradication of the infectious etiology, the presumed eradication category is based off of clinical exam. Patients who are clinically improving despite persistent bacterial presence would be categorized into the presumed eradication category when culture data is unavailable.

The culture-based microbiologic data that are available suggest there is superior early eradication of the bacterial etiology at Visit 2 in the ozenoxacin category compared to placebo. However, it does not appear that this eradication improves significantly at subsequent visits. It remains difficult to interpret these results with 33-50% of some arms being designated presumed eradication based on clinical appearance. However, earlier eradication of the bacterial etiologies is a plausible mechanism for a topical antibiotic cream to provide its effect and suggest why there is a trend for improved clinical appearance of patients at Visit 3 (primary endpoint) in the ozenoxacin group.

### 7.1.3. **Subpopulations**

Table 7.5 through Table 7.7 review subpopulation data collected and pooled from the two pivotal studies. Data was pooled to provide adequate sample size for this analysis which is reviewed in detail throughout this section.

**Table 7.5 Pooled Phase 3 Studies: Primary Endpoint Demographic Sub-Group Analysis (ITTC Population)**

| | **Ozenoxacin (N = 361)** | **Placebo (N = 362)** |
|---|---|---|
| **Age** | | |
| **2 - <12 Years** | | |
| Clinical Success, n (%) | 107 (51.7%) | 60 (29.0%) |
| Clinical Failure, n (%) | 99 (47.8%) | 139 (67.1%) |
| **12 - <18 Years** | | |
| Clinical Success, n (%) | 15 (34.9%) | 10 (25.0%) |
| Clinical Failure, n (%) | 27 (62.8%) | 30 (75.0%) |

| | | |
|---|---|---|
| Unable to Determine, n (%) | 1 (2.3%) | 0 |
| **18 - <65 Years** | | |
| Clinical Success, n (%) | 43 (42.6%) | 37 (35.6%) |
| Clinical Failure, n (%) | 56 (55.4%) | 67 (64.4%) |
| Unable to Determine, n (%) | 2 (2.0%) | 0 |
| **>65 Years** | | |
| Clinical Success, n (%) | 2 (20.0%) | 2 (18.2%) |
| Clinical Failure, n (%) | 8 (80.0%) | 9 (81.8%) |
| **Sex** | | |
| **Male** | | |
| Clinical Success, n (%) | 99 (46.9%) | 53 (27.3%) |
| Clinical Failure, n (%) | 110 (52.1%) | 137 (70.6%) |
| Unable to Determine, n (%) | 2 (0.9%) | 4 (2.1%) |
| **Female** | | |
| Clinical Success, n (%) | 68 (45.3%) | 56 (33.3%) |
| Clinical Failure, n (%) | 80 (53.3%) | 108 (64.3%) |
| Unable to Determine, n (%) | 2 (1.3%) | 4 (2.4%) |
| **Race** | | |
| **White** | | |
| Clinical Success, n (%) | 71 (39.4%) | 50 (24.8%) |
| Clinical Failure, n (%) | 105 (58.3%) | 150 (74.3%) |
| Unable to Determine, n (%) | 4 (2.2%) | 2 (1.0%) |
| **Black or African American** | | |
| Clinical Success, n (%) | 81 (62.3%) | 44 (38.3%) |
| Clinical Failure, n (%) | 49 (37.7%) | 65 (56.5%) |
| Unable to Determine, n (%) | 0 | 6 (5.2%) |
| **Asian** | | |
| Clinical Success, n (%) | 6 (35.3%) | 4 (26.7%) |
| Clinical Failure, n (%) | 11 (64.7%) | 11 (73.3%) |
| **American Indian or Alaskan Native** | | |
| Clinical Success, n (%) | 2 (100%) | 13 (86.7%) |
| Clinical Failure, n (%) | 0 | 2 (13.3%) |
| **Mixed Race** | | |
| Clinical Success, n (%) | 4 (21.1%) | 3 (20.0%) |
| Clinical Failure, n (%) | 15 (78.9%) | 12 (80.0%) |
| **Ethnicity** | | |
| **Hispanic or Latino** | | |
| Clinical Success, n (%) | 26 (40.6%) | 24 (31.2%) |
| Clinical Failure, n (%) | 38 (59.4%) | 50 (64.9%) |
| Unable to Determine, n (%) | 0 | 3 (3.9%) |
| **Not Hispanic or Latino** | | |
| Clinical Success, n (%) | 141 (47.8%) | 84 (29.8%) |
| Clinical Failure, n (%) | 150 (50.8%) | 193 (68.4%) |
| Unable to Determine, n (%) | 4 (1.4%) | 5 (1.8%) |
| **Mixed** | | |
| Clinical Failure, n (%) | 1 (100.0%) | 1 (100.0%) |
| **Other** | | |
| Clinical Success, n (%) | 0 | 1 (50.0%) |
| Clinical Failure, n (%) | 1 (100.0%) | 1 (50.0%) |

All comparisons by age, sex, race, and ethnicity showed a greater percentage of clinical success in the ozenoxacin groups relative to placebo. However, sample sizes were often not large enough to draw definitive conclusions. It is reassuring that the age group of 2 months to <12 years showed the largest sample size and largest trend towards clinical success at 22.7% given this is the age group most likely to be affected by the disease and receive treatment for it, although it is unclear why older patients would respond less to treatment with ozenoxacin. While additional skin disease was an exclusion criterion for both studies, it is possible that older patients have other skin conditions (including damaged, aged skin) which might make impetigo more difficult to treat. Of note, impetigo is much less common in the elderly and is primarily a disease of youth in age groups showing increased clinical response to treatment with ozenoxacin. Both males and females showed similar rates of clinical success relative to each other and placebo. African-American race was associated with a higher rate of treatment success at 62.3% than white at 39.4%, without any clear explanation. Similar rates of clinical success were reported between Hispanic and non-Hispanic groups. Additional comparisons between race/ethnic groups were limited due to small sample sizes, but reassuring that ozenoxacin trended towards clinical success greater than placebo with similar magnitude in all sub-groups.

**Table 7.6 Pooled Phase 3 Studies: Primary Endpoint Disease Type Sub-Group Analysis (ITTC Population)**

| | **Ozenoxacin (N = 361)** | **Placebo (N = 362)** |
|---|---|---|
| **Type of Impetigo** | | |
| **Bullous** | | |
| Clinical Success, n (%) | 18 (31.0%) | 20 (29.4%) |
| Clinical Failure, n (%) | 38 (65.6%) | 45 (66.2%) |
| Unable to Determine, n (%) | 2 (3.4%) | 3 (4.4%) |
| **Non-Bullous** | | |
| Clinical Success, n (%) | 149 (49.2%) | 89 (30.3%) |
| Clinical Failure, n (%) | 152 (50.2%) | 200 (68.0%) |
| Unable to Determine, n (%) | 2 (0.7%) | 5 (1.7%) |
| **Number of Affected Areas** | | |
| **1 Area** | | |
| Clinical Success, n (%) | 63 (42.0%) | 52 (31.1%) |
| Clinical Failure, n (%) | 84 (56.0%) | 115 (68.9%) |
| Unable to Determine, n (%) | 3 (2.0%) | 0 |
| **2 – 4 Areas** | | |
| Clinical Success, n (%) | 83 (50.9%) | 42 (30.0%) |
| Clinical Failure, n (%) | 79 (48.5%) | 92 (65.7%) |
| Unable to Determine, n (%) | 1 (0.6%) | 6 (4.3%) |
| **5 – 10 Areas** | | |
| Clinical Success, n (%) | 16 (41.0%) | 13 (28.9%) |
| Clinical Failure, n (%) | 23 (59.0%) | 30 (66.7%) |
| Unable to Determine, n (%) | 0 | 2 (4.4%) |
| **>10 Areas** | | |

| | | |
|---|---|---|
| Clinical Success, n (%) | 4 (50.0%) | 2 (22.2%) |
| Clinical Failure, n (%) | 4 (50.0%) | 7 (77.8%) |

Patients with bullous impetigo treated with ozenoxacin or placebo were found to have similar outcomes; however, limited sample size prevents any definitive conclusions. Regarding the number of lesions noted at baseline, there seems to be consistency that subjects had increased rates of clinical success independent of this variable. The majority of patients in the study had 1 – 4 affected areas. Patients with more extensive involvement may be treated with systemic agents due to concerns for alternative diagnoses or practical considerations.

**Table 7.7 Pooled Phase 3 Studies: Primary Endpoint Geographic Sub-Group Analysis (ITTC Population)**

| | **Ozenoxacin (N = 361)** | **Placebo (N = 362)** |
|---|---|---|
| **Country** | | |
| **United States** | | |
| Clinical Success, n (%) | 25 (36.2%) | 19 (22.1%) |
| Clinical Failure, n (%) | 44 (63.8%) | 65 (75.6%) |
| Unable to Determine, n (%) | 0 | 2 (2.3%) |
| **Non-United States** | | |
| Clinical Success, n (%) | 142 (48.6%) | 90 (32.6%) |
| Clinical Failure, n (%) | 146 (50.0%) | 180 (65.2%) |
| Unable to Determine, n (%) | 4 (1.4%) | 6 (2.2%) |

In response to an FDA request to include more subjects from the United States, the sponsor included a larger portion of domestic subjects in the second pivotal trial, P-110881-01, which were then pooled together with the first trial, P-110880-01. Ultimately, 155 subjects were included from the United States cohort (46 additional patients were located in Puerto Rico). This accounted for 21.4% of all patients enrolled (an additional 6.2% if Puerto Rico was included). The overall trend in the United States reflected the global data with a difference in success rates of 14.1% versus 16%, respectively.

The absolute rates of clinical success were substantially higher in the non-US sites than the US with the exception of Germany but it is unclear why this discrepancy exists. There are not enough microbiological data to suggest that there is a clear difference in types of organisms causing impetigo or in the resistance patterns within those regions. In response to these concerns, site inspections were pursued for the largest recruitment sites in the US, Germany, and South Africa (see Sections 6.1.2.9 and 6.2.2.9)

### 7.1.4. **Dose and Dose-Response**

A single Phase 2 Study, P-080623-01, was used as the rationale for selecting the 1% ozenoxacin cream dose and regimen. The study was a multi-center, randomized, double-blind, parallel, placebo-controlled trial to assess the efficacy and safety of 3 different doses of ozenoxacin

cream versus placebo cream applied 2 times daily for 7 days in the treatment of adult patients with secondarily-infected traumatic lesions. (b) (4) The study allows for a better description of the safety profile in a population most at risk for systemic absorption while still allowing for adequate comparison of different strengths of the cream for efficacy analysis. Subjects were required to have a small laceration, sutured wound, abrasion or burn with a secondary bacterial infection (the lesion had to be within 2 – 10 cm in length and 2 – 100 $cm^2$ in total surface area without area of surround erythema extending >2 cm from the edge of the wound).

The study involved 16 centers in 6 countries including France, Spain, Italy, South Africa, the Czech Republic, and Germany. A total of 202 patients were included in the study and 199 were treated (placebo cream: 48 patients, 0.25% ozenoxacin cream: 50 patients, 1% ozenoxacin cream: 50 patients, 2% ozenoxacin cream: 51 patients). Patients had to be ≥18 years of age and have a SIRS score of ≥8 including pus/exudate score of ≥2 (utilizing the same SIRS criteria from pivotal study P-110880-01).

The primary efficacy endpoint was clinical response (success or failure) at the Final Visit (Day 14) in the ITTC population. Additional secondary efficacy endpoints included clinical response at Visit 2 (Day 5) and Visit 3 (Day 7 or end of therapy) in the ITTC population. An exploratory analysis was included for the dose response relationship at Visits 2, 3, and 4 in the ITTC population.

The primary endpoint utilized a clinical assessment by the investigator including use of the SIRS (same scale as pivotal study P-110880-01; see

Table 6.4) with subjects being designated a clinical success or clinical failure. Clinical success included any patient meeting the clinical outcome definition of “cure” while clinical failure included any patient meeting another definition:

- Cure: Resolution of all entry clinical signs and symptoms and no additional antibiotic was necessary
- Improvement: Some degree of improvement in clinical signs and symptoms but was still in need of therapy
- Relapse: Worsening or reappearance of signs and symptoms after amelioration or favorable response to therapy
- Failure: Persistence, incomplete resolution or worsening of entry clinical signs and symptoms and/or emergence of new signs or symptoms of disease

**Figure 1: Phase 2 Dosing Study: Clinical Success in the Course of the Study: ITTC Population**

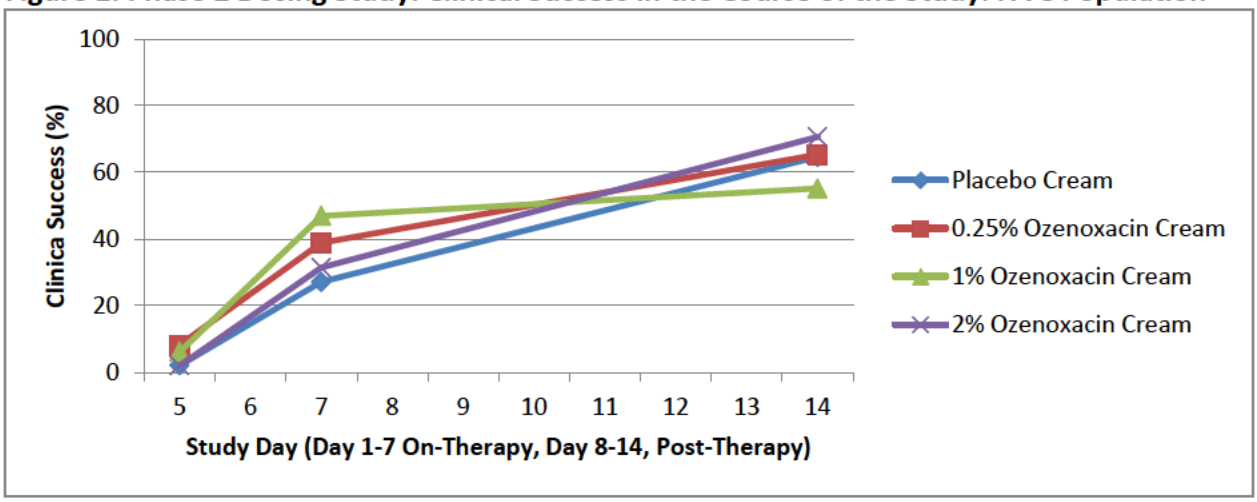


*Figure adapted from NDA 208945 Section 5.3.5.4 P-080623-01 Study Report Figure 3*

As displayed graphically in Figure 1, none of the tested ozenoxacin cream formulations showed significant differences from placebo cream for the clinical response at the final study visit (7 days after the cessation of treatment). However, ozenoxacin 1% cream (and only the 1% cream) showed both a significantly greater clinical response ($p = 0.042$) relative to placebo cream at the end of treatment. Given that, the 1% formulation was selected for further clinical development.

A twice daily treatment regimen was chosen for the first Phase 3 Study (P-110880-01) based on the results of previous *in vitro* studies conducted with ozenoxacin. That first Phase 3 study supported the dosing regimen for use in the second Phase 3 Study (P-110881-01) that, in turn, confirmed the regimen. Given the potent *in vitro* activity of ozenoxacin against common impetigo pathogens, a 5-day treatment period was considered reasonable. While Figure 1 shows that differences in clinical outcome are not apparent at 5 days, the microbiological eradication was expected to have already occurred and subsequent effect on the natural course of the disease determined.

The Phase 2 dosing and safety study (P-080623-01) had difficulty displaying the efficacy of ozenoxacin versus placebo at various time points during therapy and after. Given the combination of a relatively small sample size and the modest difference in clinical outcome shown by the 2 pivotal Phase 3 studies, this is not surprising. The tendency for impetigo to self-resolve is reflected in the Phase 2 trial with the increased clinical efficacy of placebo over time.

However, the study did not reveal any safety concerns (discussed further in Section 8) and did show some evidence for efficacy of 1% ozenoxacin cream at end of therapy in the ITTC population providing the basis for moving forward. The follow-up Phase 3 studies

demonstrated increased evidence of clinical benefit with a decreased duration of therapy of 5 days.

#### 7.1.5. Onset, Duration, and Durability of Efficacy Effects

Not applicable

### 7.2. Additional Efficacy Considerations

#### 7.2.1. Considerations on Benefit in the Postmarket Setting

Not applicable

#### 7.2.2. Other Relevant Benefits

Not applicable

### 7.3. Integrated Assessment of Effectiveness

The integrated analysis of efficacy for ozenoxacin 1% cream is based on two pivotal Phase 3 studies. The two studies, P-110880-01 and P-110881-01, have been discussed in detail in Sections 6.1 and 6.2, respectively; additional pooled data from the two studies have been described previously in this Section. It is the opinion of this reviewer that these two large, multicenter, randomized, double-blinded studies provide substantial evidence of superiority of ozenoxacin 1% cream to placebo cream in the treatment of impetigo.

Both pivotal studies utilized a primary endpoint of clinical response at end of therapy in the intent-to-treat clinical populations and these results provide the primary support for the drug's efficacy. In study P-110880-01, the difference in clinical success between the ozenoxacin arm and placebo arm was 0.156 (34.8% for ozenoxacin and 19.2% for placebo). In study P-110881-01, the difference in clinical success between the ozenoxacin arm and placebo arm was 0.160 (55.2% for ozenoxacin and 39.2% for placebo). As discussed previously, these differences in clinical success appear to persists across a variety of subpopulations including standard demographic categories (gender, race/ethnicity, age, geographic location) and disease descriptors (SIRS, extent of lesion(s), organism).

It is important to note that while the difference in clinical success between treatment and placebo arms is consistent and supportive of an improved clinical success rate of around 15% with ozenoxacin, there is wide variation in the absolute clinical success rates obtained between trials and certain subgroups. In particular, the difference in clinical success rates of ozenoxacin between the two pivotal trials (34.8% and 55.2%) is likely related to changing SIRS definitions for clinical assessment of lesions in the two trials, as discussed at length earlier in this Section. Additionally, much effort was taken to evaluate microbiological culture results as another

indicator of clinical efficacy in the secondary analysis as is detailed earlier in this Section. While the interpretation of microbiological response is dubious due to reliance on presumed eradication, there are available data on the clinical outcomes of patients with infections caused by *S. aureus* and *S. pyogenes* (see Section 7.1.2). These organisms represent the most commonly associated pathogens with impetigo in the reviewed studies and based on historical data. The clinical response mirrors the findings in the ITTC population, providing evidence for the effectiveness of ozenoxacin in treating impetigo caused by both *S. aureus and S. pyogenes.* Additionally, the available microbiologic data does suggest an earlier eradication of microorganisms with use of ozenoxacin providing a likely pathophysiological mechanism for the drug's efficacy.

While the treatment effect is not impressive, the difference in clinical success noted in the two pivotal studies is felt to represent a clinically significant difference. Impetigo is generally a self-limited disease that will resolve without treatment in the majority of cases (reflected in the large placebo clinical success rates by Visit 4 post-therapy), making treatment effects difficult to measure in this condition. However, the clinical success rate of ozenoxacin relative to placebo was comparable to retapamulin (included as a measure of internal validity in P-110880-01), which has previously demonstrated efficacy in and has FDA approval for treating impetigo. This difference is felt to be sufficient to justify the approval ozenoxacin 1% cream for the treatment of impetigo in patients ≥2 months of age.

While alternative topical therapies for impetigo already exist on the market, including mupirocin, retapamulin, and systemic antibiotics, there are benefits to an additional medication. For patients who cannot tolerate one agent, it is of benefit to have an alternative non-systemic agent available, although skin reactions have been rare in such preparations.

In order to provide the most clear and concise information in labeling, clinical efficacy data for ozenoxacin 1% cream from the pivotal trials (P-110880-01 and P-110881-01) should be presented as clinical response rates for ozenoxacin and placebo for each trial, including both absolute values and percentages. This information should not be pooled given the significant differences in clinical effect between the two trials. Microbiological response data should not be included on any labelling due to its reliance on presumed/clinical data. However, the clinical response for patients with *S. aureus* and *S. pyogenes* should be presented in the same manner as other clinical efficacy data to allow for comparison and consideration for the use of ozenoxacin 1% cream in the treatment of these etiologies of impetigo.

# 8 Review of Safety

## 8.1. Safety Review Approach

The clinical review of safety focuses on the two pivotal Phase 3 studies, P-110880-01 and P-110881-01. These randomized, controlled, blinded, multicenter trials provide the strongest evidence of safety and their comparable design allows for adequate pooling of trial data. Additional reference is made to 13 Phase 1 studies in healthy individuals, 1 Phase 1 study in subjects with non-bullous or bullous impetigo, and 1 Phase 2 studies in subjects with secondarily-infected traumatic lesions which are further detailed in Appendix Table 13.1 ( Summary of Phase 1 and 2 Clinical Trials for Safety Evaluation).

Because ozenoxacin cream is administered topically, with evidence of negligible systemic absorption, many topics dealing with systemic effects are only commented on briefly in this safety review. Similarly, safety issues of special importance with quinolone antibiotics, such as joint AEs (tendinopathy and/or arthropathy), are likely not relevant to a topical preparation with negligible systemic absorption.

## 8.2. Review of the Safety Database

### 8.2.1. Overall Exposure

**Table 8.1 Overall Extent of Exposure Across all 17 Clinical Studies**

| Actual Treatment Period | Ozenoxacin | | | | Placebo | Retapamulin Ointment 1% | Total |
|---|---|---|---|---|---|---|---|
| | Cream | | | Ointment 1% | | | |
| | 0.25% | 1% | 2% | | | | |
| ≤1 day | 0 | 32 | 32 | 24 | 64 | 0 | 152 |
| 2-8 days | 50 | 458 | 115 | 19 | 245 | 153 | 1040 |
| 21 days | 0 | 312 | 312 | 0 | 623 | 0 | 1247 |
| Total | 50 | 802 | 459 | 43 | 1137 | 153 | 2644 |

*Table adapted from NDA 208945 Section 5.3.5.3 ISS Table 1-4*

Table 8.1 summarizes the overall exposure history for subjects included in all 17 clinical studies completed for ozenoxacin at the time of this review. 1917 subjects were included in the safety population across all clinical trials; however, subjects from many Phase 1 trials acted as their own controls with exposure to both study drug and placebo on separate areas of skin. These subjects are thus counted twice in Table 8.1 and accounts for the larger subject total of 2644. Please see Table 13.1 in the Appendix for additional details of the phase 1 studies. Table 8.2 summarizes the pediatric exposure history from the 3 trials that included subjects <18 years of age. Of note, these patients represented the majority of patients within these trials.

**Table 8.2 Overall Exposure in Pediatric Subjects**

| | Study P-100797-01 | Studies P-1108801-01 and P-110881-01 | | | |
|---|---|---|---|---|---|
| Age Group | Ozenoxacin 1% Cream (N=46) | Ozenoxacin 1% Cream (N=362) | Placebo Cream (N=361) | Retapamulin 1% Ointment (N=152) | Totals |

| | | | | | |
|---|---|---|---|---|---|
| 2 months to <2 years | 20 | 11 | 16 | 0 | 47 |
| 2 to <12 years | 9 | 198 | 190 | 94 | 491 |
| 12 to <18 years | 9 | 42 | 41 | 15 | 107 |
| >18 years | 8 | 111 | 114 | 43 | 276 |

*Table adapted from NDA 208945 Section 5.3.5.3 ISS Table 1-5*

#### 8.2.2. **Relevant characteristics of the safety population:**

The demographic and disease severity characteristics of the safety population for the two pivotal Phase 3 studies (P-110880-01 and P-110881-01) are covered previously in Table 6.9, Table 6.10, Table 6.23, and Table 6.24. The safety and ITTC efficacy populations are essentially the same in these studies. The two pivotal studies are the only studies to analyze safety data in a population treated with the drug formulation, duration, and for the specific indication proposed in the application labeling.

#### 8.2.3. **Adequacy of the safety database:**

The provided safety database is adequate in size and in consideration of exposure to the appropriate dose, duration of treatment, patient demographics, and disease severity to evaluate the safety profile of ozenoxacin in the treatment of impetigo. While the proposed treatment regimen involves a single strength of ozenoxacin for a duration of five days, the safety population includes subjects treated with lower/higher strengths (0.25%, 2%) and shorter/longer durations (1-21 days). The combination of data from the pivotal Phase 3 studies with multiple earlier clinical trials with various regimens strengthens evidence for the safety of topical ozenoxacin. While the first pivotal Phase 3 Study (P-110880-01) included a large number of non-US subjects, the follow-up study (P-110881-01) and many of the early clinical trials included US subjects and is felt to be adequate.

### 8.3. **Adequacy of Applicant's Clinical Safety Assessments**

#### 8.3.1. **Issues Regarding Data Integrity and Submission Quality**

A random selection of 10% of the case report forms was requested from the sponsor and provided to the FDA. A review of these case report forms was consistent with prior information provided in the electronic submission of the application and documented elsewhere throughout this review. The submitted safety database was of sufficient quality to allow for adequate review and confirmation of the sponsor's findings. The data was submitted in a standard format and considered complete. Multiple site visits were completed to confirm data integrity as part of the application review. Please refer to the OSI findings discussed in Section 4.1 regarding these site visits.

#### 8.3.2. **Categorization of Adverse Events**

Evaluation of safety was based on Adverse event s, clinical laboratory parameters (hematology, clinical chemistry, urinalysis), vital signs (axillary temperature, pulse rate, blood pressure), and physical examinations.

The study protocols used appropriate and explicit definitions for adverse event reporting:

- Adverse event (AE) – any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which did not necessarily have a causal relationship with this treatment.
- Serious adverse event (SAE) – an AE that resulted in death was life-threatening, required in-patient or prolonged hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, or was any other medically important event that may jeopardize the patient or may require intervention to prevent one of the other above outcomes.
- Treatment emergent adverse event (TEAE) – any AE occurring in a patient or clinical trial subject after the first study medication (test or reference) administration until the last day for collecting AEs as per protocol

AEs were elicited from signing of informed consent to the completion of the clinical study (including the post-treatment visit) or premature patient withdrawal from the study. If an AE was noted it was followed to resolution or confirmed stabilization on its progression. If the AE had not resolved at 30 days post-study completion, the need for additional follow-up was discussed between the investigator and the sponsor's drug safety contact person. AEs were elicited by asking the patients non-leading, open-ended questions, by collecting AEs spontaneously reported by the patient to the investigator or delegate, and through physical examination, laboratory assessments, or other complementary test results. Of note, progression of impetigo was not considered an AE, just a clinical outcome failure.

All AEs were recorded and submitted in standard eCRF format to the FDA and coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 14.1 to give a system organ class and preferred term for each event.

Additionally, special attention was paid to the musculoskeletal physical exam of patients due to concerns for effects on joints (arthropathy and/or tendinopathy). This concern stemmed from the concerns for this adverse event with the drug class of fluoroquinolones with ozenoxacin being a non-fluorinated quinolone. However, with negligible systemic absorption, such adverse events are unexpected to be related to ozenoxacin 1% topical cream.

#### 8.3.3. **Routine Clinical Tests**

Refer to Table 6.2 for the schedule of time and events for both pivotal Phase 3 studies. The

timing and breadth of safety assessments is adequate. The timing and use of clinical examinations, telephone calls, medication/compliance checks, and patient diaries is felt to be sensitive for any clinically significant safety concerns. The vital signs and laboratory collections of hematology, clinical chemistry, and urinalysis are more than what is necessary for a topical product with negligible systemic absorption and included the following:

- Hematology: completed red blood cell, white blood cell with differential and platelet count, hemoglobin, hematocrit.
- Clinical chemistry: total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase, creatinine, blood urea nitrogen, glucose, sodium, potassium.
- Urinalysis: pH, protein, glucose, blood, ketones, urobilinogen, bilirubin, nitrite, leukocytes. If protein and/or blood were found in the urine, a sample was sent for microscopy and culture. Urine pregnancy test for female patients of child-bearing potential.
- Vital signs: axillary temperature, pulse rate, blood pressure

Deteriorations as compared to baseline in protocol-mandated vital signs and laboratory collections were considered AEs only if they fulfilled the SAE definition or were clinically significant or were the reason for discontinuation of treatment.

## 8.4. Safety Results

### 8.4.1. Deaths

No deaths occurred in any of the 17 studies included in the clinical development program for ozenoxacin.

### 8.4.2. Serious Adverse Events

Across all 17 studies, there was 1 SAE, which occurred in Study P-100847-01. A subject experienced an upper limb fracture which required hospitalization and surgery. The SAE lead to discontinuation from the study but is not related to the study drug.

### 8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Table 8.3 reviews AEs leading to discontinuation of study drug across the safety database. The discontinuation of study drug in patients across the 17 clinical trials was found to be rare and when present, generally due to AEs unrelated to the study drug or likely unrelated. In cases of skin reactions that may have a pathophysiological mechanism related to a topical cream

(worsening eczema, rosacea, seborrheic dermatitis), the AEs were mild and again rarely lead to discontinuation.

**Table 8.3 AEs Leading to Discontinuation of Study Drug across All Clinical Studies**

| Study Number | Number of subjects | Reason for Discontinuation |
|---|---|---|
| P-090738-01 | 3 | D/C due to pregnancy in 2 subjects |
| | | D/C due to the use of excluded medication (ibuprofen) for AE of ankle fracture |
| P-090739-01 | 1 | D/C due to AE of severe toothache followed by tooth extraction |
| P-090778-01 | 1 | D/C due to an AE of syncope |
| P-100847-01 | 1 | D/C due to an SAE of upper limb fracture (see section 8.4.2) |
| P-100848-01 | 1 | D/C due to pregnancy |
| P-110881-01 | 4 | D/C due to AEs of rosacea and seborrheic dermatitis |
| | | D/C due to AE of skin tightening |
| | | D/C due to AE of herpes zoster |
| | | D/C due to AE of eczema |

Please refer to Section 8.4.5 for a review of AEs not resulting in discontinuation of study drug.

Please refer to Sections 6.1.2.3 and 6.2.2.3 for a review of patient disposition for the two Phase 3 trials.

### 8.4.4. Significant Adverse Events

There were no AEs of special interest reported in any of the clinical studies. Events leading to withdrawal of study drug were reported in 9 of the 17 studies and are discussed in Section 8.4.3. See section 8.4.5. for a discussion on all TEAEs reported throughout the clinical trial history.

### 8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The safety population included 14 phase 1 trials (8 related to dermal tolerability and 6 related to pK). See Appendix Table 13.1 for a description of these trials and associated AEs/TEAEs. In brief, no significant AEs were noted during the safety review of these studies including no serious or severe TEAEs felt related to use of the study drug. Topical administration of ozenoxacin preparations appeared to be well tolerated regarding dermal irritation, dermal sensitization, dermal photo irritation, and dermal photosensitization.

There was a single Phase 2 study (P-080623-01) included in the safety analysis. In this dose finding study, 3 different strengths of ozenoxacin cream were investigated in adult subjects with SITL.

**Table 8.4 Overview of Adverse Events (Phase 2 Dose Finding Study P-080623-01)**

| | | Ozenoxacin Cream | | |
|---|---|---|---|---|
| | **Placebo Cream (N = 48)** | **0.25 % (N = 50)** | **1% (N = 50)** | **2% (N = 51)** |
| Number of AEs | 18 | 9 | 9 | 8 |
| Number of Severe AEs | 1 | 0 | 0 | 0 |
| Number of SAEs | 0 | 0 | 0 | 0 |
| Number of AEs leading to discontinuation | 1 | 0 | 1 | 1 |

No SAEs were reported during this Phase 2 study and only a single severe AE in the placebo group (oropharyngeal pain considered unrelated to study). The most commonly reported study-related AEs were application site irritation and pruritus, similar to the safety profiles from phase 1 studies. Overall, a larger proportion of AEs were reported in the placebo group without significant differences in the categories of AEs between treatment arms. No significant change in adverse events was noted in association with dose.

The 2 Phase 3 studies pooled safety data to report 64 AEs which included no severe AEs, SAEs, or AEs of special interest.

**Table 8.5 Summary of TEAEs (Safety Population) for Pooled Phase 3 Studies**

| | **Ozenoxacin 1% Cream (N = 362)** | | **Placebo Cream (N = 361)** | | **Retapamulin 1% Ointment (N = 152)** | |
|---|---|---|---|---|---|---|
| | **n (%)** | **E** | **n (%)** | **E** | **n (%)** | **E** |
| Subjects with at least 1 AE | 16 (4.4%) | 19 | 17 (4.7%) | 20 | 17 (11.2%) | 25 |
| Subjects with at least 1 SAE | 0 | 0 | 0 | 0 | 0 | 0 |
| Discontinuation due to AE | 1 (0.3%) | 2 | 3 (0.8%) | 3 | 0 | 0 |
| Intensity | | | | | | |
| Mild | 12 (3.3%) | 14 | 13 (3.6%) | 14 | 14 (9.2%) | 20 |
| Moderate | 4 (1.1%) | 5 | 5 (1.4%) | 6 | 5 (3.3%) | 5 |
| Severe | 0 | 0 | 0 | 0 | 0 | 0 |

E = events

The pooled phase 3 safety population had only 2 TEAEs that occurred with a frequency of >1% in any treatment arm. These included nasopharyngitis (1.1% of ozenoxacin arm, 0% placebo arm, and 2.6% in retapamulin arm) and rhinitis (0% in ozenoxacin arm, 0% in placebo arm, and 2.0% in retapamulin arm) similar to findings in all other clinical trials and not related to treatment. One patient treated with ozenoxacin developed worsening rosacea and worsening

seborrheic dermatitis which may have been due to the topical medication, but these adverse events did not occur in significant numbers across the safety database. The only AEs of note during treatment with ozenoxacin cream occurred in Phase 1 dermal tolerability studies in only a few patients who developed erythema and irritation at sites of repeated application.

#### 8.4.6. **Laboratory Findings**

Clinical laboratory assessments were included in Phase 1, 2, and 3 studies to various degrees including hematology, clinical chemistry and urinalysis. Appropriately, studies included any clinically meaningful abnormal laboratory results as AEs. No noteworthy differences or trends were found between any ozenoxacin topical formulation and placebo for any measured laboratory parameter. This finding is expected given the negligible systemic absorption of topical ozenoxacin.

There was a single patient in study P-080623-01 who was withdrawn from the study due to evidence of nephropathy on laboratory studies related to underlying diabetes mellitus type 1 and not due to study treatment.

#### 8.4.7. **Vital Signs**

In review of the safety database, significant changes in vital signs (blood pressure, heart and respiratory rates, temperature) were not generally found. 3 subjects in study P-080623-01 had hypertension (2 in ozenoxacin 2% cream arm and 1 in placebo cream arm) and 1 subject in P-110880-01 had hyperthermia (in retapamulin 1% ointment arm). These events were appropriately included as AEs, but are not considered related to the study medication.

#### 8.4.8. **Electrocardiograms (ECGs)**

No clinically meaningful abnormal ECG findings were reported for any subject in the studies that included ECG assessments.

#### 8.4.9. **QT**

Not applicable

#### 8.4.10. **Immunogenicity**

Not applicable

### 8.5. **Analysis of Submission-Specific Safety Issues**

Ozenoxacin is a quinolone antibiotic, and AEs related to effects on joints including arthropathy and/or tendinopathy were considered potential AEs of special interest. No AEs of this type were

reported across the safety population of all 17 clinical trials, and the lack of systemic absorption of topical ozenoxacin argues against the likelihood of occurrence.

## 8.6. Safety Analyses by Demographic Subgroups

The overall low numbers of significant AEs preclude a meaningful demographic subgroup analysis, but there is no reason to expect any demographic differences in safety profile for a topical, non-absorbed medication. Three studies included pediatric patients (P-110880-01 with patients >2 years and both P-110881-01 and P-100797-01 with patients >2 months) without any appreciable safety differences between pediatric and general populations. Similarly, three studies included elderly patients >65 years (P-080623-01, P-110880-01, and P-110881-01) without significant differences in safety profile.

## 8.7. Specific Safety Studies/Clinical Trials

As noted previously, the only AEs of note during treatment with ozenoxacin cream occurred in Phase 1 dermal tolerability studies in only a few patients who developed erythema and irritation at sites of repeated application. Please refer to the appendix Section 13.1 which further details the completed Phase 1 and 2 clinical trials for ozenoxacin.

## 8.8. Additional Safety Explorations

### 8.8.1. Human Carcinogenicity or Tumor Development

No human carcinogenicity or tumor development studies were performed, nor are they considered necessary as the product is intended for short term use.

### 8.8.2. Human Reproduction and Pregnancy

All clinical studies performed with ozenoxacin excluded pregnant subjects. Three female subjects did become pregnant during trials (see Table 8.3) with 2 unknown pregnancy outcomes and a single pregnancy reported as terminated after 1 week.

Nonclinical data on embryotoxicity/teratology of ozenoxacin in rats and rabbit showed no observable adverse effects at levels of 500 mg/kg body weight in rats and 5 mg/kg body weight in rabbits when given via the oral route. Given the negligible systemic absorption of topical ozenoxacin, transmission via placenta and breast milk are unexpected unless cream is applied directly to the breast area.

### 8.8.3. Pediatrics and Assessment of Effects on Growth

Since very young children can be affected by impetigo, pediatric patients were included in the NDA studies for ozenoxacin 1% cream. Proportionally large numbers of pediatric patients were

included in study P-110880-01 (patients >2 years) and both studies P-110881-01 and P-100797-01 (patients >2 months). The clinical efficacy and safety of ozenoxacin regarding the pediatric population is included throughout the efficacy (Section 6 and Section 7) and safety (Section 8) analyses.

A plan to request a pediatric waiver for patients <2 months of age was discussed between the sponsor and the FDA during pre-IND meetings. The application contains an adequate assessment of the efficacy and safety of ozenoxacin for the relevant age groups. This assessment will be presented to the Pediatric Review Committee (PeRC) with a recommendation to grant a waiver for studies in patients <2 months of age given the practical issues in studying patients <2 months of age.

#### 8.8.4. **Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

No cases of overdose were reported during clinical trials. Given the low concentration and negligible systemic absorption of 1% topical ozenoxacin cream, there is low concern for overdose risk unless the medication where to be taken by mouth or rectally. The formulation is not designed to be palatable and ingestion of significant amounts is unlikely.

### 8.9. **Safety in the Postmarket Setting**

#### 8.9.1. **Safety Concerns Identified Through Postmarket Experience**

Not applicable

#### 8.9.2. **Expectations on Safety in the Postmarket Setting**

There are no special concerns for the postmarket setting and routine postmarketing surveillance and reporting is sufficient.

### 8.10. **Additional Safety Issues From Other Disciplines**

Not applicable

### 8.11. **Integrated Assessment of Safety**

The safety profile of ozenoxacin was developed over 17 clinical studies. This included two Phase 3 multicenter, randomized, controlled, pivotal trials topical ozenoxacin 1% cream for the indication of impetigo. These two trials (P-110880-01 and P-110881-01) utilized the duration and dosing of topical ozenoxacin proposed for labeling. Additionally, a single Phase 2 study (P-100797-01) evaluated the safety profile of several different strengths of ozenoxacin including a preparation twice the strength (2%) of the proposed preparation. 14 additional Phase 1 studies are referenced regarding dermal tolerability and overall safety utilizing a wide variety of

preparations and durations both less than and in great excess of the proposed treatment regimen.

The overall safety database is adequate and relevant for the evaluation of topical ozenoxacin safety in the US population. The database included adequate evaluation of pediatric patients. The database included appropriate definitions and assignment of AEs, SAEs, and TEAEs. Based on a review of this database, there is no evidence of any significant safety concerns in regard to the use of topical 1% ozenoxacin cream. There were no deaths or significant adverse events identified throughout a review of the safety database. A single serious adverse event (upper limb fracture) was reported (see Section 8.4) and was unrelated to the use of ozenoxacin. Given the lack of systemic absorption demonstrated in preclinical and Phase 1 trials, there is no evidence for concern regarding systemic toxicity. The common adverse events most often reported included pruritus and erythema at application sites and were similar between treatment and placebo groups across multiple studies. Dermal tolerability studies demonstrated a well-tolerated topical preparation with rare reported cases of mild erythema and irritation associated with use.

No safety concerns were identified in this review of topical ozenoxacin 1% cream for the proposed indication of treatment of impetigo.

# 9 Advisory Committee Meeting and Other External Consultations

Not applicable

# 10 Labeling Recommendations

## 10.1. Prescribing Information

No major changes were recommended to the proposed labelling provided by the applicant. Recommended changes were related to formatting and presentation of data. In particular, Table (b) (4) within Section 14 (Clinical Studies) which (b) (4) (b) (4) display clinical responses for *S. aureus* and *S. pyogenes*. This change was recommended to better reflect clinically relevant data for prescribers as discusses elsewhere in this review.

## 10.2. Patient Labeling

Not applicable

### 10.3. Nonprescription Labeling

Not applicable

## 11 Risk Evaluation and Mitigation Strategies (REMS)

There are no recommended post-market risk management strategies other than monitoring and reporting of adverse events.

### 11.1. Safety Issue(s) that Warrant Consideration of a REMS

Not applicable.

### 11.2. Conditions of Use to Address Safety Issue(s)

Not applicable.

### 11.3. Recommendations on REMS

Not applicable.

## 12 Postmarketing Requirements and Commitments

There are no recommended post-marketing requirements or commitments.

# 13 Appendices

## 13.1. Summary of Phase 1 and 2 Clinical Trials for Safety Evaluation

| Study Identity | Study Objective | Study Design | Test Products, Regimen, Route | No. of Centers and Countries | Number of Subjects Enrolled/ Treated | Healthy Subjects or Diagnosis | Treatment Duration | Conclusion |
|---|---|---|---|---|---|---|---|---|
| P-090736-01 (Phase 1) | To determine the irritation potential in abraded and intact skin vs placebo | Randomized, within-subject comparison; Placebo-controlled | 20 mg of ozenoxacin 2% cream and placebo cream, every 24 h, topical | 1 (US) | 37/37 | Healthy adult | 21 days, 21 doses | No evidence of irritation<br><br>No AEs reported |
| P-090737-01 (Phase 1) | To determine the photo-irritation potential versus placebo in skin when followed by light exposure | Randomized, within-subject comparison; Placebo-controlled | 200 mg of ozenoxacin 2% cream and placebo cream, topical | 1 (US) | 32/32 | Healthy adult | Single dose | No photo-irritation reaction<br><br>No AEs reported |
| P-090738-01 (Phase 1) | To determine dermal sensitization potential vs placebo | Randomized within-subject comparison; Placebo-controlled | 20 mg of ozenoxacin 2% cream and placebo cream, 3x weekly for 3 weeks (induction) followed by a single dose challenge, topical | 1 (US) | 215/215 | Healthy adult | ≈21 days, 10 doses | No evidence of sensitization potential and no significant irritancy<br><br>4 TEAEs reported (all mild, none considered study drug-related) |
| P-090739-01 | To determine | Randomized, | 200 mg of | 1 (US) | 60/60 | Healthy | ≈21 days, 7 | No photoallergic |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| (Phase 1) | photoallergic skin reaction potential vs placebo | within-subject comparison; Placebo-controlled | ozenoxacin 2% cream and placebo cream, 2x weekly for 3 weeks (induction) followed by a single dose challenge, topical | | | adult | doses | reactions<br><br>8 TEAEs reported (none serious or considered study drug-related) |
| P-100845-01 (Phase 1) | To determine the irritation potential in abraded and intact skin vs placebo | Randomized, within-subject comparison; Placebo-controlled | 20 mg of ozenoxacin 1% cream and placebo cream, every 24 h, topical | 1 (Germany) | 33/33 | Healthy adult | 21 days, 21 doses | No clinically meaningful irritation potential either on abraded or intact skin<br><br>Good dermal tolerability<br><br>7 TEAEs reported (all non-serious and considered not related to study drug) |
| P-100846-01 (Phase 1) | To determine dermal irritation potential vs placebo in skin when followed by light exposure | Randomized, within-subject comparison; Placebo-controlled | 200 mg of ozenoxacin 1 % cream and placebo cream, topical | 1 (US) | 32/32 | Healthy adult | Single dose | No photo-irritation reaction.<br><br>No AEs reported |
| P-100847-01 (Phase 1) | To determine dermal sensitization potential vs placebo | Randomized, within-subject comparison; Placebo-controlled | 20 mg of ozenoxacin 1% cream and placebo cream, 3x weekly for 3 | 1 (Germany) | 220/220 | Healthy adult | ≈21 days, 10 doses | No dermal sensitization during the challenge phase<br><br>1 subject with suspected |

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| | | | weeks (induction) followed by a single challenge dose, topical | | | | | presensitization during induction phase<br><br>29 TEAEs (1 serious and 28 non-serious; all considered unlikely or not related to study drug; 1 SAE and 1 moderate TEAE led to premature study discontinuation) |
| P-100848-01 (Phase 1) | To determine photoallergic skin reaction potential vs placebo | Randomized, within-subject comparison; Placebo-controlled | 200 mg of ozenoxacin 1% cream and placebo cream, 2x weekly for 3 weeks (induction) followed by a single challenge dose, topical | 1 (US) | 59/59 | Healthy adult | ≈21 days, 7 doses | No photoallergic reactions<br><br>10 AEs including 9 TEAEs (all non-serious, all considered not related to study-drug; 1 subject discontinued study due to TEAE) |
| P-050374-03 (Phase 1) | To assess systemic absorption, safety and tolerability after topical applications of different doses of ozenoxacin 1% ointment | Open label, single rising dose, parallel group | 0.05, 0.5, or 5 g of ozenoxacin 1% ointment, single dose, topical | 1 (UK) | 24/24 | Healthy adult male | Single dose | Well tolerated<br><br>10 AEs including 8 TEAEs (all non-serious and unlikely related to study-drug) |
| P-070515-01 (Phase 1) | To assess systemic absorption, safety | Single blind, multiple dose, 2-way | 0.5 g of ozenoxacin 1% ointment or | 1 (UK) | 21/19 (2 subjects withdrew | Healthy adult male | 7 days, 19 doses | Well tolerated<br><br>98 AEs including 96 |

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| | and tolerability after repeated topical applications of ozenoxacin 1% ointment | crossover, placebo-controlled | placebo ointment, topical, every 8 h for 6 days, followed by 1 dose on day 7 | | prior to receiving treatment) | | | TEAEs (all non-serious and non-severe except for a single AE of diarrhea considered unlikely related to study drug, most commonly reported AEs were mild application site pruritus and erythema) |
| P-080582-01 (Phase 1) | To assess systemic absorption, safety and tolerability after repeated topical applications of ozenoxacin 2% cream | Double-blind, multiple dose, 2-way crossover, randomized, placebo-controlled | 0.5 g of ozenoxacin 2% cream or placebo cream, topical, every 8 h for 6 days, followed by 1 dose on day 7 | 1 (UK) | 20/20 | Healthy adult male | 7 days, 19 doses | Well tolerated<br><br>186 AEs including 183 TEAEs (all non-serious and non-severe, most commonly reported AEs were application mild site pruritus and erythema) |
| P-090778-01 (Phase 1) | To compare systemic absorption in intact versus abraded skin and to assess safety and tolerability after repeated topical applications of ozenoxacin 2% cream on intact and abraded skin | Open label, multiple dose, crossover, randomized | 1 g of ozenoxacin 2% cream, topical, every 12 h for 7 days, followed by 1 dose on day 8 | 1 (UK) | 20/20 | Healthy adult male | 8 days, 15 doses (subjects treated for 2 periods with washout of 2 weeks between) | Well tolerated with similar safety and tolerability profiles for abraded and intact skin<br><br>118 TEAEs (all non-serious, 1 severe TEAE of vasovagal syncope thought to be unrelated to study drug, most commonly reported AEs were mild application site pruritus and erythema) |
| P-100797-01 (Phase 1) | To assess systemic | Open label, multiple dose | Ozenoxacin 1% cream, | 2 (South Africa) | 46/46 | Subjects 2 months to | 6 days, 10 doses | Well tolerated |

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| | absorption, clinical response, safety, and tolerability of ozenoxacin 1% cream after repeated topical applications | | topical, 1 dose on day 1, every 12 h on days 2-5, followed by a single dose on day 6 | | | 65 years with nonbullous or bullous impetigo | | 25 TEAEs (all non-serious and non-severe, most common AEs included nasopharyngitis and rhinitis and felt to be unrelated to study drug) |
| P-090745-01 (Phase 1) | To compare skin exposure of once daily vs twice daily administration regimen and to assess the safety and tolerability of ozenoxacin 2% cream after repeated topical applications | Open label, multiple dose, parallel group | 0.2 g of ozenoxacin 2% cream, topical, every 12 to 24 h for 3 days | 1 (UK) | 24/24 | Healthy adult males | 3 days; 3 or 6 doses | Well tolerated<br><br>9 AEs including 8 TEAEs (all non-serious, non-severe and considered unrelated to study drug) |
| P-080623-01 (Phase 2) | To evaluate efficacy, safety, and tolerability of 3 doses of ozenoxacin (0.25%, 1%, and 2%) cream compared with placebo | Multicenter, double-blind, randomized, placebo-controlled | Ozenoxacin (0.25%, 1%, or 2%) cream or placebo cream, twice daily, topical | 16 (Germany, France, Italy, Spain, Czech Republic, South Africa) | 202/199 (3 subjects not randomized)<br><br>0.25%, n=50;<br>1%, n=50;<br>2% n=51;<br>placebo, n=48 | Adult subjects with SITL | 7 days, 14 doses | All formulations well tolerated<br><br>No AEs reported |

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## 13.3. Microbiological Assessment Definitions

**Table 13.1 Microbiological Assessment at Visit 2**

| Classification / Category | Definition |
|---|---|
| **If material collected and cultured; patients with clinical classification "improvement" at Visit 2** | |
| Eradication / Microbiological success | The absence of the original pathogen(s) (Visit 1) from the culture of specimens from the baseline affected area (with or without the presence of new microorganism[s}) |
| Persistence / Microbiological failure | The presence of the original pathogen(s) (Visit 1) in the culture specimen from the baseline affected area (with or without the presence of any new microorganism[s]) |
| **If material collected and cultured; patients with clinical classification "no improvement" at Visit 2** | |
| Superinfection / Microbiological failure | The absence of the original pathogen(s) (Visit 1) from the culture of specimen from the baseline affected are with the presence of a new microorganism (documented or presumed) |
| Persistence / Microbiological failure | The presence of the original pathogen(s) (Visit 1) in the culture specimen from the baseline affected area (with or without the presence of any new microorganism[s]) |
| **If material noted collected** | |
| Presumed eradication / Microbiological success | If the patient was classified as improvement at Visit 2 |
| Presumed persistence / Microbiological failure | If the patient was classified as no improvement at Visit 2 |

**Table 13.2 Microbiological Assessment at Visit 3**

| Classification / Category | Definition |
|---|---|
| **If material collected and cultured; patients with clinical classification "improvement" at Visit 3** | |
| Eradication / Microbiological success | The absence of the original pathogen(s) (Visit 1) from the culture of specimen from the baseline affected are (with or without the presence of any new microorganism[s]) |
| Persistence / Microbiological failure | The presence of the original pathogen(s) (Visit 1) from the culture specimen from the baseline affected area (with or without the presence of any new microorganism[s]) |
| **If material collected and cultured; patients with clinical classification "failure" at Visit 3** | |
| Reinfection / Microbiological failure | The absence of the original pathogen(s) (Visit 1) from the culture of specimen from the baseline affected area with the presence of a new microorganism (documented or presumed)<br>OR<br>The presence of the original pathogen(s) (Visit 1) in the culture specimen from the baseline affected area (with or without the presence of any new microorganism[s]) with the patient classified as microbiological eradication (documented or presumed) at Visit 2 |
| Persistence / Microbiological failure | The presence of the original pathogen(s) (Visit 1) in the culture specimen from the baseline affected area (with or without the presence of any new microorganism[s]) with the patient classified as microbiological persistence (documented or presumed) at Visit 2 |
| **If material not collected** | |
| Presumed eradication / Microbiological success | If the patient was classified as cure or improvement at Visit 3 |
| Presumed persistence / Microbiological failure | If the patient was classified as failure at Visit 3 and was classified microbiologically as persistence, presumed persistence or presumed eradication at Visit 2 |
| Presumed reinfection / Microbiological failure | If the patient was classified as failure at Visit 3 and was classified microbiologically as eradication, superinfection or presumed superinfection at Visit 2 |

**Table 13.3 Microbiological Assessment at Visit 4**

| Classification / Category | Definition |
|---|---|
| **If material collect and cultured; patients with clinical classification "cure" at Visit 3 and "relapse" at Visit 4** | |
| Recurrence / Microbiological recurrence | The presence of the original pathogen(s) (Visit 1) in the culture specimen from the baseline affected area (with or without the presence of any new microorganism[s]) |
| Reinfection / Microbiological reinfection | The absence of the original pathogen(s) (Visit 1) from the culture of specimen from the baseline affected area, with the presence of a new microorganism (detected or presumed) |
| **If material collected and cultured; patients with clinical classification "failure" at Visit 4** | |
| | Samples at Visit 4 will be used only for microbiological characterization |
| **If material was not collected** | |
| Presumed eradication / Microbiological success | If the patient was classified as cure, unchanged or post-therapy cure at Visit 4 |
| Presumed reinfection/recurrence / Microbiological reinfection/recurrence | If the patient was classified clinically as relapse at Visit 4 |

## 13.4. Financial Disclosure

**Covered Clinical Studies:** P-110880-01 and P-110881-01

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ |
| Total number of investigators identified: 84 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A<br>Significant payments of other sorts: N/A<br>Proprietary interest in the product tested held by investigator: N/A<br>Significant equity interest held by investigator in sponsor of covered study: N/A | | |

| | | |
|---|---|---|
| Sponsor of covered study: N/A | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☐ | No ☐ |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☐ | No ☐ |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 | | |
| Is an attachment provided with the reason: | Yes ☐ | No ☐ |

The financial disclosures for all pivotal studies were reviewed and found to be accurate and adequate. No additional concerns were found during the review.

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/s/

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NICHOLAS S RISTER
03/27/2017

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03/27/2017