CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-788

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	50-788 (formerly 21-480)
Name of drug:	Mupirocin Ointment, 2%
Applicant:	Clay-Park Labs, Inc./Agis Group
Indication:	Impetigo
Documents reviewed:	Vol. 1, 20 ~ 29
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Keywords: NDA review, clinical studies, efficacy evaluation, statistical analysis

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Review's Note: Throughout the review, the following terms are abbreviated and referred to as:
Bactroban = SmithKline Beecham Pharmaceuticals' Bactroban® Ointment (Mupirocin Ointment, 2%); EOT = end of treatment, FU = follow-up; ITT = intent-to-treat; MITT = modified intent-to-treat; MO = Medical Officer, Mupirocin = Clay-Park Labs, Inc.'s Mupirocin® Ointment, 2%; PP = per-protocol; TOC = Test of Cure.
Reviewer comments are given in italics throughout the review.

1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

The sponsor submits this NDA in order to obtain approval to market its Mupirocin Ointment, 2% formulation for the treatment of impetigo. Impetigo is a superficial infection of the skin caused primarily by *Staphylococcus aureus* and *Streptococcus pyogenes*. This highly contagious bacterial infection occurs most often in children living under conditions of poor hygiene in semitropical or tropical regions. Mupirocin is a topical antibiotic used for the treatment of impetigo and was developed as a therapeutic equivalent to Bactroban, which was approved in 1987. Mupirocin is claimed to have the same active ingredient and same indication as Bactroban.

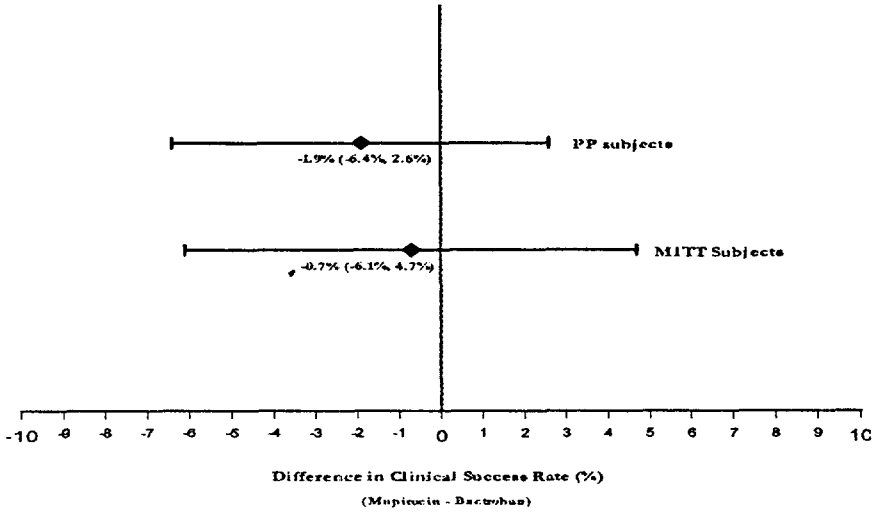
To support this indication, one pivotal phase III study was submitted for review. Study CPL-002 was a 14 days, prospective, multicenter (fourteen sites in South Africa and one site in Puerto Rico), randomized, parallel group, double-blind study. Male and female South African subjects 2 months of age and older and Puerto Rican subjects 18 months of age and older were eligible for the study if they had a clinical diagnosis of impetigo contagiosa or uncomplicated blistering impetigo. According to the inclusion/exclusion criteria, a total of 602 subjects were enrolled in the study and were randomized in a 1:1 ratio to receive either Mupirocin (300 subjects) or Bactroban (302 subjects). All of the 602 subjects were included in the ITT analyses. Five hundred fifty-eight subjects with microbiologically confirmed clinical diagnosis of impetigo (279 in the Mupirocin group and 279 in the Bactroban group) were included in the MITT analyses. Four hundred seventy five subjects (233 in the Mupirocin group and 242 in the Bactroban group) were included in the PP analysis. Both treatments were administered three times daily for 7 days. It was initiated on April 3, 2001 and completed on September 5, 2001.

The objective of the study was to demonstrate the safety and efficacy of Mupirocin in the treatment of impetigo compared to that of Bactroban. The primary efficacy measure was the proportion of subjects in each treatment group with clinical success at the FU visit. In this review, statistical evaluation of efficacy was primarily based upon the two-sided 95% confidence interval of the difference in clinical success rates at FU between Mupirocin and Bactroban for PP subjects and MITT subjects. A delta value of 0.1 is defined as an equivalence margin.

For PP population, a total of 218/233 (93.6%) Mupirocin subjects were considered clinical success, while 231/242 (95.5%) Bactroban subjects were considered clinical success. The efficacy results demonstrated therapeutic equivalence between the two treatments with a clinical favorable rate difference in favor of Bactroban of 1.9% (95% CI: -6.4%, 2.6%).

For MITT population, a total of 249/279 (89.2%) Mupirocin subjects were considered clinical success, while 251/279 (90.0%) Bactroban subjects were considered clinical success. The efficacy results demonstrated therapeutic equivalence between the two treatments with a

clinical success rate difference in favor of Bactroban of 0.7% (95% CI: -6.1%, 4.7%).



2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION AND BACKGROUND

The Sponsor submitted one pivotal phase III controlled study, CPL-002, as evidence to support that Mupirocin was safe and efficacious for the treatment of Impetigo when compared with Bactroban. Statistical review focuses on this comparative clinical trial which formed the basis of this application.

2.2 STUDY DESIGN AND DATA ANALYSIS

Primary Objectives

To demonstrate the safety and efficacy of Mupirocin in the treatment of impetigo compared to that of Bactroban.

Study Design

Subjects had a microbiologically confirmed clinical diagnosis of impetigo and at least took one post-baseline visit, to determine the safety and efficacy of Mupirocin versus Bactroban after 7 days of treatment. The study consisted of a Baseline visit (Visit 1, Day 0), an Interim visit (Visit 2, Day 3-5), an EOT visit (Visit 3, Day 7-9), and a FU visit (Visit 4, Day 12-16). Eligible subjects/parents/guardians provided written informed consent at the Baseline visit, before any study-specific procedures were initiated. After satisfying all of the inclusion/exclusion criteria, subjects were randomly assigned in blocks of four in a 1:1 ratio to receive either Mupirocin or Bactroban. The assigned subjects applied 3 times a day for 7 days. It was initiated on April 3, 2000 and completed on September 5, 2001.

Assessment of Efficacy

Clinical evaluations were performed at four visits. The lesion most representative of the subject's infection was the target lesion. Baseline cultures of the target lesion were evaluated for the presence of *Staphylococcus aureus* and *Streptococcus pyogenes* confirming the clinical diagnosis of impetigo. The target lesion was also cultured at the EOT visit or at early termination. Only subjects who had visible lesions were cultured at the FU visit.

The primary efficacy measure was the proportion of subjects in each treatment group with clinical success at the FU visit. Clinical success was defined as sufficient resolution of signs

and symptoms of infection, as evidenced by a Skin Infection Rating Scale (SIRS) score. If a valid clinical assessment could not be made, the clinical outcome was considered unevaluable. The appearance of new lesions that were not healed at the time of Visits 3 and/or 4 led to a subject being classified as treatment failure. These subjects required additional therapy for the treatment of impetigo, which, by definition, disqualified them as clinical successes.

The secondary efficacy measures were: 1. Bacteriological success proportions at the EOT visit and the FU visit; 2. Clinical success proportion at the EOT visit; Clinical evaluations (SIRS score) of impetigo at the EOT visit and the FU Visit; 4. SIRS score components at the EOT visit and the FU visit. Bacteriological success was defined as the elimination of *Staphylococcus aureus* and *Streptococcus pyogenes* at the final culture or a response.

Three subject populations were defined as ITT subjects, MITT subjects, and PP subjects. The efficacy analysis was conducted on both the PP and the MITT subject populations. These analyses were co-primary. Safety analyses were conducted on the ITT subject population.

Reviewer's Note: *The MO agreed with the evaluability criteria defined by the Sponsor, and outcome assessment classified by the Sponsor.*

Statistical Methods

The comparisons of interest in this study were conducted between Mupirocin and Bactroban, which was designed to show equivalence of the two treatment groups.

Reviewer's Note: *The following statistical analyses performed by the reviewer were to evaluate the efficacy of Mupirocin versus Bactroban.*

Equivalence between Mupirocin and Bactroban with respect to the primary efficacy parameters was assessed by computing the two-tailed 95% confidence interval of the difference in clinical success rates. The confidence intervals were computed using a normal approximation to the binomial, and included a continuity correction. The evaluation of whether the treatment groups were considered equally effective was judged based on the delta value 0.1, which is considered a clinically acceptable equivalence margin with respect to this indication. Homogeneity of treatment effect was evaluated by Breslow-Day's test.

Prior to performing efficacy analyses, this reviewer assessed the comparability of the treatment groups with respect to pretreatment characteristics of randomized subjects. Quantitative variables were assessed using the t-test, and qualitative variables were assessed using chi-square test.

All tests were two-sided and used a 5% level of significance. A 15% level of significance was applied to the test of homogeneity.

2.3 STATISTICAL EVALUATION ON EFFICACY

Of the 602 subjects who enrolled in the study, 300 were randomized to the Mupirocin treatment group, and 302 to the Bactroban treatment group. All 602 subjects were included in the ITT analyses. Forty-four subjects (21 Mupirocin and 23 Bactroban) were excluded from MITT analyses. The most common reason subjects were excluded from the MITT population was due to a negative culture at screening. One hundred twenty-seven subjects (67 Mupirocin and 60 Bactroban) were excluded from PP analyses. The primary reasons subjects were excluded from the PP population were due to negative culture at screening, non-compliance with study protocol, lost to follow-up, visit 3 occurring outside the preset window, visit 4 occurring earlier than the preset window, missed visits, compliance rate less than 66% or greater than 133%, and use of prohibited medication. Seventy-seven subjects (37 Mupirocin and 40 Bactroban) were discontinued from the study prematurely. The most common reason of discontinuation was due to negative culture at the screening/initiation visit. The 9 subjects who discontinued due to treatment failure were included in the PP analyses (4 Mupirocin and 5 Bactroban).

Reviewer's Note: *The number and the proportion of subjects included in each evaluation group are presented in Table 1. There were no notable differences for two treatment groups with respect to the percentage of subjects included in each evaluation group.*

TABLE 1: NUMBER OF SUBJECTS INCLUDED IN EACH EVALUATION GROUP

Evaluation Group	Number of Subjects	
	Mupirocin	Bactroban
All Randomized Subjects	300	302
ITT Subjects	300 (100%)	302 (100%)
MITT Subjects	279 (93.0%)	279 (92.4%)
PP Subjects	233 (77.7%)	242 (80.1%)

Reviewer's Note: *Demographic data are described for ITT subjects in Table 2, and no statistical significant differences were detected in these characteristics between the two treatment groups.*

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TABLE 2: BASELINE DEMOGRAPHICS IN ITT SUBJECTS			
Parameters	Mupirocin (N=300)	Bactroban (N=302)	P-value
Age (yrs.)			
Range (Min, Max)	(0.2, 58.6)	(0.3, 54.0)	
Mean ± SD	9.2 ± 10.1	8.8 ± 9.2	*0.926
Distribution			
≥ 12 years and < 18 years	38 (29.9%)	35 (25.9%)	0.521
≥ 18 years and < 65 years	84 (66.1%)	91 (67.4%)	
≥ 65 years	5 (3.9%)	9 (6.7%)	
Gender			
Male	146 (49%)	144 (48%)	0.793
Female	154 (51%)	158 (52%)	
Race			
White	12 (4%)	10 (3%)	0.683
Black	174 (58%)	182 (60%)	
Other	114 (38%)	110 (36%)	
* By t test. All others in the table, by chi-square test.			

Reviewer's Note: *The Primary analyses are presented in Tables 3 and 4 for PP and MITT subjects at FU visit, respectively. Both confidence interval results showed Mupirocin and Bactroban were therapeutically equivalent with respect to clinical success rates at FU.*

TABLE 3: CLINICAL RESPONSES OF PP SUBJECTS AT FU VISIT		
Clinical Response	Mupirocin (N=233)	Bactroban (N=242)
Success	218 (93.6%)	231 (95.5%)
Failure	15 (6.4%)	11 (4.5%)
Mupirocin vs. Bactroban: Difference in Success Rate	-1.9%, 95% C.I.: -6.4%, 2.6%	

TABLE 4: CLINICAL RESPONSES OF MITT SUBJECTS AT FU VISIT		
Clinical Response	Mupirocin (N=279)	Bactroban (N=279)
Success Failure	249 (89.2%) 30 (10.8%)	251 (90.0%) 28 (10.0%)
Mupirocin vs. Bactroban: Difference in Success Rate	-0.7%, 95% C.I.: -6.1%, 4.7%	

Reviewer's Note: *It is worth mentioning that four investigation sites comprised 82.1% of all randomized subjects enrolled to a total of fifteen sites (Table 5). Subset analyses display that results from MITT subjects were consistent across all four sites (Table 6). However, significant heterogeneity of treatment effects was detected for PP subjects among the four sites, which appears treatment effect favored Bactroban in Todd's site. (Table 7).*

As the four sites were pooled together and compared to the rest sites, results were consistent from both PP and MITT analyses. (Tables 8 and 9)

TABLE 5: NUMBER OF RANDOMIZED SUBJECTS IN FOUR MOST EROLLMENT SITES		
Investigation Site	Number of Subjects	
	Mupirocin	Bactroban
All Randomized Subjects	300	302
[redacted]	74 (24.7%)	74 (24.5%)
	68 (22.7%)	68 (22.5%)
	62 (20.7%)	62 (20.5%)
	42 (14.0%)	44 (14.6%)
	246 (82.0%)	248 (82.1%)

TABLE 6: SUBSET ANALYSES BY INVESTIGATIONAL SITES FOR THE CLINICAL SUCCESS RATES IN PP SUBJECTS AT FU VISIT				
*Subset	Mupirocin	Bactroban	95% C.I.	**P-value
[redacted]	62/62 (100%)	65/66 (98.5%)	(-3.0%, 6.0%)	0.098
	42/50 (84.0%)	51/53 (96.2%)	(-25.6%, 1.1%)	
	49/51 (96.1%)	48/53 (90.6%)	(-5.9%, 16.9%)	
	33/36 (91.7%)	32/34 (94.1%)	(-17.3%, 12.4%)	
* Sites with most subjects; ** By Breslow-Day's test				

TABLE 7: SUBSET ANALYSES BY INVESTIGATIONAL SITES FOR THE CLINICAL SUCCESS RATES IN MITT SUBJECTS AT FU VISIT				
*Subset	Mupirocin	Bactroban	95% C.I.	**P-value
[redacted]	67/69 (97.1%)	69/70 (98.6%)	(-7.7%, 4.8%)	0.524
	54/65 (83.1%)	58/64 (90.6%)	(-20.7%, 5.6%)	
	51/59 (86.4%)	48/57 (84.2%)	(-12.4%, 16.8%)	
	33/38 (86.8%)	32/39 (82.1%)	(-13.9%, 23.5%)	
* Sites with most subjects; ** By Breslow-Day's test				

TABLE 8: SUBSET ANALYSES BY INVESTIGATIONAL SITES FOR THE CLINICAL SUCCESS RATES IN PP SUBJECTS AT FU VISIT				
Subset	Mupirocin (N=233)	Bactroban (N=242)	95% C.I.	**P-value
*Four Sites	186/199 (93.5%)	196/206 (95.1%)	(-6.7%, 3.3%)	0.722
Rest Sites	32/34 (94.1%)	35/36 (97.2%)	(-15.5%, 9.3%)	
* Four sites with most subjects; ** By Breslow-Day's test				

TABLE 9: SUBSET ANALYSES BY INVESTIGATION SITES FOR THE CLINICAL SUCCESS RATES IN MITT SUBJECTS AT FU VISIT				
Subset	Mupirocin (N=279)	Bactroban (N=279)	95% C.I.	**P-value
*Four Sites	205/231 (88.7%)	207/230 (90.0%)	(-7.3%, 4.8%)	0.642
Rest Sites	44/48 (91.7%)	44/49 (89.8%)	(-11.7%, 15.5%)	
* Four sites with most subjects; ** By Breslow-Day's test				

Reviewer's Note: *Subset analyses for looking into the data with and without each of four individual investigator sites are shown in Tables 10 and 11, respectively. Only* [redacted] *s had an effect causing heterogeneity of treatment effects in PP subjects (p-values=0.051 and 0.061), where Bactroban was favored in* [redacted] *and Mupirocin was favored in* [redacted]

TABLE 10: SUBSET ANALYSES BY INVESTIGATIONAL SITES FOR THE CLINICAL SUCCESS RATES IN PP SUBJECTS AT FU VISIT				
*Subset	Mupirocin	Bactroban	95% C.I.	**P-value
	62/62 (100%) 156/171 (91.2%)	65/66 (98.5%) 166/176 (94.3%)	(-3.0%, 6.0%) (-9.1%, 2.9%)	0.234
	42/50 (84.0%) 176/183 (96.2%)	51/53 (96.2%) 180/189 (95.2%)	(-25.6%, 1.1%) (-3.7%, 5.6%)	0.051
	49/51 (96.1%) 169/182 (92.9%)	48/53 (90.6%) 183/189 (96.8%)	(-5.9%, 16.9%) (-9.0%, 1.1%)	0.061
	33/36 (91.7%) 185/197 (93.9%)	32/34 (94.1%) 199/208 (95.7%)	(-17.3%, 12.4%) (-6.6%, 3.1%)	0.989
* Sites with most subjects; ** By Breslow-Day's test				

TABLE 11: SUBSET ANALYSES BY INVESTIGATIONAL SITES FOR THE CLINICAL SUCCESS RATES IN MITT SUBJECTS AT FU VISIT				
*Subset	Mupirocin	Bactroban	95% C.I.	**P-value
	67/69 (97.1%) 182/210 (86.7%)	69/70 (98.6%) 182/209 (87.1%)	(-7.7%, 4.8%) (-7.4%, 6.5%)	0.583
	54/65 (83.1%) 195/214 (91.1%)	58/64 (90.6%) 193/215 (89.8%)	(-20.7%, 5.6%) (-4.7%, 7.4%)	0.185
	51/59 (86.4%) 198/220 (90.0%)	48/57 (84.2%) 203/222 (91.4%)	(-12.4%, 16.8%) (-7.3%, 4.4%)	0.572
	33/38 (86.8%) 216/241 (89.6%)	32/39 (82.1%) 219/240 (91.3%)	(-13.9%, 23.5%) (-7.3%, 4.0%)	0.431
* Sites with most subjects; ** By Breslow-Day's test				

Reviewer's Note: *The secondary analyses are displayed in Tables 12, 13, 14, 15, 16, and 17. All confidence interval results showed Mupirocin and Bactroban were therapeutically equivalent with respect to bacteriological response at FU, clinical response at EOT, and bacteriological response at EOT for both PP and MITT subjects.*

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TABLE 12: BACTERIOLOGICAL RESPONSES OF PP SUBJECTS AT FU VISIT		
Bacteriological Response	Mupirocin (N=233)	Bactroban (N=242)
Success Failure	228 (97.9%) 5 (2.1%)	237 (97.9%) 5 (2.1%)
Mupirocin vs. Bactroban: Difference in Success Rate	-0.1%, 95% C.I.: -3.1%, 2.9%	

TABLE 13: BACTERIOLOGICAL RESPONSES OF MITT SUBJECTS AT FU VISIT		
Clinical Response	Mupirocin (N=279)	Bactroban (N=279)
Success Failure	261 (93.5%) 18 (6.5%)	258 (92.5%) 21 (7.5%)
Mupirocin vs. Bactroban: Difference in Success Rate	1.1%, 95% C.I.: -3.5%, 5.7%	

TABLE 14: CLINICAL RESPONSES OF PP SUBJECTS AT EOT VISIT		
Bacteriological Response	Mupirocin (N=233)	Bactroban (N=242)
Success Failure	195 (83.7%) 38 (16.3%)	190 (78.5%) 52 (21.5%)
Mupirocin vs. Bactroban: Difference in Success Rate	5.2%, 95% C.I.: -2.3%, 12.6%	

TABLE 15: CLINICAL RESPONSES OF MITT SUBJECTS AT EOT VISIT		
Clinical Response	Mupirocin (N=279)	Bactroban (N=279)
Success Failure	224 (80.3%) 55 (19.7%)	213 (76.3%) 66 (23.7%)
Mupirocin vs. Bactroban: Difference in Success Rate	3.9%, 95% C.I.: -3.2%, 11.1%	

TABLE 16: BACTERIOLOGICAL RESPONSES OF PP SUBJECTS AT EOT VISIT		
Bacteriological Response	Mupirocin (N=233)	Bactroban (N=242)
Success Failure	232 (99.6%) 1 (0.4%)	238 (98.3%) 4 (1.7%)
Mupirocin vs. Bactroban: Difference in Success Rate	1.2%, 95% C.I.: -1.0%, 3.5%	

TABLE 17: BACTERIOLOGICAL RESPONSES OF MITT SUBJECTS AT EOT VISIT		
Clinical Response	Mupirocin (N=279)	Bactroban (N=279)
Success Failure	267 (95.7%) 12 (4.3%)	265 (95.0%) 14 (5.0%)
Mupirocin vs. Bactroban: Difference in Success Rate	0.7%, 95% C.I.: -3.1%, 4.6%	

2.4 SUMMARIES AND CONCLUSIONS

Reviewer's Note: *In this section, confidence intervals for differences in outcome rates (Mupirocin minus control) are reported as* $_{n1,n2}(l, u)_{p1,p2}$ *where* n_1 *is the number of Mupirocin subjects,* n_2 *is the number of control subjects, l and u are the lower and upper bounds of the 95% confidence interval, respectively,* p_1 *is the response rate in Mupirocin subjects, and* p_2 *is the response rate in control subjects.*

This indication was primarily supported by one controlled study (CPL-002) to demonstrate the efficacy and safety of Mupirocin.

Statistical evaluation of efficacy was primarily based upon the two-sided 95% confidence interval of the difference in clinical success rates at FU between the Mupirocin group and the Bactroban group for PP subjects and MITT subjects.

Reviewer's Summary for the Results of Study CPL-002:

- *There were no statistically significant differences in the pretreatment characteristics between the two treatment groups.*

- *The 95% confidence interval of the difference in clinical success rates of Mupirocin minus Bactroban for PP subjects was* $_{233,\ 242}(-6.4\%,\ 2.6\%)_{93.6\%,\ 95.5\%}$ *which demonstrated equivalence in efficacy of two*

treatments in the treatment of impetigo.

- *The 95% confidence interval from MITT subjects also demonstrated that Mupirocin was therapeutically equivalent to Bactroban* $_{279, 279}(-6.1\%, 4.7\%)_{89.2\%, 90.0\%}$

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