# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**22-055**

# MICROBIOLOGY REVIEW

NDA: 22-055 DATE REVIEW COMPLETED: November 1, 2006

## REMARKS

The Applicant has submitted NDA 22-055 for the use of SB-275833 1% ointment to be used for the treatment of impetigo due to methicillin-susceptible *Staphylococcus aureus* or *Streptococcus pyogenes*.

## SUMMARY AND RECOMMENDATIONS

SB-275833 (applied twice daily for 5 days) is non-inferior to sodium fusidate (applied three times for 7 days), in the treatment of primary impetigo due to *S. aureus* or *S. pyogenes*. This analysis was based on the clinical response at End of Therapy. In addition, the clinical success rates at End of Therapy appear higher in the SB-275833 treatment group compared to the sodium fusidate treatment group. The clinical and microbiological success rates against MRSA, mupRSA and fusRSA were 100% in the SB-275833 treatment group. Moreover, a 100% clinical success rate was demonstrated against 4 isolates carrying the *pvl* gene. However, the number of pvl positive isolate was small and the significance of this data is unknown due to the small sample size.

SB-275833 (applied twice daily for 5 days), has also demonstrated to be superior to placebo (applied three times for 5 days), in the treatment of primary impetigo caused by MSSA and *S. pyogenes*. This analysis was based on the clinical response at End of Therapy. In addition, the clinical and microbiological success rates at End of Therapy appear higher in the SB-275833 treatment group compared to the placebo treatment group. SB-275883 demonstrated activity against MSSA and *S. pyogenes* in individuals who were suffering from impetigo. Therefore, from an overall microbiology perspective the data show that SB-275883 is effective against *S. aureus* or *S. pyogenes* in the treatment of bullous and non-bullous impetigo.

## PROPOSED MICROBIOLOGY SECTION OF PACKAGE INSERT

The following package insert contains labeling information for [redacted] impetigo. [redacted]

**FDA's version of the package insert. FDA changes are in blue Applicant's changes are in red.):**

[redacted]

# 3 Page(s) Withheld

_____ Trade Secret / Confidential

X Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Microbiology-* 1

**DIVISION OF ANTI-INFECTIVE AND OPTHALMOLOGY PRODUCTS (HFD-520)**
**CLINICAL MICROBIOLOGY REVIEW**

NDA: 22-055 DATE REVIEW COMPLETED: November 1, 2006

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## EXECUTIVE SUMMARY

In Study TOC100224 (SB-27583 vs., fusidic acid), over 75% of the subjects had at least one pathogen isolated at baseline and *S. aureus* was the most frequently isolated pathogen followed by *S. pyogenes*. Some subjects had two or more pathogens isolated at baseline and the majority had *S. aureus* and *S. pyogenes* isolated together.

The $MIC_{90}$s for SB-275833 against isolates of *S. aureus* and *S. pyogenes* were 0.12 and 0.06 µg/mL respectively. Against *S. aureus*, the $MIC_{90}$ for fusidic acid was 0.5 µg/mL, and the MIC range was 0.12 to 16 µg/mL; the mupirocin $MIC_{90}$ value was 0.25 µg/mL, and the MIC range was 0.06 to >256 µg/mL. Therefore, some isolates were resistant to either fusidic acid or mupirocin. The $MIC_{90}$ for fusidic acid against *S. pyogenes* isolates was higher than those of mupirocin. The data show that most of pathogens were eradicated or presumed eradicated at the EOT assessment; the majority of the subjects treated with SB-275833 had a bacteriological outcome of presumed eradication.

Overall, SB-275833 appears as effective as sodium fusidate in the treatment of infections that correlated with the presence of *S. aureus*. SB-275833 did achieve a numerically higher efficacy rate against *S. pyogenes* in comparison to fusidic acid. Furthermore, although numbers were small, SB-275833 demonstrates activity against 10 (methicillin resistant *S. aureus*) MRSA, mupirocin resistant *S. aureus* (mupRSA) and fusidic acid resistant S. aureus (fusRSA), while a lower clinical success rate was observed for sodium fusidate ointment, against mupRSA and fusRSA. Of the 10 MRSA isolates, 4 were *pvl* positive; and all were eradicated in the clinical study. However, the number of MRSA isolates was too small to exemplify clinical significance against MRSA. In general, the data obtained from the clinical study correlated with a successful microbiological response.

In Study TOC103469 (SB275833 vs. placebo), over 80% of the subjects had at least one pathogen isolated at baseline. As in Study TOC100224, *S. aureus* was the most frequently isolated pathogen followed by *S. pyogenes* and some patients had *S. aureus* and *S. pyogenes* isolated together. No MRSA or mupRSA pathogens were isolated in this study; therefore, the efficacy of SB-275833 against these resistant pathogens could not be determined. In addition, no isolates tested positive for the presence of *pvl*. Of all *S. aureus* isolates recovered at baseline, 11.0% were fusidic acid-resistant. The $MIC_{90}$s for SB-275833 against isolates of *S. aureus* and *S. pyogenes* were 0.12 and 0.06 µg/mL, respectively. The $MIC_{90}$s for fusidic acid were 4µg/mL and 16µg/mL, respectively.
Approximately 89% of the pathogens were eradicated or presumed eradicated at the End of Therapy assessment in the ITTB population in the SB-275833 treatment group, compared with only 50% in the placebo group. Although SB-275833 appear to have achieved high cure rates against fusRSA (89%, compared to 33% in the placebo group), the numbers were small to achieve any meaningful significance.

As in study TOC100224, an association was demonstrated between clinical and microbiological response. This is due to the fact that microbiological response for most subjects was presumed

eradication based on the clinical response. The data from this study show that SB-275833 applied twice daily for 5 days, demonstrate activity against *S. aureus* (including fusRSA) and *S. pyogenes* in subjects exhibiting primary impetigo. From the clinical and microbiological data reviewed (study TOC100224 and TOC103469), isolates did not appear to develop resistance to SB-275833. No significant difference was observed with respect to the microbiology success rate in individuals co-infected with *S. pyogenes* and *S. aureus*.

## INTRODUCTION AND BACKGROUND:

SB-275833 (retapamulin) is a semi-synthetic derivative of pleuromutilin, isolated through fermentation from *Clitopilus passeckerianus* (formerly *Pleurotus passeckerianus*), and developed for the topical treatment of uncomplicated skin and skin-structure infections. Pleuromutilins selectively inhibit bacterial protein synthesis by interacting at a unique site on the 50S subunit of the bacterial ribosome that is distinct from the binding sites of other antibiotics that interact with the ribosome. Data indicate that the binding site involves ribosomal protein L3 and is in the region of the ribosomal P-site and peptidyl transferase center. Pleuromutilins inhibit peptidyl transfer, and prevent normal formation of active 50S ribosomal subunits, and therefore appear to inhibit bacterial protein synthesis. To date, SB-275833 demonstrates no *in vitro* target-specific cross-resistance with other classes of antibiotics.

Impetigo is a highly contagious common bacterial skin infection of the superficial layers of the dermis and the key pathogens commonly implicated in primary impetigo are *Staphylococcus aureus* and *Streptococcus pyogenes* (group A β-haemolytic streptococci) that occurs in adults and children. The infection is sometimes classified as either primary impetigo (i.e., direct bacterial invasion of previously normal skin) or secondary or common impetigo (infection is secondary to an underlying skin disease, such as scabies or eczema, that disrupts the skin barrier).
Impetigo presents clinically in two forms: bullous or nonbullous; >70% of cases are classified as nonbullous. *S. aureus* has become the main bacteriological pathogen implicated in nonbullous impetigo, either alone or with *S. pyogenes*. Nonbullous 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.

Untreated disease can persist and spread and thereby act as a reservoir for re-infection or infecting others to cause local outbreaks. Further, patients or their parents often become concerned due to the unattractive appearance of the lesions and the contagious nature of the disease, which prevents children from attending school or day care nurseries. Early intervention can stop progression and antibiotic treatment is therefore usually advised to achieve a rapid cure and to prevent recurrences in infected individuals as well as limit the spread of infection.

For sections in the impetigo application where information has not changed since the previous NDA for [redacted] reviewers will be provided cross-reference links to the previous NDA rather than repeating the identical information. This approach was agreed with the Division as referenced in your comments of May 4, 2006 to GSK's pre-NDA meeting package questions of April 6, 2006.

## ACTIVITY IN VITRO

[redacted]

Additionally, the SB-275833 $MIC_{90}$ for *S. aureus* isolates recovered from subjects enrolled in Study TOC100224 (SB-275833 vs. fusidic acid) and Study TOC103469 (SB-275833 vs. placebo) in all geographic regions combined was 0.12 µg/mL. As shown in Table 1, SB-275833 inhibited all *S. aureus* tested at a concentration of ≤ 0.25 µg/mL. A comparative analysis between this study [redacted] shows that the in vitro activity of SB-275833 against *S. aureus* isolates from Study TOC100224 and Study TOC103469 appear to be similar [redacted]

Table 1 Frequency distribution of SB-275833 MICs (µg/mL) for *S. aureus* (Study TOC100224 and Study TOC103469 combined)

| | Number and Cumulative % of Isolates at Each MIC | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | MIC ( µg/mL) | | | | | | | | |
| Organism | ≤0.015 | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | Total |
| *S. aureus* | - | 3<br>0.6% | 231<br>44.3% | 284<br>98.1% | 10<br>100% | - | - | - | 528 |

The following section describes the *in vitro* activity of SB-275833 against drug-resistant *S. aureus,* including methicillin-resistant *S. aureus* (MRSA), mupirocin-resistant *S. aureus* (mupRSA) and fusidic acid-resistant *S. aureus* (fusRSA). In the absence of CLSI approved interpretive criteria for mupirocin or fusidic acid, unless otherwise specified, the following criteria in published literature[1,2] were used to define mupirocin and fusidic acid susceptibility: mupirocin-susceptible ≤ 4 µg/mL, - resistant, ≥ 8 µg/mL; fusidic acid-susceptible ≤ 1 µg/mL, - intermediate 2 µg/mL, -resistant ≥ 4 µg/mL.

No MRSA isolates were recovered from subjects in Study TOC103469. The frequency distribution of SB-275833 MICs for MRSA isolates that were recovered at all visits from subjects in the ITT population of Study TOC100224 is shown in Table 2. Analysis of the data

based on the MIC distribution of all MRSA isolates from Study TOC100224 showed a SB-275833 MIC range of 0.06-0.12 µg/mL.

It is stated that all 10 MRSA isolates from Study TOC100224 were genetically characterized to determine the presence of the *lukS* and *lukF* genes that encode for the Panton-Valentine Leukocidin (PVL) toxin. SB-275833 demonstrated similar *in vitro* activity against PVL-positive and PVL-negative isolates with a MIC range of 0.06-0.12 µg/mL against both sub-groups. Irrespective of PVL status, SB-275833 inhibited 10/10 (100%) of MRSA isolates from Study TOC100224 at a concentration of ≤ 0.12 µg/mL (Table 2).

Table 2 Frequency distribution of SB-275833 MICs (mcg/mL) for MRSA (Study TOC100224)

| | Number and Cumulative % of Isolates at Each MIC | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | MIC ( µg/mL) | | | | | | | | |
| Phenotype | ≤0.015 | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | Total |
| MRSA | - | - | 4<br>40.0% | 6<br>100% | - | - | - | - | 10 |
| PVL positive | - | - | 3<br>30.0% | 1<br>100% | - | - | - | - | 4 |
| PVL negative | - | - | 1<br>10.0% | 5<br>100% | - | - | - | - | 6 |

As previously stated, no mupRSA were isolated from subjects in Study TOC103469. Table 3 contains the frequency distribution of SB-275833 MICs for mupRSA isolates that were isolated at all visits from subjects in the ITT population of Study TOC100224 and for fusRSA isolates that were isolated at all visits from subjects in the ITT population of Study TOC100224 and TOC103469 combined. Similar to the data presented above for MRSA, SB-275833 activity was not affected by mupirocin or fusidic acid resistance. SB-275833 demonstrated similar *in vitro* activity against mupRSA and fusRSA isolates with a $MIC_{90}$ of 0.12 µg/mL against both sub-groups. The *in vitro* activity of SB-275833 against drug-resistant *S. aureus* isolates from Study TOC100224 and Study TOC103469 .

Table 3. Frequency distribution of SB-275833 MICs (mcg/mL) for MupRSA and FusRSA (Study TOC100224 and Study TOC103469 combined).

| | Number and Cumulative % of Isolates at Each MIC | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | MIC ( µg/mL) | | | | | | | | |
| Phenotype | ≤0.015 | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | Total |
| Mupirocin-resistant *S. aureus* | - | - | 10<br>66.7% | 4<br>93.3% | 1<br>100% | - | - | - | 15 |
| Fusidic acid-resistant *S. aureus* | - | 1<br>2.3% | 33<br>77.3% | 10<br>100% | - | - | - | - | 44 |

The number of *emm* subfamily genes provides the basis for classifying *S. pyogenes* based on genetic markers (A-E). Of the 5 major genetic markers, pattern D is predominantly associated with skin infections; and of the 192 *S. pyogenes* isolates, the vast majority was obtained from India, Peru and South Africa and the Netherlands. These isolates (185/192; 96%) had the *emm* chromosomal pattern D as the predominant marker. The Applicant provided information showing that the *emm* chromosomal pattern D was the predominating *S. pyogenes emm* pattern causing skin infections and impetigo in the United States and in many regions throughout the world. Therefore, individuals enrolled in the clinical study had the *emm* pattern D as the predominant marker thereby demonstrating comparable epidemiology based on the *emm* typing between the US and other countries.

Against 192 isolates of *Streptococcus pyogenes*, from Study TOC100224 and Study TOC103469 combined, SB-275833 had a $MIC_{90}$ of 0.06 µg/mL. As shown in Table 4, SB-275833 inhibited all *S. pyogenes* tested at a concentration of ≤ 0.25 µg/mL. The *in vitro* activity of SB-275833 against *S. pyogenes* isolates from Study TOC100224 and Study TOC103469 is similar [redacted]

Table 4. Frequency distribution of SB-275833 MICs (µg/mL) for *S. pyogenes* (Study TOC100224 and Study TOC103469 combined).

| | Number and Cumulative % of Isolates at Each MIC | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | MIC ( µg/mL) | | | | | | | | |
| Organism | ≤0.015 | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | Total |
| *S. pyogenes* | 25 | 122 | 42 | 2 | 1 | - | - | - | 192 |
| | 13.0% | 76.6% | 98.4% | 99.5% | 100% | | | | |

## MECHANISM OF ACTION

Briefly, pleuromutilins selectively inhibit the elongation phase of bacterial protein synthesis by interacting at a unique site on the prokaryotic ribosome but do not bind to eukaryotic ribosomes or inhibit mammalian protein synthesis. Studies with SB-275833 have shown that this binding site is distinct from those of other ribosome-interacting antibiotics (e.g. macrolides, lincosamides and chloramphenicol) indicating that target-specific cross-resistance between this novel antimicrobial agent, SB-275833, and other classes of antibiotics is not likely. The "Mechanism of Action" was been previously [redacted]

## MECHANISM OF RESISTANCE

The mechanism of resistance was reviewed in [redacted]. Briefly, reports from the literature show that reduced susceptibility to tiamulin, a member of the pleuromutilin class, can be mediated through mutations in ribosomal protein L3 which is encoded by the *rplC* gene. Point mutations in L3 were shown to reduce the binding of tiamulin at the peptidyl transferase center, therefore affecting its inhibitory action on the ribosome. Data from studies conducted to further

investigate this mechanism of resistance to pleuromutilins and to assess its effect on SB-275833 can be found in [redacted].

## CROSS RESISTANCE

It is stated that SB-275833 activity is unaffected by the presence of phenotypic resistance to other antimicrobial agents commonly used in the treatment of skin and skin structure infections (SSSIs). It is suggested that target specific cross-resistance of SB-275833 with other classes of antibiotics is not likely to be observed in clinical isolates. Further data is needed on this matter. Non-target mediated resistance to SB-275833 in *S. aureus* due to efflux mechanisms has been observed in one isolate (isolate number IV202017033).
Data illustrating the lack of cross-resistance with other existing classes of antimicrobials were included in [redacted]. No *S. aureus* or *S. pyogenes* isolates with SB-275833 MICs > 2 µg/mL were recovered from Study TOC100224 or Study TOC103469. However, while SB-275833 does not appear to exhibit cross-resistance with other antibacterial classes, there is evidence of cross-resistance within the pleuromutilin class. Data illustrating SB-275833 MICs against isolates with elevated tiamulin MICs (MICs ≥ 16 µg/mL) [redacted].

The Applicant states that laboratory serial passage and spontaneous rate of mutation experiments have demonstrated that *S. aureus, S. pyogenes* and other organisms have a low propensity for development of resistance to SB-275833, therefore suggesting a low likelihood that resistant strains will emerge during therapy. [redacted].

## RESISTANCE DEVELOPMENT: CLINICAL TRIALS

Increases in MIC and decreases in disk diffusion zone size diameter were monitored for SB-275833 and the comparator fusidic acid during Study TOC100224 and for SB-275833 in Study TOC103469. Changes in MIC and disk susceptibility were defined as a 4-fold or greater increase in MIC or a decrease in disk zone diameter of 6 mm or greater. Antimicrobial susceptibility retesting was performed on isolates that met the above criteria. All testing was performed according to Clinical and Laboratory Standards Institute (CLSI) guidelines. Isolates with apparent changes in MIC or disk susceptibility following retesting were sent to GlaxoSmithKline (GSK) for further characterization.

A total of 517 patients (345 in the SB-275833 treatment group and 172 sodium fusidate treatment group) were enrolled in study TOC100224 and a total of 210 patients (139 in the SB-275833 treatment group and 71 in the placebo treatment group) were enrolled in study TOC103469. Nine patients (1.7%) were initially identified as having bacterial isolates with a ≥ 4-fold increase in MIC or a ≥ 6 mm reduction in disk zone size between pre- and post-therapy visits to either SB-275833 or fusidic acid in study TOC100224. One patient (0.5%) in study TOC103469 was initially identified as having bacterial isolates with a ≥ 4-fold increase in MIC or a ≥ 6 mm reduction in disk zone size between pre- and post-therapy visits to SB-275833. The

following pre-defined criteria were applied to determine if additional investigations were necessary to be conducted on these isolates:

1. Patient isolates with an apparent increase in MIC or decrease in disk zone diameter in SB-275833 or fusidic acid (TOC100224 only) had repeat testing performed at ( [redacted] .. Regardless of retest results, no further investigations were made on patient isolates that showed an apparent decreased susceptibility to fusidic acid.

2. If the original central lab susceptibility testing indicated an apparent change in the SB-275833 disk zone size (≥ 6 mm decrease between visits) or MIC (≥ 4-fold increase between visits) and the retest result did not confirm these findings, no further investigations were made.

3. If the SB-275833 retest susceptibility results confirmed the apparent decrease in susceptibility, each of the patient's isolates (both pre- and post-therapy isolates) had repeat testing performed at GSK to confirm the apparent increase in resistance. If confirmed, isolates needed to be analyzed by [redacted] ; to determine their relatedness.

Patient isolates were subcultured to blood agar plates (TSA with 5% sheep blood) to obtain inoculum for MIC testing. Cation adjusted Mueller Hinton (MH) broth with 5% lysed horse blood was used to prepare test inocula, and to dilute the test compound for preparation of the microdilution trays for MICs. Agar plates and MH broth were obtained from [redacted] ). The results show that isolates from 9 patients in study TOC100224 and 1 patient in study TOC103469 demonstrated an increase in MIC (≥ 4-fold) or ≥ 6mm decrease in disk zone size after initial susceptibility testing at the central laboratory. A line listing of the central laboratory identification and susceptibility results for these 10 patients are shown in Table 5. Isolates were stored at the central laboratories [redacted] ) and GlaxoSmithKline Pharmaceuticals (Collegeville Pa.).

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Table 5: Patients with Greater than or equal to 4-fold increase in MIC or Greater than or equal to 6 mm decrease in disk zone diameter results between baseline and subsequent visits (Central Laboratory Data).

| Study | Patient ID | Baseline Visit | Visit | Organism | Drug | Baseline MIC (µg/mL) | Visit MIC (µg/mL) | Baseline Disk (mm) | Visit Disk (mm) |
|---|---|---|---|---|---|---|---|---|---|
| **100224** | | | | | | | | | |
| | 000755 | V1 | V3 | *S. aureus* | SB-275833 | 0.12 | 0.06 | 23 | 23 |
| | | | | | Amoxicillin/clavulanic acid | 1 | **1** | NA | NA |
| | | | | | Ceftriaxone | 4 | 4 | NA | NA |
| | | | | | Bacitracin | 32 | 64 | NA | NA |
| | | | | | Cephalothin | 0.5 | 0.5 | NA | NA |
| | | | | | Cloxacillin | 0.5 | 0.5 | NA | NA |
| | | | | | Erythromycin | 0.5 | **1** | NA | NA |
| | | | | | Flucloxacillin | 0.5 | 0.12 | NA | NA |
| | | | | | Fusidic acid | **0.25** | **2** | 28 | 29 |
| | | | | | Gentamicin | 0.25 | 0.25 | NA | NA |
| | | | | | Linezolid | 2 | 2 | NA | NA |
| | | | | | Mupirocin | 0.12 | 0.12 | NA | NA |
| | | | | | Neomycin | 0.25 | 0.25 | NA | NA |
| | | | | | Penicillin | >32 | >32 | NA | NA |
| | | | | | Tetracycline | 0.5 | 8 | NA | NA |
| | | | | | Oxacillin | NA | NA | 21 | 22 |
| | 000426 | V1 (Isolate 1)[a] | V4 | *S. aureus* | SB-275833 | NA | NA | **27** | **20** |
| | | | | | Fusidic acid | NA | NA | **30** | **22** |
| | | | | | Mupirocin | NA | NA | 24 | 17 |
| | | | | | Oxacillin | NA | NA | 23 | 22 |
| | | V1 (Isolate 2)[a] | V4 | *S. aureus* | SB-275833 | NA | NA | 24 | 20 |
| | | | | | Fusidic acid | NA | NA | **28** | **22** |
| | | | | | Mupirocin | NA | NA | 23 | 17 |
| | | | | | Oxacillin | NA | NA | 24 | 22 |
| | 000427 | V1 | V4 | *S. aureus* | SB-275833 | NA | NA | 22 | 23 |
| | | | | | Fusidic acid | NA | NA | **26** | **16** |
| | | | | | Mupirocin | NA | NA | 21 | 20 |
| | | | | | Oxacillin | NA | NA | 23 | 22 |
| | 000429 | V1 | V4 | *S. aureus* | SB-275833 | NA | NA | 23 | 25 |
| | | | | | Fusidic acid | NA | NA | **28** | **14** |
| | | | | | Mupirocin | NA | NA | 21 | 23 |
| | | | | | Oxacillin | NA | NA | 27 | 25 |
| | 000791 | V1 | V3 | Group A *Streptococcus* | SB-275833 | 0.015 | 0.03 | **23** | **16** |
| | | | | | Amoxicillin/clavulanic acid | ≤0.015 | ≤0.015 | NA | NA |
| | | | | | Ceftriaxone | 0.03 | 0.03 | NA | NA |
| | | | | | Bacitracin | 0.5 | **1** | NA | NA |
| | | | | | Cephalothin | 0.12 | 0.06 | NA | NA |
| | | | | | Cloxacillin | 0.06 | 0.12 | NA | NA |
| | | | | | Erythromycin | 0.03 | 0.12 | NA | NA |
| | | | | | Flucloxacillin | 0.06 | 0.06 | NA | NA |

Table 5 continued:

| Study | Patient ID | Baseline Visit | Visit | Organism | Drug | Baseline MIC (µg/mL) | Visit MIC (µg/mL) | Baseline Disk (mm) | Visit Disk (mm) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Fusidic acid | 8 | 8 | 16 | 14 |
| | | | | | Gentamicin | 2 | 2 | NA | NA |
| | | | | | Linezolid | 1 | 1 | NA | NA |
| | | | | | Mupirocin | 0.12 | 0.12 | NA | NA |
| | | | | | Neomycin | 16 | 16 | NA | NA |
| | | | | | Penicillin | 0.03 | ≤0.015 | NA | NA |
| | | | | | Tetracycline | 0.25 | 0.25 | NA | NA |
| | 011347 | V1 | V4 | *S. aureus* | SB-275833 | NA | NA | 23 | 18 |
| | | | | | Fusidic acid | NA | NA | **27** | **21** |
| | | | | | Mupirocin | NA | NA | 20 | 19 |
| | | | | | Oxacillin | NA | NA | 25 | 24 |
| | 000356 | V1 (Isolate 1)[a] | V4 | *S. aureus* | SB-275833 | NA | NA | 26 | 21 |
| | | | | | Fusidic acid | NA | NA | **28** | **22** |
| | | | | | Mupirocin | NA | NA | 23 | 18 |
| | | | | | Oxacillin | NA | NA | 27 | 25 |
| | | V1 (Isolate 2)[a] | V4 | *S. aureus* | SB-275833 | NA | NA | 26 | 21 |
| | | | | | Fusidic acid | NA | NA | **28** | **22** |
| | | | | | Mupirocin | NA | NA | 23 | 18 |
| | | | | | Oxacillin | NA | NA | 28 | 25 |
| | 000343 | V1 | V4 | *S. aureus* | SB-275833 | NA | NA | 21 | 22 |
| | | | | | Fusidic acid | NA | NA | **23** | **8** |
| | | | | | Mupirocin | NA | NA | 21 | 19 |
| | | | | | Oxacillin | NA | NA | 23 | 6 |
| | 000716 | V1 | V4 | Group A *Streptococcus* | SB-275833 | **0.008** | **0.03** | 22 | 18 |
| | | | | | Amoxicillin/clavulanic acid | 0.06 | ≤0.015 | NA | NA |
| | | | | | Ceftriaxone | 0.12 | ≤0.015 | NA | NA |
| | | | | | Bacitracin | 0.5 | 0.5 | NA | NA |
| | | | | | Cephalothin | 0.12 | 0.12 | NA | NA |
| | | | | | Cloxacillin | 0.03 | 0.03 | NA | NA |
| | | | | | Erythromycin | 0.06 | 0.06 | NA | NA |
| | | | | | Flucloxacillin | ≤0.015 | ≤0.015 | NA | NA |
| | | | | | Fusidic acid | 8 | 8 | 16 | 14 |
| | | | | | Gentamicin | 2 | 1 | NA | NA |
| | | | | | Linezolid | 1 | 1 | NA | NA |
| | | | | | Mupirocin | 0.12 | 0.12 | NA | NA |
| | | | | | Neomycin | 8 | 16 | NA | NA |
| | | | | | Penicillin | 0.03 | ≤0.015 | NA | NA |
| | | | | | Tetracycline | 0.25 | 0.25 | NA | NA |
| **103469** | | | | | | | | | |
| | 000113 | V1 | V3 | *S. aureus* | SB-275833 | NA | NA | **25** | **19** |
| | | | | | Fusidic acid | NA | NA | 13 | 14 |
| | | | | | Mupirocin | NA | NA | 22 | 20 |
| | | | | | Oxacillin | NA | NA | 23 | 19 |

Note: SB-275833 and fusidic acid results that demonstrated a decrease in susceptibility appear in bold.
NA: Not Applicable. Amoxicillin/clavulanic acid was tested in a 2:1 ratio, MICs are reported based on the amoxicillin concentration.
[a] Isolate 1 and 2 appeared morphologically different on culture.

Of the 9 sets of isolates identified as having a ≥ 4-fold increase in MIC or ≥ 6 mm decrease in disk zone size between the screening and a subsequent visit, 6 were not characterized further because the Applicant stated that the increase in MIC or disk zone diameter occurred only for fusidic acid and no further analysis was conducted on the comparator. Of the remaining 3 sets of isolates, 2 were not investigated further because the retest susceptibility results showed no apparent reduced susceptibility in disk zone diameter or MIC (Table 6).

Table 6: SB-275833 and Fusidic acid Initial and Retest Results ( [redacted]

| Study | Patient | Pathogen | Visit | Compound | Source | Initial Disk (mm) | Retest Disk (mm) | Initial MIC (µg/mL) | Retest MIC (µg/mL) |
|---|---|---|---|---|---|---|---|---|---|
| 100224 | 000755 | *S. aureus* | 1 | Fusidic acid | Skin Swab | NA | NA | 0.25 | 0.12 |
| | | | 3 | | | NA | NA | 2 | 0.12 |
| 100224 | 000426 | *S. aureus* (Isolate 1)[a] | 1 | Fusidic acid | Nasal Swab | 30 | 30 | NA | NA |
| | | *S. aureus* (Isolate 2)[a] | 1 | | | 26 | 23 | NA | NA |
| | | | 4 | | | 22 | 24 | NA | NA |
| | | *S. aureus* (Isolate 1)[a] | 1 | SB-275833 | Nasal Swab | 27 | 24 | NA | NA |
| | | *S. aureus* (Isolate 2)[a] | 1 | | | 24 | 20 | NA | NA |
| | | | 4 | | | 20 | 20 | NA | NA |
| 100224 | 000427 | *S. aureus* | 1 | Fusidic acid | Nasal Swab | 26 | 14 | NA | NA |
| | | | 4 | | | 16 | 16 | NA | NA |
| 100224 | 000429 | *S. aureus* | 1 | Fusidic acid | Nasal Swab | 28 | 26 | NA | NA |
| | | | 4 | | | 14 | 13 | NA | NA |
| 100224 | 000791 | Group A *Streptococcus* | 1 | SB-275833 | Skin Swab | 23 | 23 | NA | NA |
| | | | 3 | | | 16 | 17 | NA | NA |
| 100224 | 001347 | *S. aureus* | 1 | Fusidic acid | Nasal Swab | 27 | 25 | NA | NA |
| | | | 4 | | | 21 | 25 | NA | NA |
| 100224 | 000356 | *S. aureus* (Isolate 1)[a] | 1 | Fusidic acid | Nasal Swab | 26 | 28 | NA | NA |
| | | *S. aureus* (Isolate 2)[a] | 1 | | | 26 | 29 | NA | NA |
| | | | 4 | | | 22 | 24 | NA | NA |
| 100224 | 000343 | *S. aureus* | 1 | Fusidic acid | Nasal Swab | 23 | 24 | NA | NA |
| | | | 4 | | | 8 | 10 | NA | NA |
| 100224 | 000716 | Group A *Streptococcus* | 1 | SB-275833 | Skin Swab | NA | NA | 0.008 | 0.03 |
| | | | 4 | | | NA | NA | 0.03 | 0.03 |
| 103469 | 000113 | *S. aureus* | 1 | SB-275833 | Nasal Swab | 25 | 23 | NA | NA |
| | | | 3 | | | 19 | 22 | NA | NA |

NA = Not Applicable
[a] Isolate 1 and 2 appeared morphologically different on culture.

The remaining set of isolates (PID000791) continued to demonstrate a ≥ 6mm reduction in the disk zone diameter between the Visit 1 and 3 isolates upon repeat testing [redacted]. This isolate was sent to GSK for MIC testing. The SB-275833 MIC was determined to be 0.016 µg/mL for both isolates, thereby demonstrating that there was no reduction in susceptibility to SB-275833 between the Visit 1 and Visit 3 isolates from this patient. In study TOC103469; 1 set of isolates demonstrated a reduction in susceptibility to SB-275833 but was not investigated further because no reduced susceptibility was noted in disk diffusion results upon repeat testing. It is reasonable to conclude that no development of resistance was observed during treatment with SB-275833 in the SB-275833 Phase III clinical studies TOC100224 and TOC103469. However, it would be worthwhile for the Applicant to continue further testing for the potential for isolates to develop resistance to SB-275833.

## QUALITY CONTROL PARAMETERS

Studies were conducted to establish quality control (QC) parameters for SB-275833. Data was presented in [redacted]. It is stated that these QC ranges were used in

TOC100224 and Study TOC103469 to validate MIC and disk diffusion results obtained by a central laboratory.

During the SB-275833 Phase III impetigo clinical studies, [redacted] received isolates from local laboratories that were cultured from skin (swab) and nasal specimens (swab). The central laboratory in [redacted] also received isolates from Mexico, Peru and India in Clinical Study SB-275833/TOC103469 and from Canada, India and Costa Rica in Clinical Study SB-275833/TOC100224. The central laboratory in [redacted] received isolates from Italy and the Netherlands in Clinical Study SB-275833/TOC103469 and from South Africa, Germany, Poland, France, Italy and the Netherlands in Clinical Study SB-275833/TOC100224. The central laboratories performed confirmatory identification and susceptibility testing on all recovered organisms in accordance with established clinical microbiology procedures.

Appropriate QC was performed when patient isolates were tested for susceptibility to SB-275833 and other antibacterial agents. The results from QC testing performed at the central laboratories were sent to GlaxoSmithKline on a semi-monthly basis throughout the studies. QC results were then reviewed internally to verify that SB-275833 and comparator disk diffusion and MIC broth microdilution results were within the established reference ranges.

**Susceptibility Test Methods**

**Skin isolates**

Susceptibility testing was performed on all aerobic pathogens recovered from skin specimens. Disk diffusion and broth microdilution testing were performed according to CLSI guidelines[3] on all pathogens isolated and in conjunction with the instructions of [redacted] Microdilution panels contained doubling dilutions of SB-275833 providing a concentration range of 0.002 mcg/mL to 256 µg/mL.

The comparator antimicrobials included on the panels were penicillin (0.015 to 32 mcg/mL), flucloxacillin (0.015 to 32 mcg/mL), cloxacillin (0.015 to 32 mcg/mL), neomycin (0.03 to 64 mcg/mL), gentamicin (0.03 to 64 mcg/mL), bacitracin (0.06 to 128 mcg/mL), erythromycin (0.015 to 32 mcg/mL), tetracycline (0.06 to 32 mcg/mL), mupirocin (0.03 to 256 mcg/mL), fusidic acid (0.015 to 32 mcg/mL), ceftriaxone (0.015 to 64 mcg/mL), linezolid (0.015 to 16 mcg/mL), amoxicillin/clavulanic acid (0.015 to 32 mcg/mL) and cephalothin (0.03 to 256 mcg/mL). Disk diffusion testing was performed on fusidic acid (10 mcg) and SB-275833 (2 mcg). Oxacillin (1 mcg) disk diffusion testing was also performed on *S. aureus* isolates.

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**Nasal Isolates**

For isolates from nasal swab culture, disk diffusion testing was performed with mupirocin (5 µg), fusidic acid (10 mcg), oxacillin (1 µg) and SB-275833 (2 µg) for all *S. aureus* isolates.

The following QC organisms were included for MIC and disk diffusion testing for isolates from skin culture: *S. pneumoniae* ATCC 49619 and *S. aureus* ATCC 25923. *S. aureus* ATCC 29213 was also tested when MIC broth microdilution testing was performed. Mupirocin MIC and disk diffusion QC ranges were evaluated using *S. aureus* ATCC 25923. QC for each organism was conducted on each day of testing with the exception of *S. pneumoniae* ATCC 49619, which was only tested when clinical isolates of *Streptococcus* spp. were recovered. The MIC and disk diffusion ranges used for SB-275833 were based on an earlier QC study conducted in accordance with CLSI and M7-A7 guidelines[4] [GSK Report Number UH2004/00010/00, GSK Report Number UH2004/00009/00]. CLSI QC ranges were used for all established comparator agents used in testing clinical isolates (CLSI M2-A8 and M100-S17). Table 7 and 8 shows the QC ranges obtained for SB-275833 and mupirocin. For nasal swab isolates, disk diffusion testing was performed using *S. aureus* ATCC 25923 as the QC organism. Testing was done in accordance to CLSI M2-A9 guidelines[3].

Table 7: QC ranges for SB-275833

| Organism | QC Range[1] | |
|---|---|---|
| | MIC (mcg/mL) | Disk Diffusion Zone Size (mm) |
| *S. aureus* ATCC 29213 | 0.06-0.25 | NA[2] |
| *S. pneumoniae* ATCC 49619 | 0.06-0.5 | 13-19 |
| *S. aureus* ATCC 25923 | NA[2] | 23-30 |

1. 1.MIC broth microdilution and disk diffusion QC ranges from GSK Report Number UH2004/00010/00 and GSK Report Number UH2004/00009/00
2. NA=Not applicable

Table 8: QC ranges for mupirocin

| Organism | QC Range[1] | |
|---|---|---|
| | MIC (mcg/mL) | Disk Diffusion Zone Size (mm) |
| *S. aureus* ATCC 25923 | 0.12-0.5 | 22-27 |

1. MIC broth microdilution and disk diffusion QC ranges from published literature [Finlay 1997]

The data from the QC analysis can be found in Figure 1 and Table 9 (*S. aureus* ATCC 29213 MIC broth microdilution), Figure 2 and Table 10 (*S. pneumoniae* ATCC 49619 MIC broth microdilution), Figure 3 and Table 11 (*S. aureus* ATCC 25923 disk diffusion) and Figure 4 and Table 12 (*S. pneumoniae* ATCC 49619 disk diffusion).

Figure 1: QC MIC Broth Microdilution Results for SB-275833 vs. *S. aureus* ATCC 29213 for SB-275833 Clinical Studies TOC103469 and TOC100224 Combined

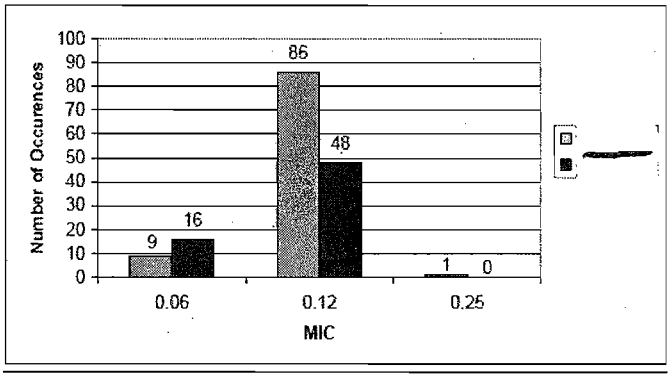


Table 9: QC MIC Broth Microdilution Results for SB-275833 vs. *S. aureus* ATCC 29213 for SB-275833 TOC103469 and TOC100224 Combined *

| MIC (mcg/mL) | Number of Occurrences from [redacted] [a] | Number of Occurrences from [redacted] [a] | Total |
|---|---|---|---|
| 0.03 | 0 | 0 | 0 |
| 0.06 | 9 | 16 | 25 |
| 0.12 | 86 | 48 | 134 |
| 0.25 | 1 | 0 | 1 |
| 0.5 | 0 | 0 | 0 |
| Total | 96 | 64 | 160 |

a. The median was 0.12mcg/mL for both [redacted]
*The shaded cells indicate the proposed QC range for SB-275833

Figure 2: QC MIC Broth Microdilution Results for SB-275833 vs. *S. pneumoniae* ATCC 49619 for SB-275833 Clinical Studies TOC103469 and TOC100224 Combined

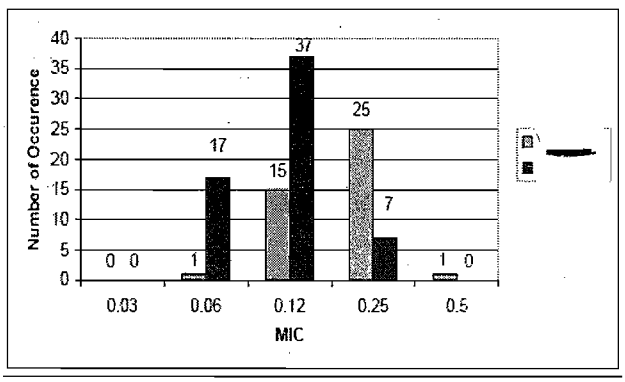

Table 10: QC MIC Broth Microdilution Results for SB-275833 vs. *S. pneumoniae* ATCC 49619 for SB-275833 Clinical Studies TOC103469 and TOC100224 Combined*

| MIC (mcg/mL) | Number of Occurrences from [redacted][a] | Number of Occurrences from [redacted][a] | Total |
|---|---|---|---|
| 0.03 | 0 | 0 | 0 |
| 0.06 | 1 | 17 | 18 |
| 0.12 | 15 | 37 | 52 |
| 0.25 | 25 | 7 | 32 |
| 0.5 | 1 | 0 | 1 |
| 1 | 0 | 0 | 0 |
| Total | 42 | 61 | 103 |

a. The median was 0.25mcg/mL and 0.12mcg/mL at [redacted], respectively
*The shaded cells indicate the proposed QC range for SB-275833

Figure 3: QC Disk Diffusion Results for SB-275833 vs. *S. aureus* ATCC 25923 for SB-275833 Clinical Studies TOC103469 and TOC100224 Combined

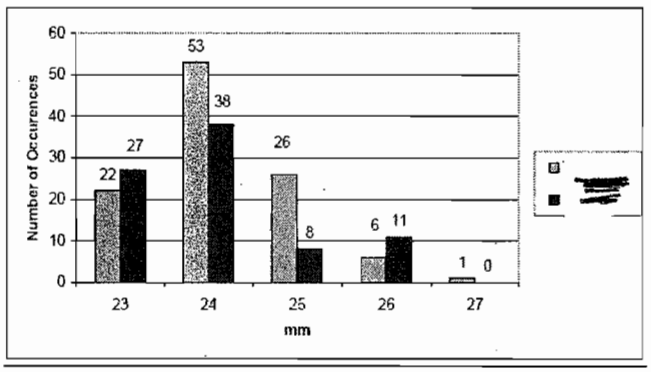


Table 11: QC Disk Diffusion Results for SB-275833 vs. *S. aureus* ATCC 25923 for SB-275833 Clinical Studies TOC103469 and TOC100224 Combined*

| Zone Diameter (mm) | Number of Occurrences from [redacted] | Number of Occurrences from [redacted] | Total |
|---|---|---|---|
| 22 | 0 | 0 | 0 |
| 23 | 22 | 27 | 49 |
| 24 | 53 | 38 | 91 |
| 25 | 26 | 8 | 34 |
| 26 | 6 | 11 | 17 |
| 27 | 1 | 0 | 1 |
| 28 | 0 | 0 | 0 |
| 29 | 0 | 0 | 0 |
| 30 | 0 | 0 | 0 |
| 31 | 0 | 0 | 0 |
| Total | 108 | 84 | 192 |

a. The median was 24mm at both [redacted]
*The shaded cells indicate the proposed QC range for SB-275833

Figure 4: QC Disk Diffusion Results for SB-275833 vs. *S. pneumoniae* ATCC 49619 for SB-275833 Clinical Studies TOC103469 and TOC100224 Combined

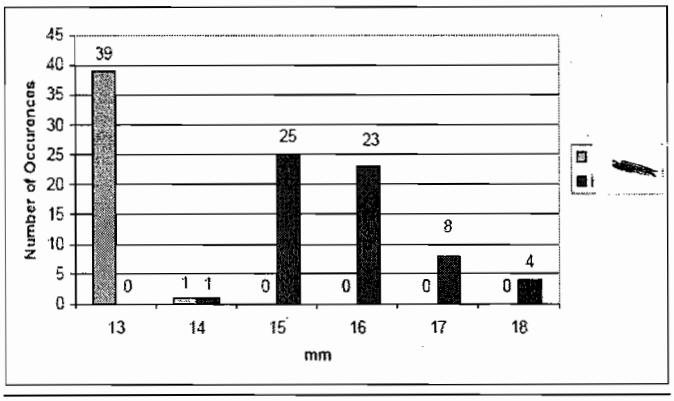


Table 12: QC Disk Diffusion Results for SB-275833 vs. *S. pneumoniae* ATCC 49619 for SB-275833 Clinical Studies TOC103469 and TOC100224 Combined*

| Zone Diameter (mm) | Number of Occurences from [redacted] a | Number of Occurences from [redacted] | Total |
|---|---|---|---|
| 12 | 0 | 0 | 0 |
| 13 | 39 | 0 | 39 |
| 14 | 1 | 1 | 2 |
| 15 | 0 | 25 | 25 |
| 16 | 0 | 23 | 23 |
| 17 | 0 | 8 | 8 |
| 18 | 0 | 4 | 4 |
| 19 | 0 | 0 | 0 |
| 20 | 0 | 0 | 0 |
| Total | 40 | 61 | 101 |

a. The median was 13mm and 16mm at \ [redacted] respectively
*The shaded cells indicate the proposed QC range for SB-275833

All of the MIC broth microdilution and disk diffusion QC results for *S. aureus* and *S. pneumoniae* appear to be within the MIC ranges for SB-275833. The MIC ranges obtained at each laboratory were within the proposed 3-4 doubling dilutions (0.06-0.25 µg/mL for *S. aureus* ATCC 29213 and 0.06-0.5 µg/mL for *S. pneumoniae* ATCC 49619). Similarly, each laboratory reported zone diameter values that were within the proposed range for each organism. Although each laboratory reported zone diameter values that were within the proposed range for each organism, some of the results of the QC test performed for SB-275833 were initially out of range; however, upon repeating the test, all values were within the established range.

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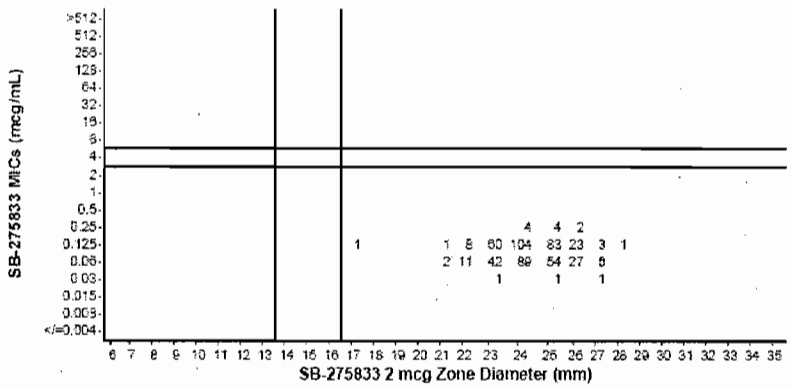
For *S. aureus* ATCC 29213, the median MIC broth microdilution result was 0.12 µg/mL and the MIC range was 0.06 to 0.25 µg/mL at both laboratories (Figure 1 and Table 9). The median values for *S. aureus* ATCC 25923 disk diffusion results were 24 mm at both [redacted] (Figure 3 and Table 11). Similarly, the ranges were 23-27 mm and 23-26 mm, respectively.

In summary, even though they were some inter-laboratory differences in the distribution of the QC parameters for *S. pneumoniae* susceptibility testing, all MIC and zone of inhibition values appear to be within the proposed range for both MIC broth microdilution and disk diffusion testing.

**Analysis of MIC and Disk Diffusion data from the Phase III study**

Studies to validate the use of SB-275833 (2 µg) disk for disk diffusion testing and microbiological breakpoints for SB-275833 were conducted against a large collection of organisms. The studies were done to correlate MIC and disk diffusion results for SB-275833 and were presented in [redacted]. An analysis of MIC and disk diffusion data from the clinical study TOC100224 and Study TOC103469 was conducted. Scattergrams depicting the results from testing of *S. aureus* and *S. pyogenes* in the impetigo Study TOC100224 and Study TOC103469 combined are shown in Figure 5 and Figure 6. Please note that interpretive criteria are not being defined; the information provided here shows a correlation between MIC and zone of inhibition.

Figure 5: SB-275833 MICs (mcg/mL) vs. Zone Size (mm) from Study TOC100224 and TOC103469 Combined – *S. aureus* (n=528) (all geographic regions)




Source: Data Listing 9.22 (TOC100224); Data Listing 9.22 (TOC103469)

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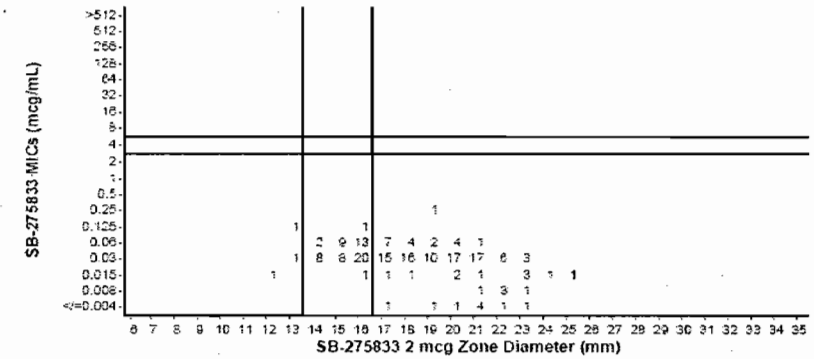
Figure 6: SB-275833 MICs (mcg/mL) vs. Zone Size (mm) from Study TOC100224 and Study TOC103469 Combined – *S. pyogenes* (n=192) (all geographic regions).




Source: Data Listing 9.22 (TOC100224); Data Listing 9.22 (TOC103469)

## HUMAN AND ANIMAL STUDIES:

### Animal Studies

Please see [redacted] review for a review of the animal studies.

### Human Studies

The Phase III clinical development program for NDA 22-055 was designed to assess the safety and efficacy of SB-275833 ointment in the treatment of impetigo. Two global Phase III trials in the indication of primary impetigo have been conducted. One adequate and well-controlled trial compared SB-275833 ointment versus placebo ointment (Study TOC103469). Subjects were enrolled from 42 centers in nine countries (Canada, France, Germany, the Netherlands, Poland, Costa Rica, India, Peru, and South Africa). The second controlled trial used a non-inferiority design to compare SB-275833 ointment versus sodium fusidate ointment (Study TOC10224). Subjects were enrolled from 17 centers in four countries (the Netherlands, India, Peru, and Mexico). Please note that sodium fusidate ointment is not an approved product within the United States.

### Overview of SB-275833 Clinical Program

The studies compared SB-275833 ointment with an active comparator (Study TOC100224) or to placebo (Study TOC103469). Subjects with a clinical diagnosis of primary impetigo with up to 10 lesions were enrolled (with a maximum area of 100cm$^2$ for either a single lesion or multiple lesions). The infected lesions had to be suitable for topical antibiotic therapy. In addition, the infections were to be those with a high likelihood of having *S. aureus* and/or *S. pyogenes* as the causative infectious agent.

Where subjects had multiple lesions, the worst lesion was nominated as the primary lesion site. At all visits, the subject's primary lesion was measured and graded for exudate/pus, crusting, erythema/inflammation, tissue warmth, tissue edema, itching, and pain according to Skin Infection Rating Scale (SIRS) criteria (please refer to the Medical Officers' review for additional information regarding the use of the SIRS criteria). If subjects had multiple lesions, all lesion dimensions were measured. The amount of topical antibacterial applied depended on the size of the infected lesion(s). Based on the maximum lesion size of $100cm^2$, the maximum amount of topical formulation applied per dose to a subject was predicted to be 2 to 5 $mg/cm^2$ (i.e., 200 to 500 $mg/100\ cm^2$ of SB-275833 ointment or sodium fusidate ointment). The total daily dose of SB-275833 ointment applied was 0.4 to $1gm/100cm^2$, which contained 4 to 10 mg of SB-275833 drug substance. For topical sodium fusidate ointment, the total daily dose applied was 0.6 to 1.5 gm of ointment, which contained 12 to 30 mg sodium fusidate. It was the subjects' responsibility to apply a suitable amount of SB-275833 ointment, sodium fusidate ointment, or placebo to cover the entire infected lesion(s).

The preparation was applied to the cleansed lesion(s) in a thin layer (approximately 1mm thick) with a sterile swab and the use of gauze, bandage, etc., to cover the lesion(s) was permitted. Children young enough to inadvertently lick the medication or the lesion site had their treated lesion covered with gauze or a semi-occlusive bandage. The type of dressing used was recorded at all visits as "occlusive," "semi-occlusive," or "none." Treatment was to continue for the full duration even if the lesion had fully healed. Treatment could be terminated at any time if, in the opinion of the investigator, the infected lesion had failed to respond to treatment.

At the Baseline visit (Day 1, Visit 1) bacteriology samples were obtained using sterile cotton swabs for culture, Gram stain, and susceptibility testing. At Baseline (Day 1, Visits 1), bacteriology samples (skin swabs) of the infected site(s) were obtained using sterile cotton swabs for culture, Gram stain, and susceptibility testing. Swabbing rather than curettage was the method selected for bacteriology sample collection in both impetigo studies based on external expert advice, as curettage sampling could damage the skin greater than would otherwise occur due to the impetigo lesion. Also, investigators in both trials were directed to lift crusts if present and culture the skin lesion underneath these crusts. At subsequent visits, bacteriology samples were only collected from subjects who were deemed clinical failures. Clinical signs and symptoms were reviewed at End of Therapy, and the clinical outcome was determined and the resulting clinical response was assigned for each subject, as follows:

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| Outcome | Defining criteria | Clinical Response End of Therapy[1] |
|---|---|---|
| Clinical success | Total absence of the treated lesions or the treated lesions had 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 was necessary. | Clinical success |
| Clinical failure | Insufficient improvement or deterioration (i.e., lesions remained crusted and/or had exudate leaving yellow or honey colored crust, lesion area increased with or without an increase in the number of lesions) compared to Baseline such that additional antibiotic therapy was required. Subjects who were clinical failures at End of Therapy were also considered clinical failures at Follow-up. | Clinical failure |
| Unable to determine | Refusal to consent to a clinical examination or lost to Follow-up. Subjects who were "unable to determine" at End of Therapy were also considered "unable to determine" at Follow-up. | Clinical failure |

1. Study TOC100224: 2 days after treatment (Day 7 [Visit 2] for SB-275833 ointment and Day 9 [Visit 3] for sodium fusidate ointment).
Study TOC103469: 2 days after treatment (Day 7, Visit 2).

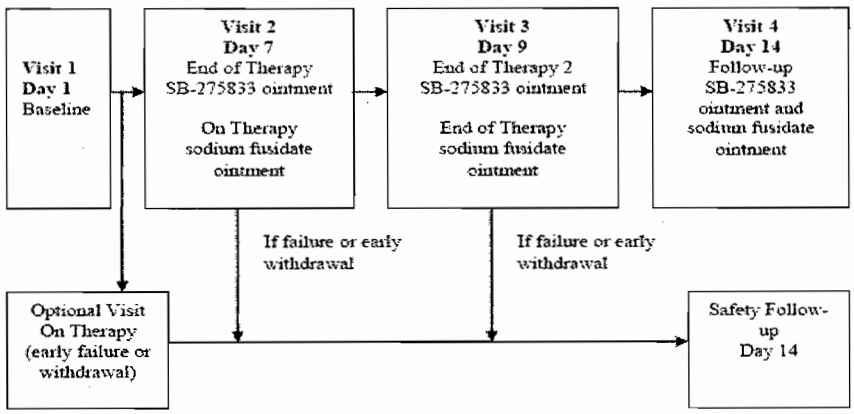
When samples were not collected, bacteriological outcome was assessed according to clinical criteria to allow a conclusion to be drawn, e.g., a conclusion of presumed eradication or presumed persistence. The presence or emergence of resistance during therapy was monitored. Any apparent change in SB-275833 minimum inhibitory concentration (MIC; ≥ 4 fold increase) or zone diameter (≥ 6mm decrease) was confirmed by concurrent testing of before and after therapy isolates. In addition, any isolates demonstrating a SB-275833 MIC of ≥ 1µg/mL were tested again and characterized for the presence of any resistance mechanisms. Diary cards were completed during the study to assess the effects of impetigo on the child's activity and its impact on the parent/guardian. Efficacy was assessed; and safety was assessed via collection of adverse events (AEs) and measurement of laboratory blood and urine parameters.

**Study TOC100224 (SB-275833 vs. sodium fusidate)**

Study TOC100224 was a randomized, observer-blind, multicenter, noninferiority study to compare the efficacy and safety of topical SB-275833 ointment with topical sodium fusidate ointment in the treatment of primary impetigo in adult and pediatric subjects. Pediatric subjects were defined as ≥ 9 months of age (≥18 months of age for the Netherlands only) and < 18 years of age. Observer blinding was used in this study because the study treatments differed in color and application frequency.

Enrolled subjects were randomized in a 2:1 ratio (SB-275833 ointment: sodium fusidate ointment) in an observer-blind manner to receive either topical SB-275833 ointment BID for 5 days or topical sodium fusidate ointment three times daily (TID) for 7 days. Subjects were enrolled into the study for up to 14 days and were required to attend the clinic for up to four visits, with an optional on-therapy visit for subjects who were clinical failures or who withdrew from the study (Figure 7). A total of 517 (345 randomized to SB-275833 ointment and 172 randomized to sodium fusidate ointment) subjects received at least one dose of study medication and were included in the ITTC population. Of the subjects in the ITTC population, 467 (317 in the SB-275833 ointment treatment group and 150 in the sodium fusidate ointment treatment group) were included in the PPC population at End of Therapy.

Figure 7 Study TOC100224 Schematic Diagram




To determine the presence of *S. aureus* nasal carriage, a nasal swab of the anterior nares was collected for culture and susceptibility testing at Baseline (Day 1, Visit 1) and at Follow-up (Day 14, Visit 4). In addition, a nasal swab was obtained for all subjects at the optional visits, and for subjects who were deemed clinical failures at Day 7 (Visit 2) and Day 9 (Visit 3).

**Study TOC103469 (SB-275833 vs. placebo)**

Study TOC103469 was a randomized, double-blind, multicenter superiority study to compare the efficacy and safety of topical SB-275833 ointment with placebo ointment for the treatment of primary impetigo in adult and pediatric subjects. Pediatric subjects were defined as ≥ 9 months of age (≥18 months of age for the Netherlands only) and < 18 years of age. Enrolled subjects were randomized to treatment in a 2:1 ratio (active:placebo) to receive either SB-275833 ointment or placebo ointment BID for 5 days. A total of 210 subjects (139 randomized to SB-275833 ointment and 71 randomized to placebo) received at least one dose of study medication and were included in the ITTC population.

This study was designed as a placebo-controlled study in order to provide an assessment of the efficacy and safety of SB-275833 ointment versus a neutral baseline in treating impetigo, and to supplement other studies where an active comparator had been used. Subjects were enrolled into the study for up to 14 days and were required to attend the clinic for up to three visits, with an optional on-therapy visit for subjects who were clinical failures or who withdrew from the study (Figure 8). (Note: in one center in the Netherlands, subjects had all postbaseline visits conducted at home, with this change being agreed to by the Independent Ethics Committee [IEC]). In addition, during the study treatment phase, subjects were contacted daily by telephone to ensure that the subject was responding to treatment. If the subject or the parent/legal guardian felt that the subject was not responding to study treatment, an immediate visit could be scheduled to assess the subject.

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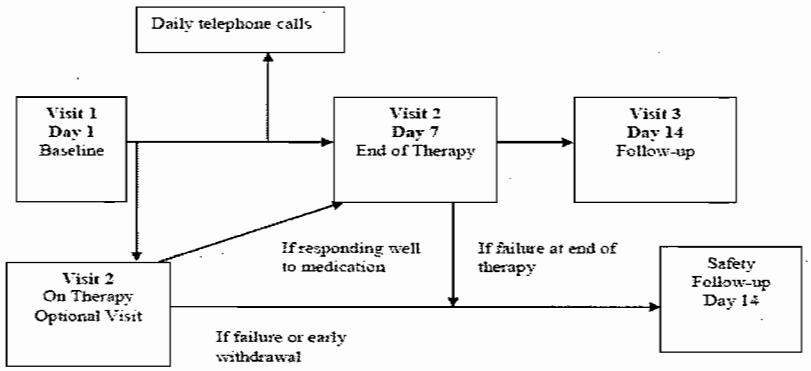
Figure 2 Study TOC103469 Schematic Diagram




Subjects had a clinical assessment at the Baseline visit (Day 1, Visit 1) and at all visits thereafter to monitor AEs and to ensure that, in the investigator's clinical judgment, the condition of the subject had not worsened or failed to improve. Following the Baseline visit (Day 1, Visit 1), subjects could return to the clinic early for any scheduled visit if the subject was not improving, suffering a recurrence, or experiencing an AE that required monitoring. While subjects were on study treatment, they were contacted daily by telephone to clinically evaluate their response to study medication. All subjects who were considered a clinical failure or who withdrew for any reason were to return to the study site on Day 14 (Visit 3) for a Follow-up safety assessment to monitor any AEs, and to record any changes in concomitant medications.

To determine the presence of *S. aureus* nasal carriage, a nasal swab of the anterior nares was collected for culture and susceptibility testing at Baseline (Day 1, Visit 1) and at Follow-up (Day 14, Visit 3). In addition, a nasal swab was obtained for all subjects at the optional visits, and for subjects who were deemed clinical failures at Day 7 (Visit 2).

**Subject Population**

In Study TOC100224, the planned sample size was 242 evaluable subjects in the SB-275833 ointment treatment group and 121 evaluable subjects in the sodium fusidate ointment treatment group. These subjects were enrolled from 42 centers in nine countries (Canada, France, Germany, the Netherlands, Poland, Costa Rica, India, Peru, and South Africa).

In Study TOC103469, the planned sample size was for 140 evaluable subjects in the SB-275833 ointment treatment group and 70 evaluable subjects in the placebo group. Subjects were enrolled from 17 centers in four countries (the Netherlands, India, Peru, and Mexico).

The primary inclusion criteria for both studies were as follows:

- The subject was ≥ 9 months of age (≥ 18 months of age for the Netherlands only).

- The subject had a clinical diagnosis of primary impetigo (bullous or nonbullous) defined as a lesion or a group of lesions characterized by red spots or blisters without crusts that later progress to lesions that ooze and form yellow or honey-colored crusts surrounded by an erythematous margin.

- The subject had no more than 10 discrete localized impetigo lesions suitable for topical treatment.
- The infected lesion(s) did not exceed 100cm$^2$ in area (with surrounding erythema not extending more than 2cm from the edge of any lesion) or a maximum of 2% body surface area for subjects < 18 years of age. If a subject had multiple lesions, the total area did not exceed 100cm$^2$.
- The subject had a SIRS score of at least 8.
- A pediatric subject under the legal age of consent (dependent on local country practice) was included if the following criteria were met: the parent/legal guardian was willing to comply with the protocol, the child had given assent to participate in the study (this was only required if the child was of an age to assent to enroll in the study – the age of assent was determined by the Independent Review Board/IEC or was consistent with local legal requirements), and the parent/legal guardian had given written, dated informed consent for the subject to participate in the study.

The primary exclusion criteria for both studies were:

- The subject demonstrated a previous hypersensitivity reaction to sodium fusidate or to any component of the ointment (Study TOC100224 only) or the subject demonstrated a previous hypersensitivity reaction to SB-275833 or any component of the ointment.
- The subject had an underlying skin disease (e.g., pre-existing eczematous dermatitis) or skin trauma, with clinical evidence of secondary infection.
- The subject had signs and symptoms of systemic infection (such as fever; defined as an oral temperature greater than 101° F or 38.3° C).
- The subject had a bacterial skin infection that, due to depth or severity, in the opinion of the investigator, could not be appropriately treated by a topical antibiotic (e.g., extensive cellulitis, furunculosis, and abscess).
- The subject had received a systemic antibacterial or steroid or had 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.

The subjects enrolled in Study TOC100224 were predominately < 65 years of age; however, a small number of subjects, predominately in the SB-275833 Ointment, 1%, group were ≥ 65 years of age. These older subjects (i.e., those ≥ 65 years of age) had an impact on the average age of the subjects within the SB-275833 Ointment, 1%, group, hence the difference observed in the average age between the treatment groups. Overall, 359/517 (69.4%) were pediatric subjects (<18 years) of whom 233 received SB-275833 Ointment, 1%, and 126 received sodium fusidate ointment, 2%. Most were in the 2 years to < 6 years and 6 years to < 13 years strata; these age groups are known to have relatively high rates of impetigo.

The primary endpoint for both studies was clinical success at End of Therapy. End of Therapy was deemed a better measure of efficacy for impetigo (as opposed to Follow-up) because of the general perception that the disease is self limiting. For both studies, End of Therapy was defined as 2 days after treatment. Due to the different durations of treatment, the timing of this End of Therapy visit differed. For Study TOC100224, it was Day 7 (Visit 2) for the SB-275833 ointment treatment group and Day 9 (Visit 3) for the sodium fusidate ointment treatment group; for Study TOC103469, it was day 2 (Visit 2) for both treatment groups. The hypothesis to be tested by the primary endpoint for Study TOC100224 was that the clinical efficacy of SB-

275833 ointment was noninferior to that of sodium fusidate ointment in the treatment of adult and pediatric subjects with primary impetigo.

The secondary endpoints for Study TOC100224 were as follows:

- Clinical response at Day 7 (Visit 2; 2 days after treatment for SB-275833 ointment and on-therapy for sodium fusidate ointment)
- Clinical response at Day 9 (Visit 3; 4 days after treatment for SB-275833 ointment, and 2 days after treatment for sodium fusidate ointment)
- Clinical response at Follow-up (Day 14, Visit 4)
- Assessment of lesion(s) area at End of Therapy (Day 7, [Visit 2] for SB-275833 ointment, and Day 9 [Visit 3] for sodium fusidate ointment) and Follow-up (Day 14, Visit 4)

For the placebo control study, TOC103469, the hypothesis to be tested was that the clinical efficacy of SB-275833 ointment was superior to that of placebo in the treatment of adult and pediatric subjects with primary impetigo. The results from each of the studies are presented individually in this Efficacy Summary; results are not combined.

The secondary endpoints for Study TOC103469 were as follows:

- Clinical response at End of Therapy (Day 7, Visit 2) for the PPC population
- Clinical response at Follow-up (Day 14, Visit 3; 9 days after study treatment)
- Assessment of lesion(s) area at each visit

The proportion of subjects in the fusidic acid study (TOC100224) with a clinical diagnosis of bullous or non-bullous impetigo at baseline by study population is shown in Table 13. In all populations and in both treatment groups, the majority of subjects had the nonbullous form of impetigo (Table 13).

Table 13: Clinical Diagnosis of Impetigo at Baseline in Each Analysis Population

| Clinical Diagnosis | Treatment Group | |
|---|---|---|
| | SB-275833 | Sodium fusidate |
| **Bullous, n (%)** | | |
| ITTC | 75 (21.7) | 35 (20.3) |
| PPC | 67 (21.8) | 28 (19.6) |
| ITTB | 61 (23.2) | 28 (21.4) |
| PPB | 53 (22.6) | 21 (19.6) |
| **Non-bullous, n (%)** | | |
| ITTC | 270 (78.3) | 137 (79.7) |
| PPC | 241 (78.2) | 115 (80.4) |
| ITTB | 202 (76.8) | 103 (78.6) |
| PPB | 182 (77.4) | 86 (80.4) |

Source: Table 6.22

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**Microbiological Data**

Bacteriology samples were obtained for culture and susceptibility testing at the Baseline visit for all subjects. At subsequent visits, bacteriology samples were only collected from subjects who were deemed clinical failures. When samples were not collected, bacteriological outcome was assessed according to clinical criteria to allow a conclusion to be drawn, e.g., a conclusion of presumed eradication or presumed persistence.

The microbiological endpoints for Study TOC100224 were as follows:

- Microbiological response at End of Therapy (Day 7 [Visit 2] for SB-275833 ointment and Day 9 [Visit 3] for sodium fusidate ointment)
- Microbiological response at Follow-up (Day 14, Visit 4)
- Number and percent of subjects who had MRSA, mupRSA, or fusidic acid resistant *S. aureus* (fusRSA) isolated at Baseline and by clinical response at End of Therapy (Day 7 [Visit 2] for SB-275833 ointment and Day 9 [Visit 3] for sodium fusidate ointment)
- Number and percent of subjects who had various pathogens including MRSA, mupRSA, and fusRSA isolated at Baseline by clinical response at Follow-up (Day 14 Visit 4)

The microbiological endpoints for Study TOC103469 were as follows:

- Microbiological response at End of Therapy (Day 7, Visit 2)
- Microbiological response at Follow-up (Day 14, Visit 3; 9 days after study treatment)
- Number and percent of subjects who had MRSA, mupRSA, or fusRSA isolated at screening (Day 1) and by clinical response at End of Therapy (Day 7, Visit 2)
- Number and percent of subjects who had various pathogens including MRSA, mupRSA, and fusRSA isolated at Baseline by clinical response at Follow-up (Day 14, Visit 3; 9 days after treatment)

**Microbiological Success at End of Therapy**

The microbiological outcome at End of Therapy was determined by comparing the baseline (Day 1, Visit 1) culture results to the culture results at End of Therapy and the corresponding microbiological response (success or failure) was then assigned, as follows:

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| Defining criteria | Outcome | Microbiological Response End of Therapy[1] |
|---|---|---|
| Elimination of Baseline pathogen(s) | Microbiological eradication | *Microbiological success* |
| Clinical outcome was success such that no culture was obtained, secondary to adequate clinical response, and was documented in the case report form | Presumed microbiological eradication | *Microbiological success* |
| Baseline pathogen(s) was still present | Microbiological persistence | *Microbiological failure* |
| Subject was a clinical failure and no culture was obtained | Microbiological presumed persistence | *Microbiological failure* |
| An assessment of bacteriological outcome could not be made at End of Therapy or Follow-up | Unable to determine | *Microbiological failure* |
| New pathogen, not previously identified, was identified at End of Therapy in a symptomatic subject requiring additional antibiotic therapy, i.e., subject was a "clinical failure" | New infection | *Microbiological failure* |
| New pathogen not previously identified was identified at End of Therapy in a nonsymptomatic subject who did not require additional antibiotic therapy, i.e., subject was a "clinical success" | Colonization | *Microbiological success* |

1. Study TOC100224: 2 days after treatment (Day 7 [Visit 2] for SB-275833 ointment and Day 9 [Visit 3] for sodium fusidate ointment).
Study TOC103469: 2 days after treatment (Day 7, Visit 2).

**Microbiological Response at Follow-up**

The microbiological outcome at Follow-up was determined by comparing the baseline (Day 1, Visit 1) culture results to the culture results at Follow-up, and the corresponding microbiological response (success or failure) was then assigned, as follows:

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| Defining criteria | Outcome | Microbiological Response Follow-up[1] |
|---|---|---|
| **For subjects whose clinical response at End of Therapy was clinical failure and who did not have cultures obtained at Follow-up:** | | |
| Subject was a clinical failure at End of Therapy and no culture was obtained at Follow-up | Microbiological presumed persistence | Microbiological failure |
| **For subjects whose clinical response at End of Therapy was clinical success:** | | |
| The Baseline pathogen was eradicated or presumed eradicated at End of Therapy, or the Baseline pathogen(s) was present at End of Therapy and was absent at Follow-up | Follow-up microbiological eradication | Microbiological success |
| The Baseline pathogen was eradicated or presumed eradicated at End of Therapy, subject was a Follow-up clinical success, such that no culture was obtained due to lack of culturable material, secondary to adequate clinical response, and was documented in the case report form | Presumed Follow-up microbiological eradication | Microbiological success |
| Baseline pathogen(s) was present at End of Therapy and was still present | Microbiological persistence | Microbiological failure |
| The Baseline pathogen was eradicated or presumed eradicated at End of Therapy and reappeared at Follow-up | Microbiological recurrence | Microbiological failure |
| The Baseline pathogen was eradicated or presumed eradicated at End of Therapy, no sample for culture was taken at the Follow-up visit, and subject was a clinical recurrence | Microbiological presumed recurrence | Microbiological failure |
| An assessment of bacteriological outcome could not be made at End of Therapy or Follow-up | Unable to determine | Microbiological failure |
| **New pathogens isolated at Follow-up (i.e., not present at Baseline or End of Therapy) were classified according to the following categories:** | | |
| A new pathogen, not previously identified at Baseline or End of Therapy, was identified at Follow-up in a symptomatic subject requiring additional antibiotic therapy, i.e., subject was a clinical recurrence | New infection | Microbiological failure |
| A new pathogen, not previously identified at Baseline or End of Therapy, was identified at Follow-up in a nonsymptomatic subject who did not require additional antibiotic therapy, i.e., subject was a Follow-up clinical success | Colonization | Microbiological success |

1. StudyTOC100 224: Day 14 (Visit 4);
   Study TOC103469: Day 14 (Visit 3)

Note: For subjects who withdrew prior to the End of Therapy visit, evaluation of by pathogen and by subject microbiological response was determined at the time they were withdrawn.

## Pathogens Isolated at Baseline: Study TOC100224

Pathogen identification at baseline was determined by results obtained from central laboratories. The number (%) of subjects who had pathogens isolated at baseline in the ITTC population is shown in Table 14. The number of subjects in relation to the number of pathogens isolated at baseline in the ITTC population is also depicted. The data show that of the subjects with a pathogen, most had a single pathogen isolated.

Table 14. Number (%) of Subjects by Number of Pathogens Isolated at Baseline (ITTC Population)

| Number of Pathogens | Number (%) of Subjects | |
|---|---|---|
| | SB-275833 N=345 | Sodium fusidate N=172 |
| 0 | 82 (23.8) | 41 (23.8) |
| 1 | 182 (52.8) | 90 (52.3) |
| 2 | 76 (22.0) | 36 (20.9) |
| 3 | 5 (1.5) | 5 (2.9) |
| **No. of subjects with ≥1 pathogen** | **263 (76.2)** | **131 (76.2)** |

In Study TOC100224, there were 65.3% of *S. aureus* isolates from subjects in the SB-275833 ointment treatment group and 63.8% from the sodium fusidate ointment treatment group (Table 15). Approximately 63% of all the isolates were MSSA in both treatment groups. Eight isolates (2.3%) in the SB-275833 ointment group and 2 (1.1%) in the sodium fusidate ointment treatment group) were methicillin-resistant. A total of 10 (2.9%) *S. aureus* isolates in the SB-275833 ointment treatment group and 9 (5.1%) in the sodium fusidate ointment treatment group were fusidic acid-resistant. Seven (2%) *S. aureus* isolates in the SB-275833 ointment treatment group and 6 (3.4%) isolates in the sodium fusidate ointment treatment group were mupirocin-resistant. It appears that pathogens were isolated with similar frequency in both treatment groups.

Table 15: Pathogens Isolated at Baseline (ITTB Population)

| Pathogens | Number (%) of Isolates[1] | |
|---|---|---|
| | 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*

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The Applicant performed MIC testing for all isolates. Table 16 summarizes the activity of SB-275833 and selected antibacterial agents against *S. aureus* isolates identified in the study. The majority of *S. aureus* isolates were susceptible to the antibacterials that were tested, and the $MIC_{90}$ values were 0.12 µg/mL for SB-27833 and sodium fusidate for *S. aureus* isolates recovered from subjects at baseline. Notable levels of resistance appear to have occurred with erythromycin and tetracycline. In general, all of the MIC values appear similar between the two treatment groups.

Table 16: Activity of Selected Antibacterial Agents against *S. aureus* at Baseline (ITTB Population)

| Test Antibacterial Treatment Group | Antibacterial Activity (µg/mL) and *S. aureus* Susceptibility (%) | | | | |
|---|---|---|---|---|---|
| | n[1] | $MIC_{50}$ | $MIC_{90}$ | MIC Range | %S/I/R/U[2,3] |
| SB-275833 | | | | | |
| SB-275833 | 228 | 0.12 | 0.12 | 0.03-0.25 | NA |
| Sodium fusidate | 113 | 0.12 | 0.12 | 0.03-0.25 | NA |
| Total | 341 | 0.12 | 0.12 | 0.03-0.25 | NA |
| Amoxicillin/clavulanic acid | | | | | |
| SB-275833 | 228 | 1 | 1 | 0.12-8 | 96.5/0/3.5/0 |
| Sodium fusidate | 113 | 1 | 1 | 0.06-16 | 98.2/0/1.8/0 |
| Total | 341 | 1 | 1 | 0.06-16 | 97.1/0/2.9/0 |
| Ceftriaxone | | | | | |
| SB-275833 | 229 | 4 | 4 | 0.50-16 | 96.5/0/3.5/0 |
| Sodium fusidate | 113 | 2 | 4 | 0.50-16 | 98.2/0/1.8/0 |
| Total | 341 | 4 | 4 | 0.50-16 | 97.1/0/2.9/0 |
| Cephalothin | | | | | |
| SB-275833 | 229 | 0.5 | 0.5 | 0.12-4 | 96.5/0/3.5/0 |
| Sodium fusidate | 113 | 0.5 | 0.5 | 0.06-4 | 98.2/0/1.8/0 |
| Total | 341 | 0.5 | 0.5 | 0.06-4 | 97.1/0/2.9/0 |
| Cloxacillin | | | | | |
| SB-275833 | 228 | 0.5 | 0.5 | 0.12-2 | NA |
| Sodium fusidate | 113 | 0.25 | 0.5 | 0.12-1 | NA |
| Total | 341 | 0.5 | 0.5 | 0.12-2 | NA |
| Erythromycin | | | | | |
| SB-275833 | 228 | 0.5 | >32 | 0.06->32 | 83.8/3.1/13.2/0 |
| Sodium fusidate | 113 | 0.5 | >32 | 0.12->32 | 80.5/2.7/16.8/0 |
| Total | 341 | 0.5 | >32 | 0.06->32 | 82.7/2.9/14.4/0 |
| Flucloxacillin | | | | | |
| SB-275833 | 228 | 0.25 | 0.5 | 0.06-1 | NA |
| Sodium fusidate | 113 | 0.25 | 0.5 | 0.12-0.5 | NA |
| Total | 341 | 0.25 | 0.5 | 0.06-1 | NA |
| Fusidic Acid[4] | | | | | |
| SB-275833 | 228 | 0.25 | 0.5 | 0.12-16 | 92.5/3.1/4.4/0 |
| Sodium fusidate | 113 | 0.25 | 0.5 | 0.12-8 | 92.0/0/8.0/0 |
| Total | 341 | 0.25 | 0.5 | 0.12-16 | 92.4/2.1/5.6/0 |
| Gentamicin | | | | | |
| SB-275833 | 228 | 0.25 | 0.5 | 0.06->64 | 94.7/1.8/3.5/0 |
| Sodium fusidate | 113 | 0.25 | 0.5 | 0.12-8 | 96.5/3.5/0/0 |
| Total | 341 | 0.25 | 0.5 | 0.06->64 | 95.3/2.3/2.3/0 |
| Mupirocin[4] | | | | | |
| SB-275833 | 228 | 0.25 | 0.25 | 0.12->256 | 96.9/0/3.1/0 |
| Sodium fusidate | 113 | 0.25 | 0.25 | 0.06->256 | 94.7/0/5.3/0 |
| Total | 341 | 0.25 | 0.25 | 0.06->256 | 96.2/0/3.8/0 |
| Tetracycline | | | | | |
| SB-275833 | 229 | 0.5 | 32 | 0.25->32 | 87.3/1.1/11.8/0 |
| Sodium fusidate | 113 | 0.5 | 1 | 0.25->32 | 92.9/1.8/5.3/0 |
| Total | 341 | 0.5 | 8 | 0.25->32 | 89.1/1.2/9.7/0 |

1. n = number of isolates of the pathogen tested against a particular antibacterial.
2. % S/I/R/U = percentage of isolates susceptible, of intermediate susceptibility, resistant or unknown (*i.e.*, not tested) to the particular antibacterial (based on breakpoints defined by CLSI, of the total number of isolates of the pathogen.
3. NA=not applicable; CLSI breakpoints are not available for this agent and organism combination.
4. Mupirocin breakpoints defined as ≤ 4 µg/mL susceptible, ≥ 8 µg/mL resistant; Fusidic acid breakpoints defined as ≤1 µg/mL susceptible, 2 µg/mL intermediate, and ≥4 µg/mL resistant.

A total of 341 *S. aureus* isolates were collected from Study TOC100224, and All *S. aureus* isolates were also tested for beta-lactamase production (Table 17). The data show that in both treatment groups, a similar proportion of *S. aureus* isolates were beta-lactamase positive (SB-275833: 93.4% [213/228]; sodium fusidate: 93.8% [106/113].

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Table 17: Beta-Lactamase Production at Baseline for *S. aureus* Isolated at Baseline

| | SB-275833 | | | Fusidic | | |
|---|---|---|---|---|---|---|
| Pathogen | Negative | Positive | Total | Negative | Positive | Total |
| *Staphylococcus aureus* | 15 (6.6%) | 213 (93.4%) | 228 | 7 (6.2%) | 106 (93.8%) | 113 |
| MRSA | 0 | 8 (100.0%) | 8 | 0 | 2 (100.0%) | 2 |
| MSSA | 15 (6.8%) | 205 (93.2%) | 220 | 7 (6.3%) | 104 (93.7%) | 111 |
| mupRSA[1] | 0 | 7 (100.0%) | 7 | 0 | 6 (100.0%) | 6 |
| mupSSA[1] | 15 (6.8%) | 206 (93.2%) | 221 | 7 (6.5%) | 100 (93.5%) | 107 |
| fusRSA[2] | 1 (10.0%) | 9 (90.0%) | 10 | 0 | 9 (100.0%) | 9 |
| fusSSA[2] | 13 (6.2%) | 198 (93.8%) | 211 | 7 (6.7%) | 97 (93.3%) | 104 |

[1]Mupirocin breakpoints defined as </=4 mcg/mL susceptible, >/=8 resistant mcg/mL
[2]Fusidic Acid breakpoints defined as </=1 mcg/mL susceptible, 2 mcg/mL intermediate, >/=4 mcg/mL resistant

In the ITT population, a small proportion of the *S. aureus* isolates recovered at baseline were mupirocin-resistant and likewise, a small number were fusidic acid-resistant (Table 17. Against mupRSA and fusRSA, the $MIC_{90}$ for SB-275833 (0.12 µg/mL) were similar to its $MIC_{90}$ for all *S. aureus* isolates that was shown above in Table 16. It is apparent for this study that the *in vitro* activity of SB-275833 was not affected by resistance to either of these agents.

The antibacterial activity of SB-275833 and selected antibacterial agents against the isolates of *S. pyogenes* is summarized in Table 18.

Table 18: Activity of Selected Antibacterial Agents against *S. pyogenes* at Baseline (ITTB Population)

| Test Antibacterial Treatment Group | Antibacterial Activity (µg/mL) and *S. pyogenes* Susceptibility (%) | | | | |
|---|---|---|---|---|---|
| | n[1] | $MIC_{50}$ | $MIC_{90}$ | MIC Range | %S/I/R/U[2,3] |
| SB-275833 | | | | | |
| SB-275833 | 96 | 0.03 | 0.06 | ≤0.002-0.06 | NA |
| Sodium fusidate | 41 | 0.03 | 0.06 | 0.004-0.06 | NA |
| Total | 137 | 0.03 | 0.06 | ≤0.002-0.06 | NA |
| Amoxicillin/clavulanic acid | | | | | |
| SB-275833 | 96 | ≤0.015 | 0.03 | ≤0.015-0.25 | NA |
| Sodium fusidate | 41 | ≤0.015 | 0.03 | ≤0.015-0.03 | NA |
| Total | 137 | ≤0.015 | 0.03 | ≤0.015-0.25 | NA |
| Ceftriaxone | | | | | |
| SB-275833 | 96 | ≤0.015 | 0.03 | ≤0.015-0.5 | 100/0/0/0 |
| Sodium fusidate | 41 | 0.03 | 0.03 | ≤0.015-0.03 | 100/0/0/0 |
| Total | 137 | ≤0.015 | 0.03 | ≤0.015-0.5 | 100/0/0/0 |
| Cephalothin | | | | | |
| SB-275833 | 96 | 0.25 | 0.25 | ≤0.03-2 | NA |
| Sodium fusidate | 41 | 0.25 | 0.25 | 0.06-0.5 | NA |
| Total | 137 | 0.25 | 0.25 | ≤0.03-2 | NA |
| Cloxacillin | | | | | |
| SB-275833 | 96 | 0.12 | 0.12 | ≤0.015-2 | NA |
| Sodium fusidate | 41 | 0.12 | 0.12 | ≤0.015-0.5 | NA |
| Total | 137 | 0.12 | 0.12 | ≤0.015-2 | NA |
| Erythromycin | | | | | |
| SB-275833 | 96 | 0.06 | 4 | 0.03->32 | 88.5/0/11.5/0 |
| Sodium fusidate | 41 | 0.06 | 0.12 | 0.03->32 | 90.2/0/9.8/0 |
| Total | 137 | 0.06 | 4 | 0.03->32 | 89.1/0/10.9/0 |
| Flucloxacillin | | | | | |
| SB-275833 | 96 | 0.06 | 0.12 | ≤0.015-2 | NA |
| Sodium fusidate | 41 | 0.06 | 0.12 | ≤0.015-0.25 | NA |
| Total | 137 | 0.06 | 0.12 | ≤0.015-2 | NA |
| Fusidic Acid | | | | | |
| SB-275833 | 96 | 8 | 16 | ≤0.015-32 | NA |
| Sodium fusidate | 41 | 8 | 8 | 0.25-16 | NA |
| Total | 137 | 8 | 8 | ≤0.015-32 | NA |
| Gentamicin | | | | | |
| SB-275833 | 96 | 2 | 8 | ≤0.03-16 | NA |
| Sodium fusidate | 41 | 4 | 8 | 0.06-8 | NA |
| Total | 137 | 4 | 8 | ≤0.03-16 | NA |
| Mupirocin | | | | | |
| SB-275833 | 96 | 0.12 | 0.12 | ≤0.03-0.25 | NA |
| Sodium fusidate | 41 | 0.12 | 0.25 | 0.06-0.25 | NA |
| Total | 137 | 0.12 | 0.12 | ≤0.03-0.25 | NA |
| Tetracycline | | | | | |
| SB-275833 | 96 | 0.25 | >32 | ≤0.06->32 | 60.4/0/39.6/0 |
| Sodium fusidate | 41 | 0.25 | >32 | ≤0.06->32 | 65.9/0/34.1/0 |
| Total | 137 | 0.25 | >32 | ≤0.06->32 | 62.0/0/38.0/0 |

1. n=number of isolates of the pathogen tested against a particular antibacterial.

2. % S/I/R/U = percentage of isolates susceptible, of intermediate susceptibility, resistant or unknown (*i.e.*, not tested) to the particular antibacterial (based on breakpoints defined by the National Committee for Clinical Laboratory Standards [NCCLS]), of the total number of isolates of the pathogen.
3. NA=not applicable; NCCLS breakpoints are not available for this agent and organism combination.

SB-275833 had an *in vitro* $MIC_{90}$ of 0.06 µg/mL against *S. pyogenes*. Fusidic acid demonstrated $MIC_{90}$s of 8-16 µg/mL against *S. pyogenes*. With the exception of erythromycin, the distribution of MIC values was similar between the two treatment groups (Table 18).

Resistance to methicillin was assessed by disk diffusion testing using oxacillin in accordance to CLSI guidelines[3]. There were 10 MRSA isolates and the MIC ranges were reported for these 10 isolates and all 10 MRSA isolates were beta-lactamase positive. In addition, the isolates were further genetically characterized to determine the presence of the *lukS* and *lukF* genes that encode for the Panton-Valentine Leukocidin (PVL) toxin. The data show that 4 (40%) were PVL-positive and 6 (60%) were PVL-negative. Of the 4 PVL-positive MRSA isolates, three were from India and one was from South Africa. Of the 6 PVL-negative MRSA isolates, three were from Costa Rica, one was from France and two were from India. SB-275833 appears to have inhibited these isolates at a concentration of $\leq 0.12$ µg/mL (Table 19).

Table 19: Frequency distribution of SB-275833 MICs (µ/mL) for MRSA (Study TOC100224)

| | Number and Cumulative % of Isolates at Each MIC | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | MIC ( µg/mL) | | | | | | | | |
| Phenotype | ≤0.015 | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | Total |
| MRSA | - | - | 4<br>40.0% | 6<br>100% | - | - | - | - | 10 |
| PVL positive | - | - | 3<br>30.0% | 1<br>100% | | - | - | - | 4 |
| PVL negative | - | - | 1<br>10.0% | 5<br>100% | - | - | - | - | 6 |

## Clinical Efficacy Results: Study TOC100224

The primary efficacy endpoint was the clinical response (clinical success or failure) to study medication at the End of Therapy for the PPC population. The data for the intent to treat clinical (ITTC), per protocol clinical (PPC), intent to treat bacteriological (ITTB) and per protocol bacteriological (PPB) are summarized in Table 20.

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Table 20: Clinical Response at End of Therapy by Analysis Population

| Analysis Population | SB-275833 | | Sodium fusidate | | Difference in Success Rates (%) |
|---|---|---|---|---|---|
| | n/N | Success Rate (%) | n/N | Success Rate (%) | |
| **PPC** | **314/317** | **99.1** | **141/150** | **94.0** | **5.1** |
| ITTC | 327/345 | 94.8 | 155/172 | 90.1 | 4.7 |
| PPB | 240/242 | 99.2 | 106/114 | 93.0 | 6.2 |
| ITTB | 250/263 | 95.1 | 116/131 | 88.5 | 6.5 |

A clinical response rate of 99.1% (314/317) was achieved for the Per Protocol Clinical (PPC) population at End of Therapy for the SB-275833 ointment group compared to 94.0% (141/150) of the PPC population for the sodium fusidate ointment group. There were 18/345 subjects in total in the SB-275833 group and 17/172 subjects in the sodium fusidate group that were considered as clinical failures. Table 21 shows the clinical success rate at follow-up (Day 14, Visit 4). In the ITTC population, 10.1% [35/345] of subjects in the SB-275833 group and 12.8% [22/172] in the sodium fusidate ointment, group was classed as clinical failures at Follow-Up.

Table 21: Clinical Response at Follow-Up (Visit 4. Day 14) by Analysis Population

| Analysis Population | SB-275833 | | Sodium fusidate | | Difference in Success Rates (%) |
|---|---|---|---|---|---|
| | n/N | Success Rate (%) | n/N | Success Rate (%) | |
| PPC | 297/308 | 96.4 | 134/143 | 93.7 | 2.7 |
| ITTC | 310/345 | 89.9 | 150/172 | 87.2 | 2.6 |
| PPB | 227/235 | 96.6 | 99/107 | 92.5 | 4.1 |
| ITTB | 237/263 | 90.1 | 111/131 | 84.7 | 5.4 |

## Clinical response by pathogen isolated at baseline

The clinical response rate by pathogens isolated at baseline is shown in Table 22. Overall, clinical success rates at End of Therapy for SB-275833 appear higher for subjects with *S. aureus* or *S. pyogenes* as their baseline pathogen. For all pathogens and resistant phenotypes (including other *Streptococcus* spp, other Gram positive pathogens and MRSA), the success rates for SB-275833 were higher than those obtained from the fusidic acid treatment group.

Table 22: Clinical Success Rate at End of Therapy by Baseline Pathogen (PPC Population)

| Baseline Pathogen | SB-275833 | | Sodium fusidate | | Difference in Success Rates (%) |
|---|---|---|---|---|---|
| | n/N[1] | Success Rate (%) | n/N | Success Rate (%) | |
| *S. aureus* (all) | 209/211 | 99.1 | 90/97 | 92.8 | 6.3 |
| MRSA[2] | 8/8 | 100.0 | 2/2 | 100.0 | 0 |
| MSSA[2] | 201/203 | 99.0 | 88/95 | 92.6 | 6.4 |
| mupRSA[3] | 6/6 | 100.0 | 2/3 | 66.7 | 33.3 |
| mupSSA[3] | 203/205 | 99.0 | 88/94 | 93.6 | 5.4 |
| fusRSA[4] | 9/9 | 100.0 | 4/7 | 57.1 | 42.9 |
| fusSSA[4] | 194/196 | 99.0 | 86/90 | 95.6 | 3.4 |
| *S. pyogenes* | 90/92 | 97.8 | 32/36 | 88.9 | 8.9 |
| Other *Streptococcus* spp. | 4/4 | 100.0 | 3/3 | 100.0 | 0 |
| Other Gram (+) pathogens | 3/3 | 100.0 | 1/1 | 100.0 | 0 |
| Gram (-) pathogens | 15/15 | 100.0 | 16/18 | 88.9 | 11.1 |
| All pathogens | 321/325 | 98.8 | 142/155 | 91.6 | 7.2 |
| No pathogens | 74/75 | 98.7 | 35/36 | 97.2 | 1.4 |

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 ≤4 µg/mL susceptible, ≥8 µg/mL resistant.
4. Fusidic acid breakpoints defined as ≤1 µg/mL susceptible, 2 µg/mL intermediate, ≥4 µg/mL resistant.

## Microbiological response at End of Therapy

Bacteriological samples were obtained for culture, and Gram stain and susceptibility testing at the baseline visit for all subjects were conducted. Samples were only collected at the End of Therapy and Follow-Up visits if the subject was a 'clinical failure' and culturable material was present. In some cases, a bacteriology sample was collected at the on-therapy visit if the subject was a 'clinical failure' at that visit. Regardless of clinical assessment, if no culturable material was present, a sample was not obtained. When no culture was taken, the microbiological outcome was then derived from the clinical outcome; (if a subject was a clinical success, the bacteriological outcome was presumed eradication; if the subject was a clinical failure or unable to determine (UTD) then the bacteriological outcome was presumed persistence). Furthermore, subjects with more than one pathogen were only considered a microbiological success if the necessary criteria were met for all pathogens. The microbiological response at End of Therapy for the per-protocol bacteriological (PPB) population is shown in Table 23.

Table 23: Per-Subject Microbiological Response at End of Therapy (PPB Population)

| SB-275833 | | Sodium fusidate | | Difference in Success Rates |
|---|---|---|---|---|
| n/N[1] | Microbiological Success Rate | n/N[1] | Microbiological Success Rate | |
| 238/242 | 98.3 | 107/114 | 93.9 | 4.5 |

At the End of therapy (in the per protocol bacteriological population), the per-subject microbiological response rate was higher in the SB-275833 group compared with the sodium fusidate group. A microbiological success rate of 98.3% and 93.6% was observed for SB-278533 and sodium fusidate, respectively. These microbiological rates appear similar to the clinical efficacy rates at End of Therapy. Similarly, an analysis of the microbiological success rate at the End of Therapy by baseline pathogen for the PPB population was conducted and summarized in Table 24.

Table 24: Microbiological Success Rate at End of Therapy by Baseline Pathogen (PPB Population)

| Pathogen | SB-275833 | | Sodium fusidate | | Difference in Success Rates (%) |
|---|---|---|---|---|---|
| | n/N[1] | Success Rate (%) | n/N[1] | Success Rate (%) | |
| *S. aureus* (all) | 207/211 | 98.1 | 91/97 | 93.8 | 4.3 |
| MRSA[2] | 8/8 | 100.0 | 2/2 | 100.0 | 0 |
| MSSA[2] | 199/203 | 98.0 | 89/95 | 93.7 | 4.3 |
| mupRSA[3] | 6/6 | 100.0 | 2/3 | 66.7 | 33.3 |
| mupSSA[3] | 201/205 | 98.0 | 89/94 | 94.7 | 3.4 |
| fusRSA[4] | 9/9 | 100.0 | 5/7 | 71.4 | 28.6 |
| fusSSA[4] | 192/196 | 98.0 | 86/90 | 95.6 | 2.4 |
| *S. pyogenes* | 90/92 | 97.8 | 32/36 | 88.9 | 8.9 |
| Other *Streptococcus* spp. | 4/4 | 100.0 | 3/3 | 100.0 | 0 |
| Other Gram (+) pathogens | 3/3 | 100.0 | 1/1 | 100.0 | 0 |
| Gram (-) pathogens | 15/15 | 100.0 | 18/18 | 100.0 | 0 |
| All pathogens | 319/325 | 98.2 | 145/155 | 93.5 | 4.6 |

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 ≤4 µg/mL susceptible, ≥8 µg/mL resistant.

4. Fusidic acid breakpoints defined as ≤1 µg/mL susceptible, 2 µg/mL intermediate, ≥4 µg/mL resistant.

The microbiological success rates at the End of Therapy by pathogen for the PPB population are similar to the clinical success rates at the End of therapy. The per-pathogen microbiological outcomes at End of Therapy for the PPB population are shown in Table 25. All MRSA and thus, *pvl* positive isolates demonstrated a 100% success rate.

Table 25: Per-Pathogen Microbiological Outcome at End of Therapy (PPB Population)

| **Microbiological Outcome** | **SB-275833** | | | **Sodium fusidate** | | |
|---|---|---|---|---|---|---|
| | **n[1]** | | **(%)[2]** | **n[1]** | | **(%)[2]** |
| ***S. aureus, n*** | | **211** | | | **97** | |
| Microbiological Success | 207 | | 98.1 | 91 | | 93.8 |
| Presumed eradication | 207 | | 98.1 | 90 | | 92.8 |
| Eradication | 0 | | 0 | 1 | | 1.0 |
| Microbiological Failure | 4 | | 1.9 | 6 | | 6.2 |
| Eradication3 | 1 | | 0.5 | 2 | | 2.1 |
| Persistent | 2 | | 1.0 | 2 | | 2.1 |
| Presumed persistent | 1 | | 0.5 | 2 | | 2.1 |
| **MRSA, n** | | **8** | | | **2** | |
| Microbiological Success | 8 | | 100.0 | 2 | | 100.0 |
| Presumed eradication | 8 | | 100.0 | 2 | | 100.0 |
| **MSSA, n** | | **203** | | | **95** | |
| Microbiological Success | 199 | | 98.0 | 89 | | 93.7 |
| Presumed eradication | 199 | | 98.0 | 88 | | 92.6 |
| Eradication | 0 | | 0 | 1 | | 1.0 |
| Microbiological Failure | 4 | | 2.0 | 6 | | 6.3 |
| Eradication | 1 | | 0.5 | 2 | | 2.1 |
| Persistent | 2 | | 1.0 | 2 | | 2.1 |
| Presumed persistent | 1 | | 0.5 | 2 | | 2.1 |
| **mupRSA, n** | | **6** | | | **3** | |
| Microbiological Success | 6 | | 100.0 | 2 | | 66.7 |
| Presumed eradication | 6 | | 100.0 | 2 | | 66.7 |
| Microbiological Failure | 0 | | 0 | 1 | | 33.3 |
| Eradication | 0 | | 0 | 1 | | 33.3 |
| Presumed persistent | 0 | | 0 | 0 | | 0 |
| **mupSSA, n** | | **205** | | | **94** | |
| Microbiological Success | 201 | | 98.0 | 89 | | 94.7 |
| Presumed eradication | 201 | | 98.0 | 88 | | 93.6 |
| Eradication | 0 | | 0 | 1 | | 1.1 |
| Microbiological Failure | 4 | | 2.0 | 5 | | 5.3 |
| Eradication | 1 | | 0.5 | 1 | | 1.1 |
| Persistent | 2 | | 1.0 | 2 | | 2.1 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Presumed persistent | 1 | | 0.5 | 2 | | 2.1 |
| **fusRSA, n** | | **9** | | | **7** | |
| Microbiological Success | 9 | | 100.0 | 5 | | 71.4 |
| Presumed eradication | 9 | | 100.0 | 4 | | 57.1 |
| Eradication | 0 | | 0 | 1 | | 14.3 |
| Microbiological Failure | 0 | | 0 | 2 | | 28.6 |
| Eradication | 0 | | 0 | 1 | | 14.3 |
| Presumed persistent | 0 | | 0 | 1 | | 14.3 |
| **fusSSA, n** | | **196** | | | **90** | |
| Microbiological Success | 192 | | 98.0 | 86 | | 95.6 |
| Presumed eradication | 192 | | 98.0 | 86 | | 95.6 |
| Eradication | 0 | | 0 | 0 | | 0 |
| Microbiological Failure | 4 | | 2.0 | 4 | | 4.4 |
| Eradication | 1 | | 0.5 | 2 | | 2.2 |
| Persistent | 2 | | 1.0 | 1 | | 1.1 |
| Presumed persistent | 1 | | 0.5 | 1 | | 1.1 |
| ***S. pyogenes*, n** | | **92** | | | **36** | |
| Microbiological Success | 90 | | 97.8 | 32 | | 88.9 |
| Presumed eradication | 90 | | 97.8 | 32 | | 88.9 |
| Microbiological Failure | 2 | | 2.0 | 4 | | 11.1 |
| Eradication | 0 | | 0 | 2 | | 5.6 |
| Persistent | 1 | | 1.0 | 1 | | 2.8 |
| Presumed persistent | 1 | | 1.0 | 1 | | 2.8 |

1. n=isolates of a specific pathogen.
2. %=number of isolates of a given pathogen with specified outcome/total number of isolates of that pathogen.
3. An eradicated pathogen occurred in subjects who were bacteriological failures due to the presence of additional pathogens that were failures.
Note: Counts within this table included pathogens isolated from the primary lesion. Percents were out of the total number of pathogens observed within subjects from the given treatment arm and analysis population.

Among the pathogens of interest, the numbers of isolates that were either persistent or presumed persistent was low in both treatment groups (Table 25). *S. aureus* was labeled as presumed eradicated in 207/211 (98.1%) of the SB-275833 cases compared with (90/97) 92.8% in the sodium fusidate treatment group. A 100% eradication rate was observed for MRSA and mupRSA isolates, respectively. A 98% and 93.7 eradiation rate was observed for MSSA in the SB-275833 and Sodium fusidate treatment group, respectively.

For *S. pyogenes*, an eradication rate of 97.8 and 88.9 % was observed for SB-275833 and sodium fusidate, respectively. Therefore, based on the data above, it appears that the majority of subjects had a bacteriological outcome of presumed eradication. It is important to note that this observation was based on clinical outcome only.

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**Microbiological response rate by visit**

Table 26 shows the microbiological response rate by visit (Days 7 and 9) and at follow-up (Day 14). At day 9, a 99.2% success rate was observed for SB-275833 compared to a 93.9 % rate for the comparator. However, at Follow-Up, the per-subject microbiological response rate had decreased to 96.6% for the SB-275833 for the treatment group; however, this rate was higher when compared with the sodium fusidate treatment group.

Table 26: Microbiological Response Rate by Visit (PPB Population)

| | SB-275833 | | Sodium fusidate | | |
|---|---|---|---|---|---|
| Study Visit | n/N | Success Rate (%) | n/N | Success Rate (%) | Difference in Success Rates (%) |
| Visit 2 (Day 7) | 238/242 | 98.3 | 112/115 | 97.4 | 1.0 |
| Visit 3 (Day 9) | 239/241 | 99.2 | 107/114 | 93.9 | 5.3 |
| Visit 4 (Day 14) | 227/235 | 96.6 | 100/107 | 93.5 | 3.1 |

Clinical success for SB-275833 and sodium fusidate analyzed by SB-275833 and fusidic acid MIC for *S. aureus* isolated at baseline is shown in Table 27.

Table 27: Clinical Successes at End of Therapy by Study Drug MIC for Subjects with *S. aureus* at Baseline (PPB Population)

| Drug | MIC (µg/mL) | Number of Clinical Successes | |
|---|---|---|---|
| | | SB-275833 n/N[1] | Sodium fusidate n/N[1] |
| SB-275833 | 0.03 | 1/1 | - |
| | 0.06 | 89/91 | - |
| | 0.12 | 114/114 | - |
| | 0.25 | 5/5 | - |
| Fusidic acid | 0.12 | - | 22/22 |
| | 0.25 | - | 41/45 |
| | 0.5 | - | 22/22 |
| | 1 | - | 1/1 |
| | 2 | - | 0 |
| | 4 | - | 4/7 |

1. n/N = number of isolates with a clinical response of success / total number of isolates at the given MIC

The results in Table 27 show that clinical success rates were 89/91 against *S. aureus* with an MIC of 0.06 µg/mL and 114/114 had an MIC of 0.12 µg/mL. Clinical success rates for sodium fusidate are also shown in Table 27. Overall, most isolates had an SB-275833 MIC of 0.06 µg/mL or 0.12 µg/mL or fusidic acid MIC of 0.25 µg/mL. The numbers were too small to draw any clinical significance from the above findings. The results in Table 28 show the clinical success rate of SB-275833 and sodium fusidate against *S. pyogenes*.

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Table 28: Clinical Successes at End of Therapy by Study Drug MIC for Subjects with *S. pyogenes* at Baseline (PPB Population)

| Drug | MIC (µg/mL) | Number of Clinical Successes | |
|---|---|---|---|
| | | SB-275833 n/N[1] | Sodium fusidate n/N[1] |
| SB-275833 | 0.002 | 1/1 | - |
| | 0.004 | 5/5 | - |
| | 0.008 | 3/3 | - |
| | 0.015 | 9/9 | - |
| | 0.03 | 49/51 | - |
| | 0.06 | 23/23 | - |
| Fusidic acid | 0.25 | - | 1/1 |
| | 4 | - | 9/11 |
| | 8 | - | 19/21 |
| | 16 | - | 3/3 |

1. n/N = number of isolates with a clinical response of success / total number of isolates at the given MIC

The clinical success rate for *S. pyogenes* was 90/92 or (97.8%) SB-275833 for isolates with an MIC of ≤ 0.06 µg/mL. Most isolates had an SB-275833 MIC of 0.03 µg/mL or a fusidic acid MIC of 8 µg/mL.

For subjects with *S. aureus* and *S. pyogenes* isolated at baseline, the clinical and microbiological success rates for SB-275833, and sodium fusidate were analyzed by the susceptibility of the organisms to other antibacterial drugs (in the PPB population at End of Therapy). There were no significant differences in the microbiological success rates of SB-285833 for subjects with isolates resistant to other antimicrobial agents. In addition, with the exception of *S. aureus* isolates resistant to fusidic acid, there was also no notable effect on the clinical and microbiological success rates for sodium fusidate for subjects with resistant isolates. For *S. pyogenes* isolated at baseline, a small number of isolates were resistant to erythromycin and tetracycline. However, the bacteriological and clinical success rates for both treatment groups were high regardless of erythromycin or tetracycline susceptibility at baseline. The findings observed here were also similar to those observed at the end of therapy.

**Clinical and Microbiological success rate (*S. aureus* and *S. pyogenes* co-infection)**

In study TOC100224 a total of 90 patients (65 in the SB-275833 treatment group and 25 in the sodium fusidate treatment group) had both *S. aureus* and *S. pyogenes* isolated at baseline. For Study TOC100224, the success rates at End of Therapy for SB-275833 ointment were 96.9% (63/65) for subjects in the PPB population with co-isolation of *S. aureus* and *S. pyogenes* as their baseline pathogens. The success rate for sodium fusidate was 88% (22/25). The clinical success rates at Follow-up in the PPB population were also similar to those observed at End of Therapy (Table 29).

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Table 29: Clinical Success Rates for Patients with both *S. aureus* and *S. pyogenes* at baseline (PPB Population)

| Endpoint/Study | SB-275833 | | Sodium Fusidate | |
|---|---|---|---|---|
| | n/N[1] | Success Rate (%) | n/N | Success Rate (%) |
| End of Therapy | | | | |
| TOC100224 | 63/65 | 96.9 | 22/25 | 88.0 |
| Follow-up | | | | |
| TOC100224 | 62/65 | 95.4 | 21/25 | 84.0 |

1. n/N = number of clinical successes/number of pathogens isolated at baseline
NA=Not applicable. Comparator not used in the study.

The microbiological success rates at End of Therapy for patients with co isolation of *S. aureus* and *S. pyogenes* at baseline were similar to the corresponding clinical success rates in the PPB population. The microbiological outcome at Follow-up for each treatment group was also similar to the outcome results at End of Therapy (Table 30).

Table 30: Microbiological Success Rates for Patients with both *S. aureus* and *S. pyogenes* at baseline (PPB Population)

| Endpoint/Study | SB-275833 | | Sodium Fusidate | |
|---|---|---|---|---|
| | n/N[1] | Success Rate (%) | n/N | Success Rate (%) |
| End of Therapy | | | | |
| TOC100224 | 63/65 | 96.9 | 22/25 | 88.0 |
| Follow-up | | | | |
| TOC100224 | 62/65 | 95.4 | 22/25 | 88.0 |

1. n/N = number of microbiological successes/number of pathogens isolated at baseline
NA=Not applicable. Comparator not used in the study.

The MIC data for patients with co-infection of *S. aureus* and *S. pyogenes* at baseline is shown in Table 31.

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Table 31: SB-275833 Clinical and Microbiology Success Rates at End of Therapy by SB-275833 MIC for Impetigo Patients with both *S. aureus* and *S. pyogenes* at Baseline (PPB Population)

| Study | Pathogen | SB-275833 MIC (µg/mL) | Clinical Efficacy | | Microbiological Efficacy | |
|---|---|---|---|---|---|---|
| | | | n/N[1] | Success Rate (%) | n/N[1] | Success Rate (%) |
| TOC100224 | *S. aureus* | 0.06 | 2/26 | 92.3 | 24/26 | 92.3 |
| | | 0.12 | 38/38 | 100.0 | 38/38 | 100.0 |
| | | 0.25 | 1/1 | 100.0 | 1/1 | 100.0 |
| | **All** | **0.06-0.25** | **63/65** | **96.9** | **63/65** | **96.9** |
| | *S. pyogenes* | 0.002 | 1/1 | 100.0 | 1/1 | 100.0 |
| | | 0.004 | 3/3 | 100.0 | 3/3 | 100.0 |
| | | 0.008 | 3/3 | 100.0 | 3/3 | 100.0 |
| | | 0.015 | 7/7 | 100.0 | 7/7 | 100.0 |
| | | 0.03 | 30/32 | 93.8 | 30/32 | 93.8 |
| | | 0.06 | 20/20 | 100.0 | 20/20 | 100.0 |
| | **All** | **0.002-0.06** | **64/66[2]** | **97.0** | **64/66[2]** | **97.0** |

1. n/N = number of successes/number of pathogens isolated at baseline
2. One patient had 2 isolates of *S. pyogenes* recovered from their baseline lesion sample

The clinical and microbiological success rate at End of Therapy and Follow-up for the sodium fusidate treatment group analyzed by fusidic acid MIC for patients with *S. aureus* and *S. pyogenes* mixed infection at baseline in TOC100224 is shown in Table 32. The results at the Follow-up visit are shown in Table 33. Against *S. aureus*, the fusidic acid MIC ranged from 0.12-4 µg/ml. Against *S. pyogenes*, the MIC ranged from 0.25-16 µg/ml; the MIC results were the same at the End of Therapy and at the Follow-up visit.

Table 32: Sodium Fusidate Clinical and Microbiology Success Rates at End of Therapy by Fusidic Acid MIC for Impetigo Patients with both *S. aureus* and *S. pyogenes* at Baseline (PPB Population)

| Study | Pathogen | Fusidic Acid MIC (mcg/mL) | Clinical Efficacy | | Microbiological Efficacy | |
|---|---|---|---|---|---|---|
| | | | n/N1 | Success Rate (%) | n/N1 | Success Rate (%) |
| TOC100224 | *S. aureus* | 0.12 | 5/5 | 100.0 | 5/5 | 100.0 |
| | | 0.25 | 12/15 | 80.0 | 12/15 | 80.0 |
| | | 0.5 | 4/4 | 100.0 | 4/4 | 100.0 |
| | | 1 | - | - | - | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | 2 | - | - | - | - |
| | | 4 | 1/1 | 100.0 | 1/1 | 100.0 |
| | All | 0.12-4 | 22/25 | 88.0 | 22/25 | 88.0 |
| | | | | | | |
| | *S. pyogenes* | 0.25 | 1/1 | 100.0 | 1/1 | 100.0 |
| | | 0.5 | - | - | - | - |
| | | 1 | - | - | - | - |
| | | 2 | - | - | - | - |
| | | 4 | 7/8 | 87.5 | 7/8 | 87.5 |
| | | 8 | 12/14 | 85.7 | 12/14 | 85.7 |
| | | 16 | 2/2 | 100.0 | 2/2 | 100.0 |
| | All | 0.25-16 | 22/25 | 88.0 | 22/25 | 88.0 |

Table 33: Sodium Fusidate Clinical and Microbiology Success Rates at Follow-up by Fusidic Acid MIC for Impetigo Patients with both *S. aureus* and *S. pyogenes* at Baseline (PPB Population)

| Study | Pathogen | Fusidic Acid MIC (mcg/mL) | Clinical Efficacy | | Microbiological Efficacy | |
|---|---|---|---|---|---|---|
| | | | n/N[1] | Success Rate (%) | n/N[1] | Success Rate (%) |
| TOC100224 | *S. aureus* | 0.12 | 5/5 | 100.0 | 5/5 | 100.0 |
| | | 0.25 | 12/15 | 80.0 | 12/15 | 80.0 |
| | | 0.5 | 3/4 | 75.0 | 4/4 | 100.0 |
| | | 1 | - | - | - | - |
| | | 2 | - | - | - | - |
| | | 4 | 1/1 | 100.0 | 1/1 | 100.0 |
| | **All** | **0.12-4** | **21/25** | **84.0** | **22/25** | **88.0** |
| | | | | | | |
| | *S. pyogenes* | 0.25 | 1/1 | 100.0 | 1/1 | 100.0 |
| | | 0.5 | - | - | - | - |
| | | 1 | - | - | - | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | 2 | - | - | - | - |
| | | 4 | 7/8 | 87.5 | 7/8 | 87.5 |
| | | 8 | 12/14 | 85.7 | 12/14 | 85.7 |
| | | 16 | 1/2 | 50.0 | 2/2 | 100.0 |
| | **All** | **0.25-16** | **21/25** | **84.0** | **22/25** | **88.0** |

1. n/N = number of successes/number of pathogens isolated at baseline

The SB-275833 MICs against *S. aureus* ranged from 0.06-0.25 μg/ml; against *S. pyogenes*, the MIC ranged from 0.002-0.06 μg/ml. Clinical and microbiological success rates for *S. aureus* and *S. pyogenes* were 96.9% and 97%, respectively. The results presented in Table 34 shows information on patients with co-isolation of *S. aureus* and *S. pyogenes* at baseline who were considered clinical or microbiological failures at End of Therapy or Follow-up for SB-275833 and sodium fusidate.

Table 34: Listing of SB-275833 MICs against *S. aureus* and *S. pyogenes* for Patients in the SB-275833 and fusidic acid treatment Arm who had both *S. aureus* and *S. pyogenes* at Baseline and who were Clinical and/or Microbiological Failures (PPB population, Study TOC100224)

| **Study** | **Subject ID** | **SB-275833 MIC (mcg/mL)** | | **End of Therapy Response** | | **Follow-up Response** | |
|---|---|---|---|---|---|---|---|
| | | *S. aureus* | *S. pyogenes* | Clinical | Microbiological | Clinical | Microbiological |
| TOC100224 | 716 | 0.06 | 0.008 | Success | Success | Failure | Failure |
| | 752 | 0.06 | 0.03 | Failure | Failure | Failure | Failure |
| | 764 | 0.06 | 0.03 | Failure | Failure | Failure | Failure |
| **Study** | **Subject ID** | **Fusidic Acid MIC (mcg/mL)** | | **End of Therapy Response** | | **Follow-up Response** | |
| | | *S. aureus* | *S. pyogenes* | Clinical | Microbiological | Clinical | Microbiological |
| TOC100224 | 661 | 0.25 | 4 | Failure | Failure | Failure | Failure |
| | 783 | 0.25 | 8 | Failure | Failure | Failure | Failure |
| | 701 | 0.25 | 8 | Failure | Failure | Failure | Failure |
| | 913 | 0.25 | 16 | Success | Success | Failure | Success |

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**Conclusion**

Although sodium fusidate is currently not an FDA approved product, the data above demonstrated that SB-275833 (applied twice daily for 5 days) is non-inferior to sodium fusidate (applied three times for 7 days), in the treatment of impetigo. This analysis was based on the clinical response at End of Therapy. In addition, the clinical success rates at End of Therapy appear higher in the SB-275833 treatment group compared to the sodium fusidate treatment group. In addition, the clinical and microbiological success rates against MRSA, mupRSA and fusRSA were 100% in the SB-275833 treatment group. In addition, a 100% clinical success rate was demonstrated against isolates carrying the *pvl* gene. However, the number of pvl positive isolate was small and the significance of this data is unknown due to the small sample size and the severity of the infections. The data appear similar to or higher than the results obtained with the comparator drug and is therefore active against pathogens thought to be associated with impetigo, including *S. aureus* or *S. pyogenes*.

**Study TOC103469 (SB-275833 vs. placebo)**

This study was a randomized, double-blind, multi-centre study to compare the efficacy and safety of topical SB-275833 Ointment, 1%, with placebo ointment in the treatment of impetigo. Subjects with up to 10 lesions were enrolled (with a maximum area of 100 $cm^2$ for either a single lesion or multiple lesions). The infected lesions had to be suitable for topical antibiotic therapy. In addition, the infections were to be those with a high likelihood of having *Staphylococcus aureus* and/or *Streptococcus pyogenes* as the causative infectious agent.

As mentioned previously, subjects enrolled in this study were randomized in a 2:1 ratio in a double-blind manner to receive either topical SB-275833 Ointment, 1%, twice daily for 5 days or topical placebo ointment, twice daily for 5 days. Subjects were enrolled into the study for up to 14 days and were required to attend the clinic for up to three visits (baseline, End of Therapy and Follow-Up), with an optional visit while on-therapy for those subjects who were not improving or who were withdrawing. In addition, subjects were contacted daily by telephone during the treatment phase of the study (Day 1 – Day 5). During these visits, clinical evaluations were performed, bacteriology samples were collected for culture, Gram stain and susceptibility testing, and blood samples were drawn for clinical laboratory (safety) evaluations and adverse events (AEs) were monitored. Pathogens isolated at baseline in this study were determined by results from a central laboratory; and all isolates were obtained by skin swab, a non-invasive procedure.

**Pathogens Isolated at Baseline: Study TOC103469**

The number of subjects who had pathogens isolated at baseline in the ITTC population is shown in Table 35. As in the TOC100224 study above, a large proportion of the subjects in this study (TOC103469) had one or more pathogens identified at baseline and of the subjects with a pathogen, most had a single pathogen isolated. Please note that subjects in the SB-275833 treatment group had two or more pathogens isolated (31/139 [22.3%]) than in the placebo group (7/71 [9.9%]).

Table 35: Number (%) of Subjects by Number of Pathogens Isolated at Baseline (ITTC Population)

| Number of Pathogens | Number (%) of Subjects | |
|---|---|---|
| | SB-275833 N=139 | Placebo N=71 |
| 0 | 25 (18.0) | 13 (18.3) |
| 1 | 83 (59.7) | 51 (71.8) |
| 2 | 29 (20.9) | 6 (8.5) |
| 3 | 2 (1.4) | 0 |
| 4 | 0 | 1 (1.4) |
| Number of subjects with ≥1 pathogen | 114 (82.0) | 58 (81.7) |

The pathogens isolated at baseline are shown in Table 36. The data shows that *S. aureus* was the most frequently isolated pathogen in the study (64.6% of isolates from subjects in the SB-275833 treatment group compared with 77.3% of isolates from the placebo group. Resistance to methicillin was assessed by disk diffusion testing using oxacillin, according to CLSI) guidelines[3] and none of the isolates in this study were determined to be MRSA. Therefore, all the isolates of *S. aureus* were methicillin-susceptible and all were susceptible to mupirocin. The data also reveal that more *S. pyogenes* were isolated in the SB-275833 treatment group (23%) compared to 12% in the placebo group. The majority of subjects with two or more pathogens had *S. aureus* and *S. pyogenes* isolated from the same baseline sample.

Table 36: Number (%) of Pathogens Isolated at Baseline (ITTB Population)

| Baseline Pathogens[1] | Number (%) of Isolates | |
|---|---|---|
| | SB-275833 | Placebo |
| All Pathogens | 147 | 66 |
| *S. aureus* | 95 (64.6) | 51 (77.3) |
| MRSA2 | 0 | 0 |
| MSSA2 | 95 (64.6) | 51 (77.3) |
| mupRSA3 | 0 | 0 |
| mupSSA3 | 95 (64.6) | 51 (77.3) |
| fusRSA4 | 10 (6.8) | 6 (9.1) |
| fusSSA4 | 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*.

As in Study TOC100224, the antibacterial activity of SB-275833 and a pre-selected set of antibacterial agents against the isolates of *S. aureus* were determined and the results are summarized in Table 37.

Table 37: Activity of some antibacterial agents against *S. aureus* at Baseline (ITTB Population)

| Antibacterial Treatment Group | Antibacterial Activity (µg/mL) and *S. aureus* Susceptibility (%) | | | | |
|---|---|---|---|---|---|
| | n[1] | $MIC_{50}$[2] | $MIC_{90}$[3] | MIC Range[4] | %S/I/R/U[5] |
| **SB-275833** | | | | | |
| SB-275833 | 95 | 0.12 | 0.12 | 0.06-0.25 | NA[6] |
| Placebo | 51 | 0.12 | 0.12 | 0.06-0.25 | NA[6] |
| Total | 146 | 0.12 | 0.12 | 0.06-0.25 | NA[6] |
| **Amoxicillin/clavulanic acid[7]** | | | | | |
| SB-275833 | 95 | 1 | 1 | 0.12-4 | 100/0/0/0 |
| Placebo | 51 | 1 | 1 | 0.25-4 | 100/0/0/0 |
| Total | 146 | 1 | 1 | 0.12-4 | 100/0/0/0 |
| **Ceftriaxone** | | | | | |
| SB-275833 | 95 | 4 | 4 | 2-8 | 100/0/0/0 |
| Placebo | 51 | 4 | 4 | 2-4 | 100/0/0/0 |
| Total | 146 | 4 | 4 | 2-8 | 100/0/0/0 |
| **Cephalothin** | | | | | |
| SB-275833 | 95 | 0.5 | 0.5 | 0.12-1 | 100/0/0/0 |
| Placebo | 51 | 0.5 | 0.5 | 0.25-2 | 100/0/0/0 |
| Total | 146 | 0.5 | 0.5 | 0.12-2 | 100/0/0/0 |
| **Cloxacillin** | | | | | |
| SB-275833 | 95 | 0.5 | 0.5 | 0.12-1 | NA[6] |
| Placebo | 51 | 0.5 | 0.5 | 0.25-0.5 | NA[6] |
| Total | 146 | 0.5 | 0.5 | 0.12-1 | NA[6] |
| **Erythromycin** | | | | | |
| SB-275833 | 95 | 0.5 | >32 | 0.25->32 | 75.8/6.3/17.9/0 |
| Placebo | 51 | 0.5 | >32 | 0.25->32 | 76.5/2.0/21.6/0 |
| Total | 146 | 0.5 | >32 | 0.25->32 | 76.0/4.8/19.2/0 |
| **Flucloxacillin** | | | | | |
| SB-275833 | 95 | 0.25 | 0.5 | 0.12-1 | NA[6] |
| Placebo | 51 | 0.25 | 0.5 | 0.12-1 | NA[6] |
| Total | 146 | 0.25 | 0.5 | 0.12-1 | NA[6] |
| **Fusidic Acid[8]** | | | | | |
| SB-275833 | 95 | 0.25 | 4 | 0.12-32 | 87.4/2.1/10.5/0 |
| Placebo | 51 | 0.25 | 4 | 0.12-8 | 86.3/2.0/11.8/0 |
| Total | 146 | 0.25 | 4 | 0.12-32 | 87.0/2.1/11.0/0 |
| **Gentamicin** | | | | | |
| SB-275833 | 95 | 0.25 | 0.5 | 0.12->64 | 95.8/1.1/3.2/0 |
| Placebo | 51 | 0.25 | 0.5 | 0.12-1 | 100/0/0/0 |
| Total | 146 | 0.25 | 0.5 | 0.12->64 | 97.3/<1/2.1/0 |
| **Mupirocin[9]** | | | | | |
| SB-275833 | 95 | 0.25 | 0.25 | 0.12-0.5 | 100/0/0/0 |
| Placebo | 51 | 0.25 | 0.25 | 0.12-0.25 | 100/0/0/0 |
| Total | 146 | 0.25 | 0.25 | 0.12-0.5 | 100/0/0/0 |
| **Tetracycline** | | | | | |
| SB-275833 | 95 | 0.5 | 1 | 0.25-32 | 98.9/0/1.1/0 |
| Placebo | 51 | 1 | 32 | 0.25->32 | 82.4/0/17.6/0 |
| Total | 146 | 0.5 | 1 | 0.25->32 | 93.2/0/6.8/0 |

1. n = number of isolates of the pathogen tested against a particular antibacterial.
2. $MIC_{50}$ = concentration of drug required to inhibit the growth of 50% of the isolates tested.
3. $MIC_{90}$ = concentration of drug required to inhibit the growth of 90% of the isolates tested.
4. MIC Range = minimum and maximum MIC in µg/mL; where minimum and maximum MICs were the same, the value is presented only once
5. % S/I/R/U = percentage of isolates susceptible, of intermediate susceptibility, resistant or unknown (i.e., not tested) to the particular antibacterial (based on breakpoints defined by CLSI, 2004), of the total number of isolates of the pathogen.
6. NA = not applicable; CLSI breakpoints are not available for this agent and organism combination
7. Amoxicillin/clavulanic acid was tested at a 2:1 ratio; MICs are expressed in terms of the amoxicillin concentration.
8. Fusidic acid breakpoints defined as susceptible ≤1µg/mL, intermediate =2mcg/mL, resistant ≥4 µg/mL
9. Mupirocin breakpoints defined as susceptible ≤4µg/mL, resistant ≥8µg/mL

Minimum inhibitory concentration testing was performed for all pathogens against other antibacterial agents. The study show that a large proportion of *S. aureus* isolates were susceptible to the antibacterials tested (based on CLSI guidelines)[4]. $MIC_{90}$ values appear relatively low for most antibacterials. However as in the TOC100224 study, increased levels of resistance occurred with erythromycin, fusidic acid and tetracycline. The $MIC_{90}$ and MIC range for SB-275833 against all *S. aureus* isolates were 0.12 and 0.06-0.25µg/mL, respectively. This information indicates that SB-275833 demonstrate activity against *S. aureus* isolates recovered from subjects at baseline. Overall, the MIC values appear to be similar between the two treatment groups. This is similar to the data observed in the TOC00224 study.

The Applicant also tested for the presence of β-lactamase production. There were no significant differences observed in the presence of β-lactamase producing isolates. In both treatment groups,

a similar proportion of *S. aureus* isolates were β-lactamase positive (SB-275833 treatment group: 94.7% [90/95]; placebo treatment group: 100% [51/51] (Table 38).

Table 38: β-Lactamase Production at Baseline for *S. aureus* Isolated at Baseline

| Pathogen | SB-27833 | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Negative | Positive | Total | Negative | Positive | Total |
| *Staphylococcus aureus* | 5 (5.3%) | 90 (94.7%) | 95 | 0 | 51 (100.0%) | 51 |
| MSSA | 5 (5.3%) | 90 (94.7%) | 95 | 0 | 51 (100.0%) | 51 |
| mupSSA[1] | 5 (5.3%) | 90 (94.7%) | 95 | 0 | 51 (100.0%) | 51 |
| fusRSA[2] | 0 | 10 (100.0%) | 10 | 0 | 6 (100.0%) | 6 |
| fusSSA[2] | 5 (6.0%) | 78 (94.0%) | 83 | 0 | 44(100.0%) | 44 |

[1]Mupirocin breakpoints defined as ≤4 µg/mL susceptible, ≥8 resistant µg/mL
[2]Fusidic Acid breakpoints defined as ≤1 µg/mL susceptible, 2 mcg/mL intermediate, ≥4 µg/mL resistant

The antibacterial activity of SB-275833 and some selected antibacterial agents against the isolates of *S. pyogenes* was also determined, and the results are shown in Table 39.

Table 39: Activity of Selected Antibacterials against *S. pyogenes* at Baseline (ITTB Population)

| Antibacterial Treatment Group | Antibacterial Activity (µg/mL) and *S. pyogenes* Susceptibility (%) n[1] | $MIC_{50}$[2] | $MIC_{90}$[3] | MIC Range[4] | %S/I/R/U[5] |
|---|---|---|---|---|---|
| **SB-275833** | | | | | |
| SB-275833 | 34 | 0.03 | 0.06 | 0.015-0.25 | NA[6] |
| Placebo | 8 | ND[8] | ND[8] | 0.03-0.06 | NA[6] |
| Total | 42 | 0.03 | 0.06 | 0.015-0.25 | NA[6] |
| **Amoxicillin/clavulanic acid[7]** | | | | | |
| SB-275833 | 34 | 0.03 | 0.03 | ≤0.015-0.5 | NA[8] |
| Placebo | 8 | ND[8] | ND[8] | ≤0.015-0.3 | NA[8] |
| Total | 42 | 0.03 | 0.03 | ≤0.015-0.5 | NA[8] |
| **Ceftriaxone** | | | | | |
| SB-275833 | 34 | 0.03 | 0.03 | ≤0.015-0.12 | 100/0/0/0 |
| Placebo | 8 | ND[8] | ND[8] | ≤0.015-0.3 | 100/0/0/0 |
| Total | 42 | 0.03 | 0.03 | ≤0.015-0.12 | 100/0/0/0 |
| **Cephalothin** | | | | | |
| SB-275833 | 34 | 0.25 | 0.25 | ≤0.03-4 | NA[6] |
| Placebo | 8 | ND[8] | ND[8] | 0.12-0.25 | NA[6] |
| Total | 42 | 0.25 | 0.25 | ≤0.03-4 | NA[6] |
| **Cloxacillin** | | | | | |
| SB-275833 | 34 | 0.12 | 0.12 | 0.03-8 | NA[6] |
| Placebo | 8 | ND[8] | ND[8] | 0.12-0.12 | NA[6] |
| Total | 42 | 0.12 | 0.12 | 0.03-8 | NA[6] |
| **Erythromycin** | | | | | |
| SB-275833 | 34 | 0.06 | >32 | 0.03->32 | 76.5/0/23.5/0 |
| Placebo | 8 | ND[8] | ND[8] | 0.06->32 | 62.5/0/37.5/0 |
| Total | 42 | 0.06 | >32 | 0.03->32 | 73.8/0/26.2/0 |
| **Flucloxacillin** | | | | | |
| SB-275833 | 34 | 0.12 | 0.12 | ≤0.015-8 | NA[6] |
| Placebo | 8 | ND[8] | ND[8] | 0.06-0.12 | NA[6] |
| Total | 42 | 0.12 | 0.12 | ≤0.015-8 | NA[6] |
| **Fusidic Acid** | | | | | |
| SB-275833 | 34 | 8 | 16 | 4->32 | NA[8] |
| Placebo | 8 | ND[8] | ND[8] | 4-8 | NA[6] |
| Total | 42 | 8 | 16 | 4->32 | NA[8] |
| **Gentamicin** | | | | | |
| SB-275833 | 34 | 4 | 8 | 0.5-8 | NA[6] |
| Placebo | 8 | ND[8] | ND[8] | 1-8 | NA[8] |
| Total | 42 | 4 | 8 | 0.5-8 | NA[6] |
| **Mupirocin** | | | | | |
| SB-275833 | 34 | 0.12 | 0.12 | 0.06-4 | NA[6] |
| Placebo | 8 | ND[8] | ND[8] | 0.06-0.12 | NA[6] |
| Total | 42 | 0.12 | 0.12 | 0.06-4 | NA[8] |
| **Tetracycline** | | | | | |
| SB-275833 | 34 | 32 | >32 | 0.12->32 | 35.3/0/64.7/0 |
| Placebo | 8 | ND[8] | ND[8] | 0.25->32 | 12.5/0/87.5/0 |
| Total | 42 | 32 | >32 | 0.12->32 | 31.0/0/69.0/0 |

1. n = number of isolates of the pathogen tested against a particular antibacterial.
2. $MIC_{50}$ = concentration of drug required to inhibit the growth of 50% of the isolates tested.
3. $MIC_{90}$ = concentration of drug required to inhibit the growth of 90% of the isolates tested.
4. MIC Range = minimum and maximum MIC in µg/mL; where minimum and maximum MICs were the same, the value is presented only once

5. % S/I/R/U = percentage of isolates susceptible, of intermediate susceptibility, resistant or unknown (i.e., not tested) to the particular antibacterial (based on breakpoints defined by the NCCLS, 2004), of the total number of isolates of the pathogen.
6. NA = not applicable; CLSI breakpoints are not available for this agent and organism combination.
7. Amoxicillin/clavulanic acid was tested at a 2:1 ratio; MICs are expressed in terms of the amoxicillin concentration.
8. ND = not done since the number of isolates was <10

The data show that 23.5% of the isolates were resistant to erythromycin in the SB-27583 treatment group, compared to 37.5% being resistant to erythromycin in the placebo group. In addition, a high percentage of isolates in both treatment groups were resistant to tetracycline (64.7% in the treatment group versus 87.5% in the placebo group). It is not known why a higher proportion of isolates were resistant to tetracycline in the placebo group. SB-275833 demonstrated *in vitro* activity against *S. pyogenes* as verified by an $MIC_{90}$ of 0.06µg/mL in the SB-275833 treatment group as well as for all *S. pyogenes* combined. These results are in line with what was observed in Study TOC00224.

**Clinical Efficacy Results: Study TOC103469**

As in Study TOC100224, the primary efficacy endpoint was clinical response (success or failure) to study medication at End of Therapy (EOT) (Day 7; Visit 2). The data for the ITTC, PPC, ITTB and PPB are summarized in Table 40.

Table 40: Clinical Response at End of Therapy by Analysis Population

| Analysis Population | SB-275833 | | Placebo | | Difference in Success Rate (%) | 95% CI[2] (%) |
|---|---|---|---|---|---|---|
| | n/N1 | Success Rate (%) | n/N1 | Success Rate (%) | | |
| ITTC | 119/139 | 85.6 | 37/71 | 52.1 | 33.5 | (20.5, 46.5) |
| PPC | 111/124 | 89.5 | 33/62 | 53.2 | 36.3 | (22.8, 49.8) |
| ITTB | 101/114 | 88.6 | 28/57 | 49.1 | 39.5 | (25.2, 53.7) |
| PPB | 96/107 | 89.7 | 26/52 | 50.0 | 39.7 | (25.0, 54.5) |

1. n/N = number of successes/number of subjects that qualified for the respective analysis population in the respective treatment.
2. Confidence intervals were not adjusted for multiplicity.

There was an 85.6 (119/139) success in the ITTC population at the End of Therapy for SB-27583 compared with 52.1% (37/71) in the placebo treatment group. In the PPC population, there was an 89.5% (111/124) success rate in the SB-275833 treatment group compared with a 53.2% (33/62) in the placebo group.

At follow-up (Visit 3, Day 14), the clinical response success rates for the SB-275833 were 75.5% (105/139) and 82.4% (98/119) for the ITTC and the PPC population respectively. Clinical response rates for the placebo group were 39.4 (27/71) and 43.1 (25/58) for ITTC and PPC, respectively (Table 41).

Table 41: Clinical Response at Follow-Up (Visit 3, Day 14) by Analysis Population

| Analysis Population | SB-275833 | | Placebo | | Difference in Success Rate (%) | 95% CI[2] (%) |
|---|---|---|---|---|---|---|
| | n/N1 | Success Rate (%) | n/N1 | Success Rate (%) | | |
| ITTC | 105/139 | 75.5 | 28/71 | 39.4 | 36.1 | (22.7, 49.5) |
| PPC | 98/119 | 82.4 | 25/58 | 43.1 | 39.2 | (24.8, 53.7) |
| ITTB | 91/114 | 79.8 | 19/57 | 33.3 | 46.5 | (32.2, 60.8) |
| PPC | 86/102 | 84.3 | 18/48 | 37.5 | 46.8 | (31.4, 62.2) |

1. n/N = number of successes/number of subjects that qualified for the respective analysis population in the respective treatment.
2. Confidence intervals were not adjusted for multiplicity.

## Assessment of Lesion Area at End of Therapy

A summary of the total lesion area by analysis population and the mean percentage change in total lesion area by visit and analysis population is shown in Table 42. Total lesion area is the sum of the lesion areas for each lesion.

Table 42: Summary of Total Lesion Area by Analysis Population

| Analysis Population | Treatment | N | Planned Relative Time | n | Mean | SD | Median | Min | Max |
|---|---|---|---|---|---|---|---|---|---|
| Intent to Treat Clinical | SB 275833 | 139 | Visit 1 | 139 | 4.51 | 10.004 | 1.50 | 0.07 | 94.50 |
| | | 139 | Visit 2 | 126 | 0.73 | 2.432 | 0.00 | 0.00 | 17.55 |
| | | 139 | Visit 3 | 116 | 0.90 | 4.400 | 0.00 | 0.00 | 30.00 |
| | | 139 | EOT | 134 | 0.86 | 2.520 | 0.00 | 0.00 | 17.55 |
| | Placebo | 71 | Visit 1 | 71 | 3.73 | 6.423 | 1.70 | 0.04 | 42.04 |
| | | 71 | Visit 2 | 56 | 2.13 | 4.500 | 0.20 | 0.00 | 21.25 |
| | | 71 | Visit 3 | 37 | 0.31 | 1.724 | 0.00 | 0.00 | 10.50 |
| | | 71 | EOT | 68 | 5.05 | 13.854 | 0.50 | 0.00 | 101.50 |
| Per Protocol Clinical | SB 275833 | 126 | Visit 1 | 126 | 4.67 | 10.414 | 1.50 | 0.07 | 94.50 |
| | | 124 | Visit 2 | 116 | 0.72 | 2.479 | 0.00 | 0.00 | 17.55 |
| | | 119 | Visit 3 | 103 | 1.01 | 4.660 | 0.00 | 0.00 | 30.00 |
| | | 124 | EOT | 120 | 0.86 | 2.609 | 0.00 | 0.00 | 17.55 |
| | Placebo | 63 | Visit 1 | 63 | 3.95 | 6.759 | 1.50 | 0.06 | 42.04 |
| | | 62 | Visit 2 | 50 | 2.28 | 4.729 | 0.20 | 0.00 | 21.25 |
| | | 58 | Visit 3 | 30 | 0.38 | 1.913 | 0.00 | 0.00 | 10.50 |
| | | 62 | EOT | 61 | 5.52 | 14.562 | 0.40 | 0.00 | 101.50 |
| Intent to Treat Bact. | SB 275833 | 114 | Visit 1 | 114 | 4.36 | 10.391 | 1.50 | 0.07 | 94.50 |
| | | 114 | Visit 2 | 104 | 0.57 | 1.975 | 0.00 | 0.00 | 15.00 |
| | | 114 | Visit 3 | 97 | 0.07 | 0.294 | 0.00 | 0.00 | 2.00 |
| | | 114 | EOT | 110 | 0.74 | 2.168 | 0.00 | 0.00 | 15.00 |
| | Placebo | 57 | Visit 1 | 57 | 4.22 | 7.024 | 1.80 | 0.05 | 42.04 |
| | | 57 | Visit 2 | 44 | 2.39 | 4.831 | 0.30 | 0.00 | 21.25 |
| | | 57 | Visit 3 | 26 | 0.44 | 2.054 | 0.00 | 0.00 | 10.50 |
| | Placebo | 57 | EOT | 55 | 5.96 | 15.232 | 0.50 | 0.00 | 101.50 |

Table 42: Summary of Total Lesion Area by Analysis Population Continued

| Analysis Population | Treatment | N | Planned Relative Time | n | Mean | SD | Median | Min | Max |
|---|---|---|---|---|---|---|---|---|---|
| Per Protocol Bact. | SB 275833 | 108 | Visit 1 | 108 | 4.36 | 10.594 | 1.50 | 0.07 | 94.50 |
| | | 107 | Visit 2 | 99 | 0.54 | 1.946 | 0.00 | 0.00 | 15.00 |
| | | 102 | Visit 3 | 89 | 0.07 | 0.306 | 0.00 | 0.00 | 2.00 |
| | | 107 | EOT | 103 | 0.71 | 2.171 | 0.00 | 0.00 | 15.00 |
| | Placebo | 53 | Visit 1 | 53 | 4.43 | 7.237 | 1.80 | 0.06 | 42.04 |
| | | 52 | Visit 2 | 41 | 2.50 | 4.984 | 0.30 | 0.00 | 21.25 |
| | | 48 | Visit 3 | 23 | 0.50 | 2.183 | 0.00 | 0.00 | 10.50 |
| | | 52 | EOT | 52 | 6.25 | 15.620 | 0.50 | 0.00 | 101.50 |

At the end of therapy, a decrease in the overall lesion area was observed in both treatment arms. However, a larger decrease in the overall lesion area was observed in the SB-275833 treatment arm compared to the placebo control.

**Clinical Response by Pathogen Isolated at Baseline**

The overall clinical response rate (by pathogen) at the End of Therapy for ITT population is shown in Table 43. Clinical success rates at the End of Therapy for SB-275833 were 88.4% for individuals with *S. aureus* infection and 52.9% for individuals in the placebo control group. A similar success rate, of 88.2% was observed for those subjects with *S. pyogenes* as baseline pathogens in the SB-275833 treatment group, and 37.5% for the placebo control group. In addition a clinical success rate of 64.3% was observed in the SB-275833 for individuals who had Gram negative pathogens at baseline compared with 28.6% in the placebo group.

Table 43: Clinical response by pathogen isolated at baseline (ITT Population).

| Baseline Pathogen1 | SB-275833 | | Placebo | | Difference in Success Rates (%) |
|---|---|---|---|---|---|
| | n/N[1] | Success Rate (%) | n/N[1] | Success Rate (%) | |
| *S. aureus (all)* | 84/95 | 88.4 | 27/51 | 52.9 | 35.5 |
| MRSA2 | 0 | 0 | 0 | 0 | 0 |
| MSSA2 | 84/95 | 88.4 | 27/51 | 52.9 | 35.5 |
| mupRSA3 | 0 | 0 | 0 | 0 | 0 |
| mupSSA3 | 84/95 | 88.4 | 27/51 | 52.9 | 35.5 |
| fusRSA4 | 9/10 | 90.0 | 2/6 | 33.3 | 56.7 |
| fusSSA4 | 74/83 | 89.2 | 24/44 | 54.5 | 34.6 |
| *S. pyogenes* | 30/34 | 88.2 | 3/8 | 37.5 | 50.7 |
| Other Streptococcus spp. | 2/2 | 100.0 | 0 | 0 | NA |
| Other Gram (+) pathogens | 2/2 | 100.0 | 0 | 0 | NA |
| Gram (-) pathogens | 9/14 | 64.3 | 2/7 | 28.6 | 35.7 |

| | | | | | |
|---|---|---|---|---|---|
| All Pathogens No Pathogens | 127/147 18/25 | 86.4 72.0 | 32/66 9/14 | 48.5 64.3 | 37.9 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. Total fusRSA and fusSSA n value is 93 for SB-275833 and 50 for placebo since fusISA is not included in this table.
NA = not applicable

Clinical results rates by pathogen at Follow-up are shown in Table 44. The results were similar to those obtained at the End of Therapy.

Table 44: Clinical response at End of Therapy by pathogen isolated at baseline (PPC Population)

| Baseline Pathogens[1] | **SB-275833** | | **Placebo** | | Differences in Success Rates |
|---|---|---|---|---|---|
| | Success/N | Success Rate | Success/N | Success Rate | |
| *Staphylococcus aureus (all)* | 70/84 | 83.3% | 17/44 | 38.6% | 44.7% |
| MRSA[1] | 0/0 | | 0/0 | | |
| MSSA[1] | 70/84 | 83.3% | 17/44 | 38.6% | 44.7% |
| mupRSA[2] | 0/0 | | 0/0 | | |
| mupSSA[2] | 70/84 | 83.3% | 17/44 | 38.6% | 44.7% |
| fusRSA[3] | 7/10 | 70.0% | 2/5 | 40.0% | 30.0% |
| fusSSA[3] | 62/72 | 86.1% | 15/39 | 38.5% | 47.6% |
| Streptococcus pyogenes | 28/32 | 87.5% | 1/6 | 16.7% | 70.8% |
| Other Streptococcus spp. | 2/2 | 100.0% | 0/0 | | |
| Other Gram (+) Pathogens | 1/1 | 100.0% | 0/0 | | |
| Other Gram (-)pathogens | 8 /11 | 72.7% | 1/5 | 20.0% | 52.7% |
| All Pathogens | 109/130 | 83.8% | 19/55 | 34.5% | 49.3% |
| No Pathogens | 12 /17 | 70.6% | 7/10 | 70.0% | 0.6% |

1. MRSA/MSSA are methicillin resistant/susceptible as defined by susceptibility to oxacillin.
2. Mupirocin breakpoints defined as susceptible ≤4µg/mL, resistant ≥8µg/mL.
3. 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.
NA = not applicable

## Microbiology Response at End of Therapy

As in Study TOC100224, bacteriological samples were obtained for culture, and Gram stain and susceptibility testing at baseline visits for all subjects were conducted. Samples were collected at the End of Therapy and Follow-Up visits if the subject was a 'clinical failure' and culturable material was present. Similarly, a bacteriology sample was collected at the on-therapy visit if the

subject was a 'clinical failure' at that visit. To reiterate, when no culture was taken, the microbiological outcome was then derived from the clinical outcome (if a subject was a clinical success, the bacteriological outcome was presumed eradication; if the subject was a clinical failure or UTD then the bacteriological outcome was presumed persistence). Microbiological success rates at End of Therapy by baseline pathogens for ITTB population are shown in Table 45.

Table 45: Per-Subject Microbiological Response at End of Therapy

| Analysis Population | SB-275833 | | Placebo | | Difference in Success Rates (%) |
|---|---|---|---|---|---|
| | n/N1 | Success Rate (%) | n/N1 | Success Rate (%) | |
| ITTB | 104/114 | 91.2 | 29/57 | 50.9 | 40.4 |
| PPB | 99/107 | 92.5 | 27/52 | 51.9 | 40.6 |

Overall, a response rate for SB-275833 of 92.5% was observed in the PPB population compared with 51.9% in the placebo group. The microbiology success similar to those obtained in the clinical success rates at the End of Therapy. Table 46 depicts the microbiology success rate at end of therapy by baseline pathogens in the ITTB population. That data show that similar microbiology success rates at End of Therapy were also observed.

Table 46: Microbiological Success Rate at End of Therapy by Baseline Pathogen (ITTB Population)

| Baseline Pathogen1 | SB-275833 | | Placebo | | Difference in Success Rates (%) |
|---|---|---|---|---|---|
| | n/N[1] | Success Rate (%) | n/N[1] | Success Rate (%) | |
| *S. aureus (all)* | 87/95 | 91.6 | 28/51 | 54.9 | 36.7 |
| MRSA2 | 0 | 0 | 0 | 0 | 0 |
| MSSA2 | 87/95 | 91.6 | 28/51 | 54.9 | 36.7 |
| mupRSA3 | 0 | 0 | 0 | 0 | 0 |
| mupSSA3 | 87/95 | 91.6 | 28/51 | 54.9 | 36.7 |
| fusRSA4 | 10/10 | 100.0 | 2/6 | 33.3 | 66.7 |
| fusSSA4 | 76/83 | 91.6 | 25/44 | 56.8 | 34.7 |
| *S. pyogenes* | 31/34 | 91.2 | 3/8 | 37.5 | 53.7 |
| Other Streptococcus spp. | 2/2 | 100.0 | 0 | 0 | NA |
| Other Gram (+) pathogens | 2/2 | 100.0 | 0 | 0 | NA |
| Gram (-) pathogens | 9/14 | 64.3 | 2/7 | 28.6 | 35.7 |
| All Pathogens | 131/147 | 89.1 | 33/66 | 50.0 | 39.1 |

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. Total fusRSA and fusSSA n value is 93 for SB-275833 and 50 for placebo since fuslSA is not included in this table.

NA = not applicable

Table 47 shows the microbiological outcome per pathogen at End of Therapy for the PPB population. As previously mentioned, microbiological outcome is based in the clinical success of the test agents. Among the pathogens of interest, the numbers of isolates that were either persistent or presumed persistent in the SB-275833 Ointment, 1%, group was low. The majority of subjects in the SB-275833 treatment group had a bacteriological outcome of presumed eradication. In the placebo group, the number of isolates that were persistent was higher.

Table 47: Per-Pathogen Microbiological Outcome at End of Therapy (ITTB Population)

| Microbiological Outcome | SB-275833 | | | Placebo | | |
|---|---|---|---|---|---|---|
| | n[1] | | %[2] | $n_1$ | | %[2] |
| ***S. aureus,*[3] *n*** | | **96** | | | **55** | |
| Microbiological Success | 87 | | 90.6 | 28 | | 50.9 |
| Presumed Eradication | 83 | | 86.5 | 27 | | 49.1 |
| Eradication | 4 | | 4.2 | 1 | | 1.8 |
| Microbiological Failure | 9 | | 9.4 | 27 | | 49.1 |
| Eradication | 0 | | 0 | 4 | | 7.3 |
| Persistent | 3 | | 3.1 | 17 | | 30.9 |
| Presumed Persistent | 3 | | 3.1 | 2 | | 3.6 |
| New Infection | 1 | | 1.0 | 4 | | 7.3 |
| Unable to Determine | 2 | | 2.1 | 0 | | 0 |
| **fusRSA, n** | | **11** | | | **8** | |
| Microbiological Success | 10 | | 90.9 | 2 | | 25.0 |
| Presumed Eradication | 9 | | 81.8 | 2 | | 25.0 |
| Eradication | 1 | | 9.1 | 0 | | 0 |
| Microbiological Failure | 1 | | 9.1 | 6 | | 75.0 |
| Eradication | 0 | | 0 | 2 | | 25.0 |
| Persistent | 0 | | 0 | 1 | | 12.5 |
| Presumed Persistent | 0 | | 0 | 1 | | 12.5 |
| New Infection | 1 | | 9.1 | 2 | | 25.0 |
| **fusSSA, n** | | **83** | | | **46** | |
| Microbiological Success | 76 | | 91.6 | 25 | | 54.4 |
| Presumed Eradication | 73 | | 88.0 | 24 | | 52.2 |
| Eradication | 3 | | 3.6 | 1 | | 2.2 |
| Microbiological Failure | 7 | | 8.4 | 21 | | 45.7 |
| Eradication | 0 | | 0 | 2 | | 4.4 |
| Persistent | 3 | | 3.6 | 16 | | 34.8 |
| Presumed Persistent | 2 | | 2.4 | 1 | | 2.2 |
| New Infection | 0 | | 0 | 2 | | 4.4 |
| Unable to Determine | 2 | | 2.4 | 0 | | 0 |
| ***S. pyogenes, n*** | | **34** | | | **10** | |
| Microbiological Success | 31 | | 91.2 | 3 | | 30.0 |
| Presumed Eradication | 30 | | 88.2 | 3 | | 30.0 |
| Eradication | 1 | | 2.9 | 0 | | 0 |
| Microbiological Failure | 3 | | 8.8 | 7 | | 70.0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Eradication | 1 | | 2.9 | 1 | | 10.0 |
| Persistent | 1 | | 2.9 | 4 | | 40.0 |
| New Infection | 0 | | 0 | 2 | | 20.0 |
| Unable to Determine | 1 | | 2.9 | 0 | | 0 |

1. n=isolates of a specific pathogen.
2. %=number of isolates of a given pathogen with specified outcome/total number of isolates of that pathogen.
3. An eradicated pathogen occurred in subjects who were bacteriological failures due to the presence of additional pathogens that were failures.
Note: Counts within this table included pathogens isolated from the primary lesion. Percents were out of the total number of pathogens observed within subjects from the given treatment arm and analysis population.

## Microbiological and Clinical Response at Follow-Up

Table 48 shows the result of the microbiology response rate by pathogen. Success rates (at Follow-up) of 80.7% and 85.3% were observed in the SB-285833 treatment group for the ITTB and PPB population respectively. This compares with a response rate of 36.8% and 41.7% in the placebo control group for the ITTB and PPB, respectively. These findings appear similar to those observed at the end of therapy.

Table 48: Per-Subject Microbiological Response at Follow-Up (Visit 3; Day 14)

| Analysis Population | SB-275833 | | Placebo | | Difference in Success Rates (%) |
|---|---|---|---|---|---|
| | n/N1 | Success Rate (%) | n/N1 | Success Rate (%) | |
| ITTB | 92/114 | 80.7 | 21/57 | 36.8 | 43.9 |
| PPB | 87/102 | 85.3 | 20/48 | 41.7 | 43.6 |

An analysis of clinical success versus failure by SB-275833 MICs for pathogens isolated at baseline show that clinical success rates were 74.3 % for *S. aureus* isolates with an MIC of 0.06 µg/mL and 91.5% for *S. aureus* isolates with an MIC of 0.12 µg/mL. Only one isolate had an MIC that was 0.25 µg/mL and this isolate was eradicated. Against fusRSA, too few isolates were obtained to draw any definitive conclusions, but from the limited data, clinical success rates were similar and all isolates had low MICs. The clinical implication of this observation is not known. Please note that there were no mupirocin resistant *S. aureus* isolates found in the SB-275833 vs. placebo study. The result of the clinical study is shown in Table 49 and the microbiology success is shown in Table 50.

Table 49: Clinical Successes at End of Therapy by SB-275833 MIC for Subjects in the SB-275833 Treatment Arm with *S. aureus* Isolated at Baseline (ITTB Population)

| Drug | MIC (µg/mL) | Clinical Success Rate | |
|---|---|---|---|
| | | n/N[1] | % |
| SB-275833 | 0.06 | 26/35 | 74.3 |
| | 0.12 | 54/5 | 91.5 |
| | 0.25 | 1/1 | 100.0 |

Table 50: Microbiological Successes at End of Therapy by Study Drug MIC for Subjects in the SB-275833 Treatment Arm with *S. aureus* at Baseline (ITTB Population)

| Drug | MIC (µg/mL) | Microbiological success Rate | |
|---|---|---|---|
| | | n/N[1] | % |
| SB-275833 | 0.06 | 32/35 | 91.4 |
| | 0.12 | 54/59 | 91.5 |
| | 0.25 | 1/1 | 100.0 |

Similarly, the clinical success rates for SB-275833 analyzed by SB-275833 MIC for *S. pyogenes* isolated at baseline is shown in Table 51 and the Microbiological success rate at the end of therapy by study drug is shown in Table 52.

Table 51: Clinical Successes at End of Therapy by SB-275833 MICs for Subjects in the SB-275833 Treatment Arm with *S. pyogenes* Isolated at Baseline (ITTB Population)

| Drug | MIC (µg/mL) | Clinical Success Rate | |
|---|---|---|---|
| | | n/N[1] | % |
| SB-275833 | 0.015 | 0/1 | 0.0 |
| | 0.03 | 23/25 | 92.0 |
| | 0.06 | 5/5 | 100.0 |
| | 0.12 | 1/2 | 50.0 |
| | 0.25 | 1/1 | 100.0 |

For *S. pyogenes*, clinical success rate of 92% was observed for isolates with an MIC of 0.03 µg/mL. Five isolates had an MIC of 0.06 µg/mL and this corresponds to a 100% success rate. There were two isolates with an MIC of 0.12 µg/mL; and a clinical success rate of 50% was observed. The one isolate with a reported MIC of 0.25 µg/mL was eradicated (Table 52).

Table 52: Microbiological Successes at End of Therapy by Study Drug MIC for Subjects in the SB-275833 Treatment Arm with *S. pyogenes* at Baseline (ITTB Population)

| Drug | MIC (µg/mL) | Microbiological success Rate | |
|---|---|---|---|
| | | n/N[1] | % |
| SB-275833 | 0.15 | 0/1 | 0.0 |
| | 0.03 | 24/25 | 96.0 |
| | 0.06 | 5/5 | 100.0 |
| | 0.12 | 1/2 | 50.0 |
| | 0.25 | 1/1 | 100.0 |

**Clinical and Microbiological success rate (*S. aureus* and *S. pyogenes* co-infection)**

In study TOC103469 a total of 24 patients (20 in the SB-275833 ointment treatment group and 4 in the placebo treatment group) had both *S. aureus* and *S. pyogenes* isolated from their baseline lesion sample. For Study TOC103469, clinical success rates at End of Therapy for SB-275833 ointment were 90% for subjects in the PPB population with co-isolation of *S. aureus* and *S. pyogenes* as their Baseline pathogens (Table 53). The clinical success rate at Follow-up was 85% in study TOC103469 for individuals who were co-infected with *S. aureus* and *S. pyogenes*. Please note that the small number of patients in the placebo group is insufficient to allow for any for any clinical significance.

Table 53: Clinical Success Rates for Patients with both *S. aureus* and *S. pyogenes* at baseline (PPB Population)

| Endpoint/Study | SB-275833 | | Placebo | |
|---|---|---|---|---|
| | n/N[1] | Success Rate (%) | n/N | Success Rate (%) |
| End of Therapy | | | | |
| TOC103469 | 18/20 | 90.0 | 3/4 | 75.0 |
| Follow-up | | | | |
| TOC103469 | 17/20 | 85.0 | 1/3 | 33.3 |

The microbiological success rate at End of Therapy for patients with co-isolation of *S. aureus* and *S. pyogenes* at baseline were similar to the data obtained for the clinical success rates. No significant difference was observed; the microbiology success rate from the PPB population is shown in Table 54.

Table 54: Microbiological Success Rates for Patients with both *S. aureus* and *S. pyogenes* at baseline (PPB Population)

| Endpoint/Study | SB-275833 | | Placebo | |
|---|---|---|---|---|
| | n/N[1] | Success Rate (%) | n/N | Success Rate (%) |
| End of Therapy | | | | |
| TOC103469 | 19/20 | 95.0 | 3/4 | 75.0 |
| Follow-up | | | | |
| TOC103469 | 18/20 | 90.0 | 2/3 | 66.7 |

Table 55 and 56 shows the clinical and microbiological success rates at End of Therapy and at Follow-up analyzed by SB-275833 MIC for patients with co-isolation of *S. aureus* and *S. pyogenes* at baseline. An MIC range of 0.06-0.25 µg/ml was reported for *S. aureus* at End of Therapy and at Follow-up. For *S. pyogenes*, the MIC ranged from 0.03-0.12 µg/ml at End of Therapy and at Follow-up.

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Table 55: SB-275833 Clinical and Microbiology Success Rates at End of Therapy by SB-275833 MIC for Impetigo Patients with both *S. aureus* and *S. pyogenes* at Baseline (PPB Population)

| Study | Pathogen | SB-275833 MIC (µg/mL) | Clinical Efficacy | | Microbiological Efficacy | |
|---|---|---|---|---|---|---|
| | | | n/N[1] | Success Rate (%) | n/N[1] | Success Rate (%) |
| TOC103469 | *S. aureus* | 0.06 | 5/6 | 83.3 | 6/6 | 100.0 |
| | | 0.12 | 12/13 | 92.3 | 12/13 | 92.3 |
| | | 0.25 | 1/1 | 100.0 | 1/1 | 100.0 |
| | All | 0.06-0.25 | 18/20 | 90.0 | 19/20 | 95.0 |
| | *S. pyogenes* | 0.03 | 15/16 | 93.8 | 16/16 | 100.0 |
| | | 0.06 | 3/3 | 100.0 | 3/3 | 100.0 |
| | | 0.12 | 0/1 | 0.0 | 0/1 | 0.0 |
| | All | 0.03-0.12 | 18/20 | 90.0 | 19/20 | 95.0 |

Table 56: SB-275833 Clinical and Microbiology Success Rates at Follow-up by SB-275833 MIC for Impetigo Patients with both *S. aureus* and *S. pyogenes* at Baseline (PPB Population)

| Study | Pathogen | SB-275833 MIC (µg/mL) | Clinical Efficacy | | Microbiological Efficacy | |
|---|---|---|---|---|---|---|
| | | | n/N[1] | Success Rate (%) | n/N[1] | Success Rate (%) |
| TOC103469 | *S. aureus* | 0.06 | 4/6 | 66.7 | 5/6 | 83.3 |
| | | 0.12 | 12/13 | 92.3 | 12/13 | 92.3 |
| | | 0.25 | 1/1 | 100.0 | 1/1 | 100.0 |
| | **All** | **0.06-0.25** | **17/20** | **85.0** | **18/20** | **90.0** |
| | *S. pyogenes* | 0.03 | 14/16 | 87.5 | 15/16 | 93.8 |
| | | 0.06 | 3/3 | 100.0 | 3/3 | 100.0 |
| | | 0.12 | 0/1 | 0.0 | 0/1 | 0.0 |
| | **All** | **0.03-0.12** | **17/20** | **85.0** | **18/20** | **90.0** |

NDA: 22-055 DATE REVIEW COMPLETED: November 1, 2006

**Conclusion**

Based on the data above, SB-275833 (applied twice daily for 5 days), has demonstrated to be superior to placebo (applied three times for 5 days), in the treatment of impetigo caused by MSSA and *S. pyogenes*. This analysis was based on the clinical response at End of Therapy. In addition, the clinical and microbiological success rates at End of Therapy are higher in the SB-275833 treatment group compared to the placebo treatment group. SB-275883 demonstrated activity against MSSA and *S. pyogenes* in individuals who were suffering from impetigo. For individuals with *S. aureus* and *S. pyogenes* co-infection, the clinical success rates at End of Therapy for SB-275833 ointment were 90% for subjects in the PPB population and 85% at Follow-up.

Published studies show that the therapeutic outcome of infections associated with MRSA is usually worse than the outcome of those that can result from MSSA isolates[5]. In addition, infections may be exacerbated by the presence of virulence genes such as enterotoxins or the Panton-Valentine leukocidin. Therefore, it is unknown if SB-275883 would have a beneficial effect against isolates expressing the *pvl* gene in the treatment of primary impetigo.

**SUMMARY AND RECOMMENDATIONS**

SB-275833 (applied twice daily for 5 days) is non-inferior to sodium fusidate (applied three times for 7 days), in the treatment of primary impetigo due to *S. aureus* or *S. pyogenes*. This analysis was based on the clinical response at End of Therapy. In addition, the clinical success rates at End of Therapy appear higher in the SB-275833 treatment group compared to the sodium fusidate treatment group. The clinical and microbiological success rates against MRSA, mupRSA and fusRSA were 100% in the SB-275833 treatment group. Moreover, a 100% clinical success rate was demonstrated against 4 isolates carrying the *pvl* gene. However, the number of pvl positive isolate was small and the significance of this data is unknown due to the small sample size.

SB-275833 (applied twice daily for 5 days), has also demonstrated to be superior to placebo (applied three times for 5 days), in the treatment of primary impetigo caused by MSSA and *S. pyogenes*. This analysis was based on the clinical response at End of Therapy. In addition, the clinical and microbiological success rates at End of Therapy appear higher in the SB-275833 treatment group compared to the placebo treatment group. SB-275883 demonstrated activity against MSSA and *S. pyogenes* in individuals who were suffering from impetigo. Therefore, from an overall microbiology perspective the data show that SB-275883 is effective against *S. aureus* or *S. pyogenes* in the treatment of bullous and non-bullous impetigo.

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# CLINICAL Microbiology: 45-Day Meeting Checklist
# July 24, 2006
# NDA 22-055 (ALTABAX)

**Sponsor: GlaxoSmithKline**
**Date Sumitted: June 12, 2006**

On **initial** overview of the NDA application for RTF:

| No. | Item | Yes | No | Comments |
|---|---|---|---|---|
| 1 | Is the clinical microbiology information (preclinical/nonclinical and clinical) described in different sections of the NDA organized in a manner to allow substantive review to begin? | X | | |
| 2 | Is the clinical microbiology information (preclinical/nonclinical and clinical) described in different sections of the NDA indexed, paginated, and/or linked in a manner to allow substantive review to begin? | X | | |
| 3 | Is the clinical microbiology information (preclinical/nonclinical and clinical) in different sections of the NDA legible so that substantive review can begin? | X | | |
| 4 | On its face, has the applicant submitted *in vitro* data in necessary quantity, using necessary clinical and non-clinical strains/ isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling? | X | | |
| 5 | Has the applicant submitted draft provisional breakpoint and interpretive criteria, along with quality control (QC) parameters, if applicable, in a manner consistent with contemporary standards, which attempt to correlate criteria with clinical results of NDA studies, and in a manner to allow substantive review to begin? | X | | |
| 6 | Has the applicant submitted any required animal model studies necessary for approvability of the product based on the submitted draft labeling? | X | | |
| 7 | Has the applicant submitted all special/critical studies/data requested by the Division during pre-submission discussions? | X | | |
| 8 | Has the applicant submitted the clinical microbiology datasets in a format which intents to correlate baseline pathogen with clinical and microbiologic outcomes exhibited by relevant pathogens isolated from test of cure or end of treatment? | X | | |
| 9 | Has the applicant submitted a clinical microbiology dataset in a format which intents to determine resistance development by correlating changes in the phenotype (such as *in vitro* susceptibility) and/or | X | | |

## CLINICAL Microbiology: 45-Day Meeting Checklist
## July 24, 2006
## NDA 22-055 (ALTABAX)

**Sponsor: GlaxoSmithKline**
**Date Sumitted: June 12, 2006**

| | | | | |
|---|---|---|---|---|
| | genotype (such as mutations) of the baseline relevant pathogen with clinical and microbiologic outcome as exhibited by relevant pathogens isolated from test of cure or end of treatment? | | | |
| 10 | Has the applicant used standardized or nonstandardized methods for measuring microbiologic outcome? If nonstandardized methods were used has the applicant included full details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done? | X | | |
| 11 | Is the clinical microbiology draft labeling consistent with 201.56 and 201.57 of the CFR, current Divisional policy. | X | | |
| 12 | FROM A CLINICAL MICROBIOLOGY PERSPECTIVE, IS THIS NDA FILEABLE? **IF NO, GIVE REASONS BELOW.** | X | | |

**Any Additional Clinical Microbiology Comments:**

**Avery Goodwin, Ph.D.**
**Name**
**Reviewing Clinical Microbiologist**

**Fred Marsik, Ph.D. 24 Jul 06**
**Name**
**Team Leader Clinical Microbiology**
HFD-520

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