U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA # :	208945/Original-1, SDN 1
Drug Name:	(b) (4) (ozenoxacin cream, 1%)
Indication:	Topical treatment of impetigo in patients 2 months and older
Applicant:	Ferrer Internacional S.A.
Dates:	Stamp Date: June 23, 2016 PDUFA Goal Date: June 22, 2017 Review Completion Date: March 6, 2017
Review Priority:	Standard
Biometrics Division:	Division of Biometrics IV
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1 EXECUTIVE SUMMARY

This submission provided adequate evidence to demonstrate the efficacy and safety of the proposed drug product, [redacted] (b) (4) (ozenoxacin cream) for the treatment of impetigo in patients aged two months and over. Evidence to support this indication relied primarily upon two Phase 3 trials, Trials P-110880-01 and P-110881-01 (Trials 880 and 881). These trials were similar in design and defined the same primary endpoint of clinical response (success or failure) analyzed in the clinical ITT population (all randomized patients) at Visit 3, the end-of-therapy visit on Day 6-7.

In both trials, the Reviewer found clinical response rates to be 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. Reviewer sensitivity analyses showed that the treatment benefit was generally robust to various assumptions made regarding the analysis population, the timing of the visit and missing data. Additional Reviewer analyses in selected secondary endpoints including changes in the size of baseline lesions, absence of baseline lesions, Total Skin Infection Rating Scale (SIRS) scores and the use of concomitant antimicrobial therapy were also supportive of primary analysis findings. Other Reviewer analyses which considered treatment effects in various subgroups defined by selected demographic and baseline characteristics showed that the treatment difference favoring ozenoxacin was mostly consistent across subgroups.

The Reviewer did not identify any major issues in this submission. As discussed in **Section 5.1**, there were only a few minor issues identified. For example, Trials 880 and 881 specified different criteria in their respective designs and analyses which may have contributed to differences in efficacy findings (e.g. overall success rates were 27.0% in Trial 880 vs. 46.1% in Trial 881). There were also limited efficacy findings in a few subgroups such as patients 18 years and older where the treatment benefit was substantially smaller and patients with bullous impetigo where no treatment benefit was observed. These issues did not affect the adequacy of the overall evidence presented to support the proposed indication but could limit the ability to compare efficacy findings between studies and make inferences in a few subgroups. The Reviewer's recommendations for the Applicant related only to the proposed product labelling.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Ozenoxacin 1% cream is a topical product proposed for short term treatment of impetigo in adults and children aged 2 months and older. Ozenoxacin 1% cream is applied to the affected area twice daily for 5 days.

2.1.2 History of Product Development

The following is a timeline of some of the notable events in the history of product development for Ozenoxacin 1% cream:

- June 4, 2009: The Pre-IND was submitted for Ozenoxacin Cream under PIND 105,567.
- February 23, 2010: The initial IND was submitted (IND 105,567).
- June 10, 2011: An End of Phase 2 meeting was held in which the Agency provided guidance on the design of Trial 880 and 881.
- January 13, 2016: A Type B Meeting was held with the Agency to discuss the content and format of the NDA for Ozenoxacin Cream, 1%, for topical treatment of impetigo.

2.1.3 Specific Trials Reviewed

The following is a brief description of Trials 880 and 881:

Table 1: Brief Summary of Trials Assessed in the Statistical Review

Trial ID	Design	Treatment/ Sample Size	Endpoint/Analysis
880	Multi-center, randomized, double-blind, placebo and active controlled trial in pediatric (≥ 2 years) and adult patients with bullous or non-bullous impetigo	Ozenoxacin 0.5 g 1% cream, topical, every 12 hrs $N_{Ozenoxacin}$=155 $N_{Placebo}$=156 $N_{Retapumulin}$=154	Primary Endpoint: Clinical response in the ITTC population at EOT (Day 6-7) Primary Analysis: Testing the superiority of ozenoxacin versus placebo with respect to difference in proportions of patients with clinical success.
881	Multi-center, randomized, double-blind, placebo controlled trial in pediatric (≥ 2 months) and adult patients with bullous or non-bullous impetigo	Ozenoxacin 0.5 g 1% cream, topical, every 12 hrs $N_{Ozenoxacin}$=206 $N_{Placebo}$=206	Primary Endpoint: Clinical response in the ITTC population at EOT (Day 6-7) Primary Analysis: Testing the superiority of ozenoxacin versus placebo with respect to difference in proportions of patients with clinical success.

Source: Reviewer Table
EOT= End of Treatment, ITTC=Clinical Intent-to-treat

The Applicant also conducted a Phase 2 dose-ranging trial (Trial P080623-1) which assessed the efficacy of three strengths of ozenoxacin cream (0.25%, 1% or 2%) against placebo in patients with secondarily infected traumatic lesions (SITLs). This trial showed ozenoxacin cream 1% was the most optimal strength. Two pivotal trials (880 and 881) were then conducted to assess the efficacy of ozenoxacin cream 1% in patients with impetigo. As the primary focus of this review is on the efficacy and safety findings presented for Trials 880 and 881, the Phase 2 trial is not included above.

2.2 Data Sources

The Reviewer primarily considered the clinical summary of efficacy, clinical study reports and selected datasets which are described below for Trial 880 and 881 along with their links. The data formats used in this submission were SDTM and ADAM.

- Clinical Summary of Efficacy :
  - \\Cdsesub1\evsprod\NDA208945\0000\m2\27-clin-summary

- Clinical Study Reports:
  - \\Cdsesub1\evsprod\NDA208945\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\impetigo\5351-stud-rep-contr\p-110880-0
  - \\Cdsesub1\evsprod\NDA208945\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\impetigo\5351-stud-rep-contr\p-110881-0

- Datasets:
  - \\Cdsesub1\evsprod\NDA208945\0000\m5\datasets\p-110880-0\analysis\adam\datasets
    - adae.xpt - Adverse Events Analysis Dataset
    - adsl.xpt - Subject Level Analysis Dataset
    - adcm.xpt - Concomitant Medication Analysis Dataset
    - adxa.xpt - Clinical Assessment Analysis Dataset
    - adsv.xpt - Subject Visit Analysis Dataset
    - adxg.xpt - SIRS Analysis Dataset
    - addv.xpt - Protocol Deviations Analysis Dataset

  - \\Cdsesub1\evsprod\NDA208945\0000\m5\datasets\p-110881-0\analysis\adam\datasets
    - adae.xpt - Adverse Events Analysis Dataset
    - adsl.xpt - Subject Level Analysis Dataset
    - adcm.xpt - Concomitant Medication Analysis Dataset
    - adex.xpt - Trial Treatment Analysis Dataset
    - adcresp.xpt - Clinical Response Analysis Dataset
    - adtcresp.xpt - Time to Clinical Response Analysis Dataset
    - adnles.xpt - New Lesions Dataset
    - adsv.xpt - Subject Visit Analysis Dataset
    - adxg.xpt - SIRS Analysis Dataset
    - addv.xpt - Protocol Deviations Analysis Dataset

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Overall, there were no significant issues relating to the data quality of the studies. The Reviewer was able to reproduce all major analyses. A final statistical analysis plan (SAP) was submitted and relevant analysis decisions were made prior to unblinding.

3.2 Evaluation of Efficacy

The Reviewer's evaluation of efficacy in this submission relied on findings from Trials 880 and 881.

Trial 880 was titled "A phase III, 3 arms, multicenter, randomized, investigator-blind trial to assess the efficacy and safety of ozenoxacin 1% cream applied twice daily (b.i.d.) for 5 days versus placebo in the treatment of patients with impetigo". This trial included patients aged 2 years and above. It was conducted between March 2012 and January 2013 in 5 different countries and 27 Trial sites: U.S. (3), Germany (4), Romania (2), Ukraine (5), and South Africa (11).

Trial 881 was titled "A phase III, 2 arms, multicenter, randomized, double-blind trial 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". This trial included patients aged 2 months and above. It was conducted between June 2014 and May 2015 in 6 different countries and 44 Trial sites: U.S. (11), Puerto Rico (5), Germany (4), Spain (1), Romania (4), Russia (6), and South Africa (3).

These trials are similar in design with the main exceptions being that Trial 880 did not enroll patients between the ages of 2 months and 2 years and included a third study arm (retapamulin) for the purpose of testing internal validity. In Trial 880, the retapamulin and placebo arms were not patient blinded due to differences in appearance, however the ozenoxacin and placebo arms were double-blinded. Note that retapamulin has been established as effective for the indication of impetigo and is approved in the US as Altabax®.

Reviewer Comments: *The Reviewer primarily considers comparisons of ozenoxacin versus placebo in Trials 880 and 881 in evaluating the efficacy and safety of ozenoxacin.*

3.2.1 Study Design and Endpoints

In these studies, patients who met eligibility criteria on Day 1 were randomized 1:1:1 to either ozenoxacin, placebo or retapamulin (Trial 880) and 1:1 to either ozenoxacin or placebo (Trial 881). 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. The first application was done under the guidance of a delegated person appointed by the investigator. Patients returned for the following visits:

- Visit 2: Day 3-4 (on-therapy visit)
- Visit 3: Day 6-7 (end of therapy visit on the following day after last application)
- Visit 4: Day 10-13 (final visit)

Additionally, a telephone contact on Day 2 (24-36 hours after baseline visit) was required to assess for any worsening of infection.

Reviewer Comments: Many elements of Trials 880 and 881 were identical. Any differences will be identified throughout this section.

Trial Objectives

Primary Objective:

- The primary objective of both trials was to compare the efficacy of a b.i.d. topical application for 5 days (10 applications) of an ozenoxacin 1% cream versus placebo in patients with impetigo.

Secondary Objectives:

- A secondary objective of both trials was to evaluate the safety and tolerability of a b.i.d. topical application for 5 days (10 applications) of ozenoxacin 1% cream and retapamulin 1% ointment (Trial 880) in patients with impetigo.
- In Trial 880, another secondary objective was to compare the efficacy of a b.i.d. topical application for 5 days (10 applications) of retapamulin 1% ointment versus placebo in patients with impetigo to assess internal validity

Reviewer Comments: *Trial 880 includes an additional secondary objective related to showing internal validity based on comparisons involving a retapamulin arm.*

Inclusion Criteria

The inclusion criteria as summarized by the Reviewer are as follows:

- Written informed consent
- Male and female patients aged 2 years and above (Trial 880) or 2 months and above (Trial 881) with a clinical diagnosis of bullous or non-bullous impetigo. The total affected area had to be between 1-100 cm^2 (Trial 880) or between 2-100 cm^2 (Trial 881) with surrounding erythema not extending more than 2 cm from the edge of any affected area. For patients under 12 years of age, the total area cannot exceed a maximum of 2% of the body surface area.
- Total Skin Infection Rating Scale (SIRS) score of at least 8 (Trial 880) or a Total SIRS score (modified version) of at least 3 (Trial 881) including pus/exudate score of at least 1.
- Females of childbearing potential had to use a reliable method of contraception.

Reviewer Comments: *Due to differences in both SIRS scaling and the signs/symptoms included for SIRS scoring (See* ***Section 3.2.1****), Total SIRS scores and clinical assessments involving SIRS scoring (e.g. success rates at Visit 3) are not directly comparable across the trials.*

Key Exclusion Criteria

Some of the key exclusion criteria as summarized by the Reviewer based on importance are listed below. Patients included in the trial could not have any of the following:

- Underlying skin disease with clinical evidence of a secondary infection
- A bacterial infection that could not be treated appropriately with a topical antibiotic
- Signs/symptoms of systemic infection
- Documented or suspected bacteremia
- The use of anti-infective agents; topical treatments with antiseptics; systemic or topical analgesics, anti-inflammatory, or antihistaminic products; and/or systemic

prednisone were limited prior to entry into the trial and, in some cases, during the trial

- Subjects must not have applied any topical therapy directly on the impetigo lesions within 24 hours of entering the trial

Analysis Populations

- Intent-to-Treat Clinical Population (ITTC): all randomized patients (primary analysis population)
- Safety Population: all patients receiving trial medication (treatment arm assignment based on the treatment received)
- All Treated Population: all patients receiving trial medication (treatment arm assignment based on the planned treatment)
- Per Protocol Clinical Population (PPC): all ITTC patients who did not deviate from the protocol
- Intent-to-Treat Bacteriological Population (ITTB): all randomized patients with a pathogen identified at trial entry. (In Trial 881, this pathogen had to be *S. aureus* or *S.pyogenes*).
- Per Protocol Bacteriological Population (PPB): all PPC patients with a pathogen identified at trial entry

Efficacy Parameters

Evaluation of efficacy was based on the following assessments:

- Clinical assessment by investigator
- SIRS
- Microbiological response

Reviewer Comments: *This Review focuses on the efficacy parameters relating to clinical assessment and SIRS which are considered to be most relevant. Microbiological responses are not addressed in this review.*

Clinical Assessment by Investigator

Tables 2, 3 & 4 show the pre-specified definitions used for outcome classification and clinical evaluation at each of the post-baseline visits (Visits 2, 3 & 4). The Reviewer considers the definitions used at Visit 3 to be most relevant since the primary endpoint is evaluated at Visit 3 (Day 6-7, end-of-therapy visit)..

The clinical assessment at Visit 2 (Day 3-4) evaluated the progression of impetigo in the baseline affected area(s) from Visit 1 according to the Total SIRS score. Newly affected areas that appeared after Visit 1 were treated with the trial medication but were not considered in the clinical evaluation. By Visit 2, at least a 10% decrease in the Total SIRS score was expected for the patient to show 'clinical improvement'. Table 2 defines the clinical assessment categories.

Table 2: Clinical Assessment at Visit 2 (Day 3-4) - Definitions

	Definition
Early Cure (Trial 881	Sufficient improvement defined as: • Total SIRS score decreased >10% compared to baseline (Visit 1).

only)[1]	This was such that according to the Investigator criteria no further antimicrobial therapy could be necessary. The patient continued treatment with trial medication.
Improvement	Some degree of improvement defined as: • Total SIRS score decreased >10% compared to baseline (Visit 1). The patient may continue treatment with Trial medication or other antimicrobial therapy at the discretion of the investigator.
No improvement	- No change in Total SIRS score, OR - Total SIRS score increased compared to baseline (Visit 1), OR - Total SIRS score decreased ≤10% compared to baseline (Visit 1). The patient could continue treatment with Trial medication or other antimicrobial therapy at the discretion of the investigator.
Unable to determine	Patients who did not meet any of the outcomes listed above for Visit 2.

Source: Applicant Table 3 in CSR

[1] The 'Early Cure' definition was used in Trial 881 only. Criteria defined for 'Improvement', 'No Improvement' and 'Unable to Determine' were the same for Trials 880 and 881.

Table 3 shows the clinical assessment categories at Visit 3 (EOT, Day 6-7) in which the investigator evaluated the impetigo progression in the baseline affected areas from Visit 1 according to the Total SIRS score. 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 oedema 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).

Table 3: Clinical Assessment at Visit 3 (EOT, Day 6-7) - Definitions

Category/Classification	Definition
Clinical Success/ Cure[1]	- SIRS score = 0 for exudates/pus, crusting, tissue warmth and pain, AND ≤ 1 for erythema/inflammation, tissue oedema and itching. (Trial 880) - SIRS score=0 for blistering, exudates/pus, crusting, itching/pain AND ≤ 1 for erythema/inflammation (Trial 881) This was such that no additional antimicrobial therapy of the baseline affected area(s) necessary.
Clinical Failure/ Improvement	Some degree of improvement defined as: - Total SIRS score decreased >10% compared to baseline (Visit 1) not fulfilling the criteria of individual SIRS scores for cure. The patient could continue treatment with another antimicrobial therapy at the discretion of the investigator.
Clinical Failure/Failure	- No change in total SIRS score, OR - Total SIRS score increased compared to baseline (Visit 1), OR - Total SIRS score decreased ≤10% compared to baseline (Visit 1), This was such that additional antimicrobial therapy of the baseline affected area(s) necessary.
Unable to Determine/ Unable to Determine	Patients who did not meet any of the classifications listed above

Source: Partially Adapted from Applicant Table 4 in CSR

[1] The criteria defined for 'Cure' in Trial 880 differed slightly from those of Trial 881. Criteria defined for 'Improvement', 'No Improvement' and 'Unable to Determine' were the same for Trials 880 and 881.

Table 4 shows the clinical assessment at Visit 4 (Final Visit, Day 10-13) in which the investigator evaluated the impetigo progression in the baseline affected area(s) from Visit 1 according to the Total SIRS score as well as the patient classification at Visit 3. By Visit 4, patients classified as 'Cure' had to have a Total SIRS score of 0 and be classified as a 'Cure' at Visit 3. Patients with a Total SIRS score of 0 at Visit 4 who were not cures at Visit 3 were classified as a 'Post-therapy Cure'.

Table 4: Clinical Assessment at Visit 4 (Day 10-13, Follow-up)-Definitions

Category/Classification	Definition
Patients Classified as Cure at Visit 3	
Clinical Success/Cure	Total SIRS score = 0. * This was such that no further antimicrobial therapy of the baseline affected area(s) necessary.
Clinical Unchanged/ Unchanged[1]	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 oedema and itching. (Trial 880) Total SIRS > 0 and individual SIRS score 0 for blistering, exudates/pus, crusting and itching/pain and no more than 1for erythema/ inflammation, (Trial 881) * This was such that no further antimicrobial therapy of the baseline affected area(s) necessary.
Clinical Relapse/Relapse	Total SIRS score > 0 not fulfilling the criteria of individual SIRS scores for unchanged. * The patient could continue treatment with another antimicrobial therapy at the discretion of the investigator.
Patients Classified as Improvement or Failure at Visit 3	
Clinical Post-therapy Cure/ 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.
Clinical Failure/Failure	Patients a with total SIRS score >0 at Visit 4, OR patients who received another antimicrobial therapy, OR Patients classified as failure at Visit 3
All Patients	
Unable to determine/ Unable to determine	Patients who did not meet any of the classifications listed above.

Source: Adapted from Applicant Table 5 in CSR

[1] The criteria used for 'Unchanged' in Trial 880 differed slightly from those of Trial 881. Otherwise, the criteria were the same for both trials.

Reviewer Comments: *Clinical response at Visit 4 (Day 10-13, Follow-up) based on these classifications is listed as a secondary endpoint in Trials 880 and 881.*

Total Skin Infection Rating Scale (SIRS) Score

Trial 880

The Total SIRS score was determined at each visit in the baseline affected area(s) based on 7 signs or symptoms: exudate/pus, crusting, erythema/inflammation, tissue warmth, tissue oedema, itching and pain.

Each sign/symptom is rated on a scale from 0 to 6:

- 0 =absent
- 1
- 2 =mild
- 3
- 4 = moderate
- 5
- 6 =severe

The Total SIRS score is calculated by adding up subscores for each sign/symptom allowing a possible maximum score of 42.

Trial 881

The Total SIRS score was determined at each visit in the baseline affected area(s) based on 5 signs or symptoms: blistering, exudate/pus, crusting, erythema/inflammation and itching/pain.

Each sign/symptom is rated on a scale from 0 to 3:

- 0 = absent
- 1 = mild
- 2 = moderate
- 3 = severe

The Total SIRS score is calculated by adding up subscores for each sign/symptom allowing a possible maximum score of 15.

Reviewer Comments: *The modified version of the SIRS used in Trial 881 was implemented to be consistent with recommendations from the Draft Guidance of June 2010 for evaluation of a topical antibiotic in the treatment of impetigo using a modified SIRS.*

Trials 880 and 881

The following table summarizes the differences between Trials 880 and 881 with respect to using SIRS for the evaluation of signs and symptoms:

Table 5: SIRS Evaluation of Signs/Symptoms: Trial 880 and 881

Sign/Symptom Evaluated Yes/No)	Trial 880	Trial 881
Exudate/pus	Yes	Yes
Crusting	Yes	Yes
Erythema/Inflammation	Yes	Yes

Itching	Yes	Yes[1]
Pain	Yes	
Tissue Warmth	Yes	No
Tissue Edema	Yes	No
Blistering	No	Yes

[1]In Trial 881, itching and pain were combined
Source: Reviewer Table

Endpoints

Primary efficacy endpoint:

- Clinical response (success (cure) or failure) at end of therapy (Visit 3, Day 6-7) in the ITTC population. Criteria for cure are provided in Table 3.

Secondary Endpoints:

- Clinical response at Visits 2, 3 and 4 in the ITTC, PPC, ITTB, and PPB populations (except at Visit 3 in the ITTC which is the primary endpoint),
- 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 at Visits 2, 3 and 4 in the ITTB, and PPB populations
- Therapeutic response (combined clinical and microbiological response) at Visit 3 in the ITTB and PPB populations
- Time to clinical response
- Time to bacterial eradication

Reviewer Comments: *The secondary endpoints listed below were defined in Trial 881 only.*

Additional Secondary Endpoints (Trial 881 only):

- Clinical Response at Visit 3 in the ITTC, PPC, ITTB, and PPB populations with a combined criteria of clinical success including SIRS and size/extension of lesion, according to these criteria, clinical success was defined as meeting 1 of the following:
    - Total absence of the treated lesions (lesion extension=0)
    - Treated lesions became dry without crusts compared with baseline (SIRS=0 for exudate and for crusting)
    - 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, 3 and 4 in patients with *S.aureus* and *S.pyogenes* co-infection in the ITTB and PPB populations
- Clinical and microbiological response at Visits 2, 3 and 4 by microbiological susceptibility profile of pathogens identified at Visit in the ITTB and PPB populations
- Use of additional antimicrobial therapy at Visit 2 and 3 in the ITTC, PPC, ITTB and PPB populations
- Patient satisfaction with treatment in the ITTC, PPC, ITTB, and PPB populations

Reviewer Comments: *Reviewer analyses only considered selected secondary endpoints from the above lists. Some of these secondary endpoints could be analyzed in Trial 881 only.*

Prior and Concomitant Medication

The following medications were prohibited during the trial:

- 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 Trial
- 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)
- More than 15 mg of systemic prednisone or equivalent

3.2.2 Subject Disposition, Demographic and Baseline Characteristics

Trial 880

As shown in **Table 6**, Trial 880 included 465 randomized patients (155 ozenoxacin, 156 placebo and 154 retapamulin) in the clinical ITT (ITTC) population. Approximately 98.7% of these patients were included in the ITT Bacteriological (ITTB) population. The overall study completion rate was 97.8% with completion rates being higher in the ozenoxacin arm versus the placebo arm (98.7% versus 96.2%). In comparison to the ozenoxacin arm, the placebo arm also had more patients who were lost to follow-up (2 vs. 0 patients) or had worsening patient condition (3 vs. 0 patients).

Table 6: Subject Disposition, Trial 880

Category, n (% of ITTC)	Ozenoxacin (N=155)	Placebo (N=156)	Retapamulin (N=154)	Overall (N=465)
Patients randomized (ITTC)	155 (100%)	156 (100%)	154 (100%)	465 (100%)
Patients treated	155 (100%)	156 (100%)	153 (99.4%)	464 (99.8%)
Safety Population[1]	156 (100%)	156 (100%)	152 (98.7%)	464 (99.8%)
Per-protocol Clinical (PPC)	134 (86.5%)	132 (84.6%)	138 (89.6%)	404 (86.9%)
ITT Bacteriological (ITTB)	154 (99.4%)	152 (97.4%)	153 (99.4%)	459 (98.7%)
Per-protocol Bacteriological (PPB)	133 (85.8%)	128 (82.1%)	138 (89.6%)	399 (85.8%)
Patients completed trial	153 (98.7%)	150 (96.2%)	152 (98.7%)	455 (97.8%)
Patients discontinuing from trial:	2 (1.3%)	6 (3.8%)	2 (1.3%)	10 (2.2%)
Withdrawal of consent	2	1	0	3
Adverse event	0	0	0	0
Lost to follow-up	0	2	1	3
Worsening patient condition	0	3	0	3

Death	0	0	0	0
Other	0	0	1	1

Source: Reviewer Table

[1] The safety population differed from the ITTC due to two patients who were planned to receive retapamulin. One of these patients was not treated and the other patient mistakenly received ozenoxacin which resulted in the safety population having 156 patients in the ozenoxacin arm and the ITTC population having 155 patients in the ozenoxacin arm.

Table 7 shows the demographics and baseline characteristics for patients included in the ITTC population of Trial 880. In this population, the mean age was 16.1 years (median age of 9.0 years) with 61.0% of patients being under 12 years of age. The majority of patients were male (61.6%), black/African American (50.2%) or South African (67.3%). Many of these patients had non-bullous impetigo (79.4%), a single affected area (48.8%) or a SIRS score of < 15 (55.0%). Patients at baseline also showed a mean (median) total affected area of 11.4 cm^2 (4.0 cm^2) and a mean (median) Total SIRS score of 14.7 (14.0).

Table 7: Subject Demographics and Baseline Characteristics- ITTC, Trial 880

Category, n (%)	Ozenoxacin (N=155)	Placebo (N=156)	Retapamulin (N=154)	Overall (N=465)
Age:				
Mean (median) yrs.	16.1 (9.0)	17.3 (10.0)	15.0 (9.0)	16.1 (9.0)
Age Group:				
2 yrs. - < 12 yrs.	94 (60.6%)	94 (60.3%)	95 (61.7%)	283 (61.0%)
12 - < 18 yrs.	19 (12.2%)	18 (11.5%)	15 (9.9%)	52 (11.2%)
18 - < 65 yrs.	36 (23.1%)	40 (25.6%)	40 (26.3%)	116 (25.0%)
≥ 65 yrs.	6 (3.8%)	4 (2.6%)	3 (2.0%)	13 (2.8%)
Gender:				
Male	99 (63.9%)	96 (61.5%)	92 (59.7%)	286 (61.6%)
Female	56 (35.9%)	60 (38.5%)	62 (40.8%)	178 (38.4%)
Race:				
White	58 (37.2%)	62 (39.7%)	50 (32.9%)	170 (36.6%)
Black/African American	77 (49.7%)	77 (49.4%)	79 (51.3%)	233 (50.2%)
Mixed	19 (12.2%)	15 (9.6%)	22 (14.5%)	56 (12.1%)
Other	1 (0.6%)	2 (1.3%)	3 (1.9%)	5 (1.1%)
Region:				
South Africa	106 (68.4%)	98 (62.8%)	109 (70.8%)	313 (67.3%)
US	4 (3.8%)	11 (7.1%)	4 (2.6%)	26 (5.6%)
Europe	45 (29.0%)	47 (30.1%)	34 (22.1%)	126 (27.1%)
Type of Impetigo:				
Bullous	33 (21.3%)	34 (21.8%)	29 (18.8%)	96 (20.7%)
Non-bullous	122 (78.2%)	122 (78.2%)	125 (81.2%)	369 (79.4%)
Total Affected Area (cm^2):				
Mean (median)	9.4 (3.6)	12.8 (5.0)	12.1 (3.4)	11.4 (4.0)
Number of Affected Areas:				
1	72 (46.5%)	78 (50.0%)	77 (50.0%)	227 (48.8%)
2-4	59 (38.1%)	54 (34.6%)	44 (28.6%)	157 (33.8%)
5-10	18 (11.6%)	18 (11.5%)	24 (15.6%)	60 (12.9%)
> 10	6 (3.9%)	6 (3.9%)	9 (5.8%)	21 (4.5%)
Total SIRS Score:				

Mean (median)	15.1 (14.0)	15.0 (14.5)	14.0 (13.0)	14.7 (14.0)
Total SIRS Score Group:				
< 15	80 (51.3%)	78 (50.0%)	98(63.8%)	255(55.0%)
15 – 42	75 (48.4%)	78 (50.0%)	55 (36.2%)	209 (45.0%)
Pathogen Isolated:				
S.aureus	93 (60.0%)	98 (62.8%)	94 (61.0%)	285 (61.3%)
S.pyogenes	73 (47.1%)	67 (42.9%)	74 (48.1%)	214 (46.0%)
Staphylococcus epidermidis	31 (20.0%)	25 (16.0%)	24 (15.6%)	80 (17.2%)
Others	51 (32.9%)	58 (37.2%)	57 (30.1%)	166 (35.7%)

Source : Reviewer Table

Reviewer Comments: *There was a slight difference across study arms in Total SIRS score at baseline, with more retapamulin patients (63.8%) having a score < 15 compared to the ozenoxacin arm (51.3%).*

Trial 881

As shown in **Table 8**, Trial 881 included 412 randomized patients (206 ozenoxacin, 206 placebo) in the ITTC population. Approximately 59% of ITTC patients were included in the ITTB population. Similar to Trial 880, Trial 881 showed a higher completion rate in the ozenoxacin arm compared to the placebo arm (i.e. 97.1% versus 90.3%). The placebo arm also included more patients with worsening patient condition (13 vs. 0 patients).

Table 8: Subject Disposition, Trial 881

Category, n (%)	**Ozenoxacin (N=206)**	**Placebo (N=206)**	**Overall (N=412)**
Patients randomized (ITTC)	206 (100)	206 (100)	412 (100)
Patients treated (Safety)	206 (100)	205 (99.5)	411 (99.8)
Per-protocol Clinical (PPC)	195 (94.7)	195 (94.7)	390 (94.7)
ITT Bacteriological (ITTB)	125 (60.7)	119 (57.8)	244 (59.2)
Per-protocol Bacteriological (PPB)	119 (57.8)	112 (54.4)	231 (56.1)
Patients completing trial	200 (97.1)	186 (90.3)	386 (93.7)
Patients discontinuing from trial:	6 (2.9)	20 (9.7)	26 (6.3)
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*
Other	*1 (16.7)*	*1 (5.0)*	*2 (7.7)*

Source Partially adapted from Table 12 in CSR.

Reviewer Comments: *A substantially smaller proportion of patients were included in the ITTB population in Trial 881 versus Trial 880 (59.2% vs. 98.7%). This is due to the more specific definition used in the ITTB analysis population for Trial 881 which required that*

the pathogen be either S.aureus or S.pyogenes and the lower rate of S.pyogenes in Trial 881 (see next table).

Table 9 shows the demographics and baseline characteristics for patients included in Trial 881. In this population, the mean age was 18.7 years (median age of 10.6 years). This trial enrolled 28 subjects between the ages of 2 months and 2 years of age. The majority of patients were male (51.1%), white (63.6%) and less than 12 years of age (55.1%). Many of these patients at baseline had a non-bullous impetigo (85.7%) or a Total SIRS score of less than 9 (81.1%). Patients at baseline had a mean (median) affected area of 9.5 cm^2 (6.0 cm^2) and a mean (median) Total SIRS score of 7.6 (7.0).

Table 9: Subject Demographics and Baseline Characteristics- ITTC, Trial 881

Category, n (%)	Ozenoxacin (N=206)	Placebo (N=206)	Overall (N=412)
Age:			
Mean (median) yrs.	18.8 (10.8)	18.6 (10.4)	18.7 (10.6)
Age Group:			
2 mo. - < 12 yrs.	114 (55.3%)	113 (54.9%)	227 (55.1%)
2 mo. - < 2 yrs	12 (5.8%)	16 (7.7%)	28 (6.8%)
2 yrs - < 12 yrs	102 (49.5%)	97 (47.1%)	199 (48.3%)
12 - < 18 yrs.	23 (11.2%)	23 (11.2%)	46 (11.2%)
< 18 yrs.	137 (66.5%)	136 (66.0%)	273 (66.3%)
>= 18 yrs.	69 (33.5%)	70 34.1%)	139 (33.8%)
Gender:			
Male	112 (54.4%)	98 (47.8%)	210 (51.1%)
Female	94 (45.6%)	108 (52.4%)	202 (49.0%)
Race:			
White	122 (59.2%)	140 (68.0%)	262 (63.6%)
Black/African American	53 (25.7%)	38 (18.5%)	91 (22.1%)
Mixed	15 (7.3%)	13 (6.3%)	28 (6.8%)
Asian	16 (7.8%)	15 (7.3%)	31 (7.5%)
Type of Impetigo			
Bullous	25 12.1%)	34 (16.5%)	59 14.3%)
Non-bullous	181 (87.9%)	172 83.5%)	353 (85.7%)
Region			
South Africa	43 (20.9%)	34 (16.5%)	77 (18.7%)
US	65 (31.6%)	75 (36.4%)	140 (34.0%)
Europe	75 (36.4%)	74 (36.0%)	149 (36.2%)
Puerto Rico	23 (11.2%)	23 (11.2%)	46 (11.2%)
Total Affected Area (cm^2)[1]:			
Mean (median)	10.3 (6.0)	8.8 (6.0)	9.5 (6.0)
Number of Affected Areas[1]			
1	78 (38.1%)	89 (43.4%)	167 (40.7%)
2-4	104 (50.7%)	86 (42.0%)	190 (46.3%)
5-10	21 (10.2%)	27 (13.2%)	48 (11.7%)
> 10	2 (1.0%)	3 (1.5%)	5 (1.2%)
Total SIRS Score:			
Mean (median)	7.6 (7.0)	7.6 (7.0)	7.6 (7.0)

Total SIRS Score Group:			
< 9	168 (81.6%)	166 (80.6%)	344 (81.1%)
10 - 15	38 (18.5%)	40 (19.4%)	78 (18.9%)
Pathogen Isolated:			
S.aureus	115 (55.8%)	108 (52.4%)	223 (54.1%)
S.pyogenes	19 (9.2%)	20 (9.7%)	39 (9.5%)
Others	79 (38.3%)	68 (33.0%)	147 (35.7%)

Source: Reviewer Table

[1] Two patients had missing data regarding the number/area of the affected areas.

3.2.3 Statistical Methodologies

3.2.3.1 Statistical Methodologies (Applicant)

Primary Analysis

In Trials 880 and 881, the primary analysis involved testing the superiority of ozenoxacin versus placebo with respect to clinical response (clinical success or clinical failure) at the end of therapy visit (Visit 3) in the ITTC population. In Trial 880, a secondary comparison (for internal validity) of retapamulin versus placebo was performed. For primary as well as other related analyses, the Applicant used a chi-square test (without continuity correction) with corresponding 95% asymptotic (Wald) confidence interval (CI) to evaluate the difference in success rates. Sensitivity analyses were performed using different methods to impute missing data. Stratification analyses were performed for the primary efficacy endpoint, including clinical diagnosis, number of affected areas, baseline total affected area and baseline total SIRS score.

Reviewer Comments: *The Applicant's primary and secondary analyses conducted in the ITTC (and ITTB) populations excluded patients with missing data in the ITTC population. This resulted in slightly more conservative findings since the placebo arm tended to have more missing data. However, Reviewer analyses, as noted below, included all ITTC (and ITTB) patients in the analysis and considered patients with missing data as failures.*

Determination of Sample Size

In Trial 880, a sample size of 465 patients (155 per arm) was determined based on a 2-group chi-square test with a 5% 2-sided significance level, 90% power to detect a difference of 20% difference in proportions at Visit 3 and a drop-out rate of 20%.

- At least 258 patients from 2 years to less than 12 years old were to be included in a 1:1 ratio
- At least 24 patients from 12 to < 18 years old were to be included in a 1:1 ratio

In Trial 881, a sample size of 412 patients (206 per arm) was determined based on a 2-group chi-square test with a 5% 2-sided significance level, 90% power to detect a 15% difference in proportions at Visit 3 and a drop-out rate of 10%.

- At least 226 patients from 2 months to less than 12 years old were to be included in a 1:1 ratio
- At least 20 patients from 12 to < 18 years old were to be included in a 1:1 ratio

3.2.3.2 Statistical Methodologies (Reviewer)

The Reviewer used statistical methodologies which were similar to those proposed by the Applicant. However, the Reviewer primary analyses considered all patients with missing/indeterminate outcomes as failures. The Reviewer considers this to be a preferable approach since it adheres it the intent-to-treat principle. To better control for potential biases, the Reviewer conducted sensitivity analyses for missing data which considered observed cases only (same as Applicant's primary analysis) as well as the worst case scenario (i.e. failure for ozenaxacin and success for placebo). Reviewer analyses considered observed cases in the ITTC population for some of the secondary endpoints as these analyses were observed to provide more conservative findings.

3.2.4 Results and Conclusions

3.2.4.1 Reviewer Primary Analyses

Trial 880

Table 10 provides the Reviewer's primary analysis results for Trial 880. In the primary comparison of interest, ozenoxacin versus placebo, success rates at Visit 3 (EOT on Day 6-7) were significantly higher for ozenoxacin at 54/155 (34.8%) vs. 30/156 (19.2%), a treatment difference (Δ) = 15.6% (95% CI: 5.8%, 25.3%). The (two-sided) p-value of 0.002 was statistically significant since it met (fell below) the required significance level of $\alpha = 0.05$. The retapamulin treatment arm was also included in the trial for the purposes of testing internal validity. Since retapamulin showed superiority and performed according to expectations against placebo ($p < 0.001$), this finding was supportive of internal validity. Clinical improvement rates at Visit 2 and success rates at Visit 4 favored ozenoxacin over placebo. At Visit 2, clinical improvement rates for ozenoxacin vs. placebo were 147/155 (94.8%) vs. 46/156 (93.6%). At Visit 4, success rates ('success' included both clinical successes and post-therapy cures) were 82/155(52.9%) vs. 63/154 (40.7%)

Reviewer Comments: *Although this was not a stated objective of this trial, the Reviewer performed exploratory analyses comparing response classifications across visits among retapamulin patients. In general, patients in the retapamulin arm fared similar to or slightly better than patients in the ozenoxacin arm.*

Table 10: Clinical Improvement and Success Rates by Visit- ITTC, Trial 880

Category/Classification, n (%)	Ozenoxacin (N=155)	Retapamulin (N=154)	Placebo (N=156)
Visit 2, Day 3-4			
Clinical Improvement/Improvement	147 (94.8%)	143 (92.9%)	146 (93.6%)
No Clinical Improvement/	8 (5.2%)	11 (7.1%)	10 (6.4%)
No Improvement	5 (3.2%)	7 (4.5)	7 (4.5%)
Unable to Determine	3 (1.9%)	4 (2.6%)	3 (1.9%)
Difference in clinical improvement rate vs. placebo (95% CI), p-value	1.2% (-4.3%, 6.9%) p=0.637	-0.7% (-6.7%, 5.3%) p=0.798	
Visit 3, Day 6-7 (Primary Analysis)			
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 clinical success rate vs. placebo 95% CI), p-value	15.6% (5.8%, 25.3%) p = 0.002[1,2]	18.4% (8.5%, 28.2%) p < 0.001	
Visit 4, Day 10-13			
Success[4]	82 (52.9%)	92 (59.7%)	63 (40.4%)
Clinical Success/Cure	48 (31.0%)	52 (33.8%)	26 (16.7%)
Clinical Post-therapy/Post-therapy Cure[3]	34 (21.9%)	40 (26.0%)	37 (23.7%)
Failure[4]	73 (47.1%)	62 (40.3%)	93 (59.6%)
Clinical Unchanged/Unchanged	3 1.9%)	4 (2.6%)	2 (1.3%)
Clinical Relapse/Relapse	1 (0.6%)	0 (0%)	2 (1.3%)
Clinical Failure/Failure	64 (41.3%)	51 (33.1%)	82 (52.6%)
Unable to Determine/Unable to Determine	5 (3.2%)	7 (4.5%)	7 (4.5%)
Difference in success vs. placebo (95% CI), p-value[4]	12.5% (1.4%, 23.3%) p=0.027	19.4% (8.2%, 30.0%) p < 0.001	

Source: Reviewer Table

[1] Applicant's primary analysis of observed cases (i.e. patients classified as 'unable to determine' excluded) showed Δ = 15.5% (95% CI: 5.6%, 25.5%), p=0.003.

[2] Worst-case scenario analysis evaluating missing outcomes as 'failure' for ozenoxacin arm and 'success' for placebo showed Δ = 11.8% (95% CI: 1.7%, 21.7%), p=0.022.

[3] Post-therapy cures are 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.

[4] The Reviewer considered patients classified as a 'cure' or 'post-therapy cure' at Visit 4 as a 'success' and all other patients as 'failure'.

Reviewer Comments: *In contrast to Trial 881, Trial 880 did not assess early cures at Visit 2 and grouped them into the improvement category. Therefore, improvement rates cannot be directly compared across the two trials. Comparisons of improvement (Trial 880) versus early cure/improvement (Trial 881) are more comparable, but may still be limited by differences in SIRS scoring and signs/symptoms as discussed in* ***Section 3.2.1****.*

Trial 881

Table 11 shows the Reviewer's primary analysis results at Visit 3 (EOT, Day 6-7) along with results at Visits 2 (on-treatment, Day 3-4) and Visit 4 (follow-up, Day 10-13). Clinical success rates at Visit 3 were significantly higher in the ozenoxacin arm versus the placebo arm at 112/206 (54.4%) vs. 78/206 (37.9%), Δ = 16.5% (95% CI: 6.9%, 25.8%). The p-value for this comparison was less than 0.001 which met the required significance

level of $\alpha = 0.05$. Efficacy findings at Visits 2 and 4 supported primary efficacy findings. At Visit 2, there was a larger proportion of patients in the ozenoxacin arm with either an 'early cure' or 'improvement' classification at 192/206 (93.2%) vs. 173/206 (84.0%), Δ = 9.2% (3.2, 15.6), p=0.003. At Visit 4 the success rate was also observed to be higher in the ozenoxacin arm at 155/206 (75.2%) vs. 123/206 (59.7%), Δ = 15.5% (6.5. 24.3), p<0.001.

Table 11: Patient Response Classification by Visit- ITTC, Trial 881

Category/Classification, n (%)	Ozenoxacin (N=206)	Placebo (N=206)
Visit 2, Day 3-4		
Early Cure or Clinical Improvement[1]	192 (93.2%)	173 (84.0%)
Early Cure/Early Cure	26 (12.6%)	21 (10.2%)
Clinical Improvement/Improvement	166 (80.6%)	152 (73.8%)
No Clinical Improvement/	14 (6.8%)	33 (16.0%)
No Improvement	9 (4.4%)	17 (8.3%)
Unable to Determine	5 (2.4%)	16 (7.8%)
Difference (95% CI) in early cure or clinical improvement rate, p-value	9.2% (3.2%, 15.6%) p=0.003	
Visit 3, Day 6-7 (Primary Analysis)		
Clinical Success/Cure	112 (54.4%)	78 (37.9v)
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 (95% CI) in clinical success rate p-value	16.5% (6.9%, 25.8%) p < 0.001[2,3]	
Visit 4, Day 10-13		
Success[5]	155 (75.2%)	123 (59.7%)
Clinical Success/Cure	104 (50.5%)	72 (35.0%)
Clinical Post-therapy Cure/Post-therapy Cure	51 (24.8%)	51 (24.8%)
Failure[5]	51 (24.8%)	83 (40.3%)
Clinical Unchanged/Unchanged	4 (1.9%)	3 (1.5%)
Clinical Relapse/Relapse	3 (1.5%)	3 (1.5%)
Clinical Failure/Failure	38 (18.4%)	54 (26.2%)
Unable to Determine/Unable to Determine	6 (2.9%)	23 (11.2%)
Difference (95% CI) in success rate, p-value[5]	15.5% (6.5%, 24.3%) p < 0.001	

Source: Reviewer Table

[1] The Reviewer combined these categories to be consistent with the definition of improvement used for Study 880

[2] Applicant's primary analysis of observed cases showed Δ = 16.0% (95% CI: 6.3%, 25.6%), p=0.001.

[3] Worst-case scenario analysis evaluating missing outcomes as 'failure' for ozenoxacin and 'success' for placebo showed Δ = 13.1% (95% CI: 3.5%, 22.5%), p=0.008.

[4] Post-therapy cures are 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.

[5] The Reviewer considered patients classified as a 'cure' or 'post-therapy cure' at Visit 4 as a 'success' and all other patients as 'failure'.

Reviewer Comments: *The success rate in the ozenoxacin arm was substantially higher in Trial 881 than in Trial 880 (54.4% vs. 35.5%) however the treatment benefit over placebo was consistent in Trials 880 and 881 at 16.0% and 16.5%.*

3.2.4.2 Additional Reviewer Analyses

In addition to the sensitivity/exploratory analyses shown in Tables 11 and 12 which addressed clinical assessments across visits and the imputation of missing data, the Reviewer conducted further analyses to assess the robustness of primary analysis findings. This included an examination of other analysis populations (e.g. ITTB) and other endpoints of interest which included changes in Total SIRS scores, changes in the total affected area and absence of lesions. Analyses of success rates by pathogen were also performed. As these analyses do not statistically control for the overall type I error rate, p-values presented in this section should be interpreted with caution.

Trial 880

ITTB Analysis Population

Success Rates in the ITTB analysis population were similar to the rates observed among ITTC patients since the ITTB population included 98.7% of ITTC subjects. In ITTB subjects, success rates at Visit 3 favored ozenoxacin over placebo at 54/154 (35.1%) vs. 30/152 (19.7%), $\Delta = 15.3\%$ (95% CI: 5.3%, 25.1%), p=0.003.

Changes in Total SIRS Scores

Analyses of changes in Total SIRS scores across visits among ITTC patients with observed outcomes are shown in **Table 12.** These analyses show that patients in the ozenoxacin arm had a greater mean reduction (improvement) in scores across all visits at -8.9 vs. -7.0, $p < 0.001$ at Visit 2, -12.4 vs. -10.7, $p = 0.001$ at Visit 3, and -13.9 vs. -12.9, p=0.055 at Visit 4. These findings are consistent with primary analysis findings.

Table 12: Changes from Baseline in Total SIRS Scores by Visit- Observed Cases in ITTC, Trial 880

	Ozenoxacin (N=155)	**Placebo (N=156)**
Visit 1/Baseline		
Mean (SD)	15.1 (4.46), n=155	15.0 (4.00), n=156
Visit 2		
Mean (SD)	6.1 (4.12), n=153	7.9 (4.45), n=154
Change (Baseline to Visit 2) Mean (SD) Percent (SD)	 -8.9 (4.60) -59.2% (24.1%)	 -7.0 (4.43) -46.9% (23.8%)
p-value for difference in means	p<0.001	
Visit 3		
Mean (SD)	2.7 (2.93), n=153	4.3 (3.94), n=151
Change (Baseline to Visit 3) Mean (SD) Percent (SD)	 -12.4 (4.86) -81.7% (20.1%)	 -10.7 (4.79) -71.6% (23.8%)
p-value for difference in means	p=0.001	
Visit 4		
Mean (SD)	1.2 (2.1), n=152	2.0 (3.2), n=150
Change (Baseline to Visit 4) Mean (SD) Percent (SD)	 -13.9 (4.57) -92.5% (12.9%)	 -12.9 (4.44) -86.9% (19.7%)
p-value for difference in means[1]	p=0.055	

Source: Reviewer Table

[1]P-value based on a t-test for 2 independent samples.

Reviewer Comments: *These analyses based on observed cases likely led to more conservative findings at Visits 2 and Visit 4 where substantially more ITTC patients in the placebo arm were excluded due to missing assessments of SIRS scores. These patients would be expected to have less favorable outcomes had they been observed.*

Size of the Affected Area

Tables 13 examines the ratio of the size of the affected area each post-Baseline visit in relation to the size of the affected area at baseline. The ratio was smaller in the ozenoxacin group than in the placebo group at all visits (54.4% vs. 69.4% at Visit 2, 30.4% vs. 46.4% at Visit 3, and 16.3% vs. 31.0% at Visit 4) indicating greater efficacy in the ozenoxacin arm. Differences were significant at all visits.

Table 13: Ratio of Size of Affected Area at Visits 2, 3 and 4- Observed Cases in ITTC, Trial 880

	Ozenoxacin (N=155)	**Placebo (N=156)**
Visit 2	N=153	N=154
Mean (SD)	54.4% (31.78%)	69.4% (35.09%)
Median (min, max)	50.0% (0, 159%)	66.7% (0%, 182%)
p-value for mean difference	p<0.001	
Visit 3	N=153	N=151
Mean (SD)	30.4% (34.39%)	46.4% (42.37%)
Median (min, max)	14.9% (0%, 113%)	38.1% (0%, 321%)
p-value for mean difference	p<0.001	
Visit 4	N=152	N=150
Mean (SD)	16.3% (28.91%)	31.0% (61.96%)
Median (min, max)	0.7% (0%, 100%)	11.9% (0%, 625%)
p-value for mean difference	p=0.009	

Source: Reviewer Table

Mean (median) size of affected area at Baseline/Visit 1 was 9.4 cm^2 (3.6 cm^2) in the ozenoxacin group and 18.8 cm^2 (5.0 cm^2) in the placebo group. By Visit 4, the mean affected area was 16.3% of the affected area at baseline in the ozenoxacin group.

Absence of Lesions

Table 14 shows the proportion of patients achieving complete absence of baseline lesions at each post-Baseline visit (Visits 2, 3 and 4). At Visit 2, only a small number of patients achieved complete absence and differences between treatments were similar. At Visit 3, comparisons favored ozenoxacin at 32.0% vs. 15.9%, Δ =16.1% (95% CI: 6.6%, 25.5%), p=0.019. By Visit 4, comparisons were more strongly in favor of ozenoxacin at 57.2% vs. 36.0%, Δ= 21.2%, (95% CI: 10.0%, 31.9%), p < 0.001.

Table 14: Absence of the Baseline Lesions at Visits 2, 3 and 4- Observed Cases in ITTC, Trial 880

Absence of Baseline Lesions? n (%)	**Ozenoxacin (N=153)**	**Placebo (N=156)**	**Treatment Difference**

Visit 2 Yes	N=153 8 (5.2%)	N=154 7 (4.5%)	0.7% (-4.5%, 6.0%) p=0.781
Visit 3 Yes	N=153 49 (32.0%)	N=151 24 (15.9%)	16.1% (6.6%, 25.5%) p < 0.001
Visit 4 Yes	N=152 87 (57.2%)	N=150 54 (36.0%)	21.2% (10.0%, 31.9%) p < 0.001

Source: Reviewer Table

Concomitant Antimicrobial Therapy

In **Table 15**, statistical comparisons of the proportion of patients with the use of concomitant antimicrobial therapy in the safety population are performed. Concomitant antimicrobial therapies included "antibacterials for systemic use", "antibiotics and chemotherapeutics for dermatological use", and "antiseptics and disinfectants" Anatomical Therapeutic Chemical (ATC) Level 2 terms. As shown below, the most commonly taken concomitant medications were topical antibiotic agents.

Treatment comparisons showed lower rates of use of any concomitant antimicrobial therapy in the ozenoxacin arm versus the placebo arm at 20/156 (12.8%) vs. 33/156 (21.2%), Δ= -8.3% (95% CI: -16.7%, 0.0%), p=0.050. These findings are consistent with primary analysis findings.

Table 15: Use of Concomitant Antimicrobial Therapy at Visit 3- Safety Population, Trial 880

	Ozenoxacin (N=156)	Placebo (N=156)	Treatment Difference
Any antimicrobial therapy	20 (12.8%)	33 (21.2%)	-8.3% (-16.7%, 0.0%) p=0.0500
Antibacterials for systemic use	5 (3.2%)	8 (5.1%)	
Antibiotics and chemotherapeutics for dermatological use	14 (9.0%)	25 (15.4%)	
antiseptics and disinfectants	1 (0.6%)	0	

Source: Partially Adapted from Table 14.1.4.1

Reviewer Comments: *In contrast to Trial 881, the use of additional antimicrobial therapy during the course of therapy, as reported at Visits 2 and 3, was not evaluated by the Applicant.*

Clinical Response by Pathogen

Table 16 shows clinical response classification at Visit 3 by pathogen. Cure (clinical success) rates were significantly higher in the ozenoxacin arm among patients with either

S.aureus or *S.pyogenes* at baseline. These findings are strongly supportive of primary analysis findings.

Table 16: Clinical Response Classification at Visit 3 by Pathogen- ITTB, Trial 880

Pathogen/Classification	Ozenoxacin (N=154)	Placebo (N=152)	Treatment Difference (95% CI)	P-value
S.aureus	N=93	N=94		
Cure	35 (38.0%)	16 (17.2%)	20.6% (7.9%, 32.9%)	p=0.002
Improvement	57 (61.3%)	72 (76.6%)		
Failure	1 (1.1%)	1 (1.1%)		
Unable to Determine	0 (0%)	5 (5.4%)		
S.pyogenes	N=72	N=66		
Cure	29 (40.3%)	7 (10.6%)	29.7% (15.6%, 42.9%)	p<0.001
Improvement	42 (58.3%)	54 (81.8%)		
Failure	1 (1.4%)	1 (1.5%)		
Unable to Determine	0 (0%)	4 (6.1%)		

Source: Partially Adapted from Table 14.2.3.4.1

Trial 881

Success Rates in the ITTB Analysis Population

Success rates in the ITTB analysis population which included 244/412 (59.2%) of ITTC patients are shown in **Table 17.** Rates favored the ozenoxacin arm at 74/125 (59.2%) vs. 42/119 (35.3%), Δ = 23.9% (95% CI: 11.4%, 35.6%) which was more pronounced than in the primary analysis. These results are strongly supportive of primary analysis findings.

Table 17: Success Rates at EOT- ITTB, Trial 881

	Ozenoxacin (N=125)	Placebo (N=119)
Success, n (%)	74 (59.2%)	42 (35.3%)
Failure, n (%)	51 (63.2%)	77 (76.9%)
Difference (95% CI) in Success Rates ozenoxacin – placebo)	23.9% (11.4%, 35.6%)	
p-value	< 0.001	

Source: Reviewer Table

Changes from Baseline in Total SIRS Scores

Changes from Baseline in Total SIRS at Visits 2, 3 and 4 among observed cases in the ITTC population are shown in **Table 18**. Patients in the ozenoxacin arm achieved a greater (more favorable) mean change from baseline at Visit 2, -3.8 vs. -3.4 points (p=0.071) where findings were marginal and at Visit 3 where findings were significant at -6.0 vs. -5.2 points (p=0.004). Findings at Visit 4 were not significant but still favored the ozenoxacin arm at -7.1 vs. -6.9 points (p=0.437). These findings are supportive of the primary analysis.

Table 18: Changes from Baseline in Total SIRS Scores by Visit- Observed Cases in ITTC, Trial 881

	Ozenoxacin (N=206)	Placebo (N=206)
Visit 1/Baseline	N=206	N=206

Mean (SD)	7.6 (2.23)	7.6 (2.31)
Visit 2	N=201	N=190
Mean (SD)	3.8 (2.16)	4.1 (2.28)
Change from Baseline to Visit 2 Mean (SD)	-3.8 (2.14)	-3.4 (2.57)
p-value for mean difference	p=0.076	
Visit 3	N=204	N=203
Mean (SD)	1.6 (2.31)	2.4 (2.86)
Change from Baseline to Visit 3 Mean (SD)	-6.0 (2.73)	-5.2 (3.31)
p-value for mean difference	p=0.004	
Visit 4	N=200	N=186
Mean (SD)	0.6 (1.49)	0.6 (1.22)
Change from Baseline to Visit 4 Mean (SD)	-7.1 (2.48)	-6.9 (2.57)
p-value for mean difference	p=0.437	

Source: Reviewer Table

Reviewer Comments: *These analyses based on observed cases likely led to more conservative findings at Visits 2 and Visit 4 where substantially more ITTC patients in the placebo arm were excluded due to missing assessments of SIRS scores. These patients would be expected to have less favorable outcomes had they been observed.*

Analyses of the Size of the Affected Area

Tables 19 examines the ratio of the size of the affected area at each post-Baseline visit to the size of the affected area at baseline. The ratio was smaller in the ozenoxacin group than in the placebo group at all visits (52.9% vs. 60.1% at Visit 2, 19.6% vs. 40.6% at Visit 3, and 6.3% vs. 8.8% at Visit 4) with the most pronounced difference at Visit 3 where findings were significant at p=0.019.

Table 19: Ratio of Size of Affected Area by Visit to Size at Baseline- ITTC, Trial 881

	Ozenoxacin (N=206)	**Placebo (N=206)**
Visit 2	N=200	N=190
Mean (SD)	52.9% (31.1%)	60.1% (41.9%)
Median (min, max)	53.6% (0, 127%)	56.1% (0%, 437%)
p-value for mean difference	p=0.452	
Visit 3	N=203	N=202
Mean (SD)	19.6% (31.5%)	40.6% (78.2%)
Median (min, max)	4.3% (0%, 201%)	12.5% (619%)
p-value for mean difference	p=0.019	
Visit 4	N=199	N=185
Mean (SD)	6.3% (18.2%)	8.8% (27.1%)
Median (min, max)	0.0% (105%)	0.0% (254%)
p-value for mean difference	p=0.108	

Source: Reviewer Table

Mean (median) size of affected area at Baseline/Visit 1 was 10.3 cm^2 (6.0 cm^2) in the ozenoxacin group and 8.8 cm^2 (6.0 cm^2) in the placebo group. By Visit 4, the mean affected area was 6.3% of the affected area at baseline in the ozenoxacin group.

Absence of Lesions

Table 20 shows the proportion of patients achieving complete absence of baseline lesions at each post-Baseline visit (Visits 2, 3 and 4). A larger percentage of patients in the ozenoxacin arm vs. the placebo arm achieved absence of the baseline lesions across all visits. At Visit 3, differences were most pronounced at 41.4% vs. 30.2%, Δ = 11.2% (95% CI: 1.9%, 20.5%), p=0.019. Differences also favored ozenoxacin over placebo at Visit 2 and Visit 4 but were not significant.

Table 20: Absence of Baseline Lesions at Visits 2, 3 and 4- Observed Cases in ITTC, Trial 881

Absence of Baseline Lesions? n (%)	Ozenoxacin (N=206)	Placebo (N=206)	Treatment Difference
Visit 2	N=200	N=190	
Yes	8 (4.0%)	5 (2.6%)	1.4% (-2.2%, 4.9%) p=0.452
Visit 3	N=203	N=202	
Yes	84 (41.4%)	61 (30.2%)	11.2% (1.9%, 20.5%) p=0.019
Visit 4	N=199	N=185	
Yes	161 (80.9%)	137 (74.1%)	6.9% (-1.5%, 15.2%) p=0.108

Source: Reviewer Table

Use of Additional Antimicrobial Therapy

In **Table 21**, statistical comparisons of the proportion of patients with the use of additional antimicrobial therapy at Visit 3 are performed. The use of additional antimicrobial therapy was determined based on the concomitant medication form question at Visit 3 'Is additional antimicrobial therapy in the Baseline (Visit 1) affected area necessary?' Additional antimicrobial therapies were defined as "antibacterials for systemic use", "antibiotics and chemotherapeutics for dermatological use", and "antiseptics and disinfectants" Anatomical Therapeutic Chemical (ATC) Level 2 terms plus one ATC Level 3 term "corticosteroids, combinations with antibiotics". Additional antimicrobial therapy does not include the use of prior/concomitant antimicrobial therapy that was ongoing at the time of first dosing.

These analyses show that nearly all of the use of antimicrobial therapy was initiated after Visit 2. At Visit 3, lower rates of use were observed in the ozenoxacin arm at 20/204 (9.8%) versus 40/203 (19.7%) in the placebo arm. These findings are supportive of primary analysis findings.

Table 21: Use of Additional Antimicrobial Therapy at Visits 2 and 3, Observed Cases in Trial 881- ITTC

Use of Additional Antimicrobial Therapy?	Ozenoxacin (N=206)	Placebo (N=206)	Treatment Difference (95% CI), p-value
Visit 2	N=200	N=188	
Yes	1 (0.5%)	2 (1.1%)	-0.6%, n.e. n.e.
Visit 3	N=204	N=203	

Yes	20 (9.8%)	40 (19.7%)	-9.9% (-16.7%, -3.1%) p=0.005

Source: Partially Adapted from Table 14.2.16. 1
At Visit 2 there were 24 patients (6 in the ozenoxacin arm, 18 in the placebo arm) and at Visit 3 there were 5 patients (2 in the ozenoxacin arm, 3 in the placebo arm) with unknown use of antimicrobial therapy who were not included in the analysis.
n.e.='Not Estimable'

Clinical Response by Pathogen

Table 22 shows clinical response classification at Visit 3 by pathogen. Cure (clinical success) rates were significantly higher in the ozenoxacin arm among patients with either *S.aureus* and *S.pyogenes* at baseline. These findings are strongly supportive of primary analysis findings.

Table 22: Clinical Response Classification at Visit 3 by Pathogen- ITTB, Trial 881

Pathogen/Classification	Ozenoxacin (N=125)	Placebo (N=119)	Treatment Difference (95% CI)	p-value
S.aureus	N=115	N=108		
Cure	66 (57.4%)	36 (33.3%)	24.1% (11.0%, 36.3%)	p<0.001
Improvement	47 (40.9%)	58 (53.7%)		
Failure	2 (1.7%)	10 (9.3%)		
Unable to Determine	0	4 (3.7%)		
S.pyogenes	N=19	N=20		
Cure	15 (79.0%)	8 (40.0%)	39.0% (7.8%, 63.1%)	p=0.013
Improvement	3 (15.8%)	9 (45.0%)		
Failure	1 (5.3%)	2 (10.0%)		
Unable to Determine	0	1 (5.0%)		

Source: Reviewer Table

3.2.4.3 Efficacy Conclusions

Both studies met their primary objective of demonstrating the superiority of ozenoxacin to placebo based on clinical success rates at Visit 3. Primary analysis findings were found to be robust to various assumptions made regarding missing data which was minimal in both studies, the analysis population considered or the definition of the primary endpoint. Additional analyses were also supportive of primary efficacy findings.

3.3 Evaluation of Safety

In Trial 880, the number of patients in the safety population experiencing at least 1 treatment emergent adverse event (TEAE) was small at 35/464 (7.5%) and generally similar across treatment groups. The most common TEAE was nasopharyngitis which occurred in 8 (1.7%) of patients overall (4 (2.6%) of ozenoxacin patients, 4 (2.6%) of retapamulin patients and 0 (0%) of placebo patients). Rhinitis was another relatively common TEAE which occurred only in retapamulin patients at 3 (2.0%).

In Trial 881, the number of patients in the safety population experiencing at least 1 TEAE was lower than in Trial 880 at 15/411 (3.6%) and similar between treatment groups at 8 patients in the ozenoxacin arm versus 7 patients in the placebo arm. The only event term

reported by more than 1 patient in a group was eczema at 2/411 (0.5%) which was reported in one patient in the ozenoxacin arm and one patient in the placebo arm.

For further details regarding the evaluation of safety, please refer to the Clinical Review conducted Dr. Nicholas Rister.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age and Geographic Region

Trial 880

In Trial 880, subgroup analyses compared success rates in the ozenoxacin arm with the placebo arm by gender, race, age and geographic region. As shown in **Table 23**, differences in success rates favored the ozenoxacin arm for nearly all of the subgroups considered with the largest differences occurring in males, black/African Americans, younger patients (e.g. < 12 years or < 18 years) and patients from South Africa. However, consistent trends of larger treatment benefits in a subgroup across both studies were only observed for males and younger patients. Differences in treatment benefits among younger vs. older patients (< 18 years vs. ≥ 18 years) was especially pronounced in Trial 880 at 20.2% (95% CI: 9.0%, 31.2%), p < 0.001 vs. 3.8% (95% CI: -15.8%, 23.3%), p=0.705.

Table 23: Success Rates by Gender, Race, Age and Geographic Region, Trial 880-ITTC

	Ozenoxacin (N=155)	Placebo (N=156)	Difference (95% CI)	p-value
Gender				
Male	38/99 (38.4%)	19/96 (19.8%)	18.6% (5.9%, 30.8%)	p=0.004
Female	16/56 (28.6%)	11/60 (18.3%)	10.3% (-5.3%, 25.7%)	p=0.192
Race				
White	13/58 (22.4%)	10/62 (16.1%)	6.3% (-8.0%, 20.8%)	p=0.382
Black/African American	37/77 (48.1%)	17/77 (22.1%)	26.0% (11.0%, 39.9%)	p<0.001
Mixed/Other	4/20 (20.0%)	3/17 (17.6%)	2.4% (-25.2%, 28.2%)	p=0.856
Age				
2 yrs. - < 12 yrs.	34/94 (36.2%)	16/94 (17.0%)	19.2% (6.6%, 31.3%)	p=0.003
≥ 12 yrs.	20/61 (32.8%)	14/62 (22.6%)	10.2% (-5.7%, 25.8%)	p=0.206
12 - < 18 yrs.	6/19 (31.6%)	1/18 (5.6 %)	26.0% (0.5%, 50.1%)	p=0.043
< 18 yrs.	40/113 (35.4%)	17/112 (15.2%)	20.2% (9.0%, 31.2%)	p<0.001
≥ 18 yrs.	14/42 (33.3%)	13/44 (29.5%)	3.8% (-15.8%, 23.3%)	p=0.705
Geographic Region				
US/Europe	8/49 (16.3%)	10/58 (17.2%)	-0.9% (-15.3%, 14.2%)	p=0.900
South Africa	46/106 (43.4%)	20/98 (20.4%)	23.0% (10.3%, 35.0%)	p < 0.001

Source: Reviewer Table

Trial 881

In Trial 881, similar subgroup analyses were performed by gender, race, age and geographic region. In **Table 24**, differences in success rates favored the ozenoxacin arm

for most of subgroups and tended to be larger in patients who were male, white, younger (e.g. < 18 years or < 12 years) or from US or Europe. There were only a limited number of patients between the ages of 2 months to less than 2 years (N=28), however the treatment benefit observed in these patients appeared to be consistent with the benefit observed in among all younger patients < 12 years. In considering both Trial 880 and Trial 881, a consistent trend in a subgroup was most apparent among patients who were younger. Consistent with Trial 880, though less pronounced, Trial 881 showed a larger treatment benefit in younger vs. older patients (< 18 years vs. ≥ 18 years) at 16.9% (95% CI: 5.2%, 28.0%), p=0.005 versus 7.8% (95% CI: -8.6%, 23.8%), p=0.351.

Table 24: Success Rates by Gender, Race, Age and Geographic Region- ITTC, Trial 881

n/N (%)	Ozenoxacin (N=206)	Placebo (N=206)	Difference (95% CI)	p-value
Gender				
Male	60/112 (53.6%)	33/98 (33.7%)	19.9% (6.4%, 32.6%)	p=0.004
Female	52/94 (55.3 %)	45/108 (41.8%)	13.7% (-0.2%, 27.0%)	p=0.053
Race				
White	58/112 (51.8%)	39/140 (27.9%)	23.9% (11.9%, 35.5%)	p<0.001
Black/African American	43/53 (81.1%)	27/38 (71.1%)	10.1% (-7.4%, 28.5%)	p=0.260
Mixed/Other	11/31 (35.5%)	12/25 (48.0%)	-12.5% (-37.1%, 13.3%)	p=0.345[1]
Age				
2 mo. - < 12 yrs.	73/114 (64.0%)	44/113 (38.9%)	25.1% (12.2%, 37.2%)	p<0.001
2 mo. - < 2 yrs.	7/12 (58.3%)	6/16 (37.5%)	20.8% (-16.5%, 53.1%)	p=0.274
2 - < 12 yrs.	66/102 (64.7%)	38/97 (39.2%)	25.3% (11.7%, 38.4%)	p<0.001
≥ 12 yrs.	39/92 (42.4%)	34/93 (36.6%)	5.8% (-8.3%, 19.7%)	p=0.417
12 - < 18 yrs.	8/23 (34.8%)	8/23 (34.8%)	0.0% (-27.1%, 27.1%)	p>0.999
≥ 18 yrs.	31/69 (44.9%)	26/70 (37.1%)	7.8% (-8.6%, 23.8%)	p=0.351
< 18 yrs.	81/147 (59.1%)	52/136 (38.2%)	16.9% (5.2%, 28.0%)	p=0.005
Geographic Region				
US	25/65 (38.5)	16/75 (21.3)	17.1% (2.0%, 32.0%)	p=0.026
South Africa	37/43 (86.1)	27/34 (79.4)	8.6% (-10.5%, 25.0%)	p=0.440
Europe	40/75 (53.3)	26/74 (35.1)	18.2% (2.2%, 33.3%)	p=0.025
Puerto Rico	10/23 (43.5)	9/23 (39.1)	4.4% (-23.7%, 31.7%)	p=0.765

[1] P-value is for comparison favoring placebo over ozenoxacin
Source: Reviewer Table

Reviewer Comment: *The Reviewer also considered the treatment benefit in younger patients vs. older patients (<12 years vs. ≥ 12 years and < 18 years vs. ≥ 18 years) using findings combined across trials in* ***Table 27****. Findings indicated a substantially smaller treatment benefit in older patients. As discussed in* ***Section 5.2****, the Reviewer also*

explored possible reasons for these differences (e.g. differences in baseline characteristics between subgroups), however no clear reason was identified.

4.2 Other Special/Subgroup Populations

Other subgroup populations considered included the type of impetigo (bullous vs. non-bullous), the SIRS score at baseline, the number of affected areas and the size of the affected area. Due to substantially higher SIRS scores in Trial 881 resulting from differences in the SIRS scale version used, the cut-off used to classify high scores was ≥ 10 in Trial 880 and ≥ 15 in Trial 881.

Trial 880

Table 25 shows that for Trial 880 larger treatment benefits were observed in patients with non-bullous vs. bullous impetigo (22.1% vs. -8.1%) and patients with two or more affected areas vs. one affected area (24.3% vs. 6.0%). However, due to the limited number of patients with bullous impetigo, it is difficult to make inferences in this subgroup.

Table 25: Success Rates by Other Variables at Baseline, Trial 880- ITTC

	Ozenoxacin (N=155)	Placebo (N=156)	Difference (95% CI)	p-value
Type of Impetigo				
Bullous	5/33 (15.2%)	8/34 (23.5%)	-8.4% (-27.7%, 11.3%)	p=0.386
Non-bullous	49/122 (40.2%)	22/122 (18.0%)	22.1% (10.9%, 33.0%)	p<0.001
SIRS score				
< 15	35/80 (43.8%)	22/78 (28.2%)	15.5% (0.5%, 29.9%)	p=0.042
≥ 15	19/75 (25.3%)	8/78 (10.3%)	15.1% (3.6%, 27.4%)	p=0.015
Number of Areas Affected				
1 area	20/72 (27.8%)	17/78 (21.8%)	6.0% (-7.9%, 19.9%)	p=0.396
≥ 2 areas	34/83 (41.0%)	13/78 (16.7%)	24.3% (10.5%, 37.4%)	p<0.001
Size of Affected Areas				
≤ 2 cm^2	19/46 (41.3%)	9/34 (26.5%)	14.8% (-6.6%, 34.3%)	p=0.169
2 to 10 cm^2	24/74 (32.4%)	15/80 (18.8%)	13.7% (-0.1%, 27.3%)	p=0.051
≥ 10 cm^2	11/35 (31.4%)	6/42 (14.3%)	17.1% (-1.6%, 36.1%)	p=0.071

Source: Reviewer Table

Trial 881

Table 26 shows that for Trial 881 larger treatment benefits were observed in patients with SIRS scores < 10. Among patients with SIRS scores ≥10, the ozenoxacin arm showed slightly lower cure rates compared to placebo. However, due to the limited number of patients with SIRS scores ≥10, it is difficult to make inferences in this subgroup.

Table 26: Success Rates by Other Variables at Baseline- ITTC, Trial 881

	Ozenoxacin (N=206)	Placebo (N=206)	Difference (95% CI)	p-value
Type of Impetigo				
Bullous	12/25 (48.0%)	12/34 (35.3%)	12.7% (-12.5%, 36.9%)	p=0.326
Non-bullous	100/182 (55.3%)	66/172 (38.4%)	16.6% (6.2%, 26.6%)	p=0.002

SIRS score				
< 10	93/168 (55.4%)	57/166 (34.3%)	21.0% (10.4%, 31.2%)	p<0.001
≥ 10	19/38 (50.0%)	21/40 (52.5%)	-2.5% (-24.2%, 19.4%)	p=0.825
Number of Areas Affected				
1 area	43/78 (55.1%)	35/89 (39.3%)	15.8% (0.6%, 30.3%)	p=0.041
≥ 2 areas	68/127 (53.5)	43/116 (40.0%)	16.5% (3.9%, 28.5%)	p=0.010
Size of Affected Areas				
< 10 cm^2	83/141 (58.9)	61/145 (42.1%)	16.8% (5.2%, 27.9%)	p=0.005
≥ 10 cm^2	28/64 (43.8)	17/60 (21.8%)	15.4% (-1.6%, 31.5%)	p=0.074

Source: Reviewer Table

Reviewer Comment: *The Reviewer also considered the treatment benefit in patients with bullous vs. non-bullous impetigo using findings combined across trials in* ***Table 28****. These findings indicated a smaller treatment benefit among patients with bullous impetigo. As discussed in* ***Section 5.2****, the Reviewer explored possible reasons for these differences (e.g. differences in baseline characteristics between subgroups), however no clear reason was identified.*

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There were no major statistical issues noted. Minor issues included the following:

- Different criteria were used in the study design and analyses of Trials 880 and 881 which may have led to large differences in efficacy findings. This may have caused the treatment effects to vary across the studies. Overall success rates at Visit 3 were substantially higher in Trial 881 than in Trial 880 and treatment differences in improvement rates at Visit 2 and post-therapy cure rates (among failures at Visit 3) at Visit 4 were substantially larger in Trial 881.
    - Overall success rates at Visit 3 (Day 6-7) were 46.1% in Trial 881 versus 27.0% in Trial 880.
    - Improvement/early cure rates at Visit 2 (Day 3-4) were 94.8% vs. 92.9%, a difference of 1.2% in Trial 880 compared to 93.2% vs. 84.0%, a difference of 9.2% in Trial 881.
- Primary efficacy findings may be limited in a few subgroups such as patients between the ages of 2 months to less than 2 years of age, older patients (e.g. patients 12 years and older) and patients with bullous impetigo.
    - Patients between the ages of 2 months to less than 2 years were limited (N=28) since only Study 881 included this subgroup
    - Patients 12 years and older showed lower success rates compared to patients under 12 years at 10.2% vs. 19.2% in Trial 880 and 5.8% vs. 25.1% in Trial 881.
    - Patients with bullous impetigo at baseline (~ 20% of the clinical ITT population) showed slightly lower success rates versus placebo (29.3% vs. 29.4%)

5.2 Collective Evidence

The Applicant submitted two phase 3 results that showed superior results to placebo in the primary endpoint. Secondary endpoints were also found to be generally consistent with primary analysis findings. In contrast to Trial 880, Trial 881 included subjects from 2 months to 2 years of age, used a modified version of the SIRS based on different signs and symptoms, focused on 2 specific pathogens in the ITTB analysis, considered early cures at Visit 2, evaluated a different clinical response definition at Visit 3 and assessed the use of additional antimicrobial therapy. In contrast to Trial 880, Trial 881 had also observed a much higher overall success rate of 46.1% vs. 27.0%. Due to these trial differences, formal analyses using data pooled across trials (e.g. interaction tests among specific subgroups) were not performed.

The Reviewer generally focused on findings from individual trials, however findings combined across trials were observed for a few subgroups. These subgroups included age at baseline (< 12 years vs. ≥ 12 years and < 18 years vs. ≥ 18 years) and the type of impetigo at baseline (bullous vs. non-bullous) where differences in treatment benefits were observed. The Reviewer also analyzed the baseline characteristics within these subgroups (mainly disease severity) examining whether certain subgroups had substantially higher (or lower) risk factors which could lead to differences in the treatment effect between subgroups. This analysis did not identify any subgroup as having an exceptionally high (or low) risk profile that would unduly influence treatment comparisons across subgroups.

5.3 Conclusions and Recommendations

In conclusion, overall evidence of a treatment benefit from ozenoxacin cream was considered to be adequate. The Reviewer only identified a few minor issues which related to differences in criteria used in the design and analysis of the trials and limited efficacy findings in a few subgroups (e.g. patients with bullous impetigo). These issues did not affect the adequacy of the overall evidence presented to support the proposed indication but could limit the interpretation of efficacy findings across studies and within a few subgroups. The Reviewer has recommendations for the Applicant only relating to the proposed product labelling.

5.4 Labelling Recommendations

Discussions regarding labelling are currently ongoing. The Reviewer has the following preliminary recommendations regarding the proposed labelling.

- Only findings from the primary analysis were recommended for inclusion into Table 2 of label. (b) (4) (b) (4)
- Various edits were made for Table 2 of the label. For example, success rates for ozenoxacin and placebo in each study were rearranged to be side-by-side in the table.

(b) (4)

- (b) (4) a new table was recommended which showed clinical response rates at Visit 3 by study among patients with *S.aureus* or *S.pyogenes* pathogens at baseline.

6 APPENDIX

Table 27: Success Rates by Age at Baseline, ITTC- Trials 880 and 881 Combined

	Ozenoxacin (N=361)	Placebo (N=362)	Difference (95% CI)	p-value
Age at Baseline				
< 12 yrs.	107/208 (51.4%)	60/207 (29.0%)	22.5% (13.1%, 31.4%)	p<0.001
≥ 12 yrs.	59/153 (38.6%)	48/155 (31.0%)	7.6% (-3.1%, 18.1%)	p=0.162
< 18 yrs.	121/260 (46.5%)	69/248 (27.8%)	18.7% (10.4%, 26.8%)	p<0.001
≥ 18 yrs.	45/111 (40.5%)	39/114 (34.2%)	6.3% (-6.3%, 18.8%)	p=0.326

Source: Reviewer Table

Table 28: Success Rates by Type of Impetigo- ITTC, Trials 880 and 881 Combined

	Ozenoxacin (N=361)	Placebo (N=362)	Difference (95% CI)	p-value
Type of Impetigo				
Bullous	17/58 (29.3%)	20/68 (29.4%)	-0.1% (-16.0%, 15.9%)	p=0.99
Non-bullous	149/304 (49.0%)	88/294 (29.9%)	19.1% (11.3%, 26.6%)	p<0.001

Source: Reviewer Table

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/s/

CHRISTOPHER E KADOORIE
03/06/2017

KAREN M HIGGINS
03/06/2017
I concur

DIONNE L PRICE
03/07/2017
Concur