CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-746

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
(An Addendum)

OCT 17 1997

NDA: 50-746

Applicant: SmithKline Beecham Pharmaceuticals

Name of Drug: Bactroban® Cream

Indications: secondarily infected traumatic skin lesions (SITL)

The purpose of this addendum is to revise one of the paragraphs in page 23 of the statistical review issued on May 28, 1997. The error was due to the confusion of different names used for the same pathogen. Since *Streptococcus* Group A is the same pathogen as *Streptococcus pyogenes*, the third paragraph of page 23 should be changed as follows:

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STATISTICAL REVIEW AND EVALUATION

NDA:	50-746
Generic Drug Name:	mupirocin calcium cream
Drug Trade Name:	BACTROBAN® Cream
Dosage Form:	cream
Drug Class:	3S
Applicant:	SmithKline Beecham Pharmaceuticals

MAY 2 8 1997

Indications: secondarily infected traumatic skin lesions (SITL)

Documents Reviewed: Source of all documents reviewed was the CANDAR. The following items from the CANDAR were reviewed:
Item 2A - Proposed Text of the Labeling - Annotated
Item 2H - Clinical Data Summary and Results of Statistical Analysis
Item 8D - Summary of Controlled Clinical Trials
Item 8G - Integrated Summary of Efficacy
Item 8H - Integrated Summary of Safety
SAS datasets and SAS PHClin datasets were provided by the sponsor

Type of Review: Statistical

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I. Background

Bactroban® Cream is intended for the treatment of secondarily infected traumatic skin lesions (SITL) such as small lacerations, sutured wounds, or abrasions. Bactroban® Cream is a new formulation of mupirocin calcium in a mineral oil base. Unlike the currently available Bactroban® Ointment, mupirocin calcium cream does not contain polyethylene glycol (PEG), so the small potential for renal toxicity from the absorption of PEG when applied to wounds with denuded epithelium is eliminated.

The efficacy of mupirocin calcium cream was evaluated in two pivotal studies in which mupirocin calcium cream, applied three times daily for 10 days, was compared with oral cephalexin therapy administered four times daily for 10 days in the treatment of SITL.

Mupirocin calcium cream for use in the treatment of secondarily infected traumatic skin lesions is not approved in any country. Worldwide marketing applications are currently being prepared for this indication.

Bactroban® (mupirocin ointment) has been available in the US since 1987 with a single indication, treatment of impetigo due to: *S. aureus*, β-hemolytic streptococci and *S. pyogenes*. (NDA 50-591, approved December 31, 1987). Bactroban also is approved for treatment of skin infections in 103 foreign countries.

As of September 18, 1995, Bactroban® Nasal (mupirocin calcium ointment) is approved for the eradication of nasal colonization with methicillin-resistant *S. aureus* in adult patients and health care workers as part of a comprehensive infection control program to reduce the risk of infection among patients at high risk of methicillin-resistant *S. aureus* infection during institutional outbreaks. Bactroban Nasal also is approved by 21 foreign countries.

In no country has either product, *Bactroban* Ointment nor *Bactroban* Nasal been withdrawn or suspended from marketing for any reason related to safety or efficacy of the product.

II. Methods

II.A. Protocols

In the proposed labelling, the applicant requests the following indication:

Bactroban Cream (mupirocin calcium cream), 2% is indicated for the treatment of secondarily infected traumatic skin lesions due to *Staphylococcus aureus*, beta-homlytic *Streptococcus*, and *Streptococcus pyogenes*.

Two Phase III pivotal studies (129A and 129B) were conducted under identical protocols to support an indication of treatment of secondarily infected traumatic lesions, such as small lacerations, sutured wounds, or abrasions. Both studies were prospective, randomized, multicenter, double-blind, double-dummy, active-control trials designed to compare the efficacy, safety and tolerance of mupirocin calcium cream and oral cephalexin in the treatment of children and adults. Patients were randomized to apply active mupirocin calcium cream or placebo cream to the lesion under study three times daily for 10 days and to take oral cephalexin or oral cephalexin placebo four times daily for 10 days. All patients who weighed >40 kg received 250 mg caphalexin capsules while patients weighing ≤ 40 kg received cephalexin oral suspension for 25 mg/kg/day. The primary efficacy endpoint was clinical response at follow-up (7-12 days post therapy). Secondary efficacy endpoints were bacteriological response at follow-up and clinical and bacteriological response at end of therapy (2-3 days post therapy). The population of primary interest was the per protocol population, although an intent-to-treat analysis also was performed.

Patients of either sex of any age were eligible for the study if they presented with a secondarily infected open wound such as a small laceration, sutured wound, or abrasion, and were able to comply with the protocol.

Excluded from the study were patients who had a serious underlying disease; patients with multiple infected wounds; patients having previously demonstrated a hypersensitivity reaction to penicillins, cephalosporins, or other beta-lactam agents; patients receiving systemic antibacterial or steroid therapy or topical treatment of any kind within 24 hours of study entry; patients receiving an investigational compound within one month prior to entering the study, or during the study; patients previously enrolled in this study, and patients who were pregnant or breast feeding.

Patients were required to attend a preliminary visit pre-therapy (-2 to 0 days) to obtain a medical history, physical exam and clinical diagnosis; an on-therapy visit (3-5 days) for clinical assessment and safety; an end of therapy visit (2-3 days post-therapy) and a follow-up visit (7-12 days post-therapy) for determining clinical and bacteriological efficacy and safety.

The clinical response at follow-up (categorized as either " treatment success" or "treatment failure") in the per protocol population was the primary endpoint of these studies. A clinical success at follow-up was defined as a patient whose clinical outcome was "persistent clinical

success". A clinical failure at follow-up was defined as a patient whose clinical outcome was either "clinical recurrence" at follow-up or "clinical failure" at end-of-treatment.

At the preliminary visit (-2 to 0 days), the investigator obtained a medical history and determined if the patient had the protocol-defined diagnosis of a secondarily infected open wound, such as a small laceration, sutured wound, or abrasion and met all the other study entry criteria. A Wright stain slide was prepared from a sample of exudate from the wound. If white blood cells (WBCs) were observed on the Wright stain and the patient met all other eligibility criteria, the patient was enrolled and swab samples of the wound were obtained for culture and sensitivity testing. The wound infection was also graded for exudatepus, crusting, erythema inflammation, tissue warmth, tissue edema, itching, and pain according to the Skin Infection Rating Scale (SIRS).

Patients (children and adults) meeting the study entry criteria were randomized in a 1:1 ratio to receive either mupirocin calcium cream and cephalexin placebo or cephalexin and mupirocin calcium cream placebo. The study medications were applied three times daily and taken orally four times daily for 10 days. Patients or parents/legal guardians were instructed in the cleaning of the infected wound and in the application of the study medication/placebo. A diary card was provided for the patient or parent/legal guardian to record each application/dose of the study medication/placebo.

Patients returned for an on-therapy visit (days 3-5) at which time the investigator graded the wound infection according to the SIRS and performed a safety assessment. If in the investigator's clinical judgment, the condition of the patient had not improved or had worsened, the patient was withdrawn from the study and treated appropriately. Such patients were considered treatment failures only if they had been treated for a minimum of three days.

At the end of therapy visit (2-3 days post-therapy), the investigator again graded the wound infection according to the SIRS. The investigator also made a clinical evaluation of the patient's overall response to therapy and, if exudate was present, obtained bacteriology specimens for culture and sensitivity testing. At this time, the patient or parent/legal guardian was questioned regarding the tolerance of the study medication and returned the diary card and all unused study medication.

A follow-up clinical and bacteriological evaluation was performed 7-12 days post-therapy. The investigator assessed the wound infection according to the SIRS, made a clinical evaluation of the patient's overall response to therapy and collected bacteriology specimens from the lesion (if exudate was present) for culture and sensitivity testing. For those patients who were withdrawn from the study prior to the end of therapy, the follow-up visit was required for monitoring adverse experiences and additional medication.

Note: The protocol specified window for the follow-up visit (7-9 days) was expanded (7-12 days) with the agreement of FDA clinical reviewers in a face-to-face pre-NDA meeting on 14 May 96. It was also agreed that violation of the end of treatment visit window or missing the end-of-treatment visit would not exclude a patient from the per protocol population at follow-up.

Clinical response at follow-up (7-12 days post-therapy) in the per protocol population, categorized as either treatment success or failure, was the primary efficacy endpoint in this study. Clinical efficacy assessments were performed at follow-up only for patients who were treatment successes at end of therapy. Patients who were clinical failures at end of therapy were carried forward as clinical failures at follow-up. Patients who were "unable to determine" at end of therapy were, by definition, "unable to determine" at follow-up. By reviewing clinical signs and symptoms at the follow-up evaluation, the investigator determined whether a satisfactory response was maintained or there was a recurrence and classified the clinical response as one of the following:

- Persistent Clinical Success: Complete resolution or sustained improvement of signs and symptoms of infection for those patients who were clinical successes at the end of therapy. No exudatepus was present and no additional antibiotic therapy was required at the follow-up visit, nor was taken between the end of therapy and follow-up visits.

- Clinical Recurrence: Reappearance or worsening of signs and symptoms of infection for those patients who were a Clinical Success at the end of therapy, and additional antibiotic therapy was required.

- Unable to Determine: A valid assessment of clinical outcome could not be made (e.g., patient did not attend or consent to clinical examination; an alternate antibiotic was administered for an intercurrent illness, etc.)

A clinical treatment success was a patient with a clinical response of "Persistent Clinical Success" at follow-up. A clinical treatment failure was defined as a patient whose clinical response was "Clinical Recurrence" at follow-up. Clinical failures at end-of-treatment were added to the failure category at follow-up to determine the overall response rate.

Secondary efficacy endpoints in these studies included the clinical response at follow-up in the ITT population, the bacteriological response at follow-up (categorized as either "treatment success" or "treatment failure") in the per protocol and ITT populations, and the clinical and bacteriological responses at end-of-treatment in the per protocol and ITT populations. A bacteriological "success " at follow-up was defined as a patient whose pre-therapy pathogen outcome at follow-up was "persistent presumed eradication" and who had no reinfecting pathogens appearing at follow-up. A bacteriological "success" at end-of-treatment was defined as a patient whose pre-therapy pathogen outcome at end-of-treatment was "presumed eradication" and who had no superinfecting pathogens appearing at end-of-treatment. A clinical "success" at end-of-treatment was defined as a patient whose clinical outcome at end-of-treatment was "clinical success".

II.B. Statistical Methods

In the applicant's analysis, the primary efficacy endpoint, clinical response at follow-up of a patient in the clinical per protocol population at follow-up was analyzed using categorical data analysis techniques via PROC CATMOD. The effect for center and treatment by center

interaction could not be assessed because of the large number of centers having a few patients (29 out of 47 centers had less than 10 patients). Hence only the treatment effect for the binary response (i.e., treatment success or failure, where failure included recurrence, clinical failure at end of therapy and unable to determine) was assessed. Two-sided 95% confidence intervals were used to evaluate the differences in the proportion of interest where the difference = (proportion of mupirocin calcium cream responders) - (proportion of cephalexin responders). The distribution of clinical response categorized as "Clinical Success", "Recurrence", "Clinical Failure at End of Therapy", "Unable to Determine" was summarized for each treatment group. Clinical response at follow-up in the intent-to-treat clinical population also was analyzed in a similar manner. For the intent-to-treat population, the "Unable to Determine" clinical response at follow-up was included in the failure group.

***Reviewer Note**: The applicant did not included a continuity correction in the calculation of the confidence intervals. However, a continuity correction is used in the calculation of the confidence intervals in this report as noted.*

Secondary endpoints included the bacteriological response at follow-up as well as clinical and bacteriological response at end of therapy in the per protocol and intent-to-treat populations. Number and percent of patients according to binary response (i.e., treatment success or failure) were presented for each treatment group. The two-sided 95% confidence intervals for the difference in the proportion of interest were also presented.

Wilcoxon rank sum test was performed to test for differences in the total SIRS scores between the two treatment groups. Differences between treatment group were tested for individual SIRS items using Cochran-Mantel-Haenzel test.

The baseline demographic and medical history characteristics such as: age, sex, race, wound type, wound site, baseline SIRS scores, baseline pathogens and baseline medical history were included in the covariate analysis to determine the relative performance of each treatment. None of the potential prognostic variables were shown to be important in predicting response of the treatment. The effect of study medication compliance on the performance of the treatment was also examined. The analysis indicated that the compliance to study medication was predictive of the clinical response; this was found to be true for both treatment groups.

II.C. Integrity of applicant's data

Throughout the phase III development of this drug for this indication, there was ongoing communication between the applicant and the FDA regarding necessary requirements for demonstrating the product's efficacy and safety. There was confirmed agreement on the protocol including inclusion/exclusion criteria, evaluability criteria, and outcome assessment. As a result, the NDA submission for the two pivotal clinical studies included all information needed for the FDA reviewers to confirm that the applicant had conformed to the agreed to protocol. Since the clinical reviewer and statistical reviewer were able to verify the integrity of the applicant's

database, it was not necessary to produce a separate database based upon the clinical reviewer's patient assessments for analysis.

The following safety and efficacy summaries are based upon the applicant's data as submitted to the FDA in the NDA and within the CANDA and SAS datasets.

III. Efficacy

1) *Intent-to-Treat (ITT) Population*

All patients who were randomized were included in the clinical intent-to-treat population at end of therapy and follow-up. A subset of the clinical intent-to-treat population consisted of those patients who had pre-treatment pathogens. This was the bacteriological intent-to-treat population at end of therapy and follow-up visits.

2) *Per Protocol (PP) Population*

The clinical and bacteriological per protocol populations at end of therapy and follow-up included only those patients who met the criteria for evaluability as determined by the applicant prior to breaking the blind.

The primary efficacy endpoint was the clinical response of a patient in the clinical per protocol population at follow-up. Secondary endpoints included the bacteriological response at follow-up as well as the clinical and bacteriological responses at end of therapy in per protocol and ITT populations.

Number and percent of patients according to binary response (i.e., treatment success or failure) was presented for each treatment group at end of therapy and at follow-up . Two-sided 95% confidence intervals were used to evaluate the differences in the proportion of patients who were treatment successes in the mupirocin calcium treatment group minus the proportion of patients who were treatment successes in the cephalexin group. The confidence intervals are reported as n_t , n_c (95% CI) p_t , p_c where n_t is the number in the test group, n_c is the number in the control group, p_t is the percent cured in the test group, and p_c is the percent cured in the control group. Categorical data analyses were performed by the applicant to test the treatment effect on clinical and bacteriological response at follow-up for the per protocol and ITT populations.

III.A. Study 129A Efficacy

A total of 333 patients was randomized into the study. A summary of the number of patients randomized, completed and valid for efficacy is presented in Table 1.

Table 1: The number of patients screened and randomized into study 129A as well as the number who completed the study and who were evaluable in the efficacy analyses

Number of Patients	Mupirocin Calcium Cream	Cephalexin	Total
screened	--	--	351
randomized	162	171	333
completed study	141	150	291
premature discontinuations	21	21	42
evaluated for ITT / per protocol	162 / 115	171 / 119	333 / 234
evaluated for safety	162	171	333

Forty two patients were withdrawn from the study. Twenty one (13.0%) patients in the mupirocin calcium group and 21 (12.3%) patients in the cephalexin group were withdrawn. The most common reason for withdrawal in both groups was AEs, 3.7% and 4.1% in the mupirocin calcium and cephalexin groups, respectively. The number of patients withdrawn from the study is presented by reason withdrawn for each treatment group in Table 2.

Table 2 The number (%) of randomized patients who completed study 129A or were withdrawn by the reason for study withdrawal

	Mupirocin Calcium Cream (N = 162)		Cephalexin (N = 171)	
Reason for Study Conclusion	n	(%)	n	(%)
Completed study*	141	(87.0)	150	(87.7)
Withdrawal due to:				
Adverse experience	6	(3.7)	7	(4.1)
Lack of efficacy	5	(3.1)	5	(2.9)
Deviation from protocol	2	(1.2)	2	(1.2)
Lost to follow-up	6	(3.7)	4	(2.3)
Other reason	2	(1.2)	3	(1.8)

* Patients who completed the study as planned met all study entry criteria, completed the 10-day dosing phase of the study, and returned for an end-of-treatment and follow-up visit, irrespective of their clinical outcomes.

Demographic data were collected at the preliminary visit for each of the 333 patients randomized into the study. The number and percent of patients by gender, race, mean age and age range for each treatment group in the intent-to-treat and per protocol clinical populations are presented in Table 3. There were no notable differences in the demographic characteristics of the two treatment groups in the clinical ITT population. Furthermore, the demographic profile of the clinical per protocol population at follow-up closely mirrored that of the ITT population.

Table 3 Demographic characteristics of all randomized* patients in study 129A, as well as those in the per protocol clinical analyses at follow-up

Demographic Characteristics	Intent-to-Treat (ITT) Mupirocin Calcium Cream (N = 162) n	(%)	Cephalexin (N = 171) n	(%)	Per-Protocol (PP) Mupirocin Calcium Cream (N = 115) n	(%)	Cephalexin (N = 119) n	(%)
Sex								
Male	91	(56.2)	89	(52.0)	63	(54.8)	70	(58.8)
Female	71	(43.8)	82	(48.0)	52	(45.2)	49	(41.2)
Age (years)								
< 2	1	(0.6)	2	(1.2)	0	(0.0)	2	(1.7)
2 - 11	24	(14.8)	33	(19.3)	17	(14.8)	27	(22.7)
12 - 16	15	(9.3)	12	(7.0)	9	(7.8)	11	(9.2)
17 - 45	80	(49.4)	81	(47.4)	56	(48.7)	55	(46.2)
46 - 65	26	(16.0)	25	(14.6)	20	(17.4)	15	(12.6)
> 65	16	(9.9)	18	(10.5)	13	(11.3)	9	(7.6)
Mean SD	33.94	21.0	32.98	22.5	35.12	21.1	29.58	21.0
Minimum								
Maximum								
Race								
Caucasian	115	(71.0)	135	(78.9)	81	(70.4)	95	(79.8)
Black	15	(9.3)	11	(6.4)	13	(11.3)	7	(5.9)
Oriental	5	(3.1)	4	(2.3)	5	(4.3)	3	(2.5)
Other	27	(16.7)	21	(12.3)	16	(13.9)	14	(11.8)

*All randomized patients = intent-to-treat clinical population

***Reviewer Note**: For the primary efficacy endpoint, clinical response at follow-up in the per protocol population, there were no statistically significant differences in response rate by sex, by age groups (<45, 45-65, and >65) or by race.*

Table 4 summarizes the clinical efficacy for the four patient populations.

Table 4: Clinical response at follow-up visit in study 129A

Population	mupirocin calcium n cured / N evaluable	%	cephalexin n cured / N evaluable	%	95% confidence interval* LCL	UCL
Clinical ITT	126 / 162	77.8	135 / 171	78.9	-10.6	8.3
Clinical PP	108 / 115	93.9	112 / 119	94.1	-7.1	6.7
Bacteriological ITT	70 / 95	73.7	87 / 112	77.7	-16.7	8.7
Bacteriological PP	44 / 47	93.6	56 / 57	98.2	-14.3	5.1

* confidence interval calculated using continuity adjustment.

***Reviewer Note**: For the primary efficacy endpoint, clinical response at follow-up in the per protocol population, the 95% confidence interval $_{115,\ 119}$ (-7.1% , 6.7%) $_{93.9\%,\ 94.1\%}$ indicates that the two treatment groups are therapeutically equivalent based upon DAIDP's Points to Consider.*

In a patient by patient review of study withdrawals, it was found that patients withdrawn due to lack of efficacy who had been treated for 3 or more days were not included as treatment failures

at follow-up as they should have been. In each treatment group, there should have been 3 additional failures in the mupirocin calcium treatment group and in the cephalexin treatment group). In the withdrawals due to adverse events, patient should have been carried forward as a failure in the cephalexin treatment group. Finally, there was one patient in the mupirocin calcium treatment group who missed the end-of-treatment visit but was a success at the follow-up visit and who should have been counted as a success. At the pre-NDA meeting on 14May96, it was agreed that violation of the end-of-treatment visit window or missing the end-of-treatment visit would not exclude a patient from the per protocol population at follow-up. As a result of these reclassifications in the per protocol population at follow-up the confidence interval becomes $_{119,123}$ (-7.4%, 8.5%) $_{91.6\%, 91.1\%}$ *which is still consistent with establishing therapeutic equivalency based upon DAIDP's Points to Consider.*

The investigator for center 11 was under investigation by DSI at the time of this review. When center 11 is excluded, the 95% confidence interval for clinical response at follow-up in the per protocol population becomes $_{103,101}$ (-6.6%, 8.8%) $_{94.2\%, 93.1\%}$ *which is even stronger evidence that mupirocin calcium is therapeutically equivalent with cephalexin in the treatment of SITL. Refer to the clinical reviewer's review for tables that show the effect of excluding center 11 on patient withdrawals, demographics, types of wounds treated in the clinical and bacteriological populations, clinical and bacteriological response rates, and adverse experiences. Exclusion of center 11 had no effect on the analysis or conclusions beyond a uniform reduction in counts.*

The clinical success rate at follow-up was examined by pre-therapy pathogen for the bacteriological per protocol population. The bacteriological successes by pre-therapy pathogen, shown in Table 5, paralleled the clinical successes in the bacteriological per protocol population at follow-up. This was an artifact of the design of the study analysis. Since bacteriological specimens were obtained only from clinical failures (by definition a clinical success can have no exudate present) all pre-existing pathogens of a clinical success were presumed eradicated. In Table 5, a bacteriological success rate of less than 100% for a given pre-therapy pathogen does not necessarily mean that pathogen was not eradicated in 100% of its pre-therapy occurrences. Bacteriological success, a patient outcome, by pre-therapy pathogen is not the same as bacteriological eradication, a pathogen outcome. The patient bacteriological outcome is determined not only by the fate of pre-therapy pathogens, but also, the appearance of superinfecting or reinfecting pathogens. It could be that a patient presenting with the pre-therapy pathogen in question was superinfected with another pathogen coincident with the eradication of the pre-therapy pathogen. This is precisely the situation for *S.aureus*. While 24 of 26 mupirocin patients presenting with *S.aureus* were bacteriological successes at FU, all 26 isolates of *S.aureus* were eradicated.

Table 5 Bacteriological success at follow-up by the most common pre-therapy pathogens in the mupirocin group (per protocol bacteriological population) in study 129A

	MupirocinCalcium Cream (N = 47)		Cephalexin (N = 57)	
Pre-therapy pathogen	**n/N**	**(%)**	**n/N**	**(%)**
S. aureus	24/26	(92.3)	32/32	(100.0)
K. oxytoca	1/4	(25.0)	1/1	(100.0)
Ent. agglomerans	3/3	(100.0)	2/2	(100.0)
Acinet lwoffi	3/3	(100.0)	1/1	(100.0)
Ent. cloacae	3/3	(100.0)	1/1	(100.0)
Aci. Baumannii	3/3	(100.0)	4/4	(100.0)
Enterococcus	2/2	(100.0)	3/3	(100.0)
Bacillus sp	2/2	(100.0)	5/6	(83.3)
Strep. Group A	2/2	(100.0)	7/7	(100.0)
Xanthomonas maltophila	2/2	(100.0)	2/2	(100.0)
Total pre-therapy pathogens	**67**		**96**	
Number of patients who were a bacteriological success	**44**	**(93.6)**	**56**	**(98.2)**

n = bacteriological successes with that pathogen pre-therapy
N = all patients with that pathogen pre-therapy

III.B. Study 129B Efficacy

A total of 373 patients was randomized into the study. A summary of patients randomized, completed and valid for efficacy is presented in Table 6..

Table 6: The number of patients screened and randomized into study 129B as well as the number who completed the study and who were evaluable in the efficacy analyses

No. of Patients	Mupirocin Calcium	Cephalexin	Total
screened			418
randomized	195	178	373
completed treatment	176	163	339
premature discontinuations	19	15	34
evaluated for ITT / per protocol	195 / 130	178 / 114	373 / 244
evaluated for safety	195	178	373

A total of 34 patients was withdrawn from the study, 19 (9.7%) in the mupirocin calcium group and 15 (8.4%) in the cephalexin group. The most common reason for withdrawal in the mupirocin calcium and the cephalexin groups was deviation from protocol; (3.1%) and (4.5%), respectively. The number of patients withdrawn from the study is presented by reason withdrawn for each treatment group in Table 7.

Table 7: The number (%) of randomized patients who completed study 129B or were withdrawn by the reason for study withdrawal

	Mupirocin Calcium Cream (N = 195)		Cephalexin (N = 178)	
Reason for Study Conclusion	n	(%)	n	(%)
Completed study*	176	(90.3)	163	(91.6)
Withdrawal due to:				
Adverse experience	4	(2.1)	0	--
Lack of efficacy	1	(0.5)	2	(1.1)
Deviation from protocol	6	(3.1)	8	(4.5)
Lost to follow-up	3	(1.5)	5	(2.8)
Other reason	5	(2.6)	0	--

* Patients who completed the study as planned met all study entry criteria, completed the 10-day dosing phase of the study, and returned for the end-of-treatment and follow-up visits, irrespective of their clinical outcomes.

Demographic data were collected at the preliminary visit for each of the 373 patients enrolled in the study. The number and percent of patients by sex, race, mean age and age range for each treatment group in the intent-to-treat and per protocol clinical populations are presented in Table 8. There were no notable differences in the demographic characteristics of the two treatment groups in the clinical ITT population. Furthermore, the demographic profile of the clinical per protocol population at follow-up was similar to that of the ITT population.

Table 8: Demographic characteristics of all randomized* patients, as well as those in the per protocol clinical analyses at follow-up in study 129B

	Intent-to-Treat (ITT)				Per-Protocol (PP)			
	Mupirocin Calcium Cream (N = 195)		Cephalexin (N = 178)		Mupirocin Calcium Cream (N = 130)		Cephalexin (N = 114)	
Demographic Characteristics	n	(%)	n	(%)	n	(%)	n	(%)
Sex								
Male	96	(49.2)	93	(52.2)	59	(45.4)	56	(49.1)
Female	99	(50.8)	85	(47.8)	71	(54.6)	58	(50.9)
Age (years)								
< 2	3	(1.5)	6	(3.4)	3	(2.3)	5	(4.4)
2 - 11	21	(10.8)	17	(9.6)	13	(10.0)	10	(8.8)
12 - 16	11	(5.6)	15	(8.4)	7	(5.4)	9	(7.9)
17 - 45	92	(47.2)	81	(45.5)	62	(47.4)	53	(46.5)
46 - 65	43	(22.1)	31	(17.4)	28	(21.5)	20	(17.5)
> 65	25	(12.8)	28	(15.7)	17	(13.1)	17	(14.9)
Mean SD	38.46	21.1	38.60	22.8	38.08	21.1	38.40	22.6
Minimum								
Maximum								
Race								
Caucasian	174	(89.2)	162	(91.0)	118	(90.8)	107	(93.9)
Black	12	(6.2)	9	(5.1)	4	(3.1)	2	(1.8)
Oriental	0	--	1	(0.6)	0	--	1	(0.9)
Other	9	(4.6)	6	(3.4)	8	(6.2)	4	(3.5)

*All randomized patients = intent-to-treat clinical population

***Reviewer Note**: For the primary efficacy endpoint, clinical response at follow-up in the per protocol population, there were no statistically significant differences in response rate by sex, by age groups (<45, 45-65, and >65) or by race.*

Table 9 summarizes the clinical efficacy for the four populations.

Table 9: Clinical response at follow-up visit in study 129B

Population	mupirocin calcium n cured / N evaluable	%	cephalexin n cured / N evaluable	%	95% confidence interval* LCL	UCL
Clinical ITT	156 / 195	80.0	147 / 178	82.6	-11.0	5.9
Clinical PP	125 / 130	96.2	110 / 114	96.5	-5.9	5.2
Bacteriological ITT	89 / 115	77.4	68 / 82	82.9	-17.8	6.7
Bacteriological PP	51 / 51	100.0	35 / 35	100.0		

* confidence interval calculated using continuity adjustment.

***Reviewer Note**: For the primary efficacy endpoint, clinical response at follow-up in the per protocol population, the 95% confidence interval $_{130, 114}$ (-5.9% , 5.2%) $_{96.2\%, 96.5\%}$ indicates that the two treatment groups are therapeutically equivalent based upon DAIDP's Points to Consider.*

In a patient by patient review of study withdrawals, no additional failures were found among the patients withdrawn due to either a lack of efficacy or an adverse events. However, there were patients who missed the end-of-treatment visit but were a success at the follow-up visit in the mupirocin calcium treatment group and in the cephalexin treatment group). At the pre-NDA meeting on 14May96, it was agreed that violation of the end-of-treatment visit window or missing the end-of-treatment visit would not exclude a patient from the per protocol population at follow-up. As a result of these reclassifications in the per protocol population at follow-up the confidence interval becomes $_{133,116}$ *(-5.8% , 5.1%)* $_{96.2\%, 96.6\%}$ *which is still consistent with establishing therapeutic equivalency based upon DAIDP's Points to Consider.*

The bacteriological success rate in the per protocol population at follow-up was 100% in both treatment groups. The clinical success rate at follow-up was examined by pre-therapy pathogen for the bacteriological per protocol population and is presented in Table 10.

Table 10: Bacteriological success at follow-up by the most common pre-therapy pathogens in the mupirocin group (per protocol bacteriological population) in study 129B

	MupirocinCalcium Cream (N = 51)		Cephalexin (N = 35)	
Pre-therapy pathogen	**n/N**	**(%)**	**n/N**	**(%)**
S. aureus	38/38	(100.0)	21/21	(100.0)
Strep. Group A	9/9	(100.0)	2/2	(100.0)
Acinet lwoffi	3/3	(100.0)		
Strep. Group B	2/2	(100.0)	2/2	(100.0)
Ps fluorescens	2/2	(100.0)		
Moraxella sp	2/2	(100.0)		
Total pre-therapy pathogens	**69**		**52**	
Number of patients who were a bacteriological success	**51**	**(100.0)**	**35**	**(100.0)**

n = bacteriological successes with that pathogen pre-therapy
N = all patients with that pathogen pre-therapy

III.C. Integrated Summary of Efficacy

The applicant had initially intended to conduct one study in

Hence, two independent randomized, double-blind studies (protocols 129A and 129B) were conducted under identical protocols in patients with secondarily infected traumatic skin lesions, such as small lacerations, sutured wounds, or abrasions. Table 11 combines the efficacy results of the two individual studies and with the results pooled.

Table 11: Clinical Efficacy Data Supporting the Indication Secondarily Infected Traumatic Skin Lesions (Per Protocol Clinically Evaluable Population at Follow-Up -- Studies 129A and 129B Separately and Combined)

	Persistent Clinical Success					
	Mupirocin Calcium Cream		Cephalexin			
Study Number	n / N [1]	(%)	n / N [1]	(%)	95% CI [2]	95% CI [3]
129A	108 / 115	93.9	112 / 119	94.1	(-6.30, 5.90)	(-7.14, 6.73)
129B	125 / 130	96.2	110 / 114	96.5	(-5.00, 4.40)	(-5.89, 5.21)
TOTAL	233 / 245	95.1	222 / 233	95.3	(-4.04, 3.64)	(-4.43, 4.08)

1 N includes patients with clinical recurrence and patients who were clinical failures at end of therapy.
2 95% CI as reported by sponsor
3 95% CI calculated using continuity correction

In the mupirocin calcium cream group, a total of 136 pathogens were isolated pre-therapy from the 98 patients in the per protocol bacteriological population at follow-up. In the cephalexin group, a total of 148 pathogens were isolated pre-therapy from the 92 patients in this population. The eradication rate of each pre-therapy pathogen was 100% in the per protocol bacteriological population at follow-up. This is not identical to the bacteriological success rate at follow-up due to the appearance of several superinfecting and reinfecting pathogens.

Reviewer Note: *Adjusting the efficacy results to reflect the patient by patient review of study withdrawals to ensure that end-of-treatment failures are carried forward and that successes at follow-up are not excluded because of missing the end-of-treatment visit, the confidence interval becomes* $_{252,239}$ *(-4.3% , 5.0%)* $_{94.0\%, 93.7\%}$ *which continues to be consistent with DAIDP's Points to Consider guidelines for establishing therapeutic equivalency.*

IV. Safety

IV.A. Study 129A Safety

All patients who signed a consent form and were randomized to study medication were followed for safety throughout all phases of study participation and for 30 days post completion for serious adverse experiences. Of the 162 patients randomized to mupirocin calcium cream, 31 (19.1%) reported a total of 50 adverse experiences. Of the 171 patients randomized to cephalexin, 40 (23.4%) reported a total of 62 adverse experiences. The proportion of patients reporting adverse experiences was similar between the two treatment groups.

Table 12: The most frequently reported (>1% of patients in either group) adverse experiences (AEs) regardless of treatment attribution in descending order for mupirocin calcium cream in study 129A

AEs by Preferred Term in Descending Order	Mupirocin Calcium Cream (N = 162)		Cephalexin (N = 171)	
	n	(%)	n	(%)
Nausea	5	(3.1)	3	(1.8)
Headache	5	(3.1)	5	(2.9)
Pain	3	(1.9)	0	(0.0)
Vomiting	3	(1.9)	2	(1.2)
Infection	2	(1.2)	1	(0.6)
Injury	2	(1.2)	6	(3.5)
Dermatitis	1	(0.6)	2	(1.2)
Pharyngitis	1	(0.6)	2	(1.2)
Upper respiratory tract infection	1	(0.6)	2	(1.2)
Diarrhea	1	(0.6)	6	(3.5)
Anorexia	0	(0.0)	2	(1.2)
Constipation	0	(0.0)	2	(1.2)
Feces discolored	0	(0.0)	2	(1.2)
Fever	0	(0.0)	2	(1.2)
Gastroenteritis	0	(0.0)	2	(1.2)
Rhinitis	0	(0.0)	2	(1.2)
Total patients with adverse experiences	31	(19.1)	40	(23.4)

A tabulation of AEs considered by the investigator to be related or possibly related to study medication is presented in Table 13. Eleven AEs were reported as related or possibly related by 11 of 162 (6.8%) patients in the mupirocin group for a total incidence rate of 6.8%. Eighteen AEs were reported as related or possibly related by 14 of 171 (9.9%) patients in the cephalexin group for a total incidence rate of 10.5%.

Table 13: Adverse experiences (AEs) considered by the investigator to be related or possibly related to treatment in descending order of frequency by mupirocin calcium cream in study 129A

AEs by Preferred Term in Descending Order	Mupirocin Calcium Cream (N = 162) n	(%)	Cephalexin (N = 171) n	(%)
Nausea	2	(1.2)	2	(1.2)
Dermatitis	1	(0.6)	0	(0.0)
Dizziness	1	(0.6)	0	(0.0)
Infection	1	(0.6)	0	(0.0)
Rash maculo-papular	1	(0.6)	0	(0.0)
Stomatitis ulcerative	1	(0.6)	0	(0.0)
Therapeutic response increased	1	(0.6)	0	(0.0)
Application site reaction	1	(0.6)	1	(0.6)
Headache	1	(0.6)	1	(0.6)
Diarrhea	1	(0.6)	6	(3.5)
Abdominal pain	0	(0.0)	1	(0.6)
Anorexia	0	(0.0)	1	(0.6)
Constipation	0	(0.0)	1	(0.6)
Feces discolored	0	(0.0)	1	(0.6)
Moniliasis genital	0	(0.0)	1	(0.6)
Pruritus	0	(0.0)	1	(0.6)
Pruritus genital	0	(0.0)	1	(0.6)
Urticaria	0	(0.0)	1	(0.6)
Total patients w/adverse experiences	11	(6.8)	14	(8.2)

A total of 13 patients (6 mupirocin and 7 cephalexin) withdrew from the Phase III pivotal studies due to AEs. The only AEs that led to withdrawal of more than one patient in either treatment group were diarrhea, which led to withdrawal of three (0.9%) patients from the cephalexin group, and nausea, which led to withdrawal of two (0.6%) patients from the mupirocin calcium cream group.

There were no deaths reported in any of the clinical trials with mupirocin calcium cream, neither in subjects who applied the active cream nor in those who received an active or placebo control.

Reviewer Note: *Subgroup analysis of safety data intended to detect gender, race, or age differences was not performed because of the very small numbers of adverse events reported in this study.*

IV.B. Study 129B Safety

All patients who signed a consent form and were randomized to study medication were followed for safety throughout all phases of study participation and for 30 days post completion for serious adverse experiences. Of the 195 patients randomized to mupirocin calcium cream, 57 (29.2%) reported a total of 84 adverse experiences. Of the 178 patients randomized to cephalexin, 57 (32.0%) reported a total of 74 adverse experiences. The proportion of patients reporting adverse experiences was similar between the two treatment groups.

Table 14: The most frequently reported (>1% of patients in either group) adverse experiences (AEs) regardless of treatment attribution in descending order for mupirocin calcium cream in study 129B

AEs by Preferred Term in Descending Order	Mupirocin Calcium Cream (N = 195)		Cephalexin (N = 178)	
	n	(%)	n	(%)
Headache	11	(5.6)	7	(3.9)
Upper respiratory tract infection	8	(4.1)	4	(2.2)
Pharyngitis	5	(2.6)	3	(1.7)
Diarrhea	5	(2.6)	5	(2.8)
Pain	3	(1.5)	0	--
Coughing	3	(1.5)	1	(0.6)
Abdominal pain	3	(1.5)	2	(1.1)
Fever	3	(1.5)	2	(1.1)
Nausea	3	(1.5)	2	(1.1)
Injury	3	(1.5)	4	(2.2)
Rhinitis	3	(1.5)	4	(2.2)
Application site reaction	2	(1.0)	2	(1.1)
Allergic Reaction	1	(0.5)	2	(1.1)
Dyspepsia	0	--	2	(1.1)
Purpura	1	(0.5)	2	(1.1)
Total	**54**	**(27.7)**	**42**	**(23.6)**

A tabulation of AEs considered by the investigator to be related or possibly related to study medication is presented in Table 15. A total of 19 AEs were reported as related or possibly related by 16 of 195 (8.2%) patients in the mupirocin group for a total incidence rate of 9.7%. A total of 21 AEs were reported as related or possibly related by 19 of 178 (10.7%) patients in the cephalexin group for a total incidence rate of 11.8%. While the profile of AEs reported as related or possibly related were very different between the two treatment groups, with only 5 of 20 AEs reported by both treatments, the overall incidence of related or possibly related AEs was similar.

Table 15: Adverse experiences (AEs) considered by the investigator to be related or possibly related to treatment in descending order of frequency by mupirocin calcium cream in study 129B

AEs by Preferred Term in Descending Order	Mupirocin Calcium Cream (N=195) n	(%)	Cephalexin (N=178) n	(%)
Headache	6	(3.1)	3	(1.7)
Diarrhea	3	(1.5)	2	(1.1)
Abdominal pain	2	(1.0)	1	(0.6)
Application site reaction	2	(1.0)	2	(1.1)
Nausea	2	(1.0)	2	(1.1)
Earache	1	(0.5)	0	--
Hot flushes	1	(0.5)	0	--
Intermenstrual bleeding	1	(0.5)	0	--
Pruritus	1	(0.5)	0	--
Constipation	0	--	1	(0.6)
Dizziness	0	--	1	(0.6)
Dyspepsia	0	--	1	(0.6)
Infection fungal	0	--	1	(0.6)
Insomnia	0	--	1	(0.6)
Lacrimation abnormal	0	--	1	(0.6)
Lymphadenopathy	0	--	1	(0.6)
Moniliasis genital	0	--	1	(0.6)
Rash maculo-papular	0	--	1	(0.6)
Rhinitis	0	--	1	(0.6)
Taste perversion	0	--	1	(0.6)
Patients with AEs	16	(8.2)	19	(10.7)

In the mupirocin group, 4 (2.1%) patients reported nine AEs which led to their withdrawal from the study. Two patients in the mupirocin treatment group were withdrawn from the study for an AE considered by the investigator to be related or possibly related to study medication. None of the patients in the cephalexin treatment group reported a related or possibly related AE which led to withdrawal.

There were no deaths reported during this study or for 30 days following the completion of the study. There were no serious non-fatal adverse events reported during this study.

Reviewer Note: *Subgroup analysis of safety data intended to detect gender, race, or age differences was not performed because of the very small numbers of adverse events reported in this study.*

IV.C. Integrated Summary of Safety

The following tables combine adverse event data from the two pivotal studies 129A and 129B and provides safety information from study 130. This information is in support of the ADVERSE REACTIONS section of the applicant's proposed label.

Table 16: The most frequently reported (>1% of patients in either group) adverse experiences (AEs) regardless of treatment attribution in descending order for mupirocin calcium cream in study 129A and study 129B

AEs by Preferred Term in Descending Order	Mupirocin Calcium Cream (N = 357)		Cephalexin (N = 349)	
	n	(%)	n	(%)
Headache	16	(4.5)	12	(3.4)
Upper respiratory tract infection	9	(2.5)	6	(1.7)
Nausea	8	(2.2)	5	(1.4)
Pharyngitis	6	(1.7)	5	(1.4)
Diarrhea	6	(1.7)	11	(3.2)
Pain	6	(1.7)	0	--
Injury	5	(1.4)	10	(2.9)
Rhinitis	3	(0.8)	6	(1.7)

Reviewer Note: *Table 16 supports the paragraph in the label under ADVERSE REACTIONS that lists the most frequently reported adverse events (>1%) irrespective of relationship to drug.*

Table 17: Adverse experiences (AEs) considered by the investigator to be related or possibly related to treatment in 3 or more patients in a treatment group in study 129A and study 129B

AEs by Preferred Term in Descending Order	Mupirocin Calcium Cream (N=357)		Cephalexin (N=349)	
	n	(%)	n	(%)
Headache	7	(2.0)	4	(1.1)
Diarrhea	4	(1.1)	8	(2.3)
Nausea	4	(1.1)	4	(1.1)
Application site reaction	3	(0.9)	3	(0.9)

Reviewer Note: *Table 17 supports the table in the label under ADVERSE REACTIONS concerning related/possibly related adverse events occurring in >1% of Mupirocin Calcium Cream-treated patients.*

A Phase III clinical study (protocol 130) compared the efficacy and safety of topical mupirocin calcium cream with oral cephalexin in the treatment of secondarily infected eczema. The study was a multicenter, double-blind, double-dummy, randomized trial. The treatment period was 10 days and the primary efficacy endpoint was clinical response at end of therapy (2-3 days post-therapy) in the per protocol population. One hundred and fifty nine patients were randomized (82 to mupirocin, 77 to cephalexin).

The study was terminated early due to a change in development strategy and the indication sought, thus, safety data only are intended to support the secondarily infected traumatic lesion (SITL) indication contained in this application. There were no deaths or serious AEs in the study. Twenty-eight AEs were reported by 15 patients in the mupirocin group and 3 patients were withdrawn for an AE. In the cephalexin group, 27 AEs were reported by 18 patients and 5 patients were withdrawn for an AE.

Table 18: Incidence of adverse experiences that occurred in > 2% of all patients in either treatment group in study 130 of secondarily infected eczema

	Mupirocin Calcium	Cephalexin
Total Number of Patients	82	77
Patients With Adverse Experiences (%)	15 (18.3)	18 (23.4)
Body System Preferred Term	N (%)	N (%)
Application Site		
application site	2 (2.4)	0
Central and Peripheral Nervous System		0
headache	3 (3.7)	0
Gastrointestinal System		
diarrhea	4 (4.9)	4 (5.2)
nausea	4 (4.9)	3 (3.9)
Resistance Mechanism		
infection	1 (1.2)	4 (5.2)
Skin and Appendages		
eczema	2 (2.4)	5 (6.5)

***Reviewer Note**: Table 18 supports the paragraph in the label under ADVERSE REACTIONS concerning most frequently reported adverse events occurring in >2% of patients in a supporting study.*

V. Pediatric Claims

One hundred and sixty children (aged 2 weeks to 16 years) were among the 706 patients treated for secondarily infected traumatic lesions in the clinical trials. Seventy-five were randomized to 10 days of topical mupirocin calcium cream t.i.d. and 85 were randomized to 10 days of oral cephalexin (250 mg q.i.d. for patient > 40 kg or 25 mg/kg/day oral suspension in four divided doses for patients ≤ 40 kg). Clinical efficacy at follow-up (7 to 12 days post-therapy) in the per protocol populations was 98.0% (48/49) for mupirocin calcium cream and 95.3% (61/64) for cephalexin.

The most frequently reported adverse experiences, irrespective of relationship to drug, in this pediatric population were upper respiratory infections (4/75, 5.3%), fever (3/75, 4.0%), and pharyngitis (3/75, 4.0%), for topical mupirocin calcium cream and abdominal pain (3/85, 3.5%), diarrhea, fever, headache, and rhinitis (2/85, 2.4% each) for oral cephalexin.

VI. Summary and Conclusions

Efficacy

Statistical evaluation of efficacy is based upon the two-sided 95% confidence interval of the proportion of clinical successes attributed to mupirocin calcium cream minus the proportion of clinical successes attributed to cephalexin in the per protocol population at the follow-up visit (7-12 days post-therapy). The confidence intervals are reported as n_t , n_c (95% CI) p_t, p_c where n_t is the number in the test group, n_c is the number in the control group, p_t is the percent cured in the test group, and p_c is the percent cured in the control group.

Both studies 129A and 129B support the claim that mupirocin calcium cream applied topically three times a day for 10 days is therapeutically equivalent to cephalexin administered orally four times a day. For study 129A, the 95% confidence interval is $_{115,119}(-7.1\%, 6.7\%)_{93.9\%,94.1\%}$. For study 129B, the 95% confidence interval is $_{130,114}(-5.9\%, 5.2\%)_{96.2\%,96.5\%}$. Since the lower bounds are not less than -10%, these results are consistent with therapeutic equivalence for drugs with cure rates of greater than 90% as specified in DAIDP's Points to Consider. The conclusion is not affected when the efficacy results are revised to reflect a patient by patient review of study withdrawals. The revised confidence interval for study 129A becomes $_{133,116}(-5.8\%,5.1\%)_{96.2\%,96.6\%}$ and for study 129B becomes $_{252,239}(-4.3\%,5.0\%)_{94.0\%,93.7\%}$.

These studies established efficacy for *Staphylococcus aureas* with clinical cure rates of 92.3% (24/26) and 100% (38/38) for studies 129A and 129B, respectively. However, these studies did not include patients with beta-homlytic *Streptococcus* and *Streptococcus pyogenes* as requested for this indication in the label. Mupirocin was previously approved for these pathogens for the topical treatment of impetigo.

For the primary efficacy endpoint, clinical response at follow-up in the per protocol population, there were no statistically significant differences in response rate by sex, by age groups (<45, 45-65, and >65) or by race.

Safety

No safety issues were noted.

Labeling

Conclusion

In the treatment of secondarily infected open wounds such as small lacerations, sutured wounds, or abrasions, mupirocin calcium cream applied topically three times daily for ten days meets DAIDP's guidelines for establishing therapeutic equivalence to cephalexin administered orally four times a day.

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