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Title:

Protocol SB-275833/030 – Studies 030A and 030B: Two Identical Double-blind, Double-dummy, Multicenter, Comparative Phase III Studies of the Safety and Efficacy of Topical 1% SB-275833, Applied Twice Daily, versus Oral Cephalexin, 500 mg in Adults, or 12.5 mg/kg (250 mg/5 ml) in Children, Twice Daily, in the Treatment of Uncomplicated Secondarily Infected Traumatic Lesions

Abstract: (For Internal Use Only)

This protocol is comprised of two identical double-blind, double-dummy, multicenter comparative studies in adults and children subjects with uncomplicated Secondarily Infected Traumatic Lesions (SITL), to evaluate the safety and efficacy of topical 1% SB-275833 ointment versus oral cephalixin. Subjects ≥ 13 years of age, who meet all inclusion and exclusion criteria, will be given topical applications of 1% SB-275833 ointment/placebo twice daily for five days, and 500 mg (12.5mg/kg in children <40 kg) oral cephalixin/placebo twice daily for 10 days.

Pediatric enrollment (ages ≥ 9 months) will commence once an Independent Data Monitoring Committee has reviewed data from the initial 600 subjects enrolled, and determined that there are no safety issues that would preclude enrollment of children.

Subjects will have safety labs drawn, clinical evaluations performed and samples collected for microbiology culture and susceptibility testing at points throughout the study. The overall study period, including final follow-up visit, is 17 to 19 days. The study treatment regimen consists of topical applications of 1% SB-275833 ointment/placebo for five days, twice daily, and oral cephalixin/placebo, twice daily for 10 days.

This protocol is comprised of two identical Phase III pivotal trials, and is intended to provide data in order to support registration of SB-275833 with the following labelling:

SB-275833 is indicated for the treatment of secondarily infected traumatic lesions (SITL) due to susceptible strains of *Staphylococcus aureus*, including MRSA, and *Streptococcus pyogenes*.

Authors: [REDACTED]

Compound Numbers/Keywords (if applicable): SB-275833, SITL, secondarily infected skin lesions, cephalixin, pediatric, pivotal, skin infection, *Staphylococcus aureus*, *Streptococcus pyogenes*

Distribution:

Biometrics	[REDACTED]
CDMA Clinical – US	[REDACTED]
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Subject Recruitment	[REDACTED]
Product Development Management	[REDACTED]
Quest Diagnostics	[REDACTED]
Regulatory Affairs	[REDACTED]
Regulatory Compliance (US)	[REDACTED]

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Protocol SB-275833/030 – Studies 030A and 030B: Two Identical Double-blind, Double-dummy, Multicenter, Comparative Phase III Studies of the Safety and Efficacy of Topical 1% SB-275833, Applied Twice Daily, versus Oral Cephalexin, 500 mg in Adults, or 12.5 mg/kg (250 mg/5 ml) in Children, Twice Daily, in the Treatment of Uncomplicated Secondarily Infected Traumatic Lesions

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Protocol Amendment Number: 05

Author(s): [REDACTED]

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[REDACTED]	2004-JAN-30	Original
[REDACTED]	2004-FEB-7	Amendment 01.: Primary reason for amendment: Changes in Section 7.1 regarding composition of comparator placebo Additional changes (these changes in and of themselves would not justify a protocol amendment): Correction of typographical error in Section 3.3 Addition in section 5.2.1 Inclusion Criterion #5 to clarify use of contraception Change in Section 6.4 to add details regarding PK collection and analysis Edits to clarify wound measurements in centimeters Edits to clarify maximum infected wound size

(Continues)

[REDACTED]	2004-APR-21	Amendment 02.: Applies to Austria and Germany only Primary reason for amendment: To meet country requirements for: Austria (enrollment of patients ≥ 18 years only) and Germany (enrollment of patients ≥ 18 years prior to IDMC review and ≥ 13 years after positive recommendation by the IDMC and agreement by the appropriate IEC/IRB No changes were made to the actual body of the protocol for this amendment
[REDACTED]	2004-OCT-28	Amendment No. 03: Number of blood draws for subjects <13 years of age reduced from five to three Projected number of subjects enrolled edited to reflect additional number of subjects enrolled over study target due extended pediatric enrollment. Statistical methods were revised to comply with regulatory feedback, as well as for consistency between the protocol and the IDMC charter/
[REDACTED]	2004-DEC-28	Amendment No.04: One additional exclusion criterion for the pediatric population (<13 years of age) was added in order to gain approval for amendment #3 from the central IRB. Because Amendment #3 had already been distributed, it was necessary to incorporate this change as Amendment #4.
[REDACTED]	2005-JUL-25	Amendment No.5: At the request of US FDA, statements were added to the protocol to better clarify and define the algorithm for determining clinical or microbiological failures prior to the follow-up visit.

SPONSOR INFORMATION PAGE

Title: Protocol SB-275833/030 – Studies 030A and 030B: Two Identical Double-blind, Double-dummy, Multicenter, Comparative Phase III Studies of the Safety and Efficacy of Topical 1% SB-275833, Applied Twice Daily, versus Oral Cephalexin, 500 mg in Adults, or 12.5 mg/kg (250 mg/5 ml) in Children, Twice Daily, in the Treatment of Uncomplicated Secondarily Infected Traumatic Lesions

Study Identifier: SB-275833/030

GlaxoSmithKline

[REDACTED]

GlaxoSmithKline

[REDACTED]

Sponsor Contact Information:

[REDACTED]

IND Number: 66,095

Sponsor Signatory:

Signature:

Date:

████████████████████

Vice President, Infectious
Disease Medicine
Development Center,
Global Leader

INVESTIGATOR AGREEMENT PAGE

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol amendment and with any other study conduct procedures provided by GlaxoSmithKline (GSK).
- Not to implement this protocol amendment without agreement from the sponsor and prior submission to and written approval from (where required) the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except when necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- Not to implement any other changes to the protocol without agreement from the sponsor and prior review and written approval from the IRB or IEC, except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am thoroughly familiar with the appropriate use of the investigational product(s), as described herein, and any other information provided by the sponsor including, but not limited to, the following: the current Investigator's Brochure (IB) or equivalent document, IB supplement (if applicable), and approved product label (if the product is marketed in this country and the label is not already provided as an equivalent to an IB).
- That I am aware of, and will comply with, "good clinical practices" (GCP) and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the GSK investigational product(s) and of their study-related duties and functions as described herein.
- That I have been informed that certain regulatory authorities require the Sponsor to obtain and supply, as necessary, details about the investigator's ownership interest in the Sponsor or the investigational product, and more generally about his/her financial ties with the Sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence I:

- Agree to supply GSK with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children);
- Agree to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study; and
- Agree that GSK may disclose any information it has about such ownership interests and financial ties to regulatory authorities.

Investigator Name: _____

Investigator Signature

Date

The following co-signature is required only when the investigator is not a physician

Physician Name: _____

Physician Signature

Date

Amendment 5

The protocol changes described herein apply to all centers. The single purpose of this amendment was at the request of the US FDA, post-completion of the study, and serves to better define and clarify the algorithm for determining clinical or microbiological failures prior to the follow-up visit. This algorithm applies when assigning an outcome of clinical failure to a subject. Subjects who are clinical failures at the end of therapy, or at any other time prior to the follow-up visit, will be considered a clinical failure at follow-up as well.

The changes are presented in a “was/is” format, with the new or amended text shown in bold. The specific changes are as follows:

Section 3.3 Determining Clinical, Microbiological and Therapeutic Response, Determining Clinical Response, Determining Clinical Response at end of therapy (day 7-9 and day 12-14), Table

Was:

Defining criteria	Outcome	Clinical Response End of Therapy (day 7-9, day 12-14)
Total resolution of all signs and symptoms of infection recorded at baseline, or improvement to such an extent that no further antimicrobial therapy is necessary.	Clinical success	<i>Clinical success</i>
Insufficient improvement or deterioration of signs and symptoms of the infection recorded at baseline, such that additional antibiotic therapy is required. Subjects who are clinical failures at end of therapy are considered clinical failures at follow-up as well.	Clinical failure	<i>Clinical failure</i>
Refusal to consent to a clinical examination, lost to follow-up. Subjects who are 'unable to determine' at end of therapy are considered 'unable to determine' at follow-up as well.	Unable to determine	<i>Clinical failure</i>

Is:

Defining criteria	Outcome	Clinical Response End of Therapy (day 7-9, day 12-14)
Total resolution of all signs and symptoms of infection recorded at baseline, or improvement to such an extent that no further antimicrobial therapy is necessary.	Clinical success	<i>Clinical success</i>
Insufficient improvement, or deterioration of signs and symptoms of the infection recorded at baseline, such that additional antibiotic therapy is required. Subjects who are clinical failures at the End of Therapy Visit or any other time prior to the follow-up visit are considered clinical failures at follow-up as well	Clinical failure	<i>Clinical failure</i>
Refusal to consent to a clinical examination, lost to follow-up. Subjects who are 'unable to determine' at end of therapy are considered 'unable to determine' at follow-up as well.	Unable to determine	<i>Clinical failure</i>

Section 3.3 Determining Clinical, Microbiological and Therapeutic Response, Determining Clinical Response, Determining Clinical Response at follow-up (day 12-14 and day 17-19) Table

Was:

Defining Criteria	Outcome	Clinical Response at Follow-up (day 12-14, day 17-19)
Sufficient resolution of signs and symptoms of the infection for subjects who were clinical successes at the end of therapy visit such that no additional antibiotic therapy is required.	Follow-up Clinical success	<i>Clinical success</i>
Reappearance or worsening of signs and symptoms of the infection for subjects who were clinical successes at the end of therapy.	Clinical recurrence	<i>Clinical failure</i>
Refusal to consent to a clinical examination, lost to follow-up. Subjects who are 'unable to determine' at end of therapy are considered 'unable to determine' follow-up as well.	Unable to determine	<i>Clinical failure</i>

Is:

Defining Criteria	Outcome	Clinical Response at Follow-up (day 12-14, day 17-19)
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Refusal to consent to a clinical examination, lost to follow-up. Subjects who are 'unable to determine' at end of therapy are considered 'unable to determine' follow-up as well.	Unable to determine	<i>Clinical failure</i>

Section 6.3.2, On-Therapy Visit, First paragraph

Was:

- Previously not included

Is:

- **Subjects who are clinical failures at the on-therapy visit or at any other time prior to the follow-up visit are considered clinical failures at follow-up as well.**

Section 6.3.3, Topical End of Therapy (2-4 days post- topical therapy) Oral On-Therapy Visit, First paragraph

Was:

- Previously not included

Is:

- **Subjects who are clinical failures at the Topical End of Therapy /Oral On-Therapy Visit or any other time prior to the follow-up visit are considered clinical failures at follow-up as well.**

Section 6.3.4, Topical Follow-Up Visit (7-9 days post-topical therapy) Oral End of Therapy Visit (2-4 days post- oral therapy) , First paragraph

Was:

- Previously not included

Is:

- **Subjects who are clinical failures at the Topical Follow-Up Visit / Oral End of Therapy Visit or any other time prior to the follow-up visit are considered clinical failures at follow-up as well.**

Section 6.3.5, Final Follow-Up Assessment, First paragraph

Was:

- Previously not included

Is:

- **Subjects who are clinical failures at the Final Follow-Up Assessment or any other time prior to the follow-up visit are considered clinical failures at follow-up as well.**

Division:	World Wide Development	Document Number:	[REDACTED]
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Title:

Protocol SB-275833/030 – Studies 030A and 030B: Two Identical Double-blind, Double-dummy, Multicenter, Comparative Phase III Studies of the Safety and Efficacy of Topical 1% SB-275833, Applied Twice Daily, versus Oral Cephalexin, 500 mg in Adults, or 12.5 mg/kg (250 mg/5 ml) in Children, Twice Daily, in the Treatment of Uncomplicated Secondarily Infected Traumatic Lesions

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Product Development Management	[REDACTED]
Quest Diagnostics	[REDACTED]
Regulatory Affairs	[REDACTED]
Regulatory Compliance (US)	[REDACTED]

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Document Number: [REDACTED]
Study Identifier: SB-275833/030
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Author(s):

[REDACTED]

Biomedical Data Sciences
Infectious Disease Medical Development Center
Biomedical Data Sciences

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<p>[REDACTED]</p>	<p>2004-Feb-17</p>	<p>Amendment 01.: Primary reason for amendment: Changes in Section 7.1 regarding composition of comparator placebo Additional changes (these changes in and of themselves would not justify a protocol amendment): Correction of typographical error in Section 3.3 Addition in section 5.2.1 Inclusion Criterion #5 to clarify use of contraception Change in Section 6.4 to add details regarding PK collection and analysis Edits to clarify wound measurements in centimeters Edits to clarify maximum infected wound size</p>

(Continues)

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Study Identifier: Study SB-275833/030:

GlaxoSmithKline

[Redacted]

GlaxoSmithKline

[Redacted]

Sponsor Contact Information:

[Redacted]

IND Number: 66-095

Sponsor Signatory:

Signature:

Date:



Vice President, Infectious Disease
Medical Development Center
Global Leader

INVESTIGATOR PROTOCOL AGREEMENT PAGE

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- Agree that GSK may disclose any information it has about such ownership interests and financial ties to regulatory authorities.

Investigator Name: _____

Investigator Signature

Date

The following co-signature is required only when the investigator is not a physician.

Physician Name: _____

Physician Signature

Date

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ABBREVIATIONS

AE	Adverse Event
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area Under the Plasma Concentration Curve
BID	twice daily
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
cm	centimeter
Cmax	maximum Concentration
CPK	Creatine phosphokinase/creatine kinase
eCRF/CRF	electronic Case Report Form/Case Report Form
EISR	Expedited Investigator Safety Report
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma glutyl transferase
GSK	GlaxoSmithKline
h/hr	hour
IB/CIB	Investigator Brochure, Clinical Investigator Brochure
IND	Investigational New Drug
ITTb	Intent To Treat Bacteriological
ITTc	Intent To Treat Clinical
kg	kilogram
LDH	Lactate dehydrogenase
mg	milligram
ml	milliliter
mm	millimeter
MRSA	Methicillin resistant <i>Staphylococcus aureus</i>
mupRSA	mupirocin resistant <i>Staphylococcus aureus</i>
ng	nanogram
NOAEL	No Adverse Event Level
PPC	Per Protocol Clinical
PPB	Per Protocol Bacteriological
QC	Quality Control
RBC	Red Blood Cell
SAE	Serious Adverse Event
SID	Secondarily Infected Dermatoses
SITL	Secondarily Infected Traumatic Lesion
T3	Triiodothyronine
T4	Thyroxine
TSH	Thyroid Stimulating Hormone
w/w	weight to weight
WBC	White Blood Cell

PROTOCOL SUMMARY

Rationale

Uncomplicated skin and skin structure infections are common clinical conditions usually caused by Group A β -hemolytic streptococci and staphylococci; Gram negative organisms account for a distinct minority of skin infections [Leyden, 1974]. Most of the staphylococci involved in these infections are resistant to penicillins due to the production of β -lactamase enzymes by these organisms.

The emergence and spread of antibiotic resistance in hospital and community pathogens has eroded the utility of established antibacterial agents, a problem that has been widely publicized and currently poses a serious threat to public health worldwide. There is therefore a need for new antibiotics with modes of action distinct from those of established agents and activity against resistant strains.

SB-275833 is currently being developed as a topical antibiotic for the treatment of uncomplicated bacterial skin infections, and has been administered to approximately 400 healthy volunteers in four previous phase 1 studies: SB-275833/001 (completed), in which the aqueous formulation of SB-275833 was delivered intranasally using a nasal pump spray [GlaxoSmithKline Document SB-275833/RSD-101B20/1]; SB-275833/025 (completed, report in progress), assessed the irritation potential of topical applications of the current ointment formulation; SB-275833/026 (completed, report in progress), in which the safety, tolerability and preliminary pharmacokinetics (PK) of topical applications of the current ointment formulation was assessed; and SB-275833/027 (completed, report in progress), which assessed the sensitization potential of SB-275833 of topical applications of the current ointment formulation.

The use of 1% SB-275833 ointment has been evaluated in one patient study, SB-275833/029 (analysis complete, report in progress). This open-label study in subjects with uncomplicated bacterial skin infections evaluated systemic exposure, via PK sampling, through topical application of 1% SB-275833 ointment to the skin. In addition, preliminary efficacy and tolerability of topical applications of 1% SB-275833 ointment in subjects with uncomplicated bacterial skin infections was explored.

This study, comparing 1% SB-275833 ointment and oral cephalexin [KEFLEX Package Insert, 2002], in adults and children with secondarily infected traumatic lesions (SITL), is intended to support registration and approval of the primary indication of SITL.

Objective(s)

To compare the clinical and microbiological efficacy and safety of topical applications of 1% SB-275833 ointment with oral cephalexin, in the treatment of subjects with secondarily infected traumatic skin lesions, such as a small laceration, sutured wound or abrasion.

Endpoint(s)

Details regarding the primary endpoint and all secondary endpoints can be found in Section 3 "ENDPOINTS". Specifics and definitions for determining the clinical, microbiological and therapeutic responses, as related to all endpoints, can be found in the Section entitled "Determining Clinical, Microbiological and Therapeutic Response".

Primary Endpoint

Clinical response at follow-up (7-9 days post-therapy; day 12-14 and day 17-19) in the per protocol clinical population (PPC) as defined in the "Efficacy Study Populations" section, is the primary endpoint.

Secondary Endpoints

Secondary efficacy endpoints, including clinical, microbiological and therapeutic response, are dependent on evaluating the response to study medication at specific visits and for distinct populations.

Secondary safety endpoints are determined by a comparison of adverse events between the two treatment groups, as well as by summarizing values of critical concern, identified from laboratory blood and urine test results. Exposure to SB-275833 will also be determined through PK sampling and analysis.

- General secondary endpoints include a comparison of percent decrease in wound size and descriptive analysis of primary and secondary endpoints, in the pediatric subpopulation.
- Secondary endpoints are further outlined in Section 3.2.

Study Design

These are two identical randomized, double-blind, double-dummy, multi-center, comparative studies, each comparing the efficacy and safety of topical 1% SB-275833 ointment and oral cephalexin, in the treatment of subjects with secondarily infected traumatic lesions, such as a small laceration, sutured wound or abrasion. Details of topical and oral regimens are shown below in the entitled Treatment Groups and Dosing Details. The infected area of the lesions must not be larger than 10cm in length, or 100cm² in area, must not require surgical intervention and must be able to be appropriately treated with a topical antibiotic. In addition, the infections must be those which have a high likelihood of having *Staphylococcus aureus* and/or *Streptococcus pyogenes* as the causative infectious agent.

At the baseline (day 1) visit, the investigator will perform a medical history and determine if the subject has the protocol-defined diagnosis of a secondarily infected traumatic lesion, and if the subject meets the study inclusion and exclusion criteria. Curettage or aspirated samples from the wound will be obtained for culture and sensitivity testing. Swab samples may be obtained only if, in the opinion of the

investigator, collection by curettage or aspiration is not appropriate. The wound infection will be graded for exudate/pus, crusting, erythema/ inflammation, tissue warmth, tissue edema, itching, and pain according to the Skin Infection Rating Scale (See Appendix 5). A nasal swab of the anterior nares will be collected for culture and susceptibility testing, in order to determine the presence of *Staphylococcus aureus* nasal carriage, in order to correlate this with clinical response. Blood specimens will be drawn and urine collected for all subjects for safety lab tests.

Study Population

It is anticipated that 870 subjects may be enrolled into each of the studies in order to provide approximately 696 evaluable subjects at follow-up (i.e., assume 20% subject non-evaluability). It is estimated that, using a 2:1 randomization scheme, a sample size of 464 evaluable subjects in the topical SB-275833 group, and 232 in the cephalixin group, would be required for each study. The total targeted enrollment for this protocol, across both studies 030A and 030B, is 1740 subjects. In order to provide adequate safety and efficacy data in the youngest age cohort, enrollment will continue beyond the targeted 1740 subjects in order to achieve approximately 100 subjects in the youngest age cohorts (9 month to <6 years, ≥6 years to <13 years).

Study Assessments and Procedures

Details of all study procedures and assessments can be found in Section 6.3, "Study Visits" and in Appendix 1 Time and Events Table.

Subjects will have a clinical assessment, at the baseline visit (day 1), and at all visits thereafter, to ensure that in the investigator's clinical judgement, the condition of the subject is not worse or has failed to improve, and to monitor adverse events.

At the baseline visit (day 1), and at all visits thereafter, the treated wound will be measured and graded for exudate/pus, crusting, erythema/ inflammation, tissue warmth, tissue edema, itching, and pain according to Skin Infection Rating Scale criteria (Appendix 5).

Based on the clinical assessment at the baseline (day 1) and follow-up (day 12-14 and day 17-19) visits, the investigator will determine that subject's clinical response at the topical end of therapy/oral on-therapy visit (day 7-9), the topical follow-up/oral end of therapy (day 12-14) visit, and at the final follow-up visit (day 17-19).

For all subjects ≥13 years of age, blood specimens will be drawn and urine collected for safety lab tests at the baseline visit (day 1), both on-therapy visits 2 and 3 (day 3-4 and day 7-9), and at both the follow-up visits 4 and 5 (day 12-14 and day 17-19). For subjects <13 years of age, blood specimens will be drawn and urine collected for safety lab tests at the baseline visit (day 1), and at both on-therapy visits 2 and 3 (day 3-4 and day 7-9). A PK sample for population PK analysis will be collected at the on-therapy visit at day 3-4 for the first 500 adult subjects enrolled across both studies, and for all pediatric subjects. For adult subjects, the PK sample will be the predose sample of the first dose on day 3 or 4; for pediatric subjects, the PK sample will be randomly spread in

either one of the three windows (0 (predose)-4 h, 4-8 h, or 8-12 h) following the first dose on day 3 or 4.

Bacteriology samples will be obtained for culture and susceptibility testing at baseline (day 1), and at the end of therapy (day 7-9 and day 12-14) and follow-up (day 12-14 and day 17-19) visits, if culturable material is still present, or the subject is a 'clinical failure.' The method of sample collection will be recorded in the eCRF.

A nasal swab of the anterior nares will be obtained at baseline (day 1) and at the follow-up visits (day 12-14 and day 17-19) for all subjects, and at the end of therapy visits (day 7-9 and day 12-14) for any subject who has exudate present and a wound sample collected, or for any subject who is a 'clinical failure'.

The lesions to be treated will be measured at baseline (day 1) and at the end of therapy visits (day 7-9 and day 12-14).

If the wound is covered, the type of dressing used will be recorded in the eCRF as 'occlusive', 'semi-occlusive', or 'none'.

Investigational Product(s)

All subjects entered into the study will be treated with either topical 1% SB-275833 ointment, twice daily for 5 days, and oral cephalexin placebo twice daily for 10 days, or SB-275833 matching placebo ointment, twice daily for 5 days and oral cephalexin twice daily for 10 days. Based on the maximum size of the infected portion of the wound to be treated (100cm², or 10 cm in length), the maximum amount of ointment/placebo formulation applied per dose to a subject would be 10 mg per cm² (i.e., 1 gram per 100 cm²). Subjects ≥13 years of age will receive 500 mg (as two 250 mg capsules) oral cephalexin/placebo (as two 250 mg over-encapsulated matching capsules) twice daily for 10 days, as per labelled dosing. Pediatric subjects <13 years of age will receive 12.5 mg/kg oral cephalexin/placebo suspension, twice daily for 10 days, as per labelled dosing. A schematic diagram of the treatment regimens can be found in the entitled Section "Treatment Groups and Dosing Details".

1. INTRODUCTION

SB-275833 is a novel semi-synthetic pleuromutilin, representing a new class of antimicrobial agents, and has been formulated as a topical antibiotic, as repeated studies in animals have shown that the oral bioavailability is very low and the clearance of the agent is rapid [GlaxoSmithKline Document Number DR98062, GlaxoSmithKline Document Number DR97422, GlaxoSmithKline Document Number DR98066].

In vitro activity against susceptible and multi-resistant clinical isolates is excellent, including strains commonly associated with skin infections (*Staphylococcus aureus* and *Streptococcus pyogenes*) and upper respiratory infections (*Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* [GlaxoSmithKline APCM Data Sheet 98-45]).

In vivo studies, using a mouse suture wound model, have shown statistical significance in the efficacy of 1% SB-275833 ointment, when dosed for ≥ 4 days BID, against susceptible and resistant strains of *Staphylococcus aureus* [methicillin-resistant *Staphylococcus aureus* (MRSA), mupirocin resistant *Staphylococcus aureus* (mupRSA)], and *Streptococcus pyogenes*, when compared to placebo and non-treated controls.

SB-275833 is currently being developed as a topical antibiotic for the treatment of uncomplicated bacterial skin infections, and has been administered to approximately 400 healthy volunteers in four previous phase 1 studies.

Systemic exposure and sensitization studies in healthy volunteers supported the progression of 0.5%, 1% or 2% SB-275833 ointment formulations; however, 2% SB-275833 ointment yielded unacceptable irritation in abraded skin, and therefore precluded its progression.

1% SB-275833 has been administered to patients in one concluded study: SB-275833/029, an open-label study in subjects with uncomplicated bacterial skin infections to evaluate systemic exposure, via PK sampling, through topical application of 1% SB-275833 to the skin. In addition, preliminary efficacy and tolerability of topical applications of 1% SB-275833, in subjects with uncomplicated bacterial skin infections was explored.

One percent SB-275833 is currently being developed as a topical antibiotic for the treatment of bacterial skin infections.

This protocol, designated as SB-275833/030, is comprised of two identical randomized, comparative, double-blind, double dummy, multicenter studies in adults and children, comparing 1% SB-275833 ointment and oral cephalexin, and is planned to support approval of the primary indication of SITL. The two studies within this protocol are designated as 030A and 030B.

1.1. Background

Uncomplicated skin and skin structure infections are common clinical conditions usually caused by Group A β -hemolytic streptococci and staphylococci; Gram negative organisms account for a distinct minority of skin infections [Leyden, 1974]. Most of the staphylococci involved in these infections are resistant to penicillins due to the production of β -lactamase enzymes by these organisms.

The emergence and spread of antibiotic resistance in hospital and community pathogens has eroded the utility of established antibacterial agents, a problem that has been widely publicized and currently poses a serious threat to public health worldwide. There is therefore a need for new antibiotics with modes of action distinct from those of established agents and activity against resistant strains.

SB-275833 is a novel semi-synthetic pleuromutilin that has been formulated as a topical antibiotic. Because the pleuromutilin mode of action is unique, SB-275833 is active against bacterial isolates carrying resistance determinants to established agents including β -lactams, macrolides, quinolones and mupirocin [GlaxoSmithKline APCM Data Sheet 98-45, GlaxoSmithKline APCM Data Sheet 97-55], and is fully active vs strains resistant to current topical therapies including fucidin and mupirocin.

In vitro activity against clinical isolates that are either susceptible or multi-resistant to many common agents is excellent, including strains commonly associated with skin infections (*Staphylococcus aureus* and *Streptococcus pyogenes*) and upper respiratory infections (*Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*) [GlaxoSmithKline APCM Data Sheet 98-45].

Specifically, studies were conducted to evaluate the comparative efficacies of SB-275833 [0.1, 0.5, 1, 2 and 5% weight to weight (w/w)] and mupirocin against *S. aureus* (mupirocin resistant) and *S. pyogenes* in experimental surgical wound infection in mice. Against *S. aureus* (mupirocin resistant) all five concentrations reduced bacterial numbers significantly compared with non-treated control ($p=0.01$), whereas the corresponding placebo had no effect.

Concentrations of 1, 2 and 5% w/w were significantly better than mupirocin, 2% ($p=0.01$) and 0.1 and 0.5% w/w were similar to mupirocin, 2% ($p>0.05$) [GlaxoSmithKline Document Number SB-275833/RSD-101SVK/1].

Efficacy has also been determined against *S. pyogenes* 257. Again, all five concentrations had a significant effect and were similar to mupirocin, 2% ($p>0.05$), while the corresponding placebo was ineffective ($p>0.05$) [GlaxoSmithKline Document Number SB-275833/RSD-101SVK/1].

SB-275833 (0.1, 0.5, 1, 2 and 5% w/w) was effective at the majority of concentrations tested against mupirocin sensitive and resistant *S. aureus* and *S. pyogenes*. Isolates with higher bacterial numbers obtained after therapy showed no decrease in susceptibility [GlaxoSmithKline Document Number SB-275833/RSD-101SVK/1]. There was no evidence of adverse effects of irritancy observed in any of the treatment or placebo groups over the experimental periods.

Ointment formulations containing 1% SB-275833, dosed bid for ≥ 4 days, are as effective in this model as mupirocin, which supports the potential for a shorter and less frequent dosing regimen than with mupirocin.

SB-275833 as topical ointment has been administered to humans in three clinical studies: SB-275833/025 (analysis complete, report in progress at time of writing), in which the irritation potential of topical applications of the ointment formulation is being assessed; SB-275833/026 (analysis complete, report in progress at time of writing), in which the safety, tolerability and preliminary PKs of topical applications of the ointment formulation is being assessed; and SB-275833/027 (in-life complete at the time of writing), in which the sensitization potential of the ointment formulation is being assessed.

Preliminary data from Studies 025 and 026 available at the time of writing (including irritation assessments, clinical laboratory parameters, vital signs and ECG data) do **not** indicate any drug-related and/or dose-dependent safety risks, or that any of the tested concentrations (0.5%, 1%, or 2%) of SB-275833 ointment is a primary irritant. Preliminary PK data available to date from Study 026 indicate that systemic exposure following topical applications of SB-275833 free base ointment on intact and abraded skin was below the exposure at NOAEL for oral administration in monkeys (89 ng/mL for C_{max} and 661 ng.h/mL for AUC).

Study 027 preliminary data indicate that only 1 of 205 subjects who completed the study was identified as sensitized to 0.5%, 1% and 2% SB 275833 ointment after challenge. This single subject out of 205 showed reaction at challenge indicating sensitization to all three concentrations: 0.5%, 1% and 2%. Of note, this subject had reactions to all test articles, including vehicle from day 1 during induction. This suggests that the subject may have a very sensitive skin type and may be exhibiting a degree of reactivity to vehicle. During the study, 8 of the 205 subjects required a re-challenge for clarification of equivocal challenge results. Of the 8 re-challenged subjects, the single subject above had challenge data clarified as sensitized.

Data from study 029 is preliminary, but indicates that there is minimal systemic absorption and thus limited measurable concentrations of SB-275833, in subjects with uncomplicated bacterial skin infections. Only 9 out of 385 samples had measurable concentrations ranging from 0.5~4.3 ng/mL, with non-quantifiable concentrations in all the remaining samples (LLQ 0.5 ng/mL). There was no accumulation upon multiple application (bid). The systemic exposure of SB 275833 when 1% ointment was applied to "real life" lesions (surface area median (range) is 1.40 (0.04~100 cm²)) was far below the NOAEL level in monkeys (oral dose of 50 mg/kg/day, C_{max} \geq 89 ng/ml and AUC \geq 661 ng.h/mL)

Please refer to the Investigator Brochure [GlaxoSmithKline Document Number UM2003/00089/00] for a more detailed review of the pre-clinical data for SB-275833.

1.2. Rationale

SB-275833 is an inhibitor (through ribosome binding) of bacterial protein synthesis. It has been formulated as a topical antibiotic, since the oral bioavailability is very low in animals and the clearance of the agent is rapid. An ointment formulation of SB-275833 is being developed for treatment of uncomplicated skin and soft tissue infections such as secondarily infected traumatic lesions (SITL).

The use of 1% SB-275833 ointment is being studied in one completed patient study, SB-275833/029, as previously described. This open-label study in subjects with uncomplicated bacterial skin infections evaluated systemic exposure, via PK sampling, through topical application of 1% SB-275833 ointment to the skin. In addition, preliminary efficacy and tolerability of topical applications of 1% SB-275833 ointment in subjects with uncomplicated bacterial skin infections was being explored in this study.

The present study SB-275833/030 constitutes the second clinical investigation in a patient population with this formulation of SB-275833 and is intended to provide data in order to support registration of SB-275833 indicated for the treatment of secondarily infected traumatic lesions (SITL), due to susceptible strains of *Staphylococcus aureus*, including MRSA, and *Streptococcus pyogenes*.

2. OBJECTIVES

To compare the efficacy and safety of topical applications of 1% SB-275833 ointment with oral cephalexin, in the treatment of subjects with secondarily infected traumatic skin lesions, such as a small laceration, sutured wound or abrasion.

3. ENDPOINTS

Efficacy endpoints, including clinical, microbiological and therapeutic response, are dependent on evaluating the response to study medication at various visits and for different populations. Specifics and definitions for determining the clinical, microbiological and therapeutic responses can be found in the Section entitled "Determining Clinical, Microbiological and Therapeutic Response".

3.1. Primary

- Clinical response at follow-up (7-9 days post-therapy; day 12-14 and day 17-19) in the per protocol clinical population (PPC) as defined in the Section "Efficacy Study Populations".

3.2. Secondary

3.2.1. Efficacy endpoints

3.2.1.1. Clinical endpoints

- Clinical response at follow-up (7-9 days post-therapy; day 12-14 and day 17-19) in the intent to treat clinical population (ITTC)
- Clinical response at end of therapy (2-4 days post-therapy; day 7-9 and 12-14) in the ITTC population, and the PPC population
- Clinical response on day 7-9 (topical end of therapy, oral on therapy) in the ITTC, and PPC populations
- Clinical response on day 12-14 (topical follow-up, oral end of therapy) in the ITTC, and PPC populations
- Clinical response on day 17-19 (oral follow-up, topical final follow-up) in the in the ITTC, and PPC populations

3.2.1.2. Microbiological endpoints

- Microbiological response at end of therapy (2-4 days post-therapy; day 7-9 and day 12-14) in the intent to treat bacteriological (ITTb), and per protocol bacteriological PPB populations
- Microbiological response at follow-up (7-9 days post-therapy; day 12-14 and day 17-19) in the ITTB, and PPB populations
- Microbiological response on day 7-9 (topical end of therapy, oral on therapy) in the ITTB, and PPB populations
- Microbiological response on day 12-14 (topical follow-up, oral end of therapy) in the ITTB, and PPB populations
- Microbiological response on day 17-19 (oral follow-up, topical final follow-up) in the in the ITTB, and PPB populations
- Number and percent of subjects in the PPB population who had methicillin resistant Staphylococcus aureus (MRSA) isolated at baseline (day 1), by clinical response, at end of therapy (2-4 days post-therapy; day 7-9 and day 12-14), and at follow-up (7-9 days post-therapy; day 12-14 and day 17-19)

3.2.1.3. Therapeutic response endpoint

- Therapeutic response at follow-up (7-9 days post-therapy; day 12-14 and day 17-19) in the PPB population

3.2.2. General endpoints

- Comparison of percent decrease in wound size from baseline at day 7-9 (topical end of therapy, oral on therapy) in the per protocol population

- Descriptive analysis (number and percent) of primary and secondary endpoints, as defined above, in the pediatric subpopulation

3.2.3. Safety endpoints

3.2.3.1. Adverse Events

- Adverse experiences will be solicited at each visit after study medication start, for any subject who has had at least one dose of study medication, and will be compared between the treatment groups in the ITTC population.
- Adverse events deemed by the investigator to be related to study medication, and affecting medication compliance (e.g., vomiting, diarrhea, nausea, anorexia, rash, burning, irritation, etc.) will be grouped together for comparison between treatment groups.
- At the on-therapy visit at day 3-4, a 3ml blood sample will be collected, for the first 500 adult subjects enrolled across both studies, and for all pediatric subjects, for potential population PK analysis, if data permits. For adult subjects, the PK sample will be the predose sample of the first dose on day 3 or 4; for pediatric subjects, the PK sample will be randomly spread in either one of the three windows (0-4 h, 4-8 h, or 8-12 h) following the first dose on day 3 or 4.

3.2.3.2. Safety laboratory tests

- For all subjects ≥ 13 year of age, laboratory blood and urine parameters will be measured at the baseline visit 1, and at on-therapy visits 2 and 3 (day 3-4, day 7-9) and follow-up visits 4 and 5 (day 12-14 and day 17-19). For subjects < 13 years of age, laboratory blood and urine parameters will be measured only at the baseline visit 1 (day 1), and both on-therapy visits 2 and 3 (day 3-4 and day 7-9).
- Changes from baseline (day 1) and values of clinical concern will be summarized for the ITTC population.

3.2.3.3. Independent Data Monitoring Committee

At the outset of the study, enrollment will be limited to subjects ≥ 13 years of age. An independent data monitoring committee (IDMC) consisting of outside experts in infectious disease, dermatology, and pediatrics, as well as a statistician, will be formed to assess emergent safety in adults and to make a determination whether the safety profile supports enrollment of pediatric subjects ≥ 9 months of age. When approximately 600 adult and adolescent subjects are enrolled (400 on 1% SB-275833 ointment), in the Phase III SITL studies, the IDMC will convene to review the data, and to determine if there are any significant safety issues that would preclude enrollment of children ≥ 9 months of age and older. Enrollment of adults and adolescents ≥ 13 years of age will continue throughout the IDMC review period. Once the review is complete, and a positive recommendation made to the sponsor, enrollment of children ≥ 9 months of age will commence. Statistical outputs for the IDMC review are produced independently of the sponsor. Blinded output (e.g. SAE narratives) from the safety data base, OCEANS, will

be produced by the sponsor's global clinical safety and pharmacovigilance (GCSP) group, for provision to IDMC. All GSK study personnel will remain blinded to the treatment regimens. Further details of the IDMC remit can be found in Section 12.9, and a copy of the IDMC charter is available from GSK upon request.

3.2.3.4. Pharmacokinetic analysis

At the on-therapy visit at day 3-4, a 3ml random blood sample to monitor exposure to SB-275833 will be collected for the first 500 enrolled adult subjects ≥ 18 years of age, across both studies, and for all pediatric and adolescent subjects, ≥ 9 months and < 18 years old, for potential population PK analysis, if the data permit. For adult subjects, the PK sample will be the predose sample of the first dose on day 3 or 4; for pediatric subjects, the PK sample will be randomly spread in either one of the three windows (0 (predose)-4 h, 4-8 h, or 8-12 h) following the first dose on day 3 or 4.

3.3. Determining Clinical, Microbiological and Therapeutic Response

Determining Clinical Response

Determining Clinical *response* at end of therapy (day 7-9 and day 12-14)

By reviewing clinical signs and symptoms at the end of therapy evaluation (2-4 days post therapy; days 7-9 and 12-14), the clinical outcome *is determined and the resulting clinical response assigned, for the each subject*, as follows:

Defining criteria	Outcome	Clinical Response End of Therapy (day 7-9, day 12-14)
Total resolution of all signs and symptoms of infection recorded at baseline, or improvement to such an extent that no further antimicrobial therapy is necessary.	Clinical success	<i>Clinical success</i>
Insufficient improvement, or deterioration of signs and symptoms of the infection recorded at baseline, such that additional antibiotic therapy is required. Subjects who are clinical failures at end of therapy, are considered clinical failures at follow-up as well.	Clinical failure	<i>Clinical failure</i>
Refusal to consent to a clinical examination, lost to follow-up. Subjects who are 'unable to determine' at end of therapy are considered 'unable to determine' at follow-up as well.	Unable to determine	<i>Clinical failure</i>

Determining Clinical response at follow-up (day 12-14 and day 17-19)

Clinical efficacy assessments are performed at follow-up (day 12-14 and day 17-19) only for subjects whose clinical response at end of therapy (day 7-9 and day 12-14) was 'clinical success'. Subjects who are 'clinical failures' at end of therapy (day 7-9 and day 12-14) are classified as 'clinical failures' at follow-up as well. By reviewing clinical signs and symptoms at the follow-up (day 12-14 and day 17-19) evaluation, the investigator will determine whether a satisfactory response is maintained or a recurrence has occurred and will classify the clinical *outcome*, and the resulting clinical response at follow-up as below:

Defining Criteria	Outcome	Clinical Response at Follow-up (day 12-14, day 17-19)
Sufficient resolution of signs and symptoms of the infection for subjects who were clinical successes at the end of therapy visit such that no additional antibiotic therapy is required.	Follow-up Clinical success	<i>Clinical success</i>
Reappearance or worsening of signs and symptoms of the infection for subjects who were clinical successes at the end of therapy.	Clinical recurrence	<i>Clinical failure</i>
Refusal to consent to a clinical examination, lost to follow-up. Subjects who are 'unable to determine' at end of therapy are considered 'unable to determine' follow-up as well.	Unable to determine	<i>Clinical failure</i>

Determining Microbiological Response

Determining Microbiological response at end of therapy (day 7-9 and day 12-14)

The 'by pathogen' microbiological outcome is determined by comparing the baseline (day 1) culture results to the culture results at the end of therapy (2-4 days post-therapy; day 7-9 and day 12-14) and the corresponding microbiological *response* (success or failure) 'by subject', is then assigned, as shown below:

Defining criteria	Outcome	Microbiological Response at End of Therapy (day 7-9, day 12-14)
Elimination of baseline pathogen(s)	Microbiological Eradication	<i>Microbiological Success</i>
Clinical outcome was success such that no culture was obtained due to lack of culturable material, secondary to adequate clinical response, and is documented in the eCRF	Presumed Microbiological Eradication	<i>Microbiological Success</i>
Baseline pathogen(s) is still present	Microbiological Persistence	<i>Microbiological Failure</i>
Subject is a clinical failure and no culture was obtained	Microbiological Presumed Persistence	<i>Microbiological Failure</i>
A determination of baseline pathogen microbiological response cannot be made (e.g., no baseline pathogen identified, sample lost, etc.)	Unable to determine	<i>Microbiological Failure</i>
New pathogen, not previously identified, is identified at end of therapy in a symptomatic subject requiring additional antibiotic therapy, i.e., subject is a 'clinical failure'	New infection	<i>Microbiological Failure</i>
New pathogen not previously identified, is identified at end of therapy in a non-symptomatic subject who does not require additional antibiotic therapy, i.e., subject is a 'clinical success'	Colonization	<i>Microbiological Success</i>

Determining Microbiological response at follow-up (day 12-14 and day 17-19)

The 'by pathogen' microbiological *outcome* is determined by comparing the baseline (day 1) culture results to the culture results at follow-up (7-9 days post-therapy; day 12-14, day 17-19) and the corresponding microbiological *response* (success or failure) 'by subject', is then assigned, as follows:

Defining criteria	Outcome	Microbiological Response at Follow-up (day 12-14, day 17-19)
<i>For subjects whose clinical response at end of therapy was 'clinical failure', and who do not have cultures obtained at follow-up</i>		
Subject is a 'clinical failure' at end of therapy and no culture was obtained at follow-up	Microbiological Presumed Persistence	<i>Microbiological Failure</i>
<i>For subjects whose clinical response at end of therapy was 'clinical success'</i>		
The baseline pathogen was eradicated or presumed eradicated at end of therapy, or the baseline pathogen(s) was present at end of therapy and is absent at follow-up	Follow-Up Microbiological Eradication	<i>Microbiological Success</i>
The baseline pathogen was eradicated or presumed eradicated at end of therapy, or the baseline pathogen(s) was present at end of therapy and, subject is a follow-up clinical success, such that no culture was obtained due to lack of culturable material, secondary to adequate clinical response, and is documented in the eCRF	Presumed Follow-Up Microbiological Eradication	<i>Microbiological Success</i>
Baseline pathogen(s) was present at end of therapy and is still present	Microbiological Persistence	<i>Microbiological Failure</i>
The baseline pathogen was eradicated or presumed eradicated at end of therapy and reappears at follow-up	Microbiological Recurrence	<i>Microbiological Failure</i>
The baseline pathogen was eradicated or presumed eradicated at end of therapy, no sample for culture is taken at the follow-up visit and subject is a clinical recurrence	Microbiological Presumed Recurrence	<i>Microbiological Failure</i>
A determination of baseline pathogen microbiological response could not be made, e.g., no baseline pathogen was isolated, sample lost etc	Unable to Determine	<i>Microbiological Failure</i>
<i>New pathogens isolated at follow-up (i.e. not present at baseline or end of therapy) will be classified according to the following categories:</i>		
A new pathogen, not previously identified at baseline or end of therapy, is identified at follow-up in a symptomatic subject requiring additional antibiotic therapy, i.e., subject is a clinical recurrence	New Infection	<i>Microbiological Failure</i>
A new pathogen, not previously identified at baseline or end of therapy, is identified at follow-up in a non-symptomatic subject who does not require additional antibiotic therapy, i.e., subject is a follow-up clinical success	Colonization	<i>Microbiological Success</i>

NB: For those subjects withdrawing prior to the end of therapy visit, evaluation of their by pathogen and by subject microbiological response will be determined at the time they are withdrawn.

Determining Therapeutic Response

Therapeutic response is a measure of the overall efficacy response, and refers to subjects who have been deemed both a 'clinical success' and a 'microbiological success'. All other combinations (other than 'clinical success' + 'microbiological success') are deemed failures for therapeutic response.

4. STUDY DESIGN

These are two identical randomized, double-blind, double-dummy, multi-center, comparative studies, each comparing the efficacy and safety of topical 1% SB-275833 ointment and oral cephalexin, in the treatment of subjects with secondarily infected traumatic lesions, such as a small laceration, sutured wound or abrasion. Details of topical and oral regimens are shown in the figure entitled "Treatment Groups and Dosing Details". The infected area of the lesions must not be larger than 10cm in length, or 100cm² in area, must not require surgical intervention, and must be able to be appropriately treated with a topical antibiotic. In addition, the infections must be those which have a high likelihood of having *Staphylococcus aureus* and/or *Streptococcus pyogenes* as the causative infectious agent.

4.1. Randomization

Two identical, independent studies are being conducted in parallel using one protocol; these studies are designated as SB-275833/030A and SB-275833/030B. The subject randomization to one or the other of the treatment arms will be stratified by site and age (9 months \leq 6 years old, 6 - <13, \geq 13) under a unique schedule for both studies. At most 60% of subjects will be allowed to be enrolled from sites in Europe and International regions. Once adult and pediatric enrollment is completed, the sites will be size-ranked and randomized accordingly to either study 030A or 030B. When assigning the sites to one or the other of the studies, a randomization scheme will be utilized, using blocks of four, stratified by region, to ensure balanced regional enrollment between the two trials.

The randomization of sites to studies is done solely on the basis of the number of subjects enrolled per site; at that point, the study will still be blinded, and no data manipulation will have taken place. The implementation of the pre-specified procedure and the information used in rank-ordering and randomizing sites to studies will be documented in the final clinical study reports.

The randomization procedure described above is an attempt to decrease the enrollment time and have both trials end at the same time, by optimizing the use of available sites.

Details regarding rationale for this randomization scheme are found in Appendix 3.

4.2. Treatment and Assessment Overview

At the baseline (day 1; Section 6.3.1) visit, the investigator will perform a medical history and determine if the subject has the protocol-defined diagnosis of a secondarily

infected traumatic lesion, and if the subject meets the study inclusion and exclusion criteria.

Curettage or aspirated samples from the wound will be obtained for culture and sensitivity testing. Swab samples may be obtained only if, in the opinion of the investigator, collection by curettage or aspiration is not appropriate. The wound infection will be graded for exudate/pus, crusting, erythema/ inflammation, tissue warmth, tissue edema, itching, and pain according to the Skin Infection Rating Scale (See Appendix 5, Skin Infection Rating Scale). A nasal swab of the anterior nares will be collected for culture and susceptibility testing, in order to determine the presence of *Staphylococcus aureus* nasal carriage, in order to correlate this with clinical response. Blood specimens will be drawn and urine collected for safety lab tests for all subjects.

All subjects who have met the inclusion and exclusion criteria, as defined in Section 5.2 and have given written, dated informed consent will be entered into the study and randomized, in a 2:1 ratio, as shown below:

Treatment Groups and Dosing Details

		Oral regimen BID 10 days	Topical regimen BID 5 days
Treatment A	adults ¹	cephalexin 500 mg placebo (2- 250 mg matching capsules)	+ 1% SB-275833 ointment
	children ²	cephalexin 12.5 mg/kg placebo matching suspension	+ 1% SB-275833 ointment
OR			
Treatment B	adults ¹	cephalexin 500 mg (2- 250 mg capsules)	+ SB-275833 ointment matching placebo
	children ²	cephalexin 12.5 mg/kg suspension (250 mg/5ml)	+ SB-275833 ointment matching placebo

1. all subjects ≥ 13 years of age
2. ≥ 9 months -12 years of age, post IDMC review

The subject or parents/legal guardians will be instructed by the site as to proper technique for cleaning the infected wound, using pre-moistened towelettes provided by the site. Instructions for applying the appropriate amount of topical study medication/placebo will also be given. A sterile swab will be used to apply sufficient medication to cover the entire wound. The subject or parents/legal guardians will be instructed not to remove the scabs and to avoid scratching or touching the lesion. Use of gauze, bandage, etc., is permitted. Children young enough to inadvertently lick the medication or the wound site must have their treated wound covered with gauze or a semi-occlusive bandage. The type of dressing used will be recorded in the eCRF as 'occlusive', 'semi-occlusive', or 'none'.

A diary card will be provided for the subject or parent/legal guardian to record each application/dose of the study medication/placebo. Diary cards are for recording purposes

only, are to be kept by the site as source documentation, and will not be sent in-house to GSK.

In addition, the subject or parents/legal guardians will be told that additional topical agents of any type, as well as systemic antibiotics and steroids, are prohibited throughout the duration of the study.

Subjects will have a clinical assessment at the baseline visit (day 1; Section 6.3.1). Subjects will have additional clinical assessments on therapy (day 3-4; Section 6.3.2), and at the end of therapy (day 7-9, and day 12-14; Sections 6.3.3, 6.3.4) and follow-up visits (day 12-14 and day 17-19; Sections 6.3.4, 6.3.5), to monitor adverse events and to ensure that in the investigator's clinical judgement, the condition of the subject is not worse or has failed to improve. If the condition of the subject has not improved or has worsened, or if the Skin Infection Rating Scale score is greater than the baseline score, the subject may be withdrawn from the study and treated at the discretion of the investigator. The topical follow-up assessment may be completed at the same visit time as the oral end of therapy assessment, as both occur on day 12-14. For those subjects who were withdrawn from the study prior to the topical end of therapy/oral on therapy visit (day 7-9; Section 6.3.3), the final follow-up visit (day 17-19; Section 6.3.5) is required for monitoring adverse experiences and additional concomitant medication.

Based on the clinical assessment at the baseline (day 1; Section 6.3.1) and follow-up (day 12-14 and day 17-19; Sections 6.3.4, 6.3.5) visits, the investigator will determine that subject's clinical response at the topical end of therapy/oral on-therapy visit (day 7-9; Section 6.3.3), the topical follow-up/oral end of therapy (day 12-14; Section 6.3.4) visit, and at the final follow-up visit (day 17-19; Section 6.3.5).

Blood specimens will be drawn and urine collected for all subjects for safety lab tests at the baseline visit (day 1; Section 6.3.1), and at both on-therapy visits 2 and 3 (day 3-4 and day 7-9; Sections 6.3.2, 6.3.3). Blood specimens will be drawn and urine collected for safety lab tests at both the follow-up visits 4 and 5 (day 12-14 and day 17-19; Sections 6.3.4, 6.3.5) for all subjects ≥ 13 years of age; subjects < 13 years of age are excluded from safety lab collection at visits 4 and 5. A PK sample for population PK analysis will be collected at the on-therapy visit 2 at day 3-4, for the first 500 subjects ≥ 18 years of age, across both studies, and for all pediatric subjects, ≥ 9 months and < 18 years old. For adult subjects, the PK sample will be the predose sample of the first dose on day 3 or 4; for pediatric subjects, the PK sample will be randomly spread in either one of the three windows (0 (predose)-4 h, 4-8 h, or 8-12 h) following the first dose on day 3 or 4. Bacteriology samples will be obtained for culture and susceptibility testing at baseline (day 1; Section 6.3.1), and at the end of therapy (day 7-9 and day 12-14; Sections 6.3.3, 6.3.4) and follow-up (day 12-14 and day 17-19; Sections 6.3.4, 6.3.5) visits, if culturable material is still present, or the subject is a 'clinical failure.' A nasal swab of the anterior nares will be obtained at baseline (day 1; Section 6.3.1) and at the follow-up visits (day 12-14 and day 17-19; Sections 6.3.4, 6.3.5) for all subjects, and at the end of therapy visits (day 7-9 and day 12-14; Sections 6.3.3, 6.3.4) for any subject who has exudate present and a wound sample collected, or for any subject who is a 'clinical failure'.

The lesions to be treated will be measured at baseline (day 1; Section 6.3.1) and at the end of therapy visits (day 7-9 and day 12-14; Sections 6.3.3, 6.3.4).

This study will be conducted according to ICH Guidelines. Institutional Review Board (IRB) approval and written informed consent will be obtained from the subject prior to study initiation.

5. STUDY POPULATION

This multi-center study will be comprised of subjects diagnosed as having a secondarily infected traumatic lesion, such as a small laceration, sutured wound or abrasion, that is suitable for treatment with a topical antibiotic. The infected area of the lesions must not be larger than 10cm in length, or 100cm² in area, must not require surgical intervention, and must be able to be appropriately treated with a topical antibiotic. In addition, the infections must be those which have a high likelihood of having *Staphylococcus aureus* and/or *Streptococcus pyogenes* as the causative infectious agent.

Initially, only adults and adolescents ≥ 13 years of age will be enrolled. An independent data monitoring committee (IDMC) will be formed to assess emergent safety in the initial population and to make a determination whether the safety profile supports enrollment of pediatric subjects ≥ 9 months of age.

Once review by an independent data monitoring committee is completed, sites will begin receiving supplies of oral cephalexin suspension/placebo (in addition to their supplies of cephalexin capsules/placebo), in order that they may treat children, ages 9 months to < 13 years; children will be randomly enrolled, in either study. It is anticipated that approximately 150-225 children will be enrolled in Phase III.

Subjects will be enrolled without regard to sex, race or socioeconomic status.

5.1. Number of Subjects

It is anticipated that 870 subjects may be enrolled into each of the studies in order to provide approximately 696 evaluable subjects at follow-up (i.e., assume 20% subject non-evaluability). It is estimated that, using a 2:1 randomization scheme, a sample size of 464 evaluable subjects in the topical SB-275833 group, and 232 in the cephalexin group, would be required for each study. The total targeted enrollment for this protocol, across both studies 030A and 030B, is 1740 subjects. In order to provide adequate safety and efficacy data, in the youngest age cohort, enrollment will continue beyond the targeted 1740 subjects in order to enrol sufficient numbers of pediatric subjects in the youngest age cohorts (9 month to < 6 years, ≥ 6 years to < 13 years).

5.2. Eligibility Criteria

5.2.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. Adult and adolescent subjects will be included in the study **PRIOR** to IDMC review, if the following inclusion criteria are met:
2. The subject is ≥ 13 years of age.
3. The subject has a secondarily infected traumatic lesion such as a small laceration, sutured wound or abrasion. The infected portion of the laceration or sutured wound should not exceed 10 cm in length with surrounding erythema not extending more than 2 cm from the edge of the lesion. Abrasions should not exceed 100 sq. cm in total area with surrounding erythema not extending more than 2 cm from the edge of the abrasion.

Note: subjects with multiple wounds may be enrolled provided only one wound is infected.

4. The subject has had a negative urine pregnancy test prior to enrollment (if of childbearing potential)
5. Subject must comply with using two barrier methods of contraception (if of childbearing potential) or be of non-childbearing potential (post-menopausal or surgically sterile).
6. The subject has a Skin Infection Rating Score of at least 8.
7. The subject is willing and able to comply with the study protocol.
8. The subject and guardian, if applicable, has given written informed, dated consent, and written assent, if applicable, to participate in the study.

Additional Pediatric Inclusion Criteria, POST IDMC review

A pediatric subject < 13 years of age will be included in the study **AFTER** IDMC review, if the following additional inclusion criteria are met:

9. The subject is ≥ 9 months of age.
10. The parent/legal guardian is willing to comply with the protocol.
11. The parent/legal guardian has given written informed, dated consent for the subject to participate in the study.

5.2.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. The subject has demonstrated a previous hypersensitivity reaction to penicillins, cephalosporins, or other β -lactam antibiotics, or the subject has demonstrated a

previous hypersensitivity reaction pleuromutilin or any component of the ointment (refer to the Investigator Brochure for composition of SB-275833 ointment).

2. The subject has a secondarily infected animal/human bite, or a puncture wound.
3. The subject has a chronic ulcerative lesion that is unlikely to have *Staphylococcus aureus* or *Streptococcus pyogenes* as the causative agent.
4. The subject has an underlying skin disease, such as pre-existing eczematous dermatitis, with clinical evidence of secondary infection.
5. The subject has systemic signs and symptoms of infection (such as fever; defined as an oral temperature greater than 101° F or 38.3° C).
6. The subject has a bacterial skin infection which, due to depth or severity, in the opinion of the investigator, cannot be appropriately treated by a topical antibiotic.
7. The subject requires surgical intervention for treatment of the infection prior to enrollment in the study, or is likely to require such intervention during the course of the study.
8. The subject has received a systemic antibacterial or steroid, or has applied any topical therapeutic agent (including glucocorticoid steroids, antibacterials and antifungals) directly to the wound, less than 24 hours prior to study entry.
9. The subject has a serious underlying disease.
10. The subject is pregnant, breast feeding or planning a pregnancy during the study.
11. The subject has used an investigational drug within 30 days prior to entering the study.
12. The subject has been previously enrolled in study SB-275833/030, or SB-275833/029.

Additional Pediatric Exclusion Criterion for subjects 9 months to less than 13 years of age:

13. The subject has systemic signs and symptoms of infection (such as fever; defined as a temperature equivalent to a rectal temperature greater than 101°F or 38.3°C).

5.2.3. Other Eligibility Criteria Considerations

To assess any potential impact on subject eligibility with regard to safety, the investigator must refer to the following document(s) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the investigational product(s) being used in this study:

Investigator Brochure/Clinical Investigator Brochure (IB/CIB) [GlaxoSmithKline Document NumberUM2003/00089/00.

Approved product label for cephalexin [KEFLEX Package Insert, 2002].

6. STUDY ASSESSMENTS AND PROCEDURES

6.1. Demographic and Baseline Assessments

Before entering the study, each subject who has met all inclusion/exclusion criteria, will provide a medical history and have a physical examination which will include height, weight, temperature, pulse rate and blood pressure. Pertinent findings will be recorded in the eCRF. Information on prior and concomitant medications will also be recorded. In addition, the following evaluations will be performed:

6.1.1. Clinical Diagnosis of Infection

The investigator will make a clinical diagnosis of secondarily infected traumatic lesion, using the following definitions:

Secondarily Infected Open Wounds

Secondarily infected lesions are infections occurring within a laceration, sutured wound, abrasion, etc.

Simple Abscess (not requiring incision and drainage)

A simple abscess (not requiring incision and drainage) is a localized collection of pus caused by suppuration buried in tissues. Each is characterized by painful local inflammation and tenderness.

N.B. A simple abscess may be sampled by needle aspiration, but only as a means to obtain material for bacteriology specimens.

Subjects who may need to be hospitalized, require parenteral antibiotic therapy, or have systemic signs and symptoms of disseminated infection are not to be enrolled.

6.1.2. Clinical Evaluation of Infection

The investigator will grade the wound infection for exudate/pus, crusting, erythema/inflammation, tissue warmth, tissue edema, itching, and pain, according to the Skin Infection Rating Scale (Appendix 5, Skin Infection Rating Scale). In addition, the wound to be treated will be measured in centimeters, using a standard metric ruler, and the measurement recorded in the eCRF.

6.1.3. Bacteriology

- Appropriate pre-treatment specimens will be obtained if available, by either curettage or aseptic needle aspiration of purulent material, for gram stain, culture and susceptibility testing, prior to initiating therapy. Swab samples may be obtained only if, in the opinion of the investigator, collection by curettage or aspiration is not appropriate. Specimens that are not obtained using either curettage or aseptic needle aspiration must have the reason documented in the eCRF. Crusted lesions should have the crusts lifted with sterile forceps and the area beneath cultured. If septicemia is suspected, the subject should not be enrolled into the study.

- All specimens collected for bacteriology should be stored and transported as instructed by the Central Laboratory — Quest Clinical Laboratories.

6.2. Safety

6.2.1. Safety Laboratory Tests

The laboratory studies listed below will be performed at the baseline visit and at on-therapy visits 2 and 3 (day 3-4, day 7-9) for all subjects. Additionally, for all subjects >13, the laboratory studies listed below will be performed at follow-up visits 4 and 5 (day 12-14 and day 17-19).

Hematology

Hemoglobin, hematocrit, red cell count, platelet count, white cell count, differential white cell count (neutrophils, lymphocytes, monocytes, eosinophils, basophils).

Blood Chemistries

Alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), blood urea nitrogen (BUN), gamma glutamyl transferase, albumin, total bilirubin, total protein, creatine kinase, lactate dehydrogenase, serum creatinine, uric acid, glucose, calcium, sodium, potassium and calculated creatinine clearance

Urinalysis

Blood, glucose, protein and ketones by dipstick and RBCs and WBCs by microscopy.

6.2.2. Pharmacokinetic Sampling

PK samples will be taken in the first 500 enrolled adult subjects, and all enrolled adolescents and children, for the purpose of population PK analysis, to further characterize the exposure of 1% SB-275833, when applied topically to the skin, if the data permit.

A blood sample (approximately 3 mL) for PK analysis will be collected at the on therapy visit (day 3-4). For adult subjects, the PK sample will be the predose sample of the first dose on day 3 or 4; for pediatric subjects, the PK sample will be randomly spread in either one of the three windows (0 (predose)-4 h, 4-8 h, or 8-12 h) following the first dose on day 3 or 4.

For the adult population, only a single predose sample is to be collected, as full PK profiles were studied in the previous patient PK study 029. For the pediatric population, the randomized block design mentioned above (subjects randomly assigned to each blood collection window) will allow the capture of a full PK profile over an entire dosing interval to better evaluate systemic absorption and possible accumulation in pediatric population.

In the previous patient PK study 029 (which used same dosing regimen as the current study, i.e., bid for 5 days), a full PK profile was assessed on day 1 and day 5, as well as single predose samples on day 3 and day 4. Minimal systemic absorption was observed with most of the samples having non-measurable concentrations, indicating that steady-state had been reached by day 3. In this current study, there is no clinical visit scheduled on day 5; for feasible practice, day 3 or 4 (Visit 2) is selected because it still allows the assessment of PK after multiple doses.

6.2.3. Pregnancy

6.2.3.1. Pregnancy testing

A urine pregnancy test must be performed locally for women of childbearing potential prior to the administration of study medication (Day 1) and must be negative for dosing to proceed. Subjects who become pregnant during the study should discontinue the study immediately. A pregnancy test will also be performed at the final follow-up visit (Day 17-19), in order to confirm that the subject was not pregnant during any phase of the study.

6.2.3.2. Time period for collecting pregnancy information

Details of all pregnancies that occur during the treatment and the follow-up period must be documented and reported to GSK. In addition, any pregnancies brought to the attention of the investigator after this period, and where it is known that study medication was taken within 30 days prior to or at the time of conception, must also be reported.

Details on any pregnancies identified during the screening phase/prior to study medication administration do not need to be collected.

6.2.3.3. Action to be taken if pregnancy occurs

The investigator, or his/her designee, will collect pregnancy information on any female subject who becomes pregnant while participating in this study. The investigator, or his/her designee, will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of a subject's pregnancy. The subject will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or a SAE, as described in Section 10.6, "Recording of AEs and SAEs" and will be followed as described in Section 10.8, "Follow-up of AEs and SAEs."

A spontaneous abortion is always considered to be a SAE and will be reported as described in Section 10, "Adverse Events (AE) and Serious Adverse Events (SAE)." Furthermore, any SAE occurring as a result of a post-study pregnancy **and** is considered

reasonably related to the investigational product by the investigator, will be reported to GSK as described in Section 10.11, "Post-study AEs and SAEs." While the investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.

6.3. Study Visits

6.3.1. Baseline Visit

At the baseline visit (day 1), subjects or parents/legal guardians will be asked to provide written, dated informed consent and/or assent, and the investigator will perform a medical history and determine if the subject has the protocol-defined diagnosis of secondarily infected traumatic lesion, and meets all the other study entry criteria as defined in the inclusion and exclusion criteria. The subject will have a physical examination to include height, weight, temperature, pulse rate and blood pressure. A urine pregnancy test must be performed locally for women of childbearing potential prior to the administration of study medication, and must be negative for dosing to proceed. An additional urine pregnancy test is to be performed at the final follow-up visit.

Blood specimens will be drawn and urine collected for safety lab tests, and are to include specimens for hematology, blood chemistries, and urinalysis; details of these tests are found in Section 6.2.1.

Samples of the exudate/pus will be obtained for quantitative culture and susceptibility testing, using curettage or aspiration techniques. Swab samples may be obtained only if, in the opinion of the investigator, collection by curettage or aspiration is not appropriate. Specimens that are not obtained using either curettage or aseptic needle aspiration must have the reason documented in the eCRF. All subjects should be started on treatment prior to bacteriological confirmation of a pathogen. The infection will be graded for exudate/pus, crusting, erythema/ inflammation, tissue warmth, tissue edema, itching, and pain according to the Skin Infection Rating Scale (See Appendix 5, Skin Infection Rating Scale).

The wound will be measured in centimeters, prior to treatment, at its widest and longest dimensions, or where the diameter is largest. The measurement must not include surrounding erythema.

If the wound is covered, the type of dressing used will be recorded in the eCRF as 'occlusive', 'semi-occlusive', or 'none'.

A swab of the anterior nares will be obtained, to determine the presence of *Staphylococcus aureus* carriage.

Subjects or parents/legal guardians will be instructed when to return for the on-therapy visit.

6.3.2. On-Therapy Visit

Subjects will return for on-therapy evaluations on Day 3-4.

The subject will be assessed for safety/tolerance of the study medication and the investigator will perform a clinical evaluation of the subject. The investigator will assess the wound infection according to the Skin Infection Rating Scale, and make a clinical evaluation of the subject's response to therapy. If in the investigator's clinical judgement, the condition of the subject has worsened or has not improved, the subject may be withdrawn from the study and treated at the discretion of the investigator. This visit will then be considered the end of therapy visit for this subject, nasal swabs will be collected and, if exudate is present, wound culture specimens will be obtained for culture and susceptibility tests. The subject will be instructed to return for the final follow-up visit (day 17-19).

A blood sample will be collected for PK analysis. For adult subjects, the PK sample will be the predose sample of the first dose on day 3 or 4; for pediatric subjects, the PK sample will be randomly spread in either one of the three windows (0 (predose)-4 h, 4-8 h, or 8-12 h) following the first dose on day 3 or 4. The time of application of the previous evening dose, as recorded in the subject diary, as well as the time of the first dose of study medication for day 3 or 4, and the time of the blood draw will be recorded in the eCRF and on the laboratory requisition form.

Blood specimens will be drawn and urine will be collected for safety lab tests.

The type of dressing used will be recorded in the eCRF as 'occlusive', 'semi-occlusive', or 'none'.

The subject/parent/legal guardian will be queried as to the use of any concomitant medications and the occurrence of any adverse experiences (AEs).

Subjects or parents/legal guardians of subjects continuing in the study will be instructed when to return for the next visit.

6.3.3. Topical End of Therapy (2-4 days post- topical therapy) Oral On-Therapy Visit

At day 7-9 (2-4 days post-topical therapy; oral on-therapy), the subject will be assessed for safety/tolerance of the study medication and the investigator will perform a clinical evaluation of the subject. The investigator will assess the wound infection according to the Skin Infection Rating Scale, make a clinical evaluation of the subject's response to therapy, and determine the subject's clinical outcome. If in the investigator's clinical judgement, the condition of the subject has worsened, or if the Skin Infection Rating Scale score is higher than the score recorded from the baseline visit (day 1), then the subject may be withdrawn from the study and treated at the discretion of the investigator. This visit will then be considered the end of therapy visit for this subject, nasal swabs will be collected and, if exudate is present, wound culture specimens will be obtained for culture and susceptibility tests.

Blood specimens will be drawn and urine will be collected for safety lab tests.

Subjects who have exudate present will also have nasal and wound culture specimens obtained for culture and susceptibility tests.

The wound is to be measured in centimeters at its widest and longest dimensions, or where the diameter is largest.

The type of dressing used will be recorded in the eCRF as 'occlusive', 'semi-occlusive', or 'none'.

All topical medication/placebo must be returned at this visit.

The subject/parent/legal guardian will be queried as to the use of any concomitant medications and the occurrence of any adverse experiences (AEs).

The subject or parents/legal guardians will be instructed to return for the next visit.

6.3.4. Topical Follow-Up Visit (7-9 days post-topical therapy) Oral End of Therapy Visit (2-4 days post- oral therapy)

At day 12-14 (7-9 days post-topical therapy; 2-4 days post-oral therapy), the subject will be assessed for safety/tolerance of the study medication and the investigator will perform a clinical evaluation of the subject. The investigator will assess the wound infection according to the Skin Infection Rating Scale, make a clinical evaluation of the subject's overall response to therapy, and determine the subject's clinical outcome. If in the investigator's clinical judgement, the condition of the subject has worsened, then the subject may be treated at the discretion of the investigator. The subject or parents/legal guardians will be instructed to return for the final follow-up visit.

If exudate is present, bacteriology specimens will be obtained for culture and susceptibility tests.

A nasal swab of the anterior nares will be obtained on all subjects

For all subjects ≥ 13 years of age, blood specimens will be drawn and urine will be collected for safety lab tests. Subjects who are <13 years of age are not required to have safety labs collected at this visit.

The wound is to be measured in centimeters at its widest and longest dimensions, or where the diameter is largest.

The type of dressing used will be recorded in the eCRF as 'occlusive', 'semi-occlusive', or 'none'.

All oral study medication/placebo is to be returned at this visit.

The subject/parent/legal guardian will be queried as to the use of any concomitant medications and the occurrence of any adverse experiences (AEs).

6.3.5. Final Follow-Up Assessment (7-9 days post-oral therapy)

All subjects will be required to return for a follow-up visit 7-9 days after the last dose of oral study medication/placebo. For subjects who were a 'clinical success' at end of therapy (day 7-9 and day 12-14), the investigator will complete the Skin Infection Rating Scale. In addition, the investigator will determine the clinical outcome by comparing the subject's condition at oral end of therapy (2-4 days post-oral therapy; day 12-14) with that at follow-up (7-9 days post-oral therapy). For those subjects who were a 'clinical failures' at either end of therapy visit (day 7-9 or day 12-14), or who were withdrawn from the study prior to the end of therapy visit (day 7-9 or day 12-14), this visit is required for monitoring any adverse experience that began on-therapy (day 3-4, day 7-9) and for recording additional medication.

A urine pregnancy test will again be performed for any subject who had a urine pregnancy test at the baseline visit.

If exudate is still present, or the infection has recurred, bacteriology specimens will be obtained for culture and susceptibility tests.

The type of dressing used will be recorded in the eCRF as 'occlusive', 'semi-occlusive', or 'none'.

For all subjects \geq 13 years of age, blood specimens will be drawn and urine will be collected for safety lab tests. Subjects who are <13 years of age are not required to have safety labs collected at this visit.

A nasal swab of the anterior nares will be obtained on all subjects to determine the presence or absence of *Staphylococcus aureus* nasal carriage.

6.4. Pharmacokinetics

Sample Collection

Samples will be collected into tubes containing EDTA and immediately chilled on crushed ice. Plasma will be separated by centrifugation at approximately 4°C and transferred to polypropylene specimen containers labeled with the study number (SB-275833/030), subject number, study day, date, and nominal time of collection (eg, predose for adult subjects, and either one of the three windows [0(predose)-4 h, 4-8 h or 8-12 h postdose] for pediatric subjects). Plasma specimens will be immediately frozen and stored at approximately -20°C (or colder).

Bioanalysis

Plasma sample analysis will be performed under the management of Worldwide Bioanalysis, DMPK, GlaxoSmithKline. Plasma specimens for pharmacokinetic analysis from each center will be transferred in the frozen state to a central laboratory, which will then be transferred to Worldwide Bioanalysis, DMPK, King of Prussia, Pennsylvania.

Upon receipt, samples will be stored at approximately -20°C (or colder) until analysis. Concentrations of SB 275833 will be determined in all plasma samples using the currently approved analytical methodology. Raw data will be stored in the GLP Archives, GlaxoSmithKline.

PK methods are discussed in Section 11.9.1

7. INVESTIGATIONAL PRODUCT(S)

7.1. Description of Investigational Product

1% SB-275833 drug product will be provided as approximately 10 grams of an off-white smooth ointment in collapsible aluminium tubes with reverse taper puncture tip caps. Placebo for SB-275833 ointment will be available in 10 gram plain aluminum tubes and contain only the ointment base.

Cephalexin will be supplied as either an overencapsulated cephalexin 250 mg capsules, or for oral suspension, as a powder for reconstitution containing cephalexin 250 mg/5 mL. Matching placebos to the overencapsulated cephalxin 250 mg capsule and to the oral suspension will also be supplied.

7.2. Dosage and Administration

The duration of topical treatment will be 5 days, and for oral treatment 10 days. Treatment should continue for the full duration even if the lesion has fully healed. Treatment may be terminated at any time if, in the opinion of the investigator, the infected lesion has failed to respond.

Subjects or the study personnel will apply a suitable amount of 1% SB-275833 ointment to cover the entire wound two times daily, at 10 – 12 hour intervals. The preparation should be applied gently to the wound with a sterile swab.

Use of gauze, bandage, etc., is permitted. Children young enough to inadvertently lick the medication or the wound site must have their treated wound covered with gauze or a semi-occlusive bandage. The type of dressing used will be recorded in the eCRF as 'occlusive', 'semi-occlusive', or 'none'.

7.3. Dose Rationale

All subjects entered into the study will be treated with either topical 1% SB-275833 ointment, twice daily for 5 days, and oral cephalexin placebo twice daily for 10 days, or SB-275833 matching placebo ointment, twice daily for 5 days and oral cephalexin twice daily for 10 days. Based on the maximum size of the infected portion of the wound to be treated (100cm², or 10 cm in length), the maximum amount of ointment/placebo formulation applied per dose to a subject would be 10 mg per cm² (i.e., 1 gram per 100

cm²). Adult subjects will receive 500 mg (as two 250 mg capsules) oral cephalixin/placebo (as two 250 mg over-encapsulated matching capsules) twice daily for 10 days, as per labelled dosing. Pediatric subjects ≤40 kg will receive 12.5 mg/kg oral cephalixin/placebo suspension, twice daily for 10 days, as per labelled dosing.

7.3.1. 1% SB-275833 ointment

Irritation evaluations on abraded (tape-stripped) skin indicate that 2% SB-275833 ointment achieved scores that were more similar to positive irritant control (sodium laurel sulfate) than sterile water control. Under the same abraded skin conditions, concentrations up to 1% SB-275833 ointment were similar to petrolatum vehicle or sterile water control, when assessed under occlusion through 14 daily 24-hour applications, and were well tolerated.

In vivo studies, using a mouse suture wound model, have shown statistical significance in the efficacy of 1% SB-275833 ointment, when dosed for ≥ 4 days BID, against susceptible and resistant strains of *Staphylococcus aureus* (MRSA, mupR), and *Streptococcus pyogenes*, when compared to placebo and non-treated controls.

The choice of 1% over 2% SB-275833 ointment concentration is supported by *in vivo* efficacy animal studies, and a healthy volunteer PK study, as well as a study conducted in healthy volunteers to determine the irritation potential of several concentrations of SB-275833 ointment.

7.3.2. Cephalixin comparator

Oral antibiotics are the gold standard for treatment of secondarily infected traumatic lesions (SITL), accounting for over 70% of such use, according to market research data. Market research also indicates that cephalixin is the most widely prescribed oral antibiotic for SITL in the US. Oral cephalixin was chosen as the comparator for Phase III studies as it has been approved in several European countries, as well as the US, for the treatment of infections of skin and soft tissues. The use of a cephalixin comparator, therefore, allows multinational studies to be conducted, that will support approval in both the US and Europe.

One percent SB-275833 ointment is expected to provide a safe and effective topical alternative to orals for treatment of SITL. This could promote reduced reliance on use of oral antibiotics in SITL, with the attendant benefit of potentially avoiding the systemic side effects of an oral agent in addition to potential benefits to society associated with decreased use of a systemic cephalosporins, with the attendant microbial resistance concerns.

7.4. Blinding

Only in the case of an emergency, when knowledge of the investigational product is essential for the clinical management or welfare of the subject, the investigator may unblind a subject's treatment assignment. If the blind is broken for any reason, the

investigator must notify GSK **immediately** of the unblinding incident without revealing the subject's study treatment assignment. In addition, the investigator will record the date and reason for revealing the blinded treatment assignment for that subject in the appropriate eCRF.

If a serious adverse event (SAE; as defined in Section 10.2, "Definition of a SAE") is reported to GSK, Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for the individual subject. If an expedited regulatory report to one or more regulatory agencies is required, the report will identify the subject's treatment assignment. When applicable, a copy of the regulatory report may be sent to investigators in accordance with relevant regulations, GSK policy, or both.

7.5. Treatment Assignment

Subjects will be assigned to study treatment, as shown in Treatment Groups and Dosing Details, in accordance with the 2:1, pre-determined randomization schedule, provided by the sponsor. Randomization will be performed centrally using an automated telephone system. The block size will remain confidential.

Once a treatment number has been assigned to a subject, if the subject is withdrawn, the number may not be reassigned to any other subject at the site.

The subject randomization will be stratified by site and age (9 months -<6 years old, ≥6- <13, ≥13) under a unique schedule for both studies. At most 60% of subjects will be allowed to be enrolled from sites in Europe and International regions. Once the enrollment is completed with sufficient numbers of subjects for both studies, the sites will be size-ranked within geographical regions (North America and outside North America) and randomized accordingly, to one or the other of the studies. When assigning the sites to one or the other of the studies, a randomization scheme will be used, stratified by region, using blocks of four, to ensure balanced regional enrollment between the two trials.

7.6. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

1% SB-275833 ointment formulation/placebo will be packaged in collapsible aluminium tubes with reverse taper puncture tip caps.

Cephalexin 250 mg capsules and matching placebo will be supplied in HDPE bottles with induction heat sealed closures.

Cephalexin suspension/placebo, 250mg/5ml will be supplied as a dry powder in a bottle.

7.7. Preparation

Reconstitution will be done at the site, as per labelled directions for cephalexin suspension and placebo.

7.8. Handling and Storage

Investigational product must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive investigational product, in accordance with all applicable regulatory requirements. Only authorized site staff may supply or administer investigational product. All investigational products must be stored in a secure area with access limited to the investigator and authorized site staff and under physical conditions that are consistent with investigational product-specific requirements.

SB-275833/placebo and cephalexin capsules/placebo will be stored at controlled room temperature in a locked cabinet or room.

Dry powder cephalexin/placebo should be stored in the original container in a dry atmosphere at room temperature in a locked cabinet or room. Reconstituted suspension must be stored refrigerated.

7.9. Product Accountability

The investigator is responsible for investigational product accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated site staff must maintain investigational product accountability records throughout the course of the study. This person(s) will document the amount of investigational product received from GSK, the amount supplied and/or administered to and returned by subjects, if applicable.

7.10. Assessment of Compliance

A diary card will be provided for the subject or parent/legal guardian to record each application/dose of the study medication/placebo. Diary cards are for recording purposes only, are to be kept by the site as source documentation, and will not be sent in-house to GSK. The number of doses of 1% SB-275833, as recorded on the card will be documented in the eCRF.

The quantity of comparator drug dispensed and not used (returned) is documented on the drug accountability record and in the eCRF. This data will allow the compliance of the subject to be determined.

7.11. Treatment of Investigational Product Overdose

If an overdose is known or suspected, the subject or parent/guardian must contact the investigator as soon as possible. Any signs or symptoms of overdosage, for 1% SB-

275833, either topically or by accidental ingestion, will be treated symptomatically. No specific antidote is known. Systemic absorption is minimal, however, and SB-275833 is rapidly cleared by the liver.

In the case of suspected overdose of the comparator drug, the investigator must consult the approved product label for information on treating an overdose.

7.12. Occupational Safety

Investigational product is not expected to pose significant occupational safety risk to site staff under normal conditions of use and administration. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

Precautions are to be taken, however, to avoid direct skin contact, eye contact, and generating aerosols or mists. In the case of unintentional occupational exposure, treat as if the substance contains the active pharmaceutical even though it is absent from placebo formulations, and notify the monitor.

8. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

8.1. Permitted Medications

A reasonable effort will be made to document any medications the subject received within 30 days prior to the Baseline visit. Any medication taken within 7 days prior to dosing will be recorded as a prior medication. All concomitant medications taken during the study will be recorded in the eCRF with indication, dose information and dates of administration.

All concomitant medications taken during the study will be recorded in the eCRF with indication, dose information, and dates of administration.

8.2. Prohibited Medications

Topical agents of any type, to the treatment site, as well as systemic antibiotics and steroids, are prohibited during therapy (both topical and oral) and for seven days after the end of therapy (both topical and oral).

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Subject Completion

Subjects who have completed all visit as defined by the protocol, and at a minimum, the baseline, topical and oral end of therapy visits, and the follow-up visits, will be considered as having completed the study.

9.2. Subject Withdrawal

9.2.1. Subject Withdrawal from Study

A subject may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator. Reasonable efforts must be made by study personnel to keep subjects in the study. A subject may be discontinued prior to completion of the study for the following reasons:

- Adverse event
- Pregnancy
- Deviation from protocol [this includes lack of compliance (dosing, visit schedule)]
- Subject lost to follow-up
- Termination of the study by GlaxoSmithKline
- Other (reason to be documented in the eCRF)

All adverse events leading to withdrawal of a subject must be fully documented and followed up as appropriate. To ensure that all withdrawals due to adverse events are correctly identified, "Adverse Event" should only be checked as the reason for withdrawal on the Study Conclusion page for those subjects for whom an adverse event was considered to be the direct cause of the subject withdrawing from the study. This is particularly important when adverse events are ongoing at the time of withdrawal but the reason for withdrawal is not related to the adverse events.

Data from subjects withdrawing from the study will be viewed as evaluable unless criteria for inclusion and retention are not met or criteria for exclusion are met.

Culture material for bacteriology should be obtained, if possible, at the time of the subject's withdrawal and the results recorded on the eCRF. Subjects who withdraw must return for a follow-up visit 7-9 days after stopping treatment to obtain information about adverse experiences and additional medication.

9.3. Screen and Baseline Failures

Subjects who do not meet the inclusion/exclusion criteria (Section 5.2), including those subjects with a positive urine pregnancy test will be considered screen and baseline failures.

10. ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS (SAE)

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol. During the study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

10.1. Definition of an AE

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Examples of an AE **includes**:

- Significant or unexpected worsening or exacerbation of the condition/indication under study. See Section 10.3, “Lack of Efficacy”, for additional information.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- Significant failure of expected pharmacological or biological action. See Section 10.3, “Lack of Efficacy” for additional information.

Examples of an AE **does not include** a/an:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

For GSK clinical studies, AEs may include pre- or post-treatment events that occur as a result of protocol-mandated procedures (i.e., invasive procedures, modification of subject's previous therapeutic regimen).

10.2. Definition of a SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

- a) results in death.
- b) is life-threatening.

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- c) requires hospitalization or prolongation of existing hospitalization.

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- d) results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- e) is a congenital anomaly/birth defect.
- f) Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood

dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3. Lack of Efficacy

“Lack of efficacy” per se will not be reported as an AE. The signs and symptoms or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the AE or SAE definition (including clarifications).

10.4. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Abnormal laboratory findings (e.g., clinical chemistry, hematology, urinalysis) or other abnormal assessments (e.g., vital signs, etc.) that are judged by the investigator as **clinically significant** will be recorded as AEs or SAEs if they meet the definition of an AE, as defined in Section 10.1, "Definition of an AE", or SAE, as defined in Section 10.2, "Definition of a SAE". Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will **not** be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

10.5. Time Period, Frequency, and Method of Detecting AEs and SAEs

Any pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study (i.e., before informed consent) should be recorded as Medical/Surgical History. In addition, any medical occurrence which is reported after informed consent is obtained but prior to administration of study medication will be documented as Medical/Surgical History.

Any signs and symptoms present at the time study medication is first administered will be documented as baseline signs and symptoms. All AEs occurring after administration of study medication and on or before the final follow up visit must be reported as Adverse Events. All AEs must be recorded irrespective of whether they are considered drug related.

At each visit/assessment in the period defined above, AEs will be evaluated by the investigator and recorded. AEs will be recorded until completion of the follow-up visit. Any AEs already documented at a previous assessment and designated as ongoing, should be reviewed at subsequent visits as necessary. If these have resolved, this should

be documented. If an AE changes in intensity/frequency then this should be recorded as a separate event (i.e., a new record started).

As a consistent method of soliciting AEs, the subject should be asked a non-leading question such as: "How do you feel?".

10.6. Recording of AEs and SAEs

Details of AE/SAE's will be entered directly into the eCRF. In the case of an SAE further information will be collected on the paper SAE form provided.

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

10.7. Evaluating AEs and SAEs

10.7.1. Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study. The assessment will be based on the investigator's clinical judgement. The intensity of each AE and SAE recorded in the eCRF should be assigned to one of the following categories:

Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: An event that prevents normal everyday activities.

An AE that is assessed as severe should not be confused with a SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 10.2, "Definition of a SAE".

10.7.2. Assessment of Causality

The investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The investigator will use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated. The investigator

will also consult the CIB/IB and/or Product Information, for marketed products, in the determination of his/her assessment.

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, it is very important that the investigator always make an assessment of causality for every event prior to transmission of the SAE eCRF or paper SAE form to GSK. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE eCRF or paper SAE form accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The investigator will provide the assessment of causality as per instructions on the SAE form in the eCRF or paper SAE form.

10.8. Follow-Up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide further information to GSK on the subject's condition.

All AEs and SAEs documented at a previous visit/contact and are designated as ongoing, will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. Once resolved, the appropriate AE/SAE eCRF page(s) or paper SAE forms will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

GSK may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a subject dies during participation in the study or during a recognized follow-up period, GSK will be provided with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded on the originally completed paper "SAE" form and within the eCRF, with all changes signed and dated by the investigator. The updated SAE eCRF and paper SAE form should be resent to GSK within the time frames outlined in Section 10.9.

10.9. Prompt Reporting of SAEs to GSK

SAEs will be reported promptly to GSK as described in the following table once the investigator determines that the event meets the protocol definition of an SAE.

10.9.1. Timeframes for Submitting SAE Reports to GSK

	Initial SAE Reports		Follow-up Information on a Previously Reported SAE	
Type of SAE	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hrs	<ol style="list-style-type: none"> Paper SAE forms to be faxed to GSK eCRF data to be transferred to GSK (replicated) 	24 hrs	<ol style="list-style-type: none"> Updated paper SAE form to be faxed to GSK Updated eCRF data to be transferred to GSK (replicated)

10.9.2. Completion and Transmission of the SAE Reports

Once an investigator becomes aware that an SAE has occurred in a study subject, she/he will report the information to GSK within 24 hours as outlined in Section 10.9, "Prompt Reporting of SAEs to GSK". The SAE eCRF or paper SAE form will always be completed as thoroughly as possible with all available details of the event, signed by the investigator (or designee), and forwarded to GSK within the designated time frames. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the form. The form will be updated when additional information is received.

The investigator will always provide an assessment of causality at the time of the initial report as described in Section 10.7.2, "Assessment of Causality".

Facsimile transmission of the paper SAE form and replication of the eCRF is the preferred method to transmit this information to the project contact for SAE receipt. In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE paper form sent by overnight mail. Initial notification via the telephone does not replace the need for the investigator to complete and replicate the eCRF within the time frames outlined in Section 10.9, "Prompt Reporting of SAEs to GSK".

GSK will provide a list of project contacts for SAE receipt, fax numbers, telephone numbers, and mailing addresses.

10.10. Regulatory Reporting Requirements For SAEs

The investigator will promptly report all SAEs to GSK in accordance with the procedures detailed in Section 10.9, "Prompt Reporting of SAEs to GSK." GSK has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the appropriate project contact for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

This protocol has been filed under an Investigational New Drug (IND) application with the US Food and Drug Administration (FDA). A given SAE may qualify as an IND Safety Report if the SAE is both attributable to the investigational product and unexpected. In this case, all investigators filed to the IND (and associated INDs for the same compound) will receive an Expedited Investigator Safety Report (EISR), identical in content to the IND Safety Report submitted to the FDA.

EISRs are prepared according to GSK policy and are forwarded to investigators as necessary. An EISR is prepared for a SAE that is both attributable to investigational product and unexpected. The purpose of the EISR is to fulfill specific regulatory and Good Clinical Practice (GCP) requirements, regarding the product under investigation.

When a site receives from GSK an Initial or Follow-up EISR or other safety information (e.g., revised Clinical Investigator's Brochure/Investigator's Brochure), the responsible person according to local requirements is required to promptly notify his or her IRB or IEC.

10.11. Post-study AEs and SAEs

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE detection period defined in Section 10.5, "Time Period, Frequency, and Method of Detecting AEs and SAEs", of the protocol.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the investigator will promptly notify GSK.

10.12. SAEs Related to Study Participation

An SAE considered related to study participation (e.g., procedures, invasive tests, a change in existing therapy), even if it occurs during the pre- or post-treatment period, will be reported promptly to GSK (see Section 10.9, "Prompt Reporting of SAEs to GSK").

11. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

11.1. Hypotheses

The primary efficacy analysis will be based on a comparison of proportions between the treatment groups, stratified by age and geographic region. Two-sided 95% confidence intervals will be used to estimate the difference in the proportion of successes between the treatment groups. A conclusion of non-inferior efficacy of 1% SB-275833 ointment

will be drawn if the lower limit of the confidence interval (Treatment 1% SB-275833 minus Treatment cephalixin) is above -10%

11.2. Treatment Comparisons of Interest

11.2.1. Primary Comparisons of Interest

The comparison of primary interest is the clinical success rate at follow-up (day 12-14 and day 17-19), for 1% SB-275833 ointment vs cephalixin for the PPC population as defined in the Section "Efficacy Study Populations".

Number and percent of subjects according to the binary response (treatment success or failure) will be presented for the primary endpoint. Analysis of the primary efficacy variable will be based on a comparison of proportions between the treatment groups. A two-sided 95% confidence interval for the difference in success rates will be used to evaluate the relative proportions of subjects who were treatment successes at follow-up (day 12-14 and day 17-19). A conclusion of non-inferior efficacy of 1% SB-275833 ointment will be drawn if the lower limit of the confidence interval for the treatment difference is greater than or equal to -10%. The primary efficacy endpoint will also be summarized for each treatment group and by center.

It is currently planned that the IDMC would stop the trial only for safety reasons, and not for reasons regarding efficacy, therefore, no alpha penalty for interim looks will be taken. Should the IDMC require data regarding efficacy, the IDMC charter states that a 0.000001 alpha penalty will be employed.

11.2.2. Other Comparisons of Interest

A similar analysis as described above will be performed for the secondary endpoints.

The number and percent of subjects in the PPB population who had methicillin resistant *Staphylococcus aureus* (MRSA) isolated at baseline (day 1) will be analyzed by clinical response at end of therapy (2-3 days post-therapy; day 7-8 and day 12-14) and at (7-9 days post-therapy; day 12-14 and day 17-19).

The number and percent of subjects in the PPB population who were nasal carriers of *Staphylococcus aureus* isolated at baseline (day 1) will be analyzed by clinical response at end of therapy (2-3 days post-therapy; day 7-8 and day 12-14) and at follow-up (7-9 days post-therapy; day 12-14 and day 17-19).

Where an AE occurs in >5% of subjects in any of the treatment groups, the proportion of subjects reporting that AE will be compared between treatment groups.

Subjects who receive the wrong coded study medication will be analyzed according to the treatment they received.

11.3. Interim Analysis

At the outset of the study, enrollment will be limited to subjects ≥ 13 years of age. An independent data monitoring committee (IDMC) consisting of outside experts in infectious disease, dermatology, and pediatrics, as well as a statistician, will be formed to assess emergent safety in adults and to make a determination whether the safety profile supports enrollment of pediatric subjects ≥ 9 months of age. When approximately 600 adult subjects are enrolled (400 on 1% SB-275833 ointment), across the two studies, the IDMC will convene to review the safety data (refer to IDMC charter for what exact data will be reviewed), and to determine if there are any significant safety issues that would preclude enrollment of children ≥ 9 month of age and older. Enrollment of subjects ≥ 13 will continue throughout the IDMC review period. Once the review is complete, and a positive recommendation made to the sponsor, enrollment of children ≥ 9 months of age will commence. Outputs for the IDMC review are produced independently of the sponsor, and all GSK study personnel will remain blinded to the treatment regimens.

Further details of the IDMC remit can be found in Section 12.9, and a copy of the IDMC charter is available from GSK upon request.

11.4. Sample Size Considerations

11.4.1. Sample Size Assumptions

This is a non-inferiority trial, with at least 90% power to detect a treatment difference greater than 10% (i.e., for a non-inferiority test with $\delta = 10\%$), with 5% type 1 error rate. Assuming the clinical success rates for 1% SB-275833 ointment and cephalexin groups are approximately 96%, it is estimated that, using a 2:1 randomization scheme, a sample size of 464 evaluable subjects in the topical SB-275833 group, and 232 in the cephalexin group, would be required. It is anticipated that approximately 870 subjects may be enrolled into the study in order to provide 696 evaluable subjects at follow-up (i.e., assume 20% subject non-evaluability). The 2:1 randomization and actual number of subjects (larger than required for 90% power) is intended to ensure sufficient numbers of subjects for the safety database.

No alpha adjustment for multiple comparisons is necessary.

11.4.2. Sample Size Sensitivity

The planned sample size is sufficiently large to allow for some variation in the efficacy rates assumed above for the study drug and comparator.

11.4.3. Sample Size Re-estimation

No sample size re-estimation will be utilised for this study; however, it is anticipated when the target sample size of 1740 is reached, there will be insufficient subjects in the youngest age cohorts to provide adequate safety and efficacy data. Enrollment will

continue beyond the targeted 1740 subjects in order to include additional pediatric subjects <13 years of age.

11.5. Analysis Populations

11.5.1. Efficacy Study Populations

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

Intent to Treat Clinical (ITTC): All randomized subjects who take at least one dose of study medication.

Intent to Treat Bacteriology (ITTb): All randomized subjects who take at least one dose of coded study medication and who have a clinical diagnosis of infection at baseline and documented evidence of a bacterial infection at baseline

Clinical Per Protocol (PPC): This population includes subjects who satisfy the inclusion/exclusion criteria and who subsequently adhere to the protocol. The clinical PP population is a subset of the clinical ITT population.

Bacteriology Per Protocol (PPB): The bacteriology PP population is a subset of the bacteriology ITT population. This population includes subjects who satisfy the inclusion/exclusion criteria and who subsequently adhere to the protocol, and who have documented evidence of a bacterial infection at baseline, from a specimen collected not more than 48 hours prior to beginning therapy.

As this is a non-inferiority study, the per protocol population is the most conservative approach to statistical analysis, hence, the PPC population is of primary interest.

The primary efficacy endpoint of the study is the clinical response to study medication at follow-up (day 12-14 and day 17-19) in the PPC population. A subject will be considered evaluable for the PP population if the subject:

- has met all study entry criteria
- has received at least 80% of the study medication; non-compliance will be considered a protocol violation
- has returned for clinical evaluation, minimally the end of therapy (day 7-8 and day 12-14)and follow-up visits (day 12-14 and day 17-19)
- has not used any of the prohibited concomitant medications (e.g., use of any topical product to the treatment site, systemic antibiotics, systemic steroids)

Any subject who was originally considered eligible for and is entered into this study, and is subsequently found to be at variance with any of the study entry criteria, as defined in Section 11.5.1 "Efficacy Study Populations", will be ineligible for the PPC and PPB analysis, due to a protocol violation.

Subjects will only be excluded from the PPC and PPB populations from the time that the protocol violation occurs. For example, a subject who returns for the follow-up visit outside the protocol specified time interval would be excluded from analyses at follow-up, but not from analyses at end of therapy.

If a subject is a PPC clinical failure at end of therapy, and subsequently violates the protocol between the end of therapy and follow-up, that subject will not be excluded from the PPC population at follow-up. If a subject is a PPB bacteriological failure at end of therapy, and subsequently violates the protocol between the end of therapy and follow-up, that subject will not be excluded from the PPB population at follow-up.

All decisions on eligibility for inclusion in these populations will be made prior to data evaluation.

The baseline demographic characteristics will be summarized to facilitate evaluation of possible differences between treatment groups, which may mask any real treatment effect that may exist. No formal hypothesis testing or interval estimation will be applied to baseline or demographic characteristics. Study medication compliance, protocol violations and reasons for dropout will be examined to evaluate bias, if any, in the proposed treatment comparisons.

11.5.2. Safety Study Population

There is one subject population defined for the safety analyses in this study:

All subjects who take at least one dose of coded study medication, (i.e., the ITTC population), are included in the safety analyses.

Counting will be based upon the number of subjects, not the number of AEs, i.e., if a subject reports the same AE on three occasions within a time interval, that AE will be counted only once. Subjects reporting more than one AE in a body system will be counted only once in the body system total

11.5.3. Pharmacokinetics Population

There is one subject population defined for the PK analysis in this study:

All subjects who take at least one dose of coded study medication, (i.e., the ITTC population), and have a PK sample taken are included in the PK analysis.

11.5.4. Data Sets

All datasets will be based on observed data. The primary dataset is based on the PPB population at the Follow-up visit (day 12-14 for SB-275833 and 17-19 for cephalixin).

11.6. General Considerations for Data Analysis

11.6.1. Withdrawal

Reasons for withdrawal are discussed in Section 9.2.

Data from subjects withdrawing from the study will be viewed as evaluable unless criteria for inclusion and retention are not met, or criteria for exclusion are met.

Subjects withdrawn from the study will not be replaced with another subject.

11.6.2. Missing Data

Missing data will not be imputed.

11.6.3. Other Issues

If any deviations from the original planned analyses, as per this protocol, are to be made, documentation will be provided in the RAP and final study report.

An exploratory evaluation of the effect on treatment response of various covariates (treatment, diagnosis of infection, Skin Infection Rating Scale score, micro, compliance, age, gender, center, etc) will be performed.

All efficacy analyses will be performed on the combined adult and pediatric populations; subset analyses of the pediatric population will also be performed if sufficient numbers of pediatric subjects are enrolled.

Also, a sub-analysis will be performed based on the subjects enrolled before the IDMC assessment and recommendation and the subjects enrolled after.

Subjects who receive the wrong coded study medication will be analyzed according to the treatment they received.

11.7. Efficacy Analyses

11.7.1. Primary Analysis

The comparison of primary interest is the clinical success rate at follow-up (day 12-14 and day 17-19), for 1% SB-275833 ointment vs cephalixin for the PPC population as defined in the Section "Efficacy Study Populations".

Number and percent of subjects according to the binary response (treatment success or failure) will be presented for the primary endpoint. Analysis of the primary efficacy variable will be based on a comparison of cure or success rates between the treatment groups. A two-sided 95% confidence interval for the difference in success rates will be used to evaluate the proportions of subjects who were treatment successes vs failures at follow-up (day 12-14 and day 17-19). A conclusion of non-inferior efficacy of 1% SB-275833 ointment will be drawn if the lower limit of the confidence interval for the treatment difference is greater than or equal to -10%. The primary efficacy endpoint will also be summarized for each treatment group and by center.

It is currently planned that the IDMC would stop the trial only for safety reasons, and not for reasons regarding efficacy, therefore, no alpha penalty for interim looks will be taken. Should the IDMC require data regarding efficacy, the IDMC charter states that a 0.000001 alpha penalty will be employed.

11.7.2. Secondary Analysis

A similar analysis as described above will be performed for the secondary endpoints.

The number and percent of subjects in the PPB population who had methicillin resistant MRSA isolated at baseline (day 1) will be analyzed by clinical response at end of therapy (2-3 days post-therapy; day 7-8 and day 12-14) and at (7-9 days post-therapy; day 12-14 and day 17-19).

The number and percent of subjects in the PPB population who were nasal carriers of *Staphylococcus aureus* isolated at baseline (day 1) will be analyzed by clinical response at end of therapy (2-3 days post-therapy; day 7-8 and day 12-14) and at follow-up (7-9 days post-therapy; day 12-14 and day 17-19).

Subjects who receive the wrong coded study medication will be analyzed according to the treatment they received.

11.7.3. Other Efficacy Analyses

An exploratory evaluation of the effect on treatment response of various covariates (treatment, diagnosis of infection, Skin Infection Rating Scale score, micro, compliance, age, gender, center, etc) will be performed.

All efficacy analyses will be performed on the combined adult and pediatric populations; subset analyses of the pediatric population will also be performed if sufficient numbers of pediatric subjects are enrolled.

Also, a sub-analysis will be performed based on the subjects enrolled before the IDMC assessment and recommendation and the subjects enrolled after.

An analysis will be done by using a mixed model with site as a random effect. The possible heterogeneity of treatment effects across centers will be explored by graphical display of the results of individual centers. If such is found and no explanation in terms of

other features of the trial can be found, a model with treatment by center interactions will be fitted.

11.8. Safety Analyses

When an AE occurs in >1% of subjects in any of the treatment groups, the proportion of subjects reporting that AE will be compared between treatment groups. Otherwise, safety data will be presented in tabular form and summarized descriptively.

11.8.1. Extent of Exposure

Extent of exposure to SB-275833 will be based on exposure generated through PK data.

The number of days exposed to study medication will be summarized using the statistics mean, standard deviation, median, minimum and maximum for all ITT subjects.

11.8.2. Adverse Events

Adverse events will be coded using the MedDRA coding dictionary, to give a preferred term and a body system, which will then be used when summarizing the data. Adverse events will be tabulated as counts and percents by intensity and relationship to study drugs.

11.8.3. Clinical Laboratory Evaluations

Abnormal clinical laboratory will be summarized descriptively by timepoints. Appendix 6 defines abnormal laboratory values of clinical concern.

11.9. Clinical Pharmacology Data Analyses

11.9.1. Pharmacokinetic Analyses

SB-275833 plasma concentration time data will be recorded in tabular and/or graphical form. The individual plasma concentration time data will be pooled and subjected to population PK analysis, using currently acceptable software methods. Selection of specific PK parameters to be used for analysis will depend upon the quality of the resultant data. An exploratory analysis will be performed to examine the relationship between derived PK parameters with selected efficacy parameters and significant adverse events. The influence of various covariates (e.g., age, body weight, gender, race, concomitant disease states, co-medication) on the PK parameters of SB-275833 may be examined.

PK analysis will be the responsibility of the Clinical Pharmacokinetics Department, CPDM, GlaxoSmithKline. All drug analyses and PK data will be stored in the Archive, GlaxoSmithKline. The pooled PK analysis will be the subject of a separate study report, to be produced independently of the clinical study report.

12. STUDY ADMINISTRATION

12.1. Regulatory and Ethical Considerations

12.1.1. Regulatory Authority Approval

GSK will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements prior to a site initiating the study in that country.

12.1.2. Ethical Conduct of the Study and Ethics Approval

This study will be conducted in accordance with "good clinical practice" (GCP) and all applicable regulatory requirements, including, where applicable, the the October 1996 version of the Declaration of Helsinki.

The investigator (or sponsor, where applicable) is responsible for ensuring that this protocol, the site's informed consent form, and any other information that will be presented to potential subjects (e.g., advertisements or information that supports or supplements the informed consent) are reviewed and approved by the appropriate IEC/IRB. The investigator agrees to allow the IEC/IRB direct access to all relevant documents. The IEC/IRB must be constituted in accordance with all applicable regulatory requirements. GSK will provide the investigator with relevant document(s)/data that are needed for IEC/IRB review and approval of the study. Before investigational product(s), GSK must receive copies of the IEC/IRB approval, the approved informed consent form, and any other information that the IEC/IRB has approved for presentation to potential subjects.

If the protocol, the informed consent form, or any other information that the IEC/IRB has approved for presentation to potential subjects is amended during the study, the investigator is responsible for ensuring the IEC/IRB reviews and approves, where applicable, these amended documents. The investigator must follow all applicable regulatory requirements pertaining to the use of an amended informed consent form including obtaining IEC/IRB approval of the amended form before new subjects consent to take part in the study using this version of the form. Copies of the IEC/IRB approval of the amended informed consent form/other information and the approved amended informed consent form/other information must be forwarded to GSK promptly.

12.1.3. Informed Consent

Informed consent will be obtained from the subject, or the subject's legal guardian if the subject is <18, before the subject can participate in the study. Patient assent must be obtained in addition to informed consent for children ages 6-17. The contents and process of obtaining informed consent/assent will be in accordance with all applicable regulatory requirements.

12.1.4. Investigator Reporting Requirements

As indicated in Section 10.10, the investigator (or sponsor, where applicable) is responsible for reporting SAEs to the IEC/IRB, in accordance with all applicable regulations. Furthermore, the investigator may be required to provide periodic safety updates on the conduct of the study at his or her site and notification of study closure to the IEC/IRB. Such periodic safety updates and notifications are the responsibility of the investigator and not of GSK.

12.2. Study Monitoring

In accordance with applicable regulations, GCP, and GSK procedures, GSK monitors will contact the site prior to the subject enrollment to review the protocol and data collection procedures with site staff. In addition, the monitor will periodically contact the site, including conducting on-site visits. The extent, nature and frequency of on-site visits will be based on such considerations as the study objective and/or endpoints, the purpose of the study, study design complexity, and enrollment rate.

During these contacts, the monitor will:

- Check the progress of the study.
- Review study data collected.
- Conduct source document verification.
- Identify any issues and address their resolution.

This will be done in order to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements.

The investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant issues.

At study closure, monitors will also conduct all activities described in Section 12.4, "Study and Site Closure."

The monitor will also review subject-completed health outcomes questionnaire(s) for extraneous written comments that could indicate possible AEs. Information collected in the eCRF and in the subject-completed health outcomes questionnaire(s) are independent components of this study. Except for header section information (e.g., subject number, treatment number, visit date) and other information as defined in the standard clarification agreement (SCA), neither the monitor nor the investigator will attempt to reconcile responses to individual questions/items recorded on the subject-completed health outcomes questionnaire(s) or health outcomes portions of diary cards (if

applicable) with other data recorded in the eCRFs. Subject-completed health outcome questionnaires generally serve as the source document; therefore, unless otherwise specified elsewhere, no other source document is available for data validation.

12.3. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

12.4. Study and Site Closure

Upon completion of the study, the monitor will conduct the following activities in conjunction with the investigator or site staff, as appropriate:

- Return of all study data to GSK.
- Data queries.
- Accountability, reconciliation, and arrangements for unused investigational product(s).
- Review of site study records for completeness.
- Return of treatment codes to GSK.

In addition, GSK reserves the right to temporarily suspend or prematurely discontinue this study either at a single site or at all sites at any time for reasons including, but are not limited to, safety or ethical issues or severe non-compliance. If GSK determines such action is needed, GSK will discuss this with the Investigator (including the reasons for taking such action) at that time. When feasible, GSK will provide advance notification to the investigator of the impending action prior to it taking effect.

GSK will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to GSK. In addition, arrangements will be made for all unused investigational product(s) in accordance with the applicable GSK procedures for the study.

Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and GSK.

12.5. Records Retention

Following closure of the study, the investigator must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible and are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or GSK standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

12.6. Provision of Study Results and Information to Investigators

When a clinical study report is completed, GSK will provide the major findings of the study to the investigator.

In addition, details of the study treatment assignment will be provided to the investigator to enable him/her to review the data to determine the outcome of the study for his/her subject.

12.7. Information Disclosure and Inventions

Ownership:

All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) are the sole property of GSK.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by site staff during the course of or as a result of the study are the sole property of GSK, and are hereby assigned to GSK.

If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed between GSK and the study site, that contract's ownership provisions shall apply rather than this statement.

Confidentiality:

All information provided by GSK and all data and information generated by the site as part of the study (other than a subject's medical records) will be kept confidential by the investigator and other site staff. This information and data will not be used by the investigator or other site personnel for any purpose other than conducting the study. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the investigator or site staff; (2) information which it is necessary to disclose in confidence to an IEC or IRB solely for the evaluation of the study; (3) information which it is necessary to disclose in order to provide appropriate medical care to a study subject; or (4) study results which may be published as described in the next paragraph. If a written contract for the conduct of the study which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

Publication:

For multicenter studies, the first publication or disclosure of study results shall be a complete, joint multicenter publication or disclosure coordinated by GSK. Thereafter, any secondary publications will reference the original publication(s).

Prior to submitting for publication, presentation, use for instructional purposes, or otherwise disclosing the study results generated by the site (collectively, a "Publication"), the investigator shall provide GSK with a copy of the proposed Publication and allow GSK a period of at least thirty (30) days [or, for abstracts, at least five (5) working days] to review the proposed Publication. Proposed Publications shall not include either GSK confidential information other than the study results or personal data on any subject, such as name or initials.

At GSK's request, the submission or other disclosure of a proposed Publication will be delayed a sufficient time to allow GSK to seek patent or similar protection of any inventions, know-how or other intellectual or industrial property rights disclosed in the proposed Publication.

If a written contract for the conduct of the study, which includes publication provisions inconsistent with this statement is executed, that contract's publication provisions shall apply rather than this statement.

12.8. Data Management

Subject data are collected by the investigator or designee using the electronic Case Report Form (eCRF) defined by GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data

cleaning procedures. Database freeze will occur when data management quality control procedures are completed. Original eCRFs will be retained by GSK, while the investigator receives a copy.

12.9. Independent Data Monitoring Committee (IDMC)

An IDMC will be utilized during the conduct of this study. An IDMC is generally assembled when there are significant safety or efficacy issues that warrant external objective medical and/or statistical review in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study.

The IDMC will be created to review the safety and tolerability of 1% SB-275833, prior to enrollment of subjects <13 years old. As subject numbers reach approximately 400 in total on the topical pleuromutilin arm across two Phase III SITL studies (approx. 600 total subjects), the IDMC will evaluate safety and tolerability data and compare the data to pre-agreed Go/No-Go criteria. If the compound is shown to be safe and well tolerated, enrollment of pediatric subjects ≥ 9 months of age will commence.

The IDMC consists of outside experts in infectious disease, dermatology, and pediatrics, as well as a statistician, and has the overall responsibility to protect the ethical and safety interests of subjects recruited into the studies, while protecting as far as possible the scientific validity of the data.

- The charter is in place and will be agreed to by both GSK and the IDMC, prior to the start of Phase III studies.
- IDMC charter also defines the type of information needed for review of safety results, reviews methods and procedures, and if appropriate, recommends stopping rules for safety.
- IDMC charter will be supplied by GSK and agreed to by the IDMC, and defines roles and responsibilities of both GSK and the IDMC.

The full IDMC Charter can be found in Appendix 7.

13. REFERENCES

GlaxoSmithKline APCM Data Sheet 97-55. Minimum inhibitory concentration of SB-275833 against aerobic and anaerobic isolates commonly associated with skin and skin structure infections. 11 November 1997.

GlaxoSmithKline APCM Data Sheet 98-45. Minimum inhibitory concentration of SB-275833 against clinical isolates of *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. 11 September 1998

GlaxoSmithKline Document Number DR98062. Preliminary Investigation of the IV Pharmacokinetics and Oral Dose Performance Of SB-275833 In the Conscious Rat. D R Smith, S J Bartlett, E Ward, P Jeffery. June 1998.

GlaxoSmithKline Document Number DR97422. Investigation of the Pharmacokinetics Of SB-275833 In the Dog. D R Smith, B J Passingham, S J Bartlett, E Ward, P Jeffery. June 1998.

GlaxoSmithKline Document Number DR98066. Investigation of the Pharmacokinetics of SB-275833 Following Intravenous Administration To the Cynomolgus Monkey. D R Smith, E. Ward, P. Jeffery. June 1998.

GlaxoSmithKline Document Number SB-275833/RSD-101B20/1. SB-275833/001. A Double-Blind, Placebo-Controlled, Dose-Rising Study to Assess The Tolerability, Safety, Pharmacokinetics and Sensitization Potential of Intranasal SB-275833 in Healthy Male Adults Following Single and Repeat Dosing. Rost, KL, Dewit O, Vousden M, Richie S, and Siederer S. 15 December 2000.

GlaxoSmithKline Document Number SB-275833/RSD-101SVK/1. SB-275833: Comparative Efficacies of SB 275833 (0.1, 0.5, 1, 2 and 5% w/w) and Mupirocin Against *S. aureus* (mupirocin resistant) and *S. pyogenes* in Experimental Surgical Wound Infection in Mice.

GlaxoSmithKline Document Number UM2003/00089/00. Clinical Investigator Brochure SB-275833 Fourth Edition. Brigandi, R. 13 October 2003.

KEFLEX (cephalexin, USP) Product Information. October, 2002

Leyden , J.J. Antibiotic Usage in Dermatological Practice, *Int J Dermatology* 1974; 13:342.

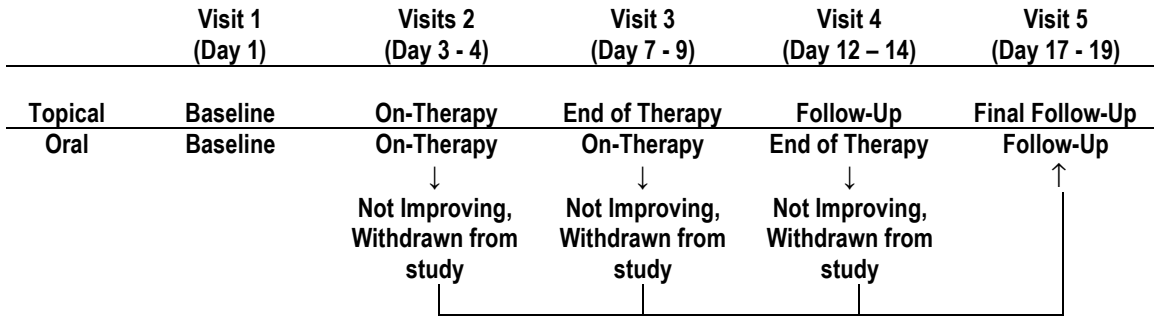
14. APPENDICES

14.1. Appendix 1 Time and Events Table

	Visit 1 (Day 1)	Visits 2 (Day 3 - 4)	Visit 3 (Day 7 - 9) ¹	Visit 4 (Day 12 - 14) ²	Visit 5 (Day 17 - 19) ³
Topical:	Baseline	On-Therapy	End of Therapy	Follow-Up	Final Follow-Up
Oral:	Baseline	On-Therapy	On-Therapy	End of Therapy	Follow-Up
Written Informed Consent	X				
Skin Infection Rating Scale ⁴	X	X	X	X	X
Urine Pregnancy test	X				X
Safety Laboratory tests	X	X	X	X ⁵	X ⁵
Nasal Swab culture	X		X ⁶	X	X
Bacteriology -wound	X		X ⁷	X ⁷	X ⁷
Medical History	X				
Perform Physical Examination	X				
Concomitant Medication	X	X	X	X	X
Adverse Experiences		X	X	X	X
Clinical Evaluation	X	X	X	X	X
Clinical Outcome Determination ⁸			X	X	X
PK sampling ⁹		X			
Assessment of Compliance		X	X	X	
Measurement of wound	X		X	X	

1. Two to four days post-topical therapy
2. Two to four days post-oral therapy/seven to nine days post-topical therapy
3. Seven to nine days post-oral therapy
4. Skin Infection Rating Scale assessment must be completed any time subject is a failure and is being withdrawn
5. Safety labs collected at visits 4 and 5 ONLY for subjects ≥ 13 years of age
6. Nasal swabs should be collected if subject is a clinical failure and/or if exudate is present and wound culture is collected
7. Bacteriology specimens should be collected if wound exudate is present or subject is a clinical failure
8. On addition to specified visits, clinical outcome determination must be completed any time subject is a failure and is being withdrawn
9. First 500 enrolled subjects and all pediatric subjects

14.2. Appendix 2 Study Schematic Diagram



14.3. Appendix 3 Rationale for Randomization Scheme

Traditionally, when two identical clinical studies are conducted simultaneously, sites are pre-assigned to one trial or the other. The site assignment is based on the anticipated enrollment rate for each site, with an attempt made to balance faster/slower enrolling sites across the two studies. Balancing sites that anticipate faster/slower enrollment between the studies is undertaken with the aim of achieving similar overall enrollment rates in the two studies, such that enrollment is completed across the trials at or close to the same time, to minimize time to progression to the next phase or to filing.

Investigators, however, are not always able to accurately predict the recruitment rates for their sites. Thus, despite the best efforts of study management personnel to balance faster or slower enrolling sites across studies based on the *predicted* enrollment capabilities, it is not uncommon for two identical studies conducted in parallel to complete enrollment at significantly different times. One study can potentially lag behind by several weeks to months, particularly in the case of relatively large trials. Another factor which can affect enrollment rates, which the Sponsor has experienced in previous studies, is that one or more sites may unexpectedly drop out of a trial, thus leaving fewer sites to complete enrollment, and compounding differences in time of completion between studies. Sites which drop out of a study at short notice cannot easily be replaced, given the procedures that must be undertaken to identify new sites, and for them to gain the necessary approvals. Similarly, individual sites may experience unforeseen delays in initiating the study and hence recruiting their first patient. Such events have led to the Sponsor considering methods to lessen the influence of these unpredictable factors in causing delays, and thus expedite drug development programs without sacrificing any scientific rigor or safety.

In the case of the SB-275833 phase 3 SITL studies 030A / 030B we are proposing a non-traditional procedure for randomizing sites to these two identical studies, which will ensure that both studies complete enrollment at approximately the same time. This has the potential to save a substantial amount of time in completing the clinical program and submitting the reports to regulatory authorities. For both of these studies, based on our anticipated weekly recruitment rate overall and the projected recruitment rates for some of the larger sites, if just one of these larger sites were to drop out after site assignment but prior to study start, this would project a minimum two week delay for that study. With a global development plan such as this project, issues can arise that delay starting enrollment in a specific country for one or two months, or even eliminate participation completely. With our proposed randomization scheme in place, then all remaining sites are available to enroll and thereby lessen the impact of that delay on an individual study.

Since allocation of a site to a specific study occurs prior to unblinding, the randomization scheme does not introduce any additional bias as to which study an individual subject or site is assigned to, over and above what occurs using traditional methods of site selection and randomization. Because there is the potential to significantly reduce the impact of unforeseen, but not uncommon, difficulties in planning for coordinated study timelines, we are using the described randomization scheme that allows for assignment of sites to one of the two studies after the total enrollment is adequate for both studies, but prior to unblinding of any data.

For these studies, the subjects will be enrolled and randomized to one or the other of the treatment arms from an unique randomization schedule, stratified by site and age. Once the enrollment is completed with enough subjects for both studies (total of 1740), sites will be size-ranked and randomized accordingly either study 030A or 030B. When assigning the sites to one or the other of the studies, a randomization scheme will be utilized, using blocks of four, stratified by region, to ensure balanced regional enrollment between the two trials.

Following are key points relating to this proposal, in particular those intended to ensure the process does not introduce bias, or compromise the independence of the two studies:

- Each site has its own patient randomization scheme, thus each site could be considered to constitute a 'mini' independent trial.
- Once enrollment is terminated, sites are rank-ordered by size (i.e. number of patients enrolled).
- Sites are then randomly assigned to study 030A or 030B using a randomization scheme with a block size of four.
- The randomization of sites to studies is done solely on the basis of the number of patients enrolled per site--at that point, the study will still be blinded, and no data manipulation will have taken place.
- The procedure and rules for ordering and randomizing sites to studies will be prospectively documented in the study protocols.
- The implementation of the pre-specified procedure and the information used in rank-ordering and randomizing sites to studies will be documented in the final clinical study reports.

In summary, we believe that the integrity and independence of the two trials are ensured by the randomization of patients to therapy at the site level and the subsequent and separate randomized allocation of sites to the individual trials, based solely on the number of patients enrolled at each site, and prior to breaking the study blind or manipulating data. Because the time delays that we are attempting to reduce are not predictable, we cannot state a precise amount for the expected time savings, however, we anticipate that it could be as great as one or two months; this is a time period that would have a significant impact on the development plans for 1% SB-275833.

14.4. Appendix 4 Country Specific Requirements

In the United States:

No country-specific requirements exist.

In Germany and Austria:

Country specific requirements for: Austria (enrollment of patients ≥ 18 years only) and Germany (enrollment of patients ≥ 18 years prior to IDMC review and ≥ 13 years after positive recommendation by the IDMC and agreement by the appropriate IEC/IRB are outlined in the country specific amendment document: UM2003/00090/02. Reduction in the number of blood draws may result in ethics committee agreement to allow Germany to enroll children <13 . These changes were not incorporated into the body the amendment.

14.5. Appendix 5 Skin Infection Rating Scale

Instructions: Rating should be based on a clinical interview and clinical examination. The rater must decide whether the rating lies on the defined scale steps (0,2,4,6) or between them (1,3,5).

Item	Score
1. Exudate/Pus	0 - Absent
	1 -
	2 - Mild
	3 -
	4 - Moderate
	5 -
	6 – Severe
2. Crusting:	0 - Absent
	1 -
	2 - Mild
	3 -
	4 - Moderate
	5 -
	6 – Severe

SKIN INFECTION RATING SCALE (continued)

Item	Score
3. Erythema/Inflammation:	0 - Absent
	1 -
	2 - Mild
	3 - _____
	4 - Moderate
	5 -
	6 - Severe
4. Tissue warmth:	0 - Absent
	1 -
	2 - Mild
	3 - _____
	4 - Moderate
	5 -
	6 - Severe
5. Tissue Edema:	0 - Absent
	1 -
	2 - Mild
	3 - _____
	4 - Moderate
	5 -
	6 - Severe

SKIN INFECTION RATING SCALE (continued)

Item	Score
6. Itching:	0 - Absent
	1 -
	2 - Mild
	3 - _____
	4 - Moderate
	5 -
	6 - Severe
7. Pain:	0 - Absent
	1 -
	2 - Mild
	3 - _____
	4 - Moderate
	5 -
	6 - Severe

Total Score _____

Definitions:

- Absent** = no evidence of the signs or symptoms
- Mild** = signs/symptoms are present but not intense
- Moderate** = signs/symptoms are clearly evident and are somewhat bothersome to the subject.
- Severe** = signs/symptoms are clearly evident, intense, and extremely bothersome to the subject.

14.6. Appendix 6 Laboratory Values of Clinical Concern**Hematology**

Hemoglobin	Males: <12.0 or >18.0 g/dL Females: <10.5 or >16.1 g/dL
Hematocrit	Males <36.0 or >54.0% Females: <31.0 or >50.6%
Leukocytes	>1x10 ³ /uL below or >3x10 ³ /uL above the limit of the ref. range
Platelets	<80 or > 500 K/uL

Chemistry

Total bilirubin	>1.5 times upper limit of the ref. range
AST	>2 times upper limit of the ref. range
ALT	>2 times upper limit of the ref. range
GGT	>2 times upper limit of the ref. range
Alk Phosphatase	>1.5 times upper limit of the ref. range
Creatinine	>1.8 mg/dL Adults >1.2 mg/dL Children age ≥9 months to 15 years
BUN	>1.5 times upper limit of the ref. range
Glucose, fasting	<60 or >126 mg/dL
Uric acid	>11 mg/dL
Sodium	>5 mEq/L above or below the limits of the ref. range
Potassium	>0.5 mEq/L above or below the limits of the ref. range
Calcium	<7.2 or > 12 mg/dL
Phosphate	>0.8 mg/dL below or 1.0 mg/dL above the limits of the ref. range
Albumin	>0.5 g/dL above or below the limits of the ref. range
Total protein	>1.0 g/dL above or below the limits of the ref. range

Urinalysis

WBC	>15/hpf
RBC	>15/hpf

Vital Signs

Heart Rate	Supine: <35 or >120 bpm Erect: <40 or >140 bpm
Blood Pressure Systolic	>30 mmHg change from baseline in same posture
Diastolic	>20 mmHg change from baseline in same posture

14.7. Appendix 7 IDMC Charter

14.8. Appendix 8 Microbiology Procedures

Microbiology Procedures: Instructions for the Local Laboratory

Microbiology Procedures: Instructions for the Central Laboratory

14.9. Appendix 9 Protocol Changes

Amendment 1

General Changes

Protocol Summary : Study Design, Investigational products; Sections: 4. Study Design; 5. Study Population; 5.2.1 Inclusion Criteria #3; and 7.3 Dose Rationale

Was: Protocol stated that the size of the lesions not be larger than 10cm in length, or 100cm² in area.

Is: The lesions or wounds may actually be larger than 10 cm in length, or 100cm² in area, however, the *infected* portion to be treated with the topical medication/placebo must not be larger than the said criteria..

Rationale: Wording regarding the infected area to be treated was edited for clarification. These changes would not have justified an amendment and would have been communicated via alternate means, had an amendment not been necessary for reasons outlined in Section 7

Sections 6.1.2. Clinical Evaluation of Infection, 6.3.1 Baseline Visit, 6.3.3 Topical End of Therapy (2-4 days post- topical therapy) Oral On-Therapy Visit, and 6.4.1 Topical Follow-Up Visit (7-9 days post-topical therapy) Oral End of Therapy Visit (2-4 days post- oral therapy)

Was: Protocol instructed that the wound be measured in millimeters.

Is: The wound is to be measured in centimeters.

Rationale: Maximum infected wound size for entry is 10 cm in length, or 100 cm². In order to ensure greater accuracy in recording of wound measurements in the eCRF, it was determined that centimeters rather than millimeters would be recorded. These changes would not have justified an amendment and would have been communicated via alternate means, had an amendment not been necessary for reasons outlined in Section 7.

3.3 Determining Clinical, Microbiological and Therapeutic Response

Determining Clinical response at follow-up (day 12-14 and day 17-19)

Was: Clinical efficacy assessments are performed at follow-up (day 12-14 and day 17-19) only for subjects whose clinical response at end of therapy (day 7-8 and day 12-14) was

'clinical success'. Subjects who are 'clinical failures' at end of therapy (day 7-8 and day 12-14) are classified ...

Is: Clinical efficacy assessments are performed at follow-up (day 12-14 and day 17-19) only for subjects whose clinical response at end of therapy (day 7-9 and day 12-14) was 'clinical success'. Subjects who are 'clinical failures' at end of therapy (day 7-9 and day 12-14) are classified ...

Rationale: Typographical error. This change would not have justified an amendment and would have been communicated via alternate means, had an amendment not been necessary for reasons outlined in Section 7.

5.2.1 Inclusion Criteria #5

Was: Inclusion Criterion #5 added; all subsequent inclusion criteria renumbered

Is: Subject must comply with using two barrier methods of contraception (if of childbearing potential) or be of non-childbearing potential (post-menopausal or surgically sterile).

Rationale: This information was clearly communicated in the Informed Consent. It was added to the protocol for re-emphasis. This change would not have justified an amendment and would have been communicated via the informed consent, had an amendment not been necessary for reasons outlined in Section 7.

6.4 Pharmacokinetics

Was: Collection of PK is outlined in Section 3.2.3.4.

Is: **Sample Collection**

Samples will be collected into tubes containing EDTA and immediately chilled on crushed ice. Plasma will be separated by centrifugation at approximately 4°C and transferred to polypropylene specimen containers labeled with the study number (SB-275833/030), subject number, study day, date, and nominal time of collection (eg, predose for adult subjects, and either one of the three windows [0(predose)-4 h, 4-8 h or 8-12 h postdose] for pediatric subjects). Plasma specimens will be immediately frozen and stored at approximately -20°C (or colder).

Bioanalysis

Plasma sample analysis will be performed under the management of Worldwide Bioanalysis, DMPK,

GlaxoSmithKline. Plasma specimens for pharmacokinetic analysis from each center will be transferred in the frozen state to a central laboratory, which will then be transferred to Worldwide Bioanalysis, DMPK, King of Prussia, Pennsylvania. Upon receipt, samples will be stored at approximately -20°C (or colder) until analysis. Concentrations of SB 275833 will be determined in all plasma samples using the currently approved analytical methodology. Raw data will be stored in the GLP Archives, GlaxoSmithKline.

Rationale for change:

Comments were received from PK after final protocol approval. These changes would not have justified an amendment and would have been communicated via alternate means, had an amendment not been necessary for reasons outlined in Section 7.

7.1 Description of Investigational Product

Paragraph 2:

Was: Cephalexin will be supplied as either pulvules in strengths of 250 mg., or an oral suspension of 250 mg/5 ml. Placebo for 250 mg cephalexin capsules contains starch 1500 in matching capsules. Active and placebo capsules have been overencapsulated. Micro crystalline cellulose replaces cephalexin in the oral suspension placebo.

Is: Cephalexin will be supplied as either an overencapsulated cephalexin 250 mg capsules, or for oral suspension, as a powder for reconstitution containing cephalexin 250 mg/5 mL. Matching placebos to the overencapsulated cephalxin 250 mg capsule and to the oral suspension will also be supplied.

Rationale: Original protocol was in error. The content of the placebo capsules was never intended to be starch, but rather microcrystalline cellulose. The placebo capsules were not to be overencapsulated. Oral suspension is no longer available from the source originally intended, and the source is yet to be determined; therefore, details regarding composition of the placebo suspension have been removed.

Amendment 2

Country specific amendment applicable to Germany and Austria only

The amendment was necessary in order to meet country requirements for: Austria (enrollment of subjects ≥ 18 years only) and Germany (enrollment of subjects ≥ 18 years prior to IDMC review and ≥ 13 years after positive recommendation by the IDMC and agreement by the appropriate IEC/IRB)

No changes were made to the actual body of the protocol for this amendment.

Amendment 3

Study Design

Paragraph 2; last line

Was: Blood specimens will be drawn, and urine collected for safety lab tests

Is: Blood specimens will be drawn and urine collected for all subjects for safety lab tests.

Rationale: Blood draws for subjects <13 years will be reduced from 5 (every visit) to 3. Labs will be drawn at Visit 1, Visit 2 and Visit 3. Visit 2 blood draw will also include PK. The decreased number of blood draws is intended to facilitate enrollment in some International and European regions that initially could not enroll younger children because of local ethics committees who felt that the blood draws as stipulated in the protocol were excessive for the younger age cohorts (9 month to <6 years, ≥ 6 years to <13 years). The section entitled “Study Design” describes the study related procedures at baseline, and because blood draws at Visit 4 and Visit 5 are being eliminated for subjects in the younger age cohorts it was necessary to reinforce that all subjects are to have safety labs collected at the Baseline visit.

Study Population

Paragraph 1

Was: It is anticipated that *approximately* 870 subjects may be enrolled into each of the studies in order to provide 696 evaluable subjects at follow-up (i.e., assume 20% subject non-evaluability). The total enrollment expected for this protocol, across both studies 030A and 030B, is approximately 1740 subjects. It is estimated that, using a 2:1 randomization scheme, a sample size of 464 evaluable subjects in the topical SB-275833 group, and 232 in the cephalixin group, would be required for each study.

Is: It is anticipated that 870 subjects may be enrolled into each of the studies in order to provide approximately 696 evaluable subjects at follow-up (i.e., assume 20% subject non-evaluability). It is estimated that, using a 2:1 randomization scheme, a sample size of 464 evaluable subjects in the topical SB-275833 group, and 232 in the cephalexin group, would be required for each study. The total targeted enrollment for this protocol, across both studies 030A and 030B, is 1740 subjects. In order to provide adequate safety and efficacy data, in the youngest age cohort, enrollment will continue beyond the targeted 1740 subjects in order to achieve approximately 100 subjects in the youngest age cohorts (9 month to <6 years, ≥6 years to <13 years).

Rationale: The study enrollment will be extended for subjects <13 years in order collect safety and efficacy data in younger subjects. The start of enrollment of younger cohorts is dependent upon the review and approval of data by an Independent Data Monitoring Committee, from the first 600 subjects enrolled. Enrollment of those subjects was initially slower than anticipated, therefore, the available data for IDMC review and approval was delayed. In addition, the selected IDMC members were not able to convene as a group until approximately a week after the projected date. As a result, enrollment of children <13 was delayed by approximately 4 weeks. In order to allow sufficient time to enroll approximately 100 subjects in the youngest age cohorts (9 month to <6 years, ≥6 years to <13 years), the last subject enrolled date has been extended for subjects in these younger cohorts. As a result, the target number of subjects enrolled will be increased from 1740. The final total of randomized subjects is dependent upon the number of additional pediatric subjects enrolled.

Study Assessments and Procedures Paragraph 5

Was: Blood specimens will be drawn, and urine collected for safety lab tests at the baseline (day 1), both on-therapy visits (day 3-4 and day 7-9), and at both the follow-up visits (day 12-14 and day 17-19).

Is: For all subjects ≥13 years of age, blood specimens will be drawn and urine collected for safety lab tests at the baseline visit (day 1), both on-therapy visits 2 and 3 (day 3-4 and day 7-9), and at both the follow-up visits 4 and 5 (day 12-14 and day 17-19). For subjects <13 years of

age, blood specimens will be drawn and urine collected for safety lab tests at the baseline visit (day 1), and at both on-therapy visits 2 and 3 (day 3-4 and day 7-9).

Rationale: Because blood draws at visit 4 and visit 5 are being eliminated for subjects in the younger age cohorts (9 month to <6 years, ≥6 years to <13 years), further clarification with regard to specimen collection at specific visits was necessary. Blood draws for subjects <13 years will be reduced from 5 (every visit) to 3, and labs will be drawn only at visit 1, visit 2 and visit 3. Visit 2 blood draw will also include PK. The decreased number of blood draws is intended to facilitate enrollment in some International and European regions that initially could not enroll younger children because of local ethics committees who felt that the blood draws as stipulated in the protocol were excessive for the younger subjects.

3.2.3.2 Safety laboratory tests **Paragraph 1; Bullet 1**

Was: Laboratory blood and urine parameters will be measured at the screening, and at all on-therapy (day 3-4, day 7-9) and follow-up visits (day 12-14 and day 17-19).

Is: For all subjects ≥13 year of age, laboratory blood and urine parameters will be measured at the baseline visit 1, at on-therapy visits 2 and 3 (day 3-4, day 7-9) and follow-up visits 4 and 5 (day 12-14 and day 17-19). For subjects <13 years of age, laboratory blood and urine parameters will be measured only at the baseline visit 1 (day 1), and both on-therapy visits 2 and 3 (day 3-4 and day 7-9).

Rationale: Because blood draws at visit 4 and visit 5 are being eliminated for subjects in the younger age cohorts (9 month to <6 years, ≥6 years to <13 years), further clarification with regard to specimen collection at specific visits was necessary. Blood draws for subjects <13 years will be reduced from 5 (every visit) to 3, and labs will be drawn only at visit 1, visit 2 and visit 3. Visit 2 blood draw will also include PK. The decreased number of blood draws is intended to facilitate enrollment in some International and European regions that initially could not enroll younger children because of local ethics committees who felt that the blood draws as stipulated in the protocol were excessive for the

younger subjects.

4.1 Randomization Paragraph 1

Was: The subject randomization to one or the other of the treatment arms will be stratified by site and age (9 months -5 years old, 6-12, ≥ 13) under a unique schedule for both studies. At most 50% of subjects will be allowed to be enrolled from sites in other than North America (Europe and international). Once the enrollment is completed with enough subjects for both studies (total of 1740), sites will be size-ranked and randomized accordingly either study 030A or 030B.

Is: The subject randomization to one or the other of the treatment arms will be stratified by site and age (9 months ≤ 6 years old, 6 - <13 , ≥ 13) under a unique schedule for both studies. At most 60% of subjects will be allowed to be enrolled from sites in Europe and International regions. Once adult and pediatric enrollment is completed, the sites will be size-ranked and randomized accordingly to either study 030A or 030B.

Rationale: Age ranges were more clearly defined. The study enrollment will be extended for subjects <13 years in order to target enrollment in the younger cohorts. As a result, the target number of subjects enrolled will be increased from 1740, and the total number of subjects will not be known until enrollment of both adults and pediatric subjects is completed. The total study allocation for sites in Europe and International regions is being increased from 50% to 60% based on current enrollment projections.

4.2 Treatment and Assessment Overview Paragraph 2; last line

Was: Blood specimens will be drawn, and urine collected for safety lab tests.

Is: Blood specimens will be drawn and urine collected for safety lab tests for all subjects.

Rationale: Blood draws for subjects <13 years will be reduced from 5 (every visit) to 3. Labs will be drawn at visit 1, visit 2 and visit 3. Visit 2 blood draw will also include PK. The decreased number of blood draws is intended to facilitate enrollment in some International and European regions that initially could not enroll younger children

because of local ethics committees who felt that the blood draws as stipulated in the protocol were excessive for the younger age cohorts (9 month to <6 years, ≥6 years to <13 years). Because Section 4.2 describes study related procedures at baseline, and because blood draws at visit 4 and visit 5 are being eliminated for subjects in the younger age cohorts it was necessary to reinforce that all subjects are to have safety labs collected at the baseline visit.

4.2 Treatment and Assessment Overview

Paragraph 9

Was: Blood specimens will be drawn, and urine collected for safety lab tests at the baseline (day 1; Section 6.3.1), both on-therapy visits (day 3-4 and day 7-9; Sections 6.3.2, 6.3.3), and at both the follow-up visits (day 12-14 and day 17-19; Sections 6.3.4, 6.3.5).

Is: Blood specimens will be drawn and urine collected for all subjects for safety lab tests at the baseline visit (day 1; Section 6.3.1) and at both on-therapy visits 2 and 3 (day 3-4 and day 7-9; Sections 6.3.2, 6.3.3), Blood specimens will be drawn and urine collected for safety lab tests at both the follow-up visits 4 and 5 (day 12-14 and day 17-19; Sections 6.3.4, 6.3.5) for all subjects ≥13 years of age; subjects <13 years of age are excluded from safety lab collection at visits 4 and 5.

Rationale: Because blood draws at visit 4 and visit 5 are being eliminated for subjects in the younger age cohorts (9 month to <6 years, ≥6 years to <13 years), further clarification with regard to specimen collection at specific visits was necessary. Blood draws for subjects <13 years will be reduced from 5 (every visit) to 3, and labs will be drawn only at visit 1, visit 2 and visit 3. Visit 2 blood draw will also include PK. The decreased number of blood draws is intended to facilitate enrollment in some International and European regions that initially could not enroll younger children because of local ethics committees who felt that the blood draws as stipulated in the protocol were excessive for the younger subjects.

5.1 Number of Subjects Paragraph 1

Was: It is anticipated that approximately 870 subjects may be enrolled into one study in order to provide 696 evaluable subjects at follow-up (i.e., assume 20% subject non-evaluability). It is estimated that, using a 2:1 randomization scheme, a sample size of 464 evaluable subjects in the topical SB-275833 group, and 232 in the cephalexin group, would be required for one study.

Is: It is anticipated that 870 subjects may be enrolled into each of the studies in order to provide approximately 696 evaluable subjects at follow-up (i.e., assume 20% subject non-evaluability). It is estimated that, using a 2:1 randomization scheme, a sample size of 464 evaluable subjects in the topical SB-275833 group, and 232 in the cephalexin group, would be required for each study. The total targeted enrollment for this protocol, across both studies 030A and 030B, is 1740 subjects. In order to provide adequate safety and efficacy data, in the youngest age cohort, enrollment will continue beyond the targeted 1740 subjects in order to enrol sufficient numbers of pediatric subjects in the youngest age cohorts (9 month to <6 years, ≥6 years to <13 years).

Rationale: The study enrollment will be extended for subjects <13 years in order collect safety and efficacy data in younger subjects. The start of enrollment of younger cohorts is dependent upon the review and approval of data by an Independent Data Monitoring Committee, from the first 600 subjects enrolled. Enrollment of those subjects was initially slower than anticipated, therefore, the available data for IDMC review and approval was delayed. In addition, the selected IDMC members were not able to convene as a group until approximately a week after the projected date. As a result, enrollment of children <13 was delayed by approximately 4 weeks. In order to allow sufficient time to enroll approximately 100 subjects in the youngest age cohorts (9 month to <6 years, ≥6 years to <13 years), the last subject enrolled date has been extended for subjects in these younger cohorts. As a result, the target number of subjects enrolled will be increased from 1740. The final total of randomized subjects is dependent upon the number of additional pediatric subjects enrolled.

6.2.1 Safety Laboratory Tests Paragraph 1

Was: The following laboratory studies will be performed at the baseline visit, and at all on-therapy (day 3-4, day 7-9) and follow-up visits (day 12-14 and day 17-19)

Is: The laboratory studies listed below will be performed at the baseline visit and at on-therapy visits 2 and 3 (day 3-4, day 7-9) for all subjects. Additionally, for all subjects >13, the laboratory studies listed below will be performed at follow-up visits 4 and 5 (day 12-14 and day 17-19).

Rationale: Because blood draws at visit 4 and visit 5 are being eliminated for subjects in the younger age cohorts (9 month to <6 years, ≥6 years to <13 years), further clarification with regard to specimen collection at specific visits was necessary. Blood draws for subjects <13 years will be reduced from 5 (every visit) to 3, and labs will be drawn only at visit 1, visit 2 and visit 3. Visit 2 blood draw will also include PK. The decreased number of blood draws is intended to facilitate enrollment in some International and European regions that initially could not enroll younger children because of local ethics committees who felt that the blood draws as stipulated in the protocol were excessive for the younger subjects.

6.3.4 Topical Follow-up Visit...Oral End of Therapy Visit Paragraph 4

Was: Blood specimens will be drawn, and urine will be collected for safety lab tests.

Is: For all subjects ≥ 13 years of age, blood specimens will be drawn and urine will be collected for safety lab tests. Subjects who are <13 years of age are not required to have safety labs collected at this visit.

Rationale: This describes visit 4 assessments. Because subjects who are <13 years of age are not required to have safety labs collected at this visit it was clarified that specimen collection is not necessary at this visit.

6.3.5 Final Follow-up Paragraph 5 Assessment

Was: New paragraph added

Is: For all subjects ≥ 13 years of age, blood specimens will be drawn and urine will be collected for safety lab tests. Subjects who are <13 years of age are not required to have safety labs collected at this visit.

Rationale: This describes visit 5 assessments. Because subjects who are <13 years of age are not required to have safety labs collected at this visit it was clarified that specimen collection is not necessary at this visit.

7.5 Treatment Paragraph 3 Assignment

Was: The subject randomization will be stratified by site and age (9 months -5 years old, 6-12, ≥ 13) under a unique schedule for both studies. At most 50% of subjects will be allowed to be enrolled from sites in other than North America (Europe and international). Once the enrollment is completed with enough subjects for both studies (total of 1740), the sites will be size-ranked within geographical regions (North America and outside N. America)

Is: The subject randomization will be stratified by site and age (9 months ≤ 6 years old, ≥ 6 - <13 , ≥ 13) under a unique schedule for both studies. At most 60% of subjects will be allowed to be enrolled from sites in Europe and International regions. Once the enrollment is completed with sufficient numbers of subjects for both studies, the sites will be size-ranked within geographical regions (North America and outside North America)

Rationale: Age ranges were more clearly defined. The study enrollment will be extended for subjects <13 years in order to target enrollment in the younger cohorts. As a result, the target number of subjects enrolled will be increased from 1740. The total study allocation for sites other than North America is being increased from 50% to 60% based on current enrollment projections.

11.2.1 Primary Last Paragraph Comparisons of Interest

Was: The IDMC may stop the trial only for safety, therefore, no alpha penalty for interim looks will be taken. Should

the IDMC require data regarding efficacy, the IDMC charter will be amended. In the event of an amendment to the IDMC charter to review efficacy data, the trial is considered successful if completed as planned, therefore no alpha penalty is required.

Is: It is currently planned that the IDMC would stop the trial only for safety reasons, and not for reasons regarding efficacy, therefore, no alpha penalty for interim looks will be taken. Should the IDMC require data regarding efficacy, the IDMC charter states that a 0.000001 alpha penalty will be employed.

Rationale: This change is to ensure consistency between the IDMC charter and the protocol.

11.4.3 Sample Size Re-estimations Paragraph 1

Was: There is no sample size re-estimation planned.

Is: No sample size re-estimation will be utilised for this study; however, it is anticipated when the target sample size of 1740 is reached, there will be insufficient subjects in the youngest age cohorts to provide adequate safety and efficacy data. Enrollment will continue beyond the targeted 1740 subjects in order to include additional pediatric subjects <13 years of age.

Rationale: The study enrollment will be extended for subjects <13 years in order collect safety and efficacy data in younger subjects. The start of enrollment of younger cohorts is dependent upon the review and approval of data by an Independent Data Monitoring Committee, from the first 600 subjects enrolled. Enrollment of those subjects was initially slower than anticipated, therefore, the available data for IDMC review and approval was delayed. In addition, the selected IDMC members were not able to convene as a group until approximately a week after the projected date. As a result, enrollment of children <13 was delayed by approximately 4 weeks. In order to allow sufficient time to enroll approximately 100 subjects in the youngest age cohorts (9 month to <6 years, ≥6 years to <13 years), the last subject enrolled date has been extended for subjects in these younger cohorts. As a result, the target number of subjects enrolled will be increased from 1740. The final total of randomized subjects is dependent upon the number of

additional pediatric subjects enrolled.

11.5.1 Efficacy Study Last Paragraph Populations

Was: Per protocol analysis will not be performed unless more than 10% of the ITT subjects have PVs. The baseline demographic characteristics will be summarized to facilitate evaluation of possible differences between treatment groups, which may mask any real treatment effect that may exist. No formal hypothesis testing or interval estimation will be applied to baseline or demographic characteristics. Study medication compliance, protocol violations and reasons for dropout will be examined to evaluate bias, if any, in the proposed treatment comparisons.

Is: The baseline demographic characteristics will be summarized to facilitate evaluation of possible differences between treatment groups, which may mask any real treatment effect that may exist. No formal hypothesis testing or interval estimation will be applied to baseline or demographic characteristics. Study medication compliance, protocol violations and reasons for dropout will be examined to evaluate bias, if any, in the proposed treatment comparisons.

Rationale: The per protocol population is the primary population so it will be analyzed regardless of differences from the ITT population.

11.6.3 Other Issues Paragraph 2

Was: The analysis will be done by using a mixed model with site as a random effect. The possible heterogeneity of treatment effects across centers will be explored by graphical display of the results of individual centers. If such is found and no explanation in terms of other features of the trial can be found, a model with treatment by center interactions will be fitted.

Is: (Removed)

Rationale: This paragraph is more appropriately located in section 11.7.3 Other Efficacy Analyses.

11.7.1 Primary Analysis Paragraph 1

Was: The analysis will be done by using a mixed model with site as a random effect. The possible heterogeneity of treatment effects across centers will be explored by graphical display of the results of individual centers. If such is found and no explanation in terms of other features of the trial can be found, a model with treatment by center interactions will be fitted.

Is: (Removed)

Rationale: It has been agreed with the FDA that it will not be the procedure used to analyze the primary endpoint.

11.7.1 Primary Analysis Last Paragraph

Was: The IDMC may stop the trial only for safety, therefore, no alpha penalty for interim looks will be taken. Should the IDMC require data regarding efficacy, the IDMC charter will be amended. In the event of an amendment to the IDMC charter to review efficacy data, the trial is considered successful if completed as planned, therefore no alpha penalty is required.

Is: It is currently planned that the IDMC would stop the trial only for safety reasons, and not for reasons regarding efficacy, therefore, no alpha penalty for interim looks will be taken. Should the IDMC require data regarding efficacy, the IDMC charter states that a 0.000001 alpha penalty will be employed.

Rationale: This change is to ensure consistency between the IDMC charter and the protocol

11.7.3 Other Efficacy Last Paragraph Analyses

Was: (Not previously present)

Is: An analysis will be done by using a mixed model with site as a random effect. The possible heterogeneity of treatment effects across centers will be explored by graphical display of the results of individual centers. If such is found and no explanation in terms of other features of the trial can be found, a model with treatment by center interactions will be fitted.

Rationale: This paragraph has been moved from the primary analysis section to this section following discussions with the FDA. The FDA requested the primary analysis be based on crude response rates rather than a model-based approach; therefore, the protocol was modified to comply.

11.8 Safety Analysis Paragraph 1

Was: Where an AE occurs in >5% of subjects in any of the treatment groups, the proportion of subjects reporting that AE will be compared between treatment groups.

Is: When an AE occurs in >1% of subjects in any of the treatment groups, the proportion of subjects reporting that AE will be compared between treatment groups.

Rationale: Correction of error in original protocol. Statistical tests will not be used for this comparison. The adverse events will be compared solely with the use of descriptive statistics including confidence interval. The choice of 1% is based upon standard AE reporting tables. Additionally, in blinded data produced for the IDMC review it appears that there are no AEs that occur in 5% or greater of the subjects.

14.1 Appendix 1 Time and Events Table Paragraph 1

Was: New Footnote added

Is: 5. Safety labs collected at visits 4 and 5 ONLY for subjects \geq 13 years of age

Rationale: New footnote added to reflect the elimination of safety labs drawn at visit 5 for subjects in the younger cohorts; all subsequent footnotes re-numbered.

14.4 Appendix 4 Country Specific Requirements Paragraph 3

Was: No specific requirements previously noted.

Is: In Germany and Austria:

Country specific requirements for: Austria (enrollment of patients \geq 18 years only) and Germany (enrollment of patients \geq 18 years prior to IDMC review and \geq 13 years after positive recommendation by the IDMC and agreement by the appropriate IEC/IRB are outlined in

the country specific amendment document:
UM2003/00090/02. Reduction in the number of blood draws may result in ethics committee agreement to allow Germany to enroll children <13.

These changes were not incorporated into the body the amendment.

Rationale: Addition to original protocol

Amendment 4

Exclusion Criteria

Addition of #13

Was: No text

Is: **Additional Pediatric Exclusion Criterion for subjects 9 months to less than 13 years of age:**

13. The subject has systemic signs and symptoms of infection (such as fever; defined as a temperature equivalent to a rectal temperature greater than 101°F or 38.3°C).

Rationale: One additional exclusion criterion for the pediatric population (<13 years of age) was added in order to gain approval for amendment #3 from the central IRB. Because Amendment #3 had already been distributed, it was necessary to incorporate this change as Amendment #4