CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-055

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA/Serial Number:	22-055
Drug Name:	Retapamulin (SB-275833) Ointment, 1%
Indication(s):	Treatment of primary impetigo caused by Staphylococcus aureus (methicillin-susceptible isolates) or Streptococcus pyogenes in adults and pediatric patients 9 months of age and older
Applicant:	GlaxoSmithKline (GSK)
Date(s):	Stamp Date: June 12, 2006 PDUFA due date: April 12, 2007
Review Priority:	Standard
Biometrics Division:	Division of Biometrics IV
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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

In NDA22055 the sponsor seeks approval of 1% SB-275833 (Retapamulin) ointment for the treatment of primary impetigo caused by *Staphylococcus aureus* (methicillin-susceptible isolates) or *Streptococcus pyogenes* in adults and pediatric patients 9 months of age and older. Two pivotal studies (studies TOC103469 and TOC100224) were included in the submission as the major source to demonstrate efficacy and safety of Retapamulin.

Study TOC103469 was a randomized, double-blind, multi-center, and placebo-controlled study in adult and pediatric subjects with impetigo. The study subjects received either topical 1% SB-275833 ointment, twice daily for 5 days or placebo ointment, twice daily for 5 days in a 2:1 ratio. There were 140 and 73 randomized subjects in the SB-275833 and the placebo groups, respectively. The primary endpoint was the clinical response at the end of therapy visit on Day 7 (2 days post therapy). This study demonstrated that the SB-275833 treatment yielded a robust and statistically significantly higher clinical response rate at the end of therapy visit compared with the placebo treatment. The differences in the clinical response rate between the SB-275833 and the placebo groups were 33.5% (95% CI: 20.5% to 46.5%) and 36.3% (95% CI: 22.8% to 49.8%) in the intent-to-treated clinical (ITTC) population and in the per protocol clinical (PPC) populations, respectively.

Study TOC100224 was a randomized, observer-blind, multi-center, and non-inferiority study in adult and pediatric subjects with impetigo. The study subjects received either topical 1% SB-275833 ointment, twice daily for 5 days or topical 2% sodium fusidate ointment, three times daily for 7 days in a 2:1 ratio. There were 346 and 173 randomized subjects in the SB-275833 and the sodium fusidate groups, respectively. The primary endpoint was the clinical response at the end of therapy visit (2 days post therapy: Day 7 for SB-275833 and Day 9 for sodium fusidate). A non-inferiority margin of 10% was used.

There is one major statistical issue in study TOC100224 as this study was designed by the sponsor as a non-inferiority trial using the active comparator, topical 2% sodium fusidate ointment, which has not been approved by the FDA. Thus, this study was considered as a superiority study in this review.

Study TOC100224 failed to demonstrate superior efficacy of the SB-275833 treatment over the sodium fusidate treatment. The difference in the clinical response rate at the end of therapy visit between the SB-275833 and the sodium fusidate groups was 4.7% (95% CI: -0.4% to 9.7%) and 5.1% (95% CI: 1.1% to 9.0%) in the ITTC and PPC populations, respectively. When any signs/symptoms were considered as failure, the difference in the clinical response rate at the end of therapy visit between the SB-275833 and the sodium fusidate groups was -20.2% (95% CI: -29% to -11%) and -20.8% (95% CI: -30% to

-12%) in the ITTC and PPC populations, respectively. When any signs/symptoms were considered as failure, the difference in the clinical response rate at Visit 2 (Day 7: 2 days post therapy for SB-275833 and end of therapy for sodium fusidate) between the SB-275833 and the sodium fusidate groups was 6.6% (95% CI: -2.5% to 15.6%) and 7.5% (95% CI: -2.2% to 17.1%) in the ITTC and PPC populations, respectively. When any signs/symptoms were considered as failure, the difference in the clinical response rate at Visit 3 (Day 9: 4 days post therapy for SB-275833 and 2 days post therapy for sodium fusidate) between the SB-275833 and the sodium fusidate groups was 2.1% (95% CI: -6.4% to 10.7%) and 2.4% (95% CI: -6.3% to 11.2%) in the ITTC and PPC populations, respectively.

1.2 Brief Overview of Clinical Studies

Study TOC103469 was a randomized, double-blind, multi-center, and placebo-controlled study in adult and pediatric subjects with impetigo. The study subjects received either topical 1% SB-275833 ointment, twice daily for 5 days or placebo ointment, twice daily for 5 days in a 2:1 ratio. There were 140 and 73 randomized subjects in the SB-275833 and the placebo groups, respectively. The total study duration was 14 days. The primary endpoint was the clinical response at the end of therapy visit on Day 7 (2 days after 5-day treatment). The primary hypothesis was that the SB-275833 treatment would be superior to placebo with respect to the successful clinical response rate.

Study TOC100224 was a randomized, observer-blind, multi-center, and non-inferiority study in adult and pediatric subjects with impetigo. The study subjects received either topical 1% SB-275833 ointment, twice daily for 5 days or topical 2% sodium fusidate ointment, three times daily for 7 days in a 2:1 ratio. There were 346 and 173 randomized subjects in the SB-275833 and the sodium fusidate groups, respectively. The total study duration was 14 days. The primary endpoint was the clinical response at the end of therapy visit (2 days post therapy: Day 7 for SB-275833 and Day 9 for sodium fusidate). The primary hypothesis was that the SB-275833 treatment would not be non-inferior to the sodium fusidate treatment with respect to the successful clinical response rate. A non-inferiority margin of 10% was used.

1.3 Statistical Issues and Findings

Statistical Issues

Study TOC100224 was designed by the sponsor as a non-inferiority trial using the active comparator, topical 2% sodium fusidate ointment, which has not been approved by the FDA. Therefore, this study was considered as a superiority study in this review.

Sensitivity Results of the Primary Efficacy Endpoint

For both studies, the primary efficacy endpoint was the clinical response (success or failure) at the end of therapy visit. It was related to the baseline signs/symptoms of

infection and was defined based on the clinical outcome assessed by the study investigators (see Tables 3.1.2-3.1.3 for details). A clinical response of "success" at the end of therapy corresponded to a clinical outcome assessment of *"Total absence of the treated lesions or the treated lesions have become dry without crusts compared to baseline, or improvement (defined as a decline in the size of the affected area, number of lesions or both) such that no further antimicrobial therapy is necessary."* judged by the study investigators.

In this definition, the sponsor failed to provide an objective criteria for *"improvement (defined as a decline in the size of the affected area, number of lesions or both) such that no further antimicrobial therapy is necessary"* that could be consistently applied across study investigators. Non-standard or subjective definition for *"improvement (defined as a decline in the size of the affected area, number of lesions or both) such that no further antimicrobial therapy is necessary"* by the study investigators would lead to misclassification of clinical responses.

To examine the robustness of the primary efficacy results, the statistical reviewer has performed numerous sensitivity analyses by modifying sponsor's definition of clinical response using the measurements of signs and symptoms of infection.

The sensitivity results in Table 1 demonstrated that (1) in study TOC103469 the superiority efficacy results of SB-275833 treatment over placebo were very robust and statistically significant; (2) in study TOC100224 the clinical response rates of the SB-275833 treatment over sodium fusidate were sensitive to how the clinical response was defined; the SB-275833 treatment seemed to be inferior to the sodium fusidate treatment when mild to severe signs and symptoms of infection at the end of therapy visit were considered as clinical failure.

In study TOC103469, the clinical response rates in the SB-275833 group were statistically significantly higher than the ones in the placebo group regardless how the clinical response was defined. The point estimates for the difference in the clinical response rate between the SB-275833 group and the placebo group were very robust and had a magnitude around 30%.

In study TOC100224 (designed as a non-inferiority study by the sponsor, reviewed by the Agency as a superiority trial), the difference in the clinical response rate between the SB-275833 and the sodium fusidate groups was sensitive to how the clinical response was defined. When any mild to severe signs and symptoms of infection at the end of therapy visit were considered as clinical failure, the difference in the clinical response rate between the SB-275833 and the sodium fusidate groups decreased from the sponsor's results of 4.7% (95% CI: -0.4%, 9.7%) to -20.2% (-29%, -11%), indicating that SB-275833 was inferior to the sodium fusidate treatment. When any signs/symptoms was considered as failure, the difference in the clinical response rate at Visit 3 (Day 9: 4 days post therapy for SB-275833 and 2 days post therapy for sodium fusidate) between the SB-275833 and the sodium fusidate groups was 2.1% (95% CI: -6.4% to 10.7%) and 2.4% (95% CI: -6.3% to 11.2%) in the ITTC and PPC populations, respectively.

To further examine the robustness of the SB-275833 treatment effect, the clinical response rates for the SB-275833 treated subjects in study TOC103469 were compared with the ones for the SB-275833 treated subjects in study TOC100224. It should be noted that these two studies were similar in terms of study inclusion and exclusion criteria, and had the same SB-275833 treatment duration (5 days) and same duration (7 days) for the end of therapy visit. Thus, it is reasonable to expect that the clinical response rates at the end of therapy visit in these two studies would be comparable for the SB-275833 treated subjects. This is exactly what was observed when less subjective response variables such as RESPON_m0 and RESPON_m1 were used. The results in Table 2 showed that when response variable RESPON_m0 was used, the difference in clinical response rate for the SB-275833 treated subjects between studies TOC103469 and TOC100224 was -0.6% (95% CI: -10% to 9.2%). In contrast, when the sponsor's definition of clinical response was used, the SB-275833 treated subject in study TOC100224 (designed as a non-inferiority trial by the sponsor) had a clinical response rate that was 9.2% (95% CI: 2.9% to 15%) higher than the one for the SB-275833 treated subjects in study TOC103469 (designed as a placebo controlled trial by the sponsor). This disparity in the clinical response rate in the SB-275833 treated subjects in these two studies might very well reflect on the fact that the component *"improvement (defined as a decline in the size of the affected area, number of lesions or both) such that no further antimicrobial therapy is necessary"* in the sponsor's definition was subjected to the study investigators' interpretation and might have lead to over estimation of the clinical response rate in the non-inferiority trial. Thus, this kind of non-standard/subjective definition of primary endpoint should be avoided in a non-inferiority trial to ensure assay sensitivity of the trial.

The sensitivity of the SB-275833 treatment effect to the severity of baseline signs and symptoms of infection was also examined in the SB-275833 treated subjects in study TOC100224. It is reasonable to expect that the subjects who had only mild baseline signs/symptoms (SIRS<4 for every sign/ symptom) would generally have a higher clinical success rate than the subjects who had at least one moderate/severe baseline signs and symptoms (SIRS≥4 for at least one sign/symptom). This is exactly what was observed when less subjective response variables such as RESPON_m0 and RESPON_m1 were used. The results in Table 3 showed that when response variable RESPON_m0 was used, the response rate for the subjects who had only mild baseline signs and symptoms was 14.9% (95% CI: 3.7% to 26.1%) higher than the one for the subjects who had at least one moderate/severe baseline signs and symptoms. In contrast, when the sponsor's definition of clinical response was used, the response rates were similar for these two groups of subjects. This lack of sensitivity of the clinical response rate to the severity of baseline signs and symptoms again reflected on the fact that the sponsor's definition of clinical response entailed a component that was subjected to investigators' interpretation. This non-standardized/subjective definition of primary endpoint might very well lead to misclassification and obscure the rue difference in the response rate between these two groups of subjects. Thus, this kind of non-standard/subjective definition of primary endpoint should be avoided in a non-inferiority trial to ensure assay sensitivity of the trial.

Table 1: Key Sensitivity Results for Clinical Response Rates (ITTC Population)

		SB-275833		PLACEBO		
Study/Visit	**Outcome Variable**	**n/N**	**Success Rate (%)**	**n/N**	**Success Rate (%)**	**Difference in Rate (95% CI) (%)**
TOC103469/ End of Therapy						
	RESPON_m0	64/139	46.0	14/ 71	19.7	26.3 (13.9, 38.7)
	RESPON_m1	87/139	62.6	22/ 71	31.0	31.6 (18.2, 45.0)
	RESPON_m2	112/139	80.6	33/ 71	46.5	34.1 (20.8, 47.4)
	RESPON_m3	115/139	82.7	35/ 71	49.3	33.4 (20.2, 46.7)
	RESPON_m4	117/139	84.2	36/ 71	50.7	33.5 (20.4, 46.6)
	RESPONSE	119/139	85.6	37/ 71	52.1	33.5 (20.5, 46.5)
TOC100224/		**SB-275833**		**Sodium Fusidate**		
End of Therapy						
	RESPON_m0	161/345	46.7	115/172	66.9	-20.2 (-29, -11)
	RESPON_m1	220/345	63.8	137/172	79.7	-15.9 (-24, -8.0)
	RESPON_m2	304/345	88.1	152/172	88.4	-0.3 (-6.1, 5.6)
	RESPON_m3	318/345	92.2	153/172	89.0	3.2 (-2.3, 8.7)
	RESPON_m4	326/345	94.5	155/172	90.1	4.4 (-0.7, 9.4)
	RESPONSE	327/345	94.8	155/172	90.1	4.7 (-0.4, 9.7)
Visit 2 (Day 7)						
	RESPON_m0	161/345	46.7	69/172	40.1	6.6 (-2.5, 15.6)
	RESPONSE	327/345	94.8	165/172	95.9	-1.1 (-4.9, 2.6)
Visit 3 (Day 9)						
	RESPON_m0	238/345	69.0	115/172	66.9	2.1 (-6.4, 10.7)
	RESPONSE	324/345	93.9	155/172	90.1	3.8 (-1.3, 8.9)

RESPONSE : Sponsor's definition of clinical response;
RESPON_m0: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >0;
RESPON_m1: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >1;
RESPON_m2: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >2;
RESPON_m3: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >3;
RESPON_m4: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >4.

Table 2: Results of Sensitivity Analyses for Clinical Response at End of Therapy for SB-275833 Treated Subjects (ITT Population)

	Study TOC103469 SB-275833		Study TOC100224 SB-275833		Difference in Success Rate (95% CI) (%)
Response Variable	n/N	Rate (%)	n/N	Rate (%)	
RESPON_m0	64/139	46.0	161/345	46.7	-0.6 (-10, 9.2)
RESPON_m1	87/139	62.6	220/345	63.8	-1.2 (-11, 8.3)
RESPON_m2	112/139	80.6	304/345	88.1	-7.5 (-15, -0.1)
RESPON_m3	115/139	82.7	318/345	92.2	-9.4 (-16, -2.5)
RESPON_m4	117/139	84.2	326/345	94.5	-10 (-17, -3.8)
RESPONSE	119/139	85.6	327/345	94.8	-9.2 (-15, -2.9)

Table 3: Clinical Response at End of Therapy for SB-275833 Treated Subjects by Severity of Baseline Signs/Symptoms of Infection (ITT Population, Study TOC100224)

	Baseline SIRS <4 for All Signs/Symptoms		Baseline SIRS ≥4 for at least One Sign/Symptom		Difference in Success Rate (95% CI) (%)
Response Variable	n/N	Rate (%)	n/N	Rate (%)	
RESPON_m0	63/111	56.8	98/234	41.9	14.9 (3.7, 26.1)
RESPON_m1	86/111	77.5	134/234	57.3	20.2 (10.2, 30.2)
RESPON_m2	107/111	96.4	197/234	84.2	12.2 (6.4, 18.0)
RESPON_m3	108/111	97.3	210/234	89.7	7.6 (2.6, 12.5)
RESPON_m4	108/111	97.3	218/234	93.2	4.1 (-0.3, 8.6)
RESPONSE	108/111	97.3	219/234	93.6	3.7 (-0.6, 8.1)

RESPONSE : Sponsor's definition of clinical response;
RESPON_m0: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >0;
RESPON_m1: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >1;
RESPON_m2: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >2;
RESPON_m3: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >3;
RESPON_m4: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >4.

2. INTRODUCTION

2.1 Class and Indication

Retapamulin (SB-27833) is a member of new chemical class (pleuromutilin) of antibacterial agents for human use. 1% SB-275833 is currently being developed as a topical antibiotic for the treatment of bacterial skin infections. To date, no drug of the pleuromutilin class has been registered for human use. Two pleuromutilins, tiamulin (Denagard) and valnemulin (Econor), are registered for veterinary use for the treatment of swine dysentery, mycoplasmal pneumonia, and, in some countries, growth promotion. Tiamulin has been registered for veterinary use in the United States since 1983 and valnemulin has been registered in Europe since 1999.

In this NDA submission, Retapamulin was indicated as a topical treatment of primary impetigo caused by *Staphylococcus aureus* (methicillin-susceptible *S. aureus* only) or *Streptococcus pyogenes* in adults and pediatric patients 9 months of age and older:

Impetigo[1] is a common bacterial skin infection of the superficial layers of the dermis (skin) that particularly affects children. Impetigo can occur as a primary infection or secondary to pre-existing skin conditions such as eczema or scabies. It has two forms; bullous or non-bullous, and over 70% are the latter. *Staphylococcus aureus* has become the main bacteriological pathogen involved in the non-bullous form either alone or with *Streptococcus pyogenes.* Non-bullous impetigo tends to affect exposed areas such as the face and extremities. The bullous form is always caused by *S .aureus* and usually found on the face, buttocks, trunk, and perineum.

There are currently available a variety of oral and topical products for the treatment of impetigo. Frequently prescribed topical treatments include Mupirocin.

The sponsor claimed the following features of Retapamulin as a tropical treatment for uncomplicated skin infections: (1) inhibiting bacterial protein synthesis by interacting at a unique site on the 50S subunit that differs from those for other classes of antibiotics; (2) convenient dosing twice daily vs. three times daily for topical products such as Mupirocin or sodium fusidic acid and reduced duration of dosing compared with currently available treatments.

[1] Ajay George and Greg Rubin: A systematic review and meta-analysis of treatments for impetigo, British Journal of General Practice, June 2003.

2.2 History of Drug Development

The initial IND for SB-275833, [redacted] was submitted to the FDA on October 24, 2002. The sponsor completed a pre-phase 3/End-of-Phase 2 meeting with the FDA on December 3, 2003. Pre-NDA meeting was held on July 11, 2005.

2.3 Specific Studies Reviewed and Major Statistical Issues

The sponsor included two phase 3 studies (TOC103469 and TOC100224, both conducted outside of the United States) in the NDA package to support the proposed indication. These two studies were the focus of this review.

Study TOC103469 was a randomized, double-blind, multi-center, and placebo-controlled study in adult and pediatric subjects with impetigo. The study subjects received either topical 1% SB-275833 ointment, twice daily for 5 days or placebo ointment, twice daily for 5 days in a 2:1 ratio. There were 140 and 73 randomized subjects in the SB-275833 and the placebo groups, respectively. The total study duration was 14 days. The primary endpoint was the clinical response at the end of therapy visit on Day 7 (2 days post therapy). The primary hypothesis was that the SB-275833 treatment would be superior to placebo with respect to the successful clinical response rate.

Study TOC100224 was a randomized, observer-blind, multi-center, and non-inferiority study in adult and pediatric subjects with impetigo. The study subjects received either topical 1% SB-275833 ointment, twice daily for 5 days or topical 2% sodium fusidate ointment, three times daily for 7 days in a 2:1 ratio. There were 346 and 173 randomized subjects in the SB-275833 and the sodium fusidate groups, respectively. The total study duration was 14 days. The primary endpoint was the clinical response at the end of therapy visit (2 days post therapy: Day 7 for SB-275833 and Day 9 for sodium fusidate). The primary hypothesis was that the SB-275833 treatment would not be non-inferior to the sodium fusidate treatment with respect to the successful clinical response rate. A non-inferiority margin of 10% was used.

There is one major statistical issue in study TOC100224: this study was designed by the sponsor as a non-inferiority trial; however, the active comparator, sodium fusidate ointment, 2%, has not been approved by the FDA. Thus, this study was considered as a superiority study in this review.

2.4 Data Sources

The sponsor's study reports and data sets for studies TOC102469 and TOC100224 are available on the EDR at 2006-06-12 on 'Cdsesub1\n22055\N_000'.

3. STATISTICAL EVALUATION OF EFFICACY

3.1 Study Design and Endpoints

3.1.1 Study TOC103469

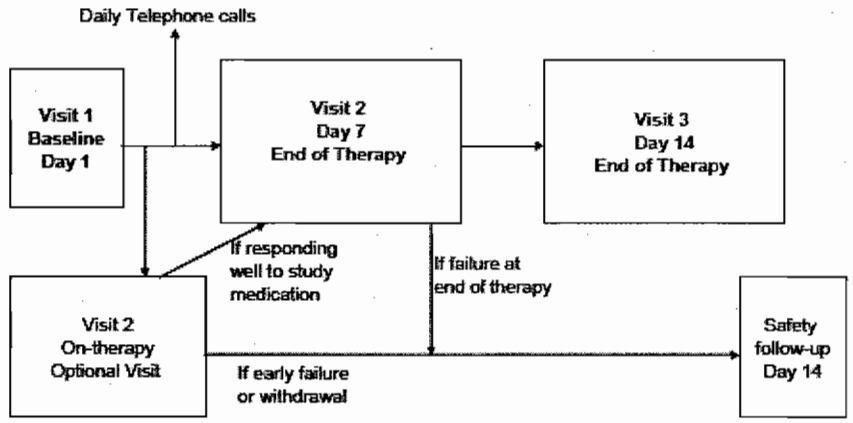
Study Design

Study TOC103469 was a randomized, double-blind, multi-center, and placebo-controlled study in adult and pediatric subjects with impetigo. The study subjects received either topical 1% SB-275833 Ointment, twice daily for 5 days or placebo ointment, twice daily for 5 days in a 2:1 ratio. There were 140 and 73 randomized subjects in SB-275833 and placebo groups, respectively. Some key inclusion and exclusion criteria are shown in Table 3.1.1. There were three study visits (baseline, End of Therapy and Follow-up) and the study duration was 14 days (Figure 1).

Table 3.1.1: Key Inclusion and Exclusion Criteria

Key Inclusion Criteria	
1	≥ 9 months of age (age ≥ 18 months in the Netherlands only).
2	With a clinical diagnosis of primary impetigo (bullous or non-bullous), defined as a lesion or group of lesions characterized by red spots or blisters without crusts, which later progress to lesions that ooze and form yellow or honey-coloured crusts surrounded by an erythematous margin.
3	No more than 10 discrete localized impetigo lesions (lesions not exceeding 100 sq. cm in total area) suitable for topical treatment.
4	A Skin Infection Rating Scale score of at least 8.
Key Exclusion Criteria	
1	Previous hypersensitivity reaction to pleuromutilin or any component of the ointment.
2	Had an underlying skin disease (e.g., pre-existing eczematous dermatitis) or skin trauma, with clinical evidence of secondary infection.
3	Systemic signs and symptoms of infection (such as fever; defined as an oral temperature greater than 101° F or 38.3° C).
4	Had a bacterial skin infection which, due to depth or severity, in the opinion of the investigator, cannot be appropriately treated by a topical antibiotic.
5	Received a systemic antibacterial, steroid, or has applied any topical therapeutic agent (including glucocorticoid steroids, antibacterials and antifungals) directly to the impetigo lesion(s), less than 24 hours prior to study entry.
6	Had a serious underlying disease that could be imminently life threatening.

Figure 1 Study Schematic Diagram



The primary Efficacy Endpoint

The primary efficacy endpoint was the clinical response at the end of therapy visit (EOT) on Day 7 (2 days post therapy) in the ITTC population.

The primary hypothesis tested in the study was that the SB-275833 treatment would be superior to placebo with respect to the efficacy measurement of proportion of subjects who had a successful clinical response.

Key Secondary Efficacy Endpoints:

(1) Clinical endpoints:

- Clinical response at Visit 2 (end of therapy; Day 7) (ITTC is primary, other populations are secondary)
- Clinical response at Visit 3 (follow-up; Day 14)

(2) Microbiological Endpoints:

- Microbiological endpoints included microbiological response at Visit 2 and Visit 3
- Number and percent of subjects who had various pathogens including methicillin resistant Staphylococcus aureus (MRSA), mupirocin-ressitant Staphylococcus aureus (mupRSA), and fusidic acid resistent Staphylococcus aureus (fusRSA) isolated at baseline, by clinical response at the end of therapy and follow-up

Determining Clinical Response

By reviewing clinical signs and symptoms at the end of therapy evaluation, the clinical outcome was determined and the resulting clinical response was assigned for each subject, as follows:

Table 3.1.2: Determining Clinical Response at the End of Therapy (Day 7)

Outcome	Defining criteria	Clinical Response
Clinical success	Total absence of the treated lesions or the treated lesions have become dry without crusts compared to baseline, or improvement (defined as a decline in the size of the affected area, number of lesions or both) such that no further antimicrobial therapy is necessary.	*Clinical success*
Clinical failure	Insufficient improvement or deterioration (i.e. lesions remain crusted and/or have exudate leaving a yellow or honey coloured crust, lesion area has increased with or with out an increase in the number of lesions) compared to baseline such that additional antibiotic therapy is required. Subjects who are clinical failures at the end of therapy are considered clinical failures at follow-up as well.	*Clinical failure*
Unable to determine	Refusal to consent to a clinical examination or lost to follow-up. Subjects who are 'unable to determine' at the end of therapy are considered 'unable to determine' at follow-up as well.	*Clinical failure*

Table 3.1.3: Determining Clinical Response at Follow-up (Day 14)
(only for subjects whose clinical response at the end of therapy)

Outcome	Defining criteria	Clinical Response
Clinical success	Continued absence of the treated lesions or the treated lesions have become dry without crusts with or without erythema compared to baseline, or improvement (defined as a decline in the size of the affected area, number of lesions or both) such that no further antimicrobial therapy is required.	*Clinical success*
Clinical recurrence	Reappearance or worsening of lesions i.e., increase in the number of lesions and/or lesion area for subjects who were clinical successes at the end of therapy.	*Clinical failure*
Unable to determine	Refusal to consent to a clinical examination or lost to follow-up. Subjects who are 'unable to determine' at the end of therapy are considered unable to determine' at follow-up as well.	*Clinical failure*
EOT Failure	The subject was an end of therapy failure. This outcome will be programmatically assessed by GlaxoSmithKline and not the investigator.	*Clinical failure*

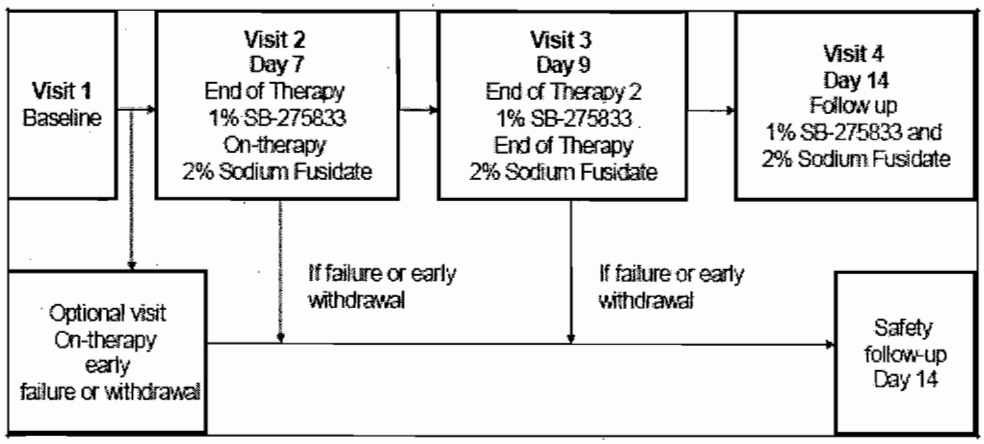
3.1.2 Study TOC100224

Study Design

Study TOC100224 was a randomized, observer-blind, multi-centre, and active-controlled study (a non-inferiority study designed by the sponsor) in adult and pediatric subjects with impetigo. The study subjects received either topical 1% SB-275833 ointment, twice daily for 5 days or topical 2% sodium fusidate ointment, three times daily for 7 days in a 2:1 ratio. There were 346 and 173 randomized subjects in the SB-275833 and the sodium fusidate groups, respectively. There were four study visits (a schematic diagram of the visit schedule is presented in Figure 1). The study duration was 14 days. The inclusion and exclusion criteria were similar to those in study TOC103469.

To maintain observer blinding, an unblinded study site member would dispense study medication and the subject or the subject's parent/legal guardian would be instructed not to discuss the study medication or medication administration with the investigator or any other investigational staff assessing the subject throughout the study.

Figure 1 Study Schematic Diagram



The primary Efficacy Endpoint

The primary efficacy endpoint was the clinical response at the end of therapy visit (2 days post therapy: Day 7 for SB-275833 and Day 9 for sodium fusidate) in the per protocol clinical evaluable (PPC) population.

The primary hypothesis tested in the study was that the SB-275833 treatment would be non-inferior to the sodium fusidate treatment with respect to the efficacy measurement of proportion of subjects who had a successful clinical response. A non-inferiority margin of 10% was used in the primary hypothesis test.

Note: this study was designed by the sponsor as a non-inferiority trial; however, the active comparator, 2% sodium fusidate ointment, has not been approved by the FDA. Thus, this study was considered as a superiority study in this review.

Key Secondary Efficacy Endpoints:

(1) Clinical endpoints:

- Clinical response at Day 7; Visit 2 (2 days post therapy for 1% SB-275833 ointment and on-therapy for 2% sodium fusidate ointment)
- Clinical response at Day 9; Visit 3 (4 days after treatment for 1% SB-275833 ointment and 2 days after treatment for 2% sodium fusidate ointment)
- Clinical response at follow-up (Day 14; Visit 4)

(2) Microbiological Endpoints:

- Microbiological response at the end of therapy (Day 7 for 1% SB-275833 ointment, Day 9 for 2% sodium fusidate ointment)
- Microbiological response at follow-up (Day 14)
- Number and percent of subjects who had methicillin resistant Staphylococcus aureus (MRSA) isolated at baseline, by clinical response, at the end of therapy (Day 7 for 1% SB-275833 ointment, Day 9 for 2% sodium fusidate ointment) and follow-up (Day 14)

Determining Clinical Response

Same as in study TOC103469.

3.2 Subject Disposition, Demographic and Baseline Characteristics

3.2.1 Subject Disposition, Analysis Population, and Protocol Violation

The results of subject disposition are presented in Table 3.2.1.

In study TOC103469, there were 140 and 73 subjects randomized to SB-275833 and placebo, respectively. Of the 140 subjects randomized to SB-275833, 139 subjects were treated. Of these treated subjects, 122 (88%) completed the study. Of the 73 subjects randomized to placebo, 71 subjects were treated. Of these treated subjects, 40 (56%) completed the study.

A higher percentage of subjects in the placebo group were withdrawn from the study compared to the SB-275833 group (44% vs. 12%). This difference was due to the higher percentage of subjects in the placebo group withdrawing due to lack of efficacy (25% versus 4%) and disease progression (13% versus 2%).

In study TOC100224, there were 346 and 173 subjects randomized to SB-275833 and sodium fusidate, respectively. In each treatment group, there was one randomized subject who was not treated. The proportions of subjects who completed the study were similar in both groups (92% for SB-275833 and 91% for sodium fusidate). The most frequent reason for withdrawal in both groups was "disease progression" (2% for SB-275833 and 3% for sodium fusidate).

Table 3.2.1: Subject Disposition

	Number (%) of Subjects			
	TOC103469		TOC100224	
	SB-275833	Placebo	SB-275833	Sodium Fusidate
Randomized	140	73	346	173
Randomized but not treated	1	2	1	1
ITTC	139 (100%)	71 (100%)	345 (100)	172 (100)
Completed	122 (88)	40 (56)	319 (92)	157 (91)
Prematurely Withdrawn	17 (12)	31 (44)	15 (9)	41 (8)
Reason for Withdrawal				
Disease progression	3 (2)	9 (13)	8 (2)	6 (3)
Lost to follow-up	5 (4)	3 (4)	8 (2)	1 (<1)
Lack of efficacy	5 (4)	18 (25)	1 (<1)	1 (<1)
Subject withdrew	2 (1)	0	3 (<1)	1 (<1)
Adverse Event	1 (<1)	1 (1)	1 (<1)	3 (2)
Protocol Deviation	1 (<1)	1 (<1)	0	
Sponsor terminated Study			1 (<1)	0
Other			3 (<1)	3 (2)

Percentages are based on ITTC population.
Data Source: Sponsor Data Source: Sponsor CSR Table 5 and Table 7.

The results of analysis population are presented in Table 3.2.2. For both studies, the proportions of PPC subjects at EOT and FU in the SB-275833 group were slightly higher than the ones in the controlled group. For study TOC103469, the PPC subjects at EOT consisted of 89% and 87% of the ITTC subjects for the SB-275833 and the placebo groups, respectively. For study TOC100224, the PPC subjects at EOT consisted of 92% and 87% of the ITTC subjects for the SB-275833 and fusidate groups, respectively.

Table 3.2.2: Analysis Population

	Number of Subjects			
	TOC103469		TOC100224	
Population	**SB-275833**	**Placebo**	**SB-275833**	**Sodium Fusidate**
ITTC	139 (100)	71 (100)	345 (100)	172 (100)
PPC at the end of therapy	124 (89)	62 (87)	317 (92)	150 (87)
PPC at Follow-Up	119 (86)	58 (82)	308 (89)	143 (83)
ITTB	114 (82)	57 (80)	263 (76)	131 (76)
PPB at the end of therapy	107 (77)	52 (73)	242 (70)	114 (66)
PPB at Follow-Up	102 (73)	48 (68)	235 (68)	107 (62)

Data Source: Sponsor CSR Table 9.

The number of subjects excluded from the per protocol clinical population PPC due to protocol violations is shown in Table 3.2.3 (Study TOC103469) and Table 3.2.4 (Study TOC100224).

In study TOC103469, the overall PPC population at follow-up consisted of 84% (177/210) of the ITTC population (85.6% for SB-275833 and 81.7% for placebo). The most common reason that led to exclusion from the PPC population in both treatment groups was exposure to other topical treatment, followed by clinical response of unable to determine.

In study TOC100224, the overall PPC population at follow-up consisted of 87% (451/517) of the ITTC population (89.3% for SB-275833 and 83.1% for sodium fusidate). The most common reasons that led to exclusion from the PPC population in the SB-275833 Ointment, 1%, group were (i) a clinical response of unable to determine and (ii) subjects being exposed to other topical treatment. The most common reasons for exclusion in the sodium fusidate ointment, 2%, group, were (i) subjects' visit day not being in a specified visit window, (ii) subjects being less than 80% compliant with study medication and (iii) subjects being exposed to other topical treatment.

Table 3.2.3: Number (%) of Subjects Excluded from the PPC Population by Reason (ITTC Population, Study 103469)

Reason For Exclusion	Treatment Group		
	SB-275833 N=139	Placebo N=71	Total N=210
PPC Population at Follow-up	119 (85.6)	58 (81.7)	177 (84.3)
Protocol Violation (PV)			
Subject exposed to other treatment[1]	7 (5.0)	7 (9.9)	14 (6.7)
Clinical response UTD	7 (5.0)	6 (8.5)	13 (6.2)
Relative day not in specified visit window	6 (4.3)	4 (5.6)	10 (4.8)
Did not return for scheduled Follow-Up visit	2 (1.4)	2 (2.8)	4 (1.9)
Inclusion or exclusion criteria not met	2 (1.4)	0	2 (1.0)

UTD = unable to determine
[1] Source Table states exposure to topical treatment, but also includes systemic treatment.
Data source: Sponsor CSR Table 8.

Table 3.2.4: Number (%) of Subjects Excluded from the PPC Population by Reason (ITTC Population, Study 100224)

Reason For Exclusion	Treatment Group		
	SB-275833 N=345	Sodium fusidate N=172	Total N=517
PPC Population at Follow-up	308 (89.3)	143 (83.1)	451 (87.2)
Protocol Violation (PV)			
Clinical response was UTD	19 (5.5)	2 (1.2)	21 (4.1)
Was exposed to other topical treatment	10 (2.9)	7 (4.1)	17 (3.3)
Relative day was not in a specified visit window	7 (2.0)	10 (5.8)	17 (3.3)
<80% study medication compliance	1 (0.3)	7 (4.1)	8 (1.5)
Inclusion or exclusion criteria not met	1 (0.3)	2 (1.2)	3 (0.6)
Did not return for scheduled Follow-Up visit	1 (0.3)	0	1 (0.2)
Subject received wrong medication[1]	1 (0.3)	0	1 (0.2)

[1] This subject was Subject 148 who was randomized to receive SB-275833 Ointment, 1%, but actually received sodium fusidate ointment, 2%.
UTD = unable to determine.
Data source: Sponsor CSR Table 8.

3.2.2 Demographic Characteristics

The demographic characteristics are presented in Table 3.2.5. Within each study, treatment groups were balanced with respect to gender, race, and ethnicity. Males and females were about evenly represented in these studies. The median age of the subjects ranged from 7 to 9 years. Overall, 175/210 (83.3%) and 359/517 (69.4%) subjects were pediatrics (<18 years) in study TOC103469 and study TOC100024, respectively.

Table 3.2.5: Demographic Characteristics (ITTC Population)

	Number (%) of Subjects			
	TOC103469		TOC100224	
	SB-275833 N=139	Placebo N=71	SB-275833 N=345	Sodium Fusidate N=172
Age (yrs)				
Mean (SD)	12.3 (14.02)	8.9 (8.95)	17.8 (19.4)	14.4 (15.7)
Median	8.0	7.0	9.0	7.0
Range	0 - 73	0 - 44	0 – 84	0 - 66
Age Strata				
9 months to <2 years	12	6	29	12
2 years to <6 years	38	24	90	53
6 years to <13 years	56	28	87	47
13 years to <18 years	5	6	27	14
18-<65 years	25	7	97	45
≥65 years	3	0	15	1
Sex: n (%)				
Female	73 (53)	34 (48)	167 (48)	72 (42)
Male	66 (47)	37 (52)	178 (52)	100 (58)
Race: n (%)				
African American / African heritage	2 (1)	3 (4)	92 (27)	48 (28)
American Indian or Alaskan native	23 (17)	13 (18)	25 (7)	11 (6)
Asian – Center/South Asian heritage	59 (42)	30 (42)	85 (25)	44 (26)
Asian – South East Asian heritage	NA	NA	1 (<1)	3 (2)
White – Arabic/North African heritage	2 (1)	0	2 (<1)	1 (<1)
White – White/Caucasian /European heritage	52 (37)	23 (32)	140 (41)	65 (38)
Mixed race	1 (<1)	2 (3)	NA	NA
Ethnicity: n (%)				
Hispanic/Latino	39 (28)	23 (32)	56 (16)	24 (14)
Not Hispanic/Latino	100 (72)	48 (68)	289 (84)	148 (86)

Data Source: Sponsor CSR Table 10 and Table 11 for Studies TOC103469 and TOC100224.

3.2.3 Baseline Clinical Characteristics

The proportions of subjects with a clinical diagnosis of bullous or non-bullous impetigo at baseline were similar between treatment groups within each study (Table 3.2.6). There were about 80% subjects who had non-bullous impetigo.

Table 3.2.6 Clinical Diagnosis of Impetigo at Baseline by Analysis Population

	Number (%) of Subjects			
	TOC103469		TOC100224	
Characteristic	SB-275833 N=662	Placebo N=326	SB-275833 N=606	Fusidate N=310
Bullous				
ITTC	26 (18.7)	11 (15.5)	75 (21.7)	35 (20.3)
PPC	20 (16.8)	8 (13.8)	67 (21.8)	28 (19.6)
ITTB	19 (16.7)	8 (14.0)	61 (23.2)	28 (21.4)
PPB	15 (14.7)	6 (12.5)	53 (22.6)	21 (19.6)
Non-bullous				
ITTC	113 (81.3)	60 (84.5)	270 (78.3)	137 (79.7)
PPC	99 (83.2)	50 (86.2)	241 (78.2)	115 (80.4)
ITTB	95 (83.3)	49 (86.0)	202 (76.8)	103 (78.6)
PPB	87 (85.3)	42 (87.5)	182 (77.4)	86 (80.4)

Data Source: Sponsor CSR Table 12 for Studies TOC103469 and TOC100224.

The summary results of individual and total skin infection rating (SIRS) scores at baseline are presented in Table 3.2.7. These results showed similarity between treatment groups within each study. The overall mean total SIR scores were also similar between the two studies (16.4 and 16.1 in studies TOC103469 and TOC100224, respectively).

However, the statistical reviewer's analysis results in Table 3.2.8 showed that compared with study TOC103469, study TOC100024, designed as a non-inferiority study by the sponsor, had a much higher percentage of subjects who had only mild signs/symptoms (SIRS <4 for every sign/symptom) of infection at baseline. There were more than 32% of these subjects in study TOC100024 whereas there were about 8% in study TOC103469. It is reasonable to expect that these subjects will have high placebo rate and have the potential to make any two drugs (effective or not) look similar in a non-inferiority trial where the definition of a successful clinical response is in part based on the improvement of sign/symptoms of infection at baseline and subjects to study investigators' interpretation.

Table 3.2.7 Summary of SIRS Scores at Baseline (ITTC Population)

	SIRS Score			
	TOC103469		TOC100224	
Skin Infection Item	**SB-275833 N=139**	**Placebo N=71**	**SB-275833 N=345**	**Sodium Fusidate N=172**
Exudate/Pus				
Mean (SD)	2.38 (1.61)	2.62 (1.47)	2.61 (1.36)	2.79 (1.48)
Median	3.0	3.0	2.0	2.0
Score <2 (%)	25.2	25.4	18.0	18.0
Crusting				
Mean (SD)	3.27 (1.44)	3.52 (1.49)	2.70 (1.66)	2.86 (1.30)
Median	3.0	4.0	2.0	3.0
Score <2 (%)	10.1	8.5	22.9	25.6
Erythema/Inflammation				
Mean (SD)	3.24 (1.43)	3.20 (1.41)	2.86 (1.30)	2.95 (1.24)
Median	4.0	3.0	3.0	3.0
Score <2 (%)	11.5	12.7	14.8	12.2
Tissue Warmth				
Mean (SD)	1.72 (1.50)	1.58 (1.56)	1.84 (1.34)	1.85 (1.34)
Median	2.0	1.0	2.0	2.0
Score <2 (%)	47.5	50.7	40.3	41.9
Tissue Edema				
Mean (SD)	1.37 (1.40)	1.37 (1.46)	1.59 (1.31)	1.63 (1.31)
Median	1.0	1.0	1.0	1.0
Score <2 (%)	56.1	54.9	51.6	51.2
Itching				
Mean (SD)	2.60 (1.67)	2.45 (1.67)	2.25 (1.63)	2.20 (1.53)
Median	3.0	2.0	2.00	2.00
Score <2 (%)	24.5	26.8	33.0	33.1
Pain				
Mean (SD)	1.47 (1.68)	1.41 (1.60)	2.23 (1.56)	2.14 (1.47)
Median	1.0	1.0	2.0	2.0
Score <2 (%)	57.6	57.7	33.0	33.7
Total Score				
Mean (SD)	16.50 (5.62)	16.14 (6.10)	16.09 (6.00)	16.27 (6.51)
Median	15.0	14.0	15.0	15.0

Data Source: Sponsor CSR Table 7.47 and Table 7.48

Table 3.2.8: Percent and Mean Total SIRS score of Signs/Symptoms of Infection at Baseline (ITTC Population)

Study	Subjects who had all signs/symptoms grated as mild (SIRS <4 for every sign/symptom)		Subjects who had at least one sign/symptom grated as moderate/ severe (SIRS ≥4 for at least one sign/symptom)		ALL
	SB-275833	**Placebo**	**SB-275833**	**Placebo**	
103469	7.9% (12.0)	8.5% (12.0)	92.1% (16.9)	91.5% (16.5)	100% (16.4)
	SB-275833	**Fusidate**	**SB-275833**	**Fusidate**	
100024	32.2% (10.7)	34.9% (10.6)	67.8% (18.6)	65.1% (19.3)	100% (16.1)

3.2.3 Bacteriology at Baseline

The numbers of subjects by number of pathogens identified at baseline in the ITTC population are summarized in Table 3.2.9. Study TOC103469 had about 82% of subjects with at least one pathogens isolated at baseline. Study TOC100224 had about 76% of subjects with at least one pathogens isolated at baseline. Of the subjects with one or more pathogens, the majority of these subjects had only one pathogen identified in the sample: 60% in SB-275833 and 72% in placebo in study TOC103469; 53% in SB-275833 and 52% in Fusidate in study TOC100224.

Table 3.2.9: Number (%) of Subjects by Number of Pathogens Isolated at Baseline (ITTC population)

	Number (%) of Subjects			
	TOC103469		TOC100224	
Number of Pathogens	SB-275833 N=139	Placebo N=71	SB-275833 N=345	Sodium Fusidate N=172
0	25 (18.0)	13 (18.3)	82 (23.8)	41 (23.8)
1	83 (59.7)	51 (71.8)	182 (52.8)	90 (52.3)
2	29 (20.9)	6 (8.5)	76 (22.0)	36 (20.9)
3	2 (1.4)	0	5 (1.5)	5 (2.9)
4	0	1 (1.4)	0	0
Number of Subjects with ≥ 1 Pathogen	114 (82.0)	58 (81.7)	263 (76.2)	131 (76.2)

Data Source: Sponsor CSR Table 13.

For study TOC103469, pathogens isolated at baseline are summarized in Table 3.2.10. *S. aureus* was the most frequently isolated pathogen in the study (64.6% of isolates from subjects in the SB-275833 group, and 77.3% of isolates from the placebo group. All the isolates of *S. aureus* were methicillin-susceptible (i.e. no MRSA pathogens were isolated) and all were susceptible to Mupirocin. Pathogens were generally isolated with similar frequency in the two treatment groups, although slightly more *S. pyogenes* were isolated in the SB-275833 group (23% compared to 12% in the placebo group).

For study TOC100224, pathogens isolated at baseline are summarized in Table 3.2.11. *S. aureus* was the most frequently isolated pathogen in the study (65.3% of isolates from

subjects in the SB-275833 group and 63.8% of isolates from the Fusidate group). Of all the isolates of *S. aureus*, most were methicillin-susceptible while only 10 (1.9% of all *S.* aureus isolates) were methicillin-resistant. Pathogens were isolated with similar frequency in the two treatment groups.

Table 3.2.10: Pathogens Isolated at Baseline (Study TOC103469)

	Number (%) of Isolates	
Baseline Pathogens[1]	**SB-275833**	**Placebo**
All Pathogens	147	66
S. aureus	95 (64.6)	51 (77.3)
MRSA[2]	0	0
MSSA[2]	95 (64.6)	51 (77.3)
mupRSA[3]	0	0
mupSSA[3]	95 (64.6)	51 (77.3)
fusRSA[4]	10 (6.8)	6 (9.1)
fusSSA[4]	83 (56.5)	44 (66.7)
S. pyogenes	34 (23.1)	8 (12.1)
Other Streptococcus spp.	2 (1.4)	0
Other Gram (+) pathogens	2 (1.4)	0
Gram (-) pathogens	14 (9.5)	7 (10.6)

1. Subjects may be represented in this table more than once as they may have had more than one pathogen at baseline
2. MRSA/MSSA are methicillin resistant/susceptible as defined by susceptibility to oxacillin.
3. Mupirocin breakpoints defined as susceptible ≤4µg/mL, resistant ≥8µg/mL
4. Fusidic acid breakpoints defined as susceptible ≤1µg/mL, intermediate =2µg/mL, resistant ≥4µg/mL. Total fusRSA and fusSSA n value is 93 for SB-275833 and 50 for placebo since fusISA is not included in this table.

Note: MSSA = Methicillin-susceptible *S. aureus*; mupSSA = Mupirocin-susceptible *S. aureus*; fusSSA = Fusidic acid-susceptible *S. aureus*; fusRSA = Fusidic acid-resistant *S. aureus*.
Data Source: Sponsor CSR Table 14.

Table 3.2.11: Pathogens Isolated at Baseline (Study TOC100224)

	Number (%) of Isolates[1]	
Pathogens	**SB-275833**	**Sodium fusidate**
All pathogens	349	177
S. aureus	228 (65.3)	113 (63.8)
MRSA	8 (2.3)	2 (1.1)
MSSA	220 (63.0)	111 (62.7)
mupRSA	7 (2.0)	6 (3.4)
mupSSA	221 (63.3)	107 (60.4)
fusRSA[2]	10 (2.9)	9 (5.1)
fusSSA[2]	211 (60.5)	104 (58.8)
S. pyogenes	96 (27.5)	41 (23.2)
Other Streptococcus spp.	4 (1.1)	3 (1.7)
Other Gram (+) pathogens	3 (1.0)	1 (0.6)
Gram (-) pathogens	18 (5.2)	19 (10.7)

1. Number (%) of isolates = number of a particular pathogen and the percentage of all pathogens for the treatment group.
2. Total fusRSA and fusSSA n value is 221 as fusISA is not included in this table.

Note: MSSA = Methicillin-susceptible *Staphylococcus aureus*; mupSSA = Mupirocin-susceptible *Staphylococcus aureus*; fusSSA = Fusidic acid-susceptible *Staphylococcus aureus*.
Data Source: Sponsor CSR Table 14.

3.3 Statistical Methodology

3.3.1 Study TOC103469

Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint in study TOC103469 was clinical response at the end of therapy on Day 7 (2 days post therapy) in the ITTC population.

The primary hypothesis tested in the study was that SB-275833 treatment would be superior to placebo with respect to the efficacy measurement of proportion of subjects who had a successful clinical response. A conclusion of superior efficacy of 1% SB-275833 ointment would be drawn if the lower limit of the 95% confidence interval for the treatment difference between SB-275833 and placebo was greater than zero.

The normal approximation, without continuity correction, was used to construct the confidence interval.

Efficacy Analysis Population:

Four analysis populations were defined for the analysis of clinical efficacy and bacteriology data.

Intent to Treat Clinical (ITTC): All randomized subjects who took at least one dose of study medication. A subject was considered to have taken at least one dose of study medication if their medication start date was not missing or if the total number of doses (actual dose) was not missing and greater than zero.

Intent to Treat Bacteriology (ITTB): All randomized subjects who took at least one dose of study medication and who had evidence of a bacterial infection (have a pathogen isolated by the central lab from the primary lesion) at baseline. The ITTB population was a subset of the ITTC population.

Per Protocol Clinical (PPC): Subjects from the ITTC population who adhered to the protocol (do not violate the protocol). The PPC population was a subset of the ITTC population.

Per Protocol Bacteriology (PPB): Subjects from the ITTB population who adhered to the protocol (do not violate the protocol). The PPB population was a subset of the ITTB and PPC populations.

Subjects were excluded from the PPC and PPB populations from the time that the protocol violation occurred. For example, a subject who returns for the follow-up visit outside the protocol specified time interval would be excluded from analyses at follow-up, but not from analyses at the end of therapy. However, patients who fail clinically are

exempt from this rule. For example, if a subject is a PPC clinical failure at the end of therapy, and subsequently violates the protocol between the end of therapy and follow-up, that subject will not be excluded from the PPC population at follow-up.

Analysis of Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints included the following:
(1) Clinical endpoints:

- Clinical response at Visit 2 (end of therapy; Day 7) (ITTC is primary as seen above, other populations are secondary)
- Clinical response at Visit 3 (follow-up; Day 14)

(2) Microbiological Endpoints:

- Microbiological endpoints included microbiological response at Visit 2 and Visit 3.
- Number and percent of subjects who had various pathogens including methicillin resistant Staphylococcus aureus (MRSA), mupirocin-ressitant Staphylococcus aureus (mupRSA), and fusidic acid resistent Staphylococcus aureus (fusRSA) isolated at baseline, by clinical response at the end of therapy and follow-up

The secondary clinical efficacy endpoints were analyzed in the same fashion as for the primary efficacy endpoint.

Sample Size Consideration

This study planed to enroll 140 subjects in the 1% SB-275833 ointment group, and 70 in the placebo group. With these sample sizes, the study would have a 90% power for the primary hypothesis test using a one-sided type 1 error rate of 2.5%. These sample sizes were based on the assumptions that the clinical success rates for 1% SB-275833 ointment were 82% and a 61% cure rate for placebo, respectively.

3.3.2 Study TOC100224

Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint in study TOC100224 was clinical response (success or failure) at the end of therapy, two days after therapy (Day 7 for 1% SB-275833 ointment and Day 9 for 2% sodium fusidate ointment) in the PPC population.

According to the sponsor, the primary hypothesis tested in the study was that SB-275833 treatment would be non-inferior to sodium fusidate treatment with respect to the efficacy measurement of proportion of subjects who had a successful clinical response. A non-inferiority margin of 10% was used. A conclusion of non-inferior 1% SB-275833 ointment to sodium fusidate ointment would be drawn if the lower limit of the 95% confidence interval for the treatment difference between the SB-275833 and the sodium

fusidate groups was greater than -10%. The normal approximation, without continuity correction, was used to construct the confidence interval.

Statistical Reviewer's Comments:
Since sodium fusidate ointment, the active controlled drug in this study, has not been approved by the FDA, this study is considered as a superiority study in this review. The demonstration of efficacy of SB-275833treatment in this study requires that SB-275833treatment is superior to the sodium fusidate treatment with respect to the efficacy measurement of proportion of subjects who had a successful clinical response.

Efficacy Analysis Population:

Four analysis populations (ITTC, ITTB, PPC, and PPB) were defined in the same manner as in study TOC103469 for the analysis of clinical efficacy and bacteriology data.

Analysis of Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints included the following:
(1) Clinical endpoints:

- Clinical response at Visit 2 (Day 7), Visit 3 (Day 9), and Visit 4 (follow-up/Day 14).

(2) Microbiological Endpoints:

- Microbiological response at the end of therapy
- Microbiological response at Visit 2, Visit 3, and Visit 4.
- Number and percent of subjects who had various pathogens including methicillin resistant Staphylococcus aureus (MRSA) isolated at baseline, by clinical response at the end of therapy and follow-up

The secondary clinical efficacy endpoints were analyzed in the same fashion as for the primary efficacy endpoint.

Sample Size Consideration

This study planed to enroll 520 subjects (2:1 randomization scheme) to ensure 363 evaluable subjects at the end of therapy visit. It was assumed that the clinical success rates for 1% SB-275833 ointment and 2% sodium fusidate ointment groups were 91%. Using a non-inferiority margin of 10% and a one sided type 1 error rate of 2.5%, the study would have a 90% power for the primary hypothesis test. It was anticipated that due to the age of the subjects (most will be pediatrics) as many as 30% of subjects could be non-evaluable (not within the per protocol population). Thus, 520 subjects should be enrolled into the study in order to provide the 363 evaluable subjects at the end of therapy.

3.3.3 Sensitivity Analyses of Primary Efficacy Endpoint

For both studies, the primary efficacy endpoint was the clinical response (success or failure) at the end of therapy visit. It was related to the baseline signs/symptoms of infection and was defined based on the clinical outcome assessed by the study investigators (see Tables 3.1.2-3.1.3 for details). A clinical response of "success" at the end of therapy corresponded to a clinical outcome assessment of *"Total absence of the treated lesions or the treated lesions have become dry without crusts compared to baseline, or improvement (defined as a decline in the size of the affected area, number of lesions or both) such that no further antimicrobial therapy is necessary."* judged by the study investigators.

In this definition, the sponsor failed to provide an objective criteria for *"improvement (defined as a decline in the size of the affected area, number of lesions or both) such that no further antimicrobial therapy is necessary"* that could be consistently applied across study investigators. Non-standard or subjective definition for *"improvement (defined as a decline in the size of the affected area, number of lesions or both) such that no further antimicrobial therapy is necessary"* by the study investigators would lead to misclassification of clinical responses.

To examine the robustness of the primary efficacy results, the statistical reviewer has performed numerous sensitivity analyses by modifying sponsor's definition of clinical response using the measurements of signs and symptoms of infection.

The sponsor collected data on signs and symptoms of infection on seven items at each study visit. The seven items are: Exudate/Pus, Crusting, Erythema/Inflammation, Tissue warmth, Tissue edema, Itching, and Pain. Each item of these signs and symptoms was rated by the study investigators using a 6 point (0, 1, 2, 3, 4, 5, and 6) skin infection rating scale (SIRS). The scale was defined as follows. Total SIRS score is the sum of SIRS score for the seven items.

0 Absent	= no evidence of the signs or symptoms
1	half point between 0 and 2
2 Mild	= signs/symptoms are present but not intense
3	half point between 2 and 4
4 Moderate	= signs/symptoms are clearly evident and are somewhat bothersome to the subject
5	half point between 4 and 6
6 Severe	= signs/symptoms are clearly evident, intense and extremely bothersome to the subject

By incorporating the data on signs and symptoms of infection at the end of therapy visit, the statistical reviewer modified the sponsor's primary endpoint "RESPONSE" (success or failure) in various ways shown in the following table. The sensitivity analyses were performed for these modified clinical response variables.

Variable	Definition
RESPON_m0:	Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >0;
RESPON_m1:	Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >1;
RESPON_m2:	Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >2;
RESPON_m3:	Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >3;
RESPON_m4:	Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >4;
RESPON_m5:	Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >5;
RESPON_ n:	Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms increased from baseline;
RESP_nm5:	Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >5 or at least one SIRS score for signs/symptoms increased from baseline;
RESPONS_s:	Modified sponsor's definition by treating subjects as failure if total SIRS score for signs/symptoms didn't improve from baseline;
RESPONS_8:	Modified sponsor's definition by treating subjects as failure if total SIRS score for signs/symptoms ≥8.

Among the above modified clinical response variables, a successful clinical response using variable "RESPON_m0" is the strictest one and requires that none of the seven signs and symptoms of infection would be present for a successful clinical response. This requirement would relate most closely to the component "Total absence of the treated lesions or the treated lesions have become dry without crusts compared to baseline" in the sponsor's definition of clinical response in the study protocols. Apparently this modified definition of clinical response would much less subject to investigators' interpretation compared to the sponsor's definition, and thus lead to less misclassification of a successful clinical response.

The variable "RESPON_m1" requires that subjects with mild to severe signs and symptoms be treated as clinical failure, which could be considered as a reasonable requirement of any sensible definition of clinical response.

The variable "RESPON_m5" requires that subjects with any severe signs and symptoms be treated as clinical failure, which could be considered as a minimum requirement of any sensible definition of clinical response.

Variables "RESPON_m1", "RESPON_m2", "RESPON_m3", and "RESPON_m4" correspond to the requirements in-between "RESPON_m0" and "RESPON_m5".

The variable "RESPON_n" requires that subjects with increased signs and symptoms of infection be treated as clinical failure. This requirement would related closely to "insufficient improvement, or deterioration of signs and symptoms of the infection recorded at baseline" mentioned in the sponsor's original definition.

The variable "RESPON_nm5" requires that subjects with severe or increased signs and symptoms of infection be treated as clinical failure. This requirement would also related closely to "insufficient improvement, or deterioration of signs and symptoms of the infection recorded at baseline" mentioned in the sponsor's definition of clinical response in the study protocols.

Since one of the inclusion criteria was that the total SIRS at baseline must be at least 8, variable "RESPONS_8" requires that subjects with total SIRS at follow-up be treated as clinical failure. The variable RESPONS_s" requires that subjects whose total SIRS at follow-up did not improve from baseline be treated as clinical failure.

3.4 Results and Conclusions

The efficacy results of clinical response at the end of therapy and the follow-up visits are presented in Table 3.4.1.

Clinical Success Rates at the end of therapy

In study TOC103469, the SB-275833 group had a statistically significantly higher clinical success rate than the placebo group in all the analysis populations (ITTC, PPC, ITTB, and PPB). The clinical success rates in the ITTC population were 85.6% and 52.1% for the SB-27833 and the placebo groups, respectively. The 95% confidence interval for the difference in the clinical success rate between the SB-27833 and the placebo groups were (20.5%, 46.5%) and (22.8%, 49.8%) in the ITTC and PPC populations, respectively.

In study TOC100224, the SB-275833 group didn't have a statistically significantly higher clinical success rate than the sodium fusidate group. The SB-275833 group and the sodium fusidate group seemed to have a similar clinical success rate in all the analysis populations (ITTC, PPC, ITTB, and PPB). The clinical success rates in the ITTC population were 94.8% and 90.1% for the SB-27833 and the sodium fusidate groups, respectively. The 95% confidence interval for the difference in the clinical success rate between the SB-27833 and the sodium fusidate groups were (-0.4%, 9.7%) and (1.1%, 9.0%) in the ITTC and PPC populations, respectively.

Clinical Success Rates at Follow-up

In study TOC103469, the SB-275833 group had a statistically significantly higher clinical success rate than the placebo group in all the analysis populations (ITTC, PPC, ITTB, and PPB). The clinical success rates in the ITTC population were 75.5% and 39.4% for the SB-27833 and the placebo groups, respectively. The 95% confidence interval for the difference in the clinical success rate between the SB-27833 and the placebo groups were (22.7%, 49.5%) and (24.8%, 53.7%) in the ITTC and PPC populations, respectively.

In study TOC100224, the SB-275833 group didn't have a statistically significantly higher clinical success rate than the sodium fusidate group. The SB-275833 group and the sodium fusidate group seemed to have a similar clinical success rate in all the analysis populations (ITTC, PPC, ITTB, and PPB). The clinical success rates in the ITTC population were 89.9% and 87.2% for the SB-27833 and the sodium fusidate groups, respectively. The 95% confidence interval for the difference in the clinical success rate between the SB-27833 and the sodium fusidate groups were (-3.3%, 8.6%) and (-1.8%, 7.2%) in the ITTC and PPC populations, respectively.

Results of Sensitivity Analysis for Clinical Success Rates at the end of therapy

The results of the sensitivity analyses for the clinical response at the end of therapy visit performed by the statistical reviewer are presented in Tables 3.4.2 - 3.4.5.

These results demonstrated that (1) in study TOC103469 the superiority efficacy results of SB-275833 treatment over placebo were very robust and statistically significant; (2) in study TOC100224 the clinical response rates of the SB-275833 treatment over sodium fusidate were sensitive to how the clinical response was defined; the SB-275833 treatment seemed to be inferior to the sodium fusidate treatment when mild to severe signs and symptoms of infection at the end of therapy visit were considered as clinical failure.

In study TOC103469, the results in Table 3.4.2 shown that the clinical response rates in the SB-275833 group were statistically significantly higher than the ones in the placebo group regardless how the clinical response was defined. The point estimates for the difference in the clinical response rate between the SB-275833 group and the placebo group were very robust and with a magnitude around 30%.

In study TOC100224 (designed as a non-inferiority study by the sponsor, reviewed by the Agency as a superiority trial), the difference in the clinical response rate between the SB-275833 and the sodium fusidate groups was sensitive to how the clinical response was defined. The results in Table 3.4.3 showed that when mild to severe signs and symptoms of infection at the end of therapy visit were considered as clinical failure, the difference in the clinical response rates between the SB-275833 and the sodium fusidate groups decreased from the sponsor's results of 4.7% (95% CI: -0.4%, 9.7%) to -20.2% (95% CI: -29%, -11%) in the ITTC population, indicating that SB-275833 was inferior to the sodium fusidate treatment.

To further examine the robustness of the SB-275833 treatment effect, the clinical response rates for the SB-275833 treated subjects in study TOC103469 were compared with the ones for the SB-275833 treated subjects in study TOC100224. It should be noted that these two studies were similar in terms of study inclusion and exclusion criteria, and had the same SB-275833 treatment duration (5 days) and same duration (7 days) for the end of therapy visit. Thus, it is reasonable to expect that the clinical response rates at the end of therapy visit in these two studies would be comparable. This is exactly what was

observed when less subjective response variables such as RESPON_m0 and RESPON_m1 were used. The results in Table 3.4.4 showed that when response variable RESPON_m0 was used, the difference in clinical response rate for the SB-275833 treated subjects between studies TOC103469 and TOC100224 was -0.6% (95% CI: -10% to 9.2%) in the ITTC population. In contrast, when the sponsor's definition of clinical response was used, the SB-275833 treated subject in study TOC100224 (designed as a non-inferiority trial by the sponsor) had a clinical response rate that was 9.2% (95% CI: 2.9% to 15%) higher than the one for the SB-275833 treated subjects in study TOC103469 (designed as a placebo controlled trial by the sponsor). This disparity in the clinical response rate in the SB-275833 treated subjects in these two studies might very well reflect on the fact that the component *"improvement (defined as a decline in the size of the affected area, number of lesions or both) such that no further antimicrobial therapy is necessary"* in the sponsor's definition was subjected to the study investigators' interpretation and might have lead to over estimation of the clinical response rate in the non-inferiority trial. Thus, this kind of non-standard definition of primary endpoint should be avoided in a non-inferiority trial to ensure assay sensitivity of the trial.

The sensitivity of the SB-275833 treatment effect to the severity of baseline signs and symptoms of infection was also examined in the SB-275833 treated subjects in study TOC100224. It is reasonable to expect that the subjects who had only mild baseline signs/symptoms (SIRS<4 for every sign/ symptom) would generally have a higher clinical success rate than the subjects who had at least one moderate/severe baseline signs and symptoms (SIRS≥4 for at least one sign/symptom). This is exactly what was observed when less subjective response variables such as RESPON_m0 and RESPON_m1 were used. The results in Table 3.4.5 showed that when response variable RESPON_m0 was used, the response rate for the subjects who had only mild baseline signs and symptoms was 14.9% (95% CI: 3.7% to 26.1%) higher than the one for the subjects who had at least one moderate/severe baseline signs and symptoms in the ITTC population. In contrast, when the sponsor's definition of clinical response was used, the response rates were similar for these two groups of subjects. This lack of sensitivity of the clinical response rate to the severity of baseline signs and symptoms again reflected on the fact that the sponsor's definition of clinical response entailed a component that was subjected to investigators' interpretation. This non-standardized definition of primary endpoint might very well lead to misclassification and obscure the rue difference in the response rate between these two groups of subjects. Thus, this kind of non-standard definition of primary endpoint should be avoided in a non-inferiority trial to ensure assay sensitivity of the trial.

Clinical Success Rates at the end of therapy by Pathogen Isolated at Baseline

SB-275833 was designed to treat subjects with skin and skin structure infections that have a high likelihood of *S. aureus* or *S. pyogenes* as the causative agent. The sponsor's results of clinical success rates by baseline pathogen (Table 3.4.6) showed that in study 103469 the SB-275833 group had a higher clinical success rate than the placebo group for subjects with all pathogens (including *S. aureus* or *S. pyogenes*) identified at baseline.

In study TOC100224, the clinical success rates in the SB-275833 group were similar to those in the sodium fusidate group.

Results of Microbiological Success Rates at the end of therapy

The sponsor's results of microbiological response at the end of therapy visit are presented in Tables 3.4.7 and 3.4.8. In study TOC103469, the microbiological success rates in the SB-275833 group were statistically significantly higher than those in the placebo group. In study TOC100224, the microbiological success rates in the SB-275833 group were similar to those in the sodium fusidate group.

Table 3.4.1: Clinical Response at the end of therapy and Follow-Up

	Number (%) of Successes							
	TOC103469				TOC100224			
	SB-275833		Placebo		SB-275833		Sodium Fusidate	
	n/N	Success Rate (%)	n/N	Success Rate (%)	n/N	Success Rate (%)	n/N	Success Rate (%)
End of Therapy								
PPC	111/124	89.5	33/ 62	53.2	314/317	99.1	141/150	94.0
ITTC	119/139	85.6	37/ 71	52.1	327/345	94.8	155/172	90.1
PPB	96/107	89.7	26/ 52	50.0	240/242	99.2	106/114	93.0
ITTB	101/114	88.6	28/ 57	49.1	250/263	95.1	116/131	88.5
Follow-Up								
PPC	98/119	82.4	25/ 58	43.1	297/308	96.4	134/143	93.7
ITTC	105/139	75.5	28/ 71	39.4	310/345	89.9	150/172	87.2
PPB	86/102	84.3	18/ 48	37.5	227/235	96.6	99/107	92.5
ITTB	91/114	79.8	19/ 57	33.3	237/263	90.1	111/131	84.7
	Difference, % (CI)				Difference, % (CI)			
End of Therapy								
PPC	36.3 (22.8, 49.8)				5.1 (1.1, 9.0)			
ITTC	33.5 (20.5, 46.5)				4.7 (-0.4, 9.7)			
PPB	39.7 (25.0, 54.5)				6.2 (1.4, 11.0)			
ITTB	39.5 (25.2, 53.7)				6.5 (0.5, 12.6)			
Follow-Up								
PPC	39.2 (24.8, 53.7)				2.7 (-1.8, 7.2)			
ITTC	36.1 (22.7, 49.5)				2.6 (-3.3, 8.6)			
PPB	46.8 (31.4, 62.2)				4.1 (-1.4, 9.6)			
ITTB	46.5 (32.2, 60.8)				5.4 (-1.8, 12.5)			

Data Source: Generated by the Statistical Reviewer.

Table 3.4.2: Results of Sensitivity Analyses for Clinical Response at End of Therapy (Study TOC103469)

		SB-275833		PLACEBO			
Response Variable	Analysis Population	n/N	Rate (%)	n/N	Rate (%)	Difference in Success Rate (%)	95% CI (%)
RESPON_m0	PPC	60/124	48.4	12/ 62	19.4	29.0	(15.8, 42.2)
RESPON_m0	ITTC	64/139	46.0	14/ 71	19.7	26.3	(13.9, 38.7)
RESPON_m1	PPC	82/124	66.1	20/ 62	32.3	33.9	(19.6, 48.2)
RESPON_m1	ITTC	87/139	62.6	22/ 71	31.0	31.6	(18.2, 45.0)
RESPON_m2	PPC	104/124	83.9	30/ 62	48.4	35.5	(21.5, 49.5)
RESPON_m2	ITTC	112/139	80.6	33/ 71	46.5	34.1	(20.8, 47.4)
RESPON_m3	PPC	107/124	86.3	32/ 62	51.6	34.7	(20.8, 48.5)
RESPON_m3	ITTC	115/139	82.7	35/ 71	49.3	33.4	(20.2, 46.7)
RESPON_m4	PPC	109/124	87.9	33/ 62	53.2	34.7	(21.0, 48.4)
RESPON_m4	ITTC	117/139	84.2	36/ 71	50.7	33.5	(20.4, 46.6)
RESPON_m5	PPC	111/124	89.5	33/ 62	53.2	36.3	(22.8, 49.8)
RESPON_m5	ITTC	119/139	85.6	37/ 71	52.1	33.5	(20.5, 46.5)
RESPONS_n	PPC	106/124	85.5	29/ 62	46.8	38.7	(24.8, 52.6)
RESPONS_n	ITTC	113/139	81.3	31/ 71	43.7	37.6	(24.4, 50.9)
RESP_nm5	PPC	106/124	85.5	29/ 62	46.8	38.7	(24.8, 52.6)
RESP_nm5	ITTC	113/139	81.3	31/ 71	43.7	37.6	(24.4, 50.9)
RESPONS_8	PPC	107/124	86.3	32/ 62	51.6	34.7	(20.8, 48.5)
RESPONS_8	ITTC	115/139	82.7	36/ 71	50.7	32.0	(18.8, 45.2)
RESPONS_s	PPC	111/124	89.5	33/ 62	53.2	36.3	(22.8, 49.8)
RESPONS_s	ITTC	119/139	85.6	37/ 71	52.1	33.5	(20.5, 46.5)

RESPON_m0: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >0;

RESPON_m1: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >1;

RESPON_m2: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >2;

RESPON_m3: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >3;

RESPON_m4: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >4;

RESPON_m5: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >5;

RESPON_n: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms increased from baseline;

RESPON_nm5: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >5 or at least one SIRS score for signs/symptoms increased from baseline;

RESPONS_8: Modified sponsor's definition by treating subjects as failure if total SIRS score for signs/symptoms ≥8;

RESPONS_s: Modified sponsor's definition by treating subjects as failure if total SIRS score did not improve from baseline.

Table 3.4.3: Results of Sensitivity Analyses for Clinical Response by Visit (Study TOC100224)

		SB-275833		Fusidate			
Response Variable	Analysis Population	n/N	Rate (%)	n/N	Rate (%)	Difference in Success Rate (%)	95% CI (%)
End of Therapy (2 days post therapy; 7 days for SB-275833 and 9 days for Fusidate)							
RESPON_m0	PPC	158/317	49.8	106/150	70.7	-20.8	(-30, -12)
RESPON_m0	ITTC	161/345	46.7	115/172	66.9	-20.2	(-29, -11)
RESPON_m1	PPC	216/317	68.1	125/150	83.3	-15.2	(-23, -7.3)
RESPON_m1	ITTC	220/345	63.8	137/172	79.7	-15.9	(-24, -8.0)
RESPON_m2	PPC	295/317	93.1	138/150	92.0	1.1	(-4.1, 6.2)
RESPON_m2	ITTC	304/345	88.1	152/172	88.4	-0.3	(-6.1, 5.6)
RESPON_m3	PPC	308/317	97.2	139/150	92.7	4.5	(-0.1, 9.0)
RESPON_m3	ITTC	318/345	92.2	153/172	89.0	3.2	(-2.3, 8.7)
RESPON_m4	PPC	314/317	99.1	141/150	94.0	5.1	(1.1, 9.0)
RESPON_m4	ITTC	326/345	94.5	155/172	90.1	4.4	(-0.7, 9.4)
RESPON_m5	PPC	314/317	99.1	141/150	94.0	5.1	(1.1, 9.0)
RESPON_m5	ITTC	327/345	94.8	155/172	90.1	4.7	(-0.4, 9.7)
RESPONS_n	PPC	287/317	90.5	140/150	93.3	-2.8	(-7.9, 2.3)
RESPONS_n	ITTC	299/345	86.7	154/172	89.5	-2.9	(-8.7, 2.9)
RESP_nm5	PPC	287/317	90.5	140/150	93.3	-2.8	(-7.9, 2.3)
RESP_nm5	ITTC	299/345	86.7	154/172	89.5	-2.9	(-8.7, 2.9)
RESPONS_8	PPC	302/317	95.3	138/150	92.0	3.3	(-1.7, 8.2)
RESPONS_8	ITTC	312/345	90.4	152/172	88.4	2.1	(-3.6, 7.8)
RESPONS_s	PPC	314/317	99.1	141/150	94.0	5.1	(1.1, 9.0)
RESPONS_s	ITTC	327/345	94.8	155/172	90.1	4.7	(-0.4, 9.7)
Visit 2 (Day 7: 2 days post therapy for SB-275833 and end of therapy for Fusidate)							
RESPONSE	PPC	314/317	99.1	148/151	98.0	1.0	(-1.4, 3.5)
RESPONSE	ITTC	327/345	94.8	165/172	95.9	-1.1	(-4.9, 2.6)
RESPON_m0	PPC	158/317	49.8	64/151	42.4	7.5	(-2.2, 17.1)
RESPON_m0	ITTC	161/345	46.7	69/172	40.1	6.6	(-2.5, 15.6)
RESPON_m1	PPC	216/317	68.1	87/151	57.6	10.5	(1.1, 19.9)
RESPON_m1	ITTC	220/345	63.8	96/172	55.8	8.0	(-1.0, 16.9)
RESPON_m2	PPC	295/317	93.1	133/151	88.1	5.0	(-0.9, 10.9)
RESPON_m2	ITTC	304/345	88.1	149/172	86.6	1.5	(-4.6, 7.6)
RESPON_m3	PPC	308/317	97.2	139/151	92.1	5.1	(0.4, 9.8)
RESPON_m3	ITTC	318/345	92.2	155/172	90.1	2.1	(-3.2, 7.3)

		SB-275833		Fusidate			
Response Variable	**Analysis Population**	**n/N**	**Rate (%)**	**n/N**	**Rate (%)**	**Difference in Success Rate (%)**	**95% CI (%)**
RESPON_m4	PPC	314/317	99.1	148/151	98.0	1.0	(-1.4, 3.5)
RESPON_m4	ITTC	326/345	94.5	165/172	95.9	-1.4	(-5.2, 2.4)
RESPON_m5	PPC	314/317	99.1	148/151	98.0	1.0	(-1.4, 3.5)
RESPON_m5	ITTC	327/345	94.8	165/172	95.9	-1.1	(-4.9, 2.6)
Visit 3 (Day 9: 4 days post therapy for SB-275833 and 2 days post therapy for Fusidate)							
RESPONSE	PPC	313/316	99.1	141/150	94.0	5.1	(1.1, 9.0)
RESPONSE	ITTC	324/345	93.9	155/172	90.1	3.8	(-1.3, 8.9)
RESPON_m0	PPC	231/316	73.1	106/150	70.7	2.4	(-6.3, 11.2)
RESPON_m0	ITTC	238/345	69.0	115/172	66.9	2.1	(-6.4, 10.7)
RESPON_m1	PPC	273/316	86.4	125/150	83.3	3.1	(-4.0, 10.1)
RESPON_m1	ITTC	281/345	81.4	137/172	79.7	1.8	(-5.5, 9.1)
RESPON_m2	PPC	305/316	96.5	138/150	92.0	4.5	(-0.3, 9.3)
RESPON_m2	ITTC	315/345	91.3	152/172	88.4	2.9	(-2.7, 8.6)
RESPON_m3	PPC	310/316	98.1	139/150	92.7	5.4	(1.0, 9.9)
RESPON_m3	ITTC	320/345	92.8	153/172	89.0	3.8	(-1.6, 9.2)
RESPON_m4	PPC	313/316	99.1	141/150	94.0	5.1	(1.1, 9.0)
RESPON_m4	ITTC	324/345	93.9	155/172	90.1	3.8	(-1.3, 8.9)
RESPON_m5	PPC	313/316	99.1	141/150	94.0	5.1	(1.1, 9.0)
RESPON_m5	ITTC	324/345	93.9	155/172	90.1	3.8	(-1.3, 8.9)

RESPON_m0: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >0;

RESPON_m1: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >1;

RESPON_m2: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >2;

RESPON_m3: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >3;

RESPON_m4: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >4;

RESPON_m5: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >5;

RESPON_n: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms increased from baseline;

RESPON_nm5: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >5 or at least one SIRS score for signs/symptoms increased from baseline;

RESPONS_8: Modified sponsor's definition by treating subjects as failure if total SIRS score for signs/symptoms ≥8;

RESPONS_s: Modified sponsor's definition by treating subjects as failure if total SIRS score did not improve from baseline.

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Table 3.4.4: Results of Sensitivity Analyses for Clinical Response at End of Therapy for SB-275833 Treated Subjects

		Study TOC103469 SB-275833		Study TOC100224 SB-275833		Difference in Success Rate
Response Variable	Analysis Population	n/N	Rate (%)	n/N	Rate (%)	(95% CI) (%)
RESPON_m0	PPC	60/124	48.4	158/317	49.8	-1.5 (-12, 8.9)
RESPON_m0	ITTC	64/139	46.0	161/345	46.7	-0.6 (-10, 9.2)
RESPON_m1	PPC	82/124	66.1	216/317	68.1	-2.0 (-12, 7.8)
RESPON_m1	ITTC	87/139	62.6	220/345	63.8	-1.2 (-11, 8.3)
RESPON_m2	PPC	104/124	83.9	295/317	93.1	-9.2 (-16, -2.1)
RESPON_m2	ITTC	112/139	80.6	304/345	88.1	-7.5 (-15, -0.1)
RESPON_m3	PPC	107/124	86.3	308/317	97.2	-11 (-17, -4.5)
RESPON_m3	ITTC	115/139	82.7	318/345	92.2	-9.4 (-16, -2.5)
RESPON_m4	PPC	109/124	87.9	314/317	99.1	-11 (-17, -5.3)
RESPON_m4	ITTC	117/139	84.2	326/345	94.5	-10 (-17, -3.8)
RESPON_m5	PPC	111/124	89.5	314/317	99.1	-9.5 (-15, -4.0)
RESPON_m5	ITTC	119/139	85.6	327/345	94.8	-9.2 (-15, -2.9)
RESPONSE	PPC	111/124	89.5	314/317	99.1	-9.5 (-15, -4.0)
RESPONSE	ITTC	119/139	85.6	327/345	94.8	-9.2 (-15, -2.9)

RESPON_m0: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >0;
RESPON_m1: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >1;
RESPON_m2: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >2;
RESPON_m3: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >3;
RESPON_m4: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >4;
RESPON_m5: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >5;
RESPONOSE: sponsor's definition.

Table 3.4.5: Clinical Response at End of Therapy for SB-275833 Treated Subjects by Severity of Baseline Signs/Symptoms of Infection (Study TOC100224)

		Baseline SIRS <4 for All Signs/Symptoms		Baseline SIRS ≥4 for at least One Sign/Symptom		Difference in
Response Variable	Analysis Population	n/N	Rate (%)	n/N	Rate (%)	Success Rate (%)
RESPON_m0	PPC	63/105	60.0	95/212	44.8	15.2 (3.7, 26.7)
RESPON_m0	ITTC	63/111	56.8	98/234	41.9	14.9 (3.7, 26.1)
RESPON_m1	PPC	85/105	81.0	131/212	61.8	19.2 (9.2, 29.1)
RESPON_m1	ITTC	86/111	77.5	134/234	57.3	20.2 (10.2, 30.2)
RESPON_m2	PPC	104/105	99.0	191/212	90.1	9.0 (4.5, 13.4)
RESPON_m2	ITTC	107/111	96.4	197/234	84.2	12.2 (6.4, 18.0)
RESPON_m3	PPC	105/105	100.0	203/212	95.8	4.2 (1.5, 7.0)
RESPON_m3	ITTC	108/111	97.3	210/234	89.7	7.6 (2.6, 12.5)
RESPON_m4	PPC	105/105	100.0	209/212	98.6	1.4 (-0.2, 3.0)
RESPON_m4	ITTC	108/111	97.3	218/234	93.2	4.1 (-0.3, 8.6)
RESPON_m5	PPC	105/105	100.0	209/212	98.6	1.4 (-0.2, 3.0)
RESPON_m5	ITTC	108/111	97.3	219/234	93.6	3.7 (-0.6, 8.1)
RESPONSE	PPC	105/105	100.0	209/212	98.6	1.4 (-0.2, 3.0)
RESPONSE	ITTC	108/111	97.3	219/234	93.6	3.7 (-0.6, 8.1)

RESPON_m0: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >0;
RESPON_m1: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >1;
RESPON_m2: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >2;
RESPON_m3: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >3;
RESPON_m4: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >4;
RESPON_m5: Modified sponsor's definition by treating subjects as failure if at least one SIRS score for signs/symptoms >5;
RESPONOSE: sponsor's definition.

Table 3.4.6: Clinical Success Rate at End of Therapy by Pathogen Isolated at Baseline

Number (Percentage) of Successes										
Baseline Pathogen	Study TOC100224 (PPC Population)					Study TOC103469 (ITTC Population)				
	SB-275833		Sodium Fusidate		Difference in Success Rates (%)	SB-275833		Placebo		Difference in Success Rates (%)
	n/N[1]	Success Rate (%)	n/N[1]	Success Rate (%)		n/N[1]	Success Rate (%)	n/N[1]	Success Rate (%)	
S. aureus (all)	209/211	99.1	90/97	92.8	6.3	84/95	88.4	27/51	52.9	35.5
MRSA[2]	8/8	100.0	2/2	100.0	0	0/0	-	0/0	-	-
MSSA[2]	201/203	99.0	88/95	92.6	6.4	84/95	88.4	27/51	52.9	35.5
mupRSA[3]	6/6	100.0	2/3	66.7	33.3	0/0	-	0/0	-	-
mupSSA[3]	203/205	99.0	88/94	93.6	5.4	84/95	88.4	27/51	52.9	35.5
fusRSA[4]	9/9	100.0	4/7	57.1	42.9	9/10	90.0	2/6	33.3	56.7
fusSSA[4]	194/196	99.0	86/90	95.6	3.4	74/83	89.2	24/44	54.5	34.6
S. pyogenes	90/92	97.8	32/36	88.9	8.9	30/34	88.2	3/8	37.5	50.7
Other Streptococcus spp.	4/4	100.0	3/3	100.0	0	2/2	100.0	0/0	-	-
Other Gram (+) pathogens	3/3	100.0	1/1	100.0	0	2/2	100.0	0/0	-	-
Gram (-) pathogens	15/15	100.0	16/18	88.9	11.1	9/14	64.3	2/7	28.6	35.7
All pathogens	321/325	98.8	142/155	91.6	7.2	127/147	86.4	32/66	48.5	37.9
No pathogens	74/75	98.7	35/36	97.2	1.4	18/25	72.0	9/14	64.3	7.7

1. n/N = number of clinical successes/number of pathogens isolated at Baseline.
2. MRSA/MSSA are methicillin resistant/susceptible as defined by susceptibility to oxacillin.
3. Mupirocin breakpoints defined as susceptible ≤4μg/mL, resistant ≥8μg/mL.
4. Fusidic acid breakpoints defined as susceptible ≤1μg/mL, intermediate =2μg/mL, resistant ≥4μg/mL. The total fusRSA and fusSSA n value will not equal the total n for all *S.aureus* isolates as fusISA is not included in this table.

Data Source: Sponsor Module 2.7.3 table 18.

Table 3.4.7: Microbiological Success Rate at End of Therapy

Number (Percentage) of Microbiological successes										
Population	Study TOC100224					Study TOC103469				
	SB-275833		Sodium Fusidate		Difference in Success Rates (%)	SB-275833		Placebo		Difference in Success Rates (%)
	n/N	Success Rate (%)	n/N	Success Rate (%)		n/N	Success Rate (%)	n/N	Success Rate (%)	
PPB[1]	238/242	98.3	107/114	93.9	4.5	99/107	92.5	27/52	51.9	40.6
ITTB[2]	248/263	94.3	118/131	90.1	4.2	104/114	91.2	29/57	50.9	40.4

1. Primary analysis population for Study TOC100224.
2. Primary analysis population for Study TOC103469.

n/N = number of successes/total number of subjects.

Data Source: Sponsor Module 2.7.3 table 19.

Table 3.4.8: Microbiological Success Rate at End of Therapy by Pathogen Isolated at Baseline

Number (Percentage) of successes										
Baseline Pathogen	Study TOC100224 (PPC Population)					Study TOC103469 (ITTC Population)				
	SB-275833		Sodium Fusidate		Difference in Success Rates (%)	SB-275833		Placebo		Difference in Success Rates (%)
	n/N[1]	Success Rate (%)	n/N[1]	Success Rate (%)		n/N[1]	Success Rate (%)	n/N[1]	Success Rate (%)	
S. aureus (all)	207/211	98.1	91/97	93.8	4.3	87/95	91.6	28/51	54.9	36.7
MRSA[2]	8/8	100.0	2/2	100.0	0	0/0	-	0/0	-	-
MSSA[2]	199/203	98.0	89/95	93.7	4.3	87/95	91.6	28/51	54.9	36.7
mupRSA[3]	6/6	100.0	2/3	66.7	33.3	0/0	-	0/0	-	-
mupSSA[3]	201/205	98.0	89/94	94.7	3.4	87/95	91.6	28/51	54.9	36.7
fusRSA[4]	9/9	100.0	5/7	71.4	28.6	10/10	100.0	2/6	33.3	66.7
fusSSA[4]	192/196	98.0	86/90	95.6	2.4	76/83	91.6	25/44	56.8	34.7
S. pyogenes	90/92	97.8	32/36	88.9	8.9	31/34	91.2	3/8	37.5	53.7
Other Streptococcus spp.	4/4	100.0	3/3	100.0	0	2/2	100.0	0/0	-	-
Other Gram (+) pathogens	3/3	100.0	1/1	100.0	0	2/2	100.0	0/0	-	-
Gram (-) pathogens	15/15	100.0	18/18	100.0	0	9/14	64.3	2/7	28.6	35.7
All pathogens	319/325	98.2	145/155	93.5	4.6	131/147	89.1	33/66	50.0	39.1

1. n/N = number of microbiological successes/number of pathogens isolated at Baseline.
2. MRSA/MSSA are methicillin resistant/susceptible as defined by susceptibility to oxacillin.
3. Mupirocin breakpoints defined as ≤4μg/mL susceptible, ≥8μg/mL resistant.
4. Fusidic acid breakpoints defined as ≤1μg/mL susceptible, 2μg/mL intermediate, ≥4μg/mL resistant. The total fusRSA and fusSSA n value will not equal the total n for all *S.aureus* isolates as fusISA is not included in this table.

Data Source: Sponsor Module 2.7.3 table 21.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Clinical response at the end of therapy visit was analyzed by the pre-defined set of subgroup factors which included gender, race, and age. Success rates by subgroup factor and treatment group are presented in Table 4.1 (study TOC103469) and Table 4.2 (study TOC100224). In general, when the numbers of subjects within a subgroup were sufficient, the difference in response rates between the treatment groups were similar to the difference seen for the overall clinical response at the end of therapy visit.

Table 4.1: Clinical Response at End of Therapy by Subgroup Factors (Studies TOC103469, ITTC Population)

Subgroup Factors	SB-275833 Success		Placebo Success		Difference in Success
	n/N[1]	Rate	n/N[1]	Rate	Rates
Clinical Diagnosis of Impetigo					
Bullous	20/26	76.9%	6/11	54.5%	22.4%
Non-Bullous	99/113	87.6%	31/60	51.7%	35.9%
Primary Lesion Dressing Type at Baseline					
Occlusive	1/4	25.0%	1/2	50.0%	-25.0%
Semi-occlusive	3/4	75.0%	2/2	100.0%	-25.0%
None	115/131	87.8%	34/67	50.7%	37.0%
Age					
9 months to < 2 years	11/12	91.7%	2/6	33.3%	58.3%
2 years to < 6 years	29/38	76.3%	8/24	33.3%	43.0%
6 years to < 13 years	52/56	92.9%	19/28	67.9%	25.0%
13 years to < 18 years	4/5	80.0%	3/6	50.0%	30.0%
18 years to < 65 years	21/25	84.0%	5/7	71.4%	12.6%
>= 65 years	2/3	66.7%			
Region					
Europe	34/42	81.0%	9/18	50.0%	31.0%
International	85/97	87.6%	28/53	52.8%	34.8%
Gender					
Female	62/73	84.9%	16/34	47.1%	37.9%
Male	57/66	86.4%	21/37	56.8%	29.6%
Race					
African American/Heritage	2/2	100.0%	2/3	66.7%	33.3%
African Indian or Alaskan Native	21/23	91.3%	5/13	38.5%	52.8%
Asian - Central/South Asian Heritage	51/59	86.4%	16/30	53.3%	33.1%
Mixed race	1/1	100.0%	2/2	100.0%	0.0%
White - Arabic/North African Heritage	1/2	50.0%			
White - White/Caucasian/European Heritage	43/52	82.7%	12/23	52.2%	30.5%
Compliance					
80% - 120%	119/136	87.5%	37/68	54.4%	33.1%
>120%	0/1	0.0%	0/3	0.0%	0.0%
Unknown	0/2	0.0%			

Date Source: Sponsor's CSR Table 7.08.
[1] N = number of subjects that qualified for the respective analysis population in the respective treatment.

Table 4.2: Clinical Response at End of Therapy by Subgroup Factors (Studies TOC100224, ITTC Population)

Subgroup Factors	SB-275833 Success		Placebo Success		Difference in Success
	n/N[1]	Rate	n/N[1]	Rate	Rates
Clinical Diagnosis of Impetigo					
Bullous	71/75	94.7%	31/35	88.6%	6.1%
Non-Bullous	256/270	94.8%	124/137	90.5%	4.3%
Primary Lesion Dressing Type at Baseline					
Occlusive	21/22	95.5%	11/12	91.7%	3.8%
Semi-occlusive	32/32	100.0%	11/15	73.3%	26.7%
None	274/291	94.2%	133/145	91.7%	2.4%
Age					
9 months to < 2 years	28/29	96.6%	11/12	91.7%	4.9%
2 years to < 6 years	84/90	93.3%	49/53	92.5%	0.9%
6 years to < 13 years	84/87	96.6%	42/47	89.4%	7.2%
13 years to < 18 years	26/27	96.3%	11/14	78.6%	17.7%
18 years to < 65 years	90/97	92.8%	41/45	91.1%	1.7%
>= 65 years	15/15	100.0%	1/1	100.0%	0.0%
Region					
Europe	95/102	93.1%	39/45	86.7%	6.5%
International	232/243	95.5%	116/127	91.3%	4.1%
Gender					
Female	158/167	94.6%	65/72	90.3%	4.3%
Male	169/178	94.9%	90/100	90.0%	4.9%
Race					
African American/Heritage	90/92	97.8%	43/48	89.6%	8.2%
African Indian or Alaskan Native	23/25	92.0%	10/11	90.9%	1.1%
Asian - Central/South Asian Heritage	79/85	92.9%	43/44	97.7%	-4.8%
Asian - South East Asian Heritage	1/1	100.0%	3/3	100.0%	0.0%
White - Arabic/North African Heritage	2/2	100.0%	1/1	100.0%	0.0%
White - White/Caucasian/European Heritage	132/140	94.3%	55/65	84.6%	9.7%
Compliance					
<80%	1/1	100.0%	7/7	100.0%	0.0%
80% - 120%	309/317	97.5%	148/163	90.8%	6.7%
>120%	16/17	94.1%			
Unknown	1/10	10.0%	0/2	0.0%	10.0%

Date Source: Sponsor's CSR Table 7.08.
[1] N = number of subjects that qualified for the respective analysis population in the respective treatment.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Statistical Issues

Study TOC100224 was designed by the sponsor as a non-inferiority trial using the active comparator, 2% sodium fusidate ointment, which has not been approved by the FDA. Therefore, this study was considered as a superiority study in this review.

Sensitivity Results of the Primary Efficacy Endpoint

For both studies, the primary efficacy endpoint was the clinical response (success or failure) at the end of therapy visit. It was related to the baseline signs/symptoms of infection and was defined based on the clinical outcome assessed by the study investigators (see Tables 3.1.2-3.1.3 for details). A clinical response of "success" at the end of therapy corresponded to a clinical outcome assessment of *"Total absence of the treated lesions or the treated lesions have become dry without crusts compared to baseline, or improvement (defined as a decline in the size of the affected area, number of lesions or both) such that no further antimicrobial therapy is necessary."* judged by the study investigators.

In this definition, the sponsor failed to provide an objective criteria for *"improvement (defined as a decline in the size of the affected area, number of lesions or both) such that no further antimicrobial therapy is necessary"* that could be consistently applied across study investigators. Non-standard or subjective definition for *"improvement (defined as a decline in the size of the affected area, number of lesions or both) such that no further antimicrobial therapy is necessary"* by the study investigators would lead to misclassification of clinical responses.

To examine the robustness of the primary efficacy results, the statistical reviewer has performed numerous sensitivity analyses by modifying sponsor's definition of clinical response using the measurements of signs and symptoms of infection.

The sensitivity results in Table 1 demonstrated that (1) in study TOC103469 the superiority efficacy results of SB-275833 treatment over placebo were very robust and statistically significant; (2) in study TOC100224 the clinical response rates of the SB-275833 treatment over sodium fusidate were sensitive to how the clinical response was defined; the SB-275833 treatment seemed to be inferior to the sodium fusidate treatment when mild to severe signs and symptoms of infection at the end of therapy visit were considered as clinical failure.

In study TOC103469, the clinical response rates in the SB-275833 group were statistically significantly higher than the ones in the placebo group regardless how the clinical response was defined. The point estimates for the difference in the clinical

response rate between the SB-275833 group and the placebo group were very robust and had a magnitude around 30%.

In study TOC100224 (designed as a non-inferiority study by the sponsor, reviewed by the Agency as a superiority trial), the difference in the clinical response rate between the SB-275833 and the sodium fusidate groups was sensitive to how the clinical response was defined. When any mild to severe signs and symptoms of infection at the end of therapy visit were considered as clinical failure, the difference in the clinical response rate between the SB-275833 and the sodium fusidate groups decreased from the sponsor's results of 4.7% (95% CI: -0.4%, 9.7%) to -20.2% (-29%, -11%), indicating that SB-275833 was inferior to the sodium fusidate treatment.

To further examine the robustness of the SB-275833 treatment effect, the clinical response rates for the SB-275833 treated subjects in study TOC103469 were compared with the ones for the SB-275833 treated subjects in study TOC100224. It should be noted that these two studies were similar in terms of study inclusion and exclusion criteria, and had the same SB-275833 treatment duration (5 days) and same duration (7 days) for the end of therapy visit. Thus, it is reasonable to expect that the clinical response rates at the end of therapy visit in these two studies would be comparable for the SB-275833 treated subjects. This is exactly what was observed when less subjective response variables such as RESPON_m0 and RESPON_m1 were used. The results in Table 2 showed that when response variable RESPON_m0 was used, the difference in clinical response rate for the SB-275833 treated subjects between studies TOC103469 and TOC100224 was -0.6% (95% CI: -10% to 9.2%). In contrast, when the sponsor's definition of clinical response was used, the SB-275833 treated subject in study TOC100224 (designed as a non-inferiority trial by the sponsor) had a clinical response rate that was 9.2% (95% CI: 2.9% to 15%) higher than the one for the SB-275833 treated subjects in study TOC103469 (designed as a placebo controlled trial by the sponsor). This disparity in the clinical response rate in the SB-275833 treated subjects in these two studies might very well reflect on the fact that the component *"improvement (defined as a decline in the size of the affected area, number of lesions or both) such that no further antimicrobial therapy is necessary"* in the sponsor's definition was subjected to the study investigators' interpretation and might have lead to over estimation of the clinical response rate in the non-inferiority trial. Thus, this kind of non-standard/subjective definition of primary endpoint should be avoided in a non-inferiority trial to ensure assay sensitivity of the trial.

The sensitivity of the SB-275833 treatment effect to the severity of baseline signs and symptoms of infection was also examined in the SB-275833 treated subjects in study TOC100224. It is reasonable to expect that the subjects who had only mild baseline signs/symptoms (SIRS<4 for every sign/ symptom) would generally have a higher clinical success rate than the subjects who had at least one moderate/severe baseline signs and symptoms (SIRS≥4 for at least one sign/symptom). This is exactly what was observed when less subjective response variables such as RESPON_m0 and RESPON_m1 were used. The results in Table 3 showed that when response variable RESPON_m0 was used, the response rate for the subjects who had only mild baseline

signs and symptoms was 14.9% (95% CI: 3.7% to 26.1%) higher than the one for the subjects who had at least one moderate/severe baseline signs and symptoms. In contrast, when the sponsor's definition of clinical response was used, the response rates were similar for these two groups of subjects. This lack of sensitivity of the clinical response rate to the severity of baseline signs and symptoms again reflected on the fact that the sponsor's definition of clinical response entailed a component that was subjected to investigators' interpretation. This non-standardized/subjective definition of primary endpoint might very well lead to misclassification and obscure the rue difference in the response rate between these two groups of subjects. Thus, this kind of non-standard/ subjective definition of primary endpoint should be avoided in a non-inferiority trial to ensure assay sensitivity of the trial.

5.2 Conclusions and Recommendations

In this NDA22055 the sponsor seeks approval of 1% SB-275833 (Retapamulin) ointment for the treatment of primary impetigo caused by *Staphylococcus aureus* (methicillin-susceptible isolates) or *Streptococcus pyogenes* in adults and pediatric patients 9 months of age and older. Two pivotal studies (studies TOC103469 and TOC100224) were included in the submission as the major source to demonstrate efficacy and safety of Retapamulin.

Study TOC103469 was a randomized, double-blind, multi-center, and placebo-controlled study in adult and pediatric subjects with impetigo. The study subjects received either topical 1% SB-275833 ointment, twice daily for 5 days or placebo ointment, twice daily for 5 days in a 2:1 ratio. There were 140 and 73 randomized subjects in the SB-275833 and the placebo groups, respectively. The primary endpoint was the clinical response at the end of therapy visit on Day 7 (2 days post therapy). This study demonstrated that the SB-275833 treatment yielded a robust and statistically significantly higher clinical response rate at the end of therapy visit compared with the placebo treatment. The differences in the clinical response rate between the SB-275833 and the placebo groups were 33.5% (95% CI: 20.5% to 46.5%) and 36.3% (95% CI: 22.8% to 49.8%) in the intent-to-treated clinical (ITTC) population and in the per protocol clinical (PPC) populations, respectively.

Study TOC100224 was a randomized, observer-blind, multi-center, and non-inferiority study in adult and pediatric subjects with impetigo. The study subjects received either topical 1% SB-275833 ointment, twice daily for 5 days or topical 2% sodium fusidate ointment, three times daily for 7 days in a 2:1 ratio. There were 346 and 173 randomized subjects in the SB-275833 and the sodium fusidate groups, respectively. The primary endpoint was the clinical response at the end of therapy visit (2 days post therapy: Day 7 for SB-275833 and Day 9 for sodium fusidate). A non-inferiority margin of 10% was used.

There is one major statistical issue in study TOC100224 as this study was designed by the sponsor as a non-inferiority trial using the active comparator, 2% sodium fusidate

ointment, which has not been approved by the FDA. Therefore, this study was considered as a superiority study in this review.

Study TOC100224 failed to demonstrate superior efficacy of the SB-275833 treatment over the sodium fusidate treatment. The difference in the clinical response rate between the SB-275833 and the sodium fusidate groups was 4.7% (95% CI: -0.4% to 9.7%) and 5.1% (95% CI: 1.1% to 9.0%) in the ITTC and PPC populations, respectively. When any signs/symptoms were considered as failure, the difference in the clinical response rate at the end of therapy visit between the SB-275833 and the sodium fusidate groups was -20.2% (95% CI: -29% to -11%) and -20.8% (95% CI: -30% to -12%) in the ITTC and PPC populations, respectively. When any signs/symptoms were considered as failure, the difference in the clinical response rate at Visit 2 (Day 7: 2 days post therapy for SB-275833 and end of therapy for sodium fusidate) between the SB-275833 and the sodium fusidate groups was 6.6% (95% CI: -2.5% to 15.6%) and 7.5% (95% CI: -2.2% to 17.1%) in the ITTC and PPC populations, respectively. When any signs/symptoms were considered as failure, the difference in the clinical response rate at Visit 3 (Day 9: 4 days post therapy for SB-275833 and 2 days post therapy for sodium fusidate) between the SB-275833 and the sodium fusidate groups was 2.1% (95% CI: -6.4% to 10.7%) and 2.4% (95% CI: -6.3% to 11.2%) in the ITTC and PPC populations, respectively.

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