Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for retapamulin

Proprietary Product Name: Altargo

Sponsor: GlaxoSmithKline Australia Pty Ltd

Date of CER: 31 October 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
ACD	allergic contact dermatitis
AD	atopic dermatitis
AE	adverse event
AUC	area under the plasma concentration time curve
BD	two times daily (bis in die)
CA-MRSA	community-associated methicillin-resistant S. aureus
CI	confidence interval
CLSI	Clinical and Laboratory Standards Institute
Cmax	maximum plasma concentration
CPK	creatine phosphokinase
CYP3A4	cytochrome P450 3A4
ECG	electrocardiogram
EoT	end of treatment
EU	European Union
FDA	United States Food and Drug Administration
FU	follow up
fusRSA	fusidic acid-resistant S. aureus
GGT	gamma-glutamyl transferase
H	hour
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
ITTB	intent to treat bacteriological
ITTC	intent to treat clinical
ITTMRSA	intent-to-treat MRSA

Abbreviation	Meaning
LC/MS	liquid chromatography/mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MRSA	methicillin-resistant S. aureus
MSSA	methicillin-susceptible S. aureus
mupRSA	mupirocin-resistant S. aureus
NOAEL	no observed adverse effect level
Pgp	P-glycoprotein
PK	pharmacokinetic
PPB	per protocol bacteriological
PPC	per protocol clinical
PPMRSA	per protocol MRSA
PVL	Panton-Valentine Leukocidin
SAE	serious adverse event
SID	secondarily-infected dermatoses
SIRS	Skin Infection Rating Scale
SITL	secondarily-infected traumatic lesions
TID	three times daily
US	Unites States
uSSSI	uncomplicated skin and skin structure infections
UTD	unable to determine

1. Introduction

Retapamulin (Altargo) is a semi-synthetic pleuromutilin, based on a nucleus isolated through fermentation from Clitopilus passeckerianus (formerly Pleurotus passeckerianus), and developed to treat uncomplicated skin and skin structure infections (uSSSI).

The proposed indications are:

- primary impetigo
- secondarily infected traumatic lesions e.g. small lacerations, abrasions, sutured wounds
- secondarily infected dermatoses including infected psoriasis, infected atopic dermatitis and infected contact dermatitis

Safety and efficacy has not been established in secondarily-infected traumatic lesions more than 10 cm in length or 100 cm^2 in surface area, or in secondarily-infected dermatoses or primary impetigo affecting more than 100 cm^2 in surface area (or exceeding 2% of body surface area in paediatric patients).

Retapamulin 1% is an ointment intended for topical use.

The dosing recommendation in this submission is topical use, twice daily for five days in adult and paediatric patients aged 9 months and older.

2. Clinical rationale

Retapamulin is the first drug of the pleuromutilin class to be registered [anywhere in the world] for human use. Tiamulin (Denagard) and valnemulin (Econor) from the same class are registered for veterinary use. Retapamulin ointment was first approved in the United States in April 2007, and was approved in the European Union (EU) in May 2007. Since that time retapamulin ointment has been approved for use in 60 countries. Retapamulin has excellent in vitro activity against Gram-positive bacteria commonly associated with skin infections and a low propensity for development of resistance in vitro, suggesting a low likelihood that resistance would develop during treatment.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The clinical dosser documented a full clinical development program of pharmacology, efficacy and safety studies (summarised in Table 1).

Phase I and Phase II (and one Phase IV) studies to establish the most appropriate concentration and pharmacokinetics of retapamulin ointment. The topical retapamulin Phase III program consists of 7 controlled blinded studies. The submission contained the following clinical information:

Module 5

- Phase I/II studies

Six clinical Phase I studies in healthy adults, assessing irritation, safety, tolerability, pharmacokinetics (PK), and sensitisation after use of retapamulin ointment are included in this application. Study TOC101825 evaluated interaction of retapamulin with ketoconazole, a potent

cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (Pgp) inhibitor. Two studies (Study 001 and Study 034) were conducted in healthy adults using alternative formulations (an aqueous nasal spray solution and an alternative succinate salt, retapamulin-AAA ointment) that are no longer being developed. The open-label noncomparative Phase II Study 029 evaluated the PK of retapamulin ointment in adult subjects with uncomplicated bacterial skin infections. There was minimal systemic exposure following topical administration according to the proposed clinical dosing regimen, along with an excellent safety profile.

· Phase III studies

The clinical and microbiological efficacy of retapamulin ointment was evaluated in 7 phase III clinical studies involving 4088 adult and paediatric subjects, of whom 2724 received retapamulin. There were 2 studies in primary impetigo; one a comparator study versus topical sodium fusidate ointment (Study TOC100224) and the other a placebo controlled study (Study TOC103469). Two identical studies were in SITL, using oral cephalexin as a comparator (Studies 030A and 030B). A further study (TOC110977) was conducted in subjects with SITL using a placebo control. Single PK plasma samples were collected in the SITL studies to assess exposure to retapamulin under the proposed conditions of clinical use. A study was conducted in subjects with SITL and impetigo to evaluate the efficacy and safety of retapamulin versus linezolid in subjects with MRSA (Study TOC110978). One study was in SID in which retapamulin was compared with oral cephalexin (Study 032).

· Phase IV study

Phase IV Study TOC106489 was conducted to evaluate the PK of retapamulin in children 2 to 24 months of age. Safety and efficacy were secondary endpoints.

· Other studies

Study ALB110247 was a Phase I study conducted to evaluate efficacy of retapamulin ointment on nasal decolonization of S. aureus. Study ALT111065 was a study to evaluate efficacy of retapamulin in subjects with *P. acnes* colonization of the forehead.

Also provided were:

Module 1

· Application letter, application form, confidentiality request, draft Australian PI and CMI, FDA-approved product label, GMP letters, presubmission declaration of compliance, information on experts, summary of biopharmaceutics, information on risk monitoring system, overseas evaluation reports, overseas product status and regulatory information, paediatric development plan. [A *Risk Assessment of Microbial Resistance Altargo 1% Ointment* was included in Module 1 and is evaluated in Appendix 1, below].

Module 2

· Table of contents, introduction, Clinical Overview, non-clinical overview, clinical summary, non-clinical summary.

Module 3 (Quality data)

Module 4 (Non-clinical data)

Table 1: Complete Summary of Studies – Design and Methodology

Protocol No. Document No. Location of CSR	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects: Gender M/F: Mean Age (Range) (ITTC Population)	Treatment Details (Drug: Dose; Form; Route; Frequency; Duration)	Study Status: Type of Report
Completed Phase I/II Studies							
SB-275833/026 PM2003/00144/01 m5.3.3.1.1	Safety, tolerability, and PK	Safety and PK after single and repeat application on intact and abraded skin	Randomized, single-blind, placebo-controlled, parallel-group, dose-rising	Healthy adult subjects	106 randomized, 99 completed Part 1: 27M, 0F 30±9.9y (18-50) Part 2: 27M,0F 29±9.8y (19-49) Part 3: 23M, 2F 31±9.8y (18-45) Part 4: 27M, 0F 24±4.7y (20-43)	Retapamulin 0.5%, 1%, and 2% w/w in white soft paraffin, placebo was white soft paraffin only. Each subject received 1 dose level of retapamulin or placebo. The 0.5% ointment was applied to 400 cm^2, 1% to 800 cm^2, and 2% to 1600 cm^2 intact skin on the leg for 1 24-hour application (Part 1) or for 7 24-hour applications (Part 2). The 0.5% ointment was applied to 100 cm^2, 1% to 200 cm^2, and 2% to 100 cm^2 abraded (tape-stripped) skin on the leg for 1 24-hour application (Part 3) or 7 24-hour applications (Part 4).	Complete, full
SB-275833/029 UM2004/00014/00 m5.3.3.2.1	Phase IIa PK. preliminary efficacy and safety	Systemic exposure in uncomplicated bacterial skin structure infections	Open-label, non-comparative	Subjects ≥18 years old with uncomplicated bacterial skin infections	35 randomized, 30 completed M/F: 15/20; 45.1 y (20-80)	Retapamulin ointment, 1% concentration; topical application; BID; 5 days	Complete; full
TOC101825 PM2004/00119/01 m5.3.3.4.1	Drug interaction	PK with and without oral ketoconazole	Randomized, open-label, crossover	Healthy adult subjects	29 randomized, 26 completed 29M, 0F 37±12.1 y (20-60)	Retapamulin ointment, 1%, Ketoconazole 200 mg tablet. Single 24-hour application of retapamulin ointment to 50 cm^2 abraded skin on upper leg, with and without repeat oral doses of ketoconazole 200 mg tablet BID for 4 days.	Complete, full
SB-275833/025 PM2003/00143/00 m5.3.4.1.1	Safety and tolerability	Irritation of primary and repeat applications on intact and abraded skin	Randomized, single-blind, placebo-controlled, parallel	Healthy adult subjects	96 randomized, 90 completed 72M. 24F 41±14.3 y (18-64)	Retapamulin 0.5%, 1%, and 2% w/w ointment,; +positive control sodium lauryl sulfate 0.5%, 0.1%, negative control sterile distilled water. All 7 treatments applied concurrently to upper arm for 2 24-hour applications on intact skin (Cohort 1) or abraded skin (tape-stripped, Cohort 2), or for 21 24-hour applications on intact skin (Cohort 3), or for 14 24-hour applications on abraded skin (Cohort 4)	Complete, full

Table 1 continued: Complete Summary of Studies – Design and Methodology

Protocol No. Document No. Location of CSR	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects: Gender M/F: Mean Age (Range) (ITTC Population)	Treatment Details (Drug: Dose; Form; Route; Frequency; Duration)	Study Status: Type of Report
SB-275833/027 PM2004/00004/00 m5.3.4.1.2	Safety and tolerability	Induction of contact sensitivity	Randomized, single-blind, placebo-controlled, parallel	Healthy adult subjects	226 randomized, 200 completed 52M, 174F 42±12 y (18-66)	Retapamulin 0.5%, 1%, and 2%; w/w in white soft paraffin, placebo was white soft paraffin only. All 4 treatments applied concurrently to intact skin on the back for a 3-week induction period (9 repeated 48-72 hour applications). Following 14-17 day rest period, 1 challenge application for 48 hours to naive sites on the back.	Complete, full
SB-275833/001 SB-275833/RSD-101B20/1 m5.3.3.1.3	Safety and tolerability	Safety, potential for intranasal sensitization, and PK of single and repeat intranasal spray	Randomized, double-blind, placebo-controlled, parallel, dose rising	Healthy adult subjects	48 randomized, 39 completed 48M, 0F 29±5.5 y (21-43)	Retapamulin: 0.01%, 0.02%, 0.05% and 0.10% in saline and benzalkonium chloride (0.02%) clear solutions for intranasal application; placebo: saline and benzalkonium chloride (0.02%) clear solutions for intranasal application	Complete, full
SB-275833/034 PM2004/00120/00 m5.3.4.1.3	Safety and tolerability	Safety and irritation potential of primary and repeat applications of SB 275833-AAA on intact and abraded skin	Randomized, single-blind, placebo-controlled, parallel	Healthy adult subjects	105 randomized, 89 completed 26M, 79F 40±11.2 y(18-67)	Retapamulin-AAA: 0.5%, 1%, and 2% w/w ointment positive control: sodium lauryl sulfate 0.1%, 0.5%; negative control: white soft paraffin; comparators: Neosporin® ointment, 0.1% gentamicin ointment, retapamulin ointment, 1%. All treatments applied concurrently to the back for 2 24-hour applications on intact skin (Cohort 1), for 21 24-hour application to intact skin (Cohort 2), or for 14 24-hour applications on abraded skin (Cohort 3)	Complete, full
ALB110247 RM2008/00304/00 m5.3.3.2.2	Phase I/IIa	Safety, efficacy, and PK in subjects nasally colonized with *S. aureus*	Randomized, double-blind, placebo-controlled	Subjects between 18 and 65 years of age (inclusive) with persistent nasal carriage of *S. aureus*	Randomized: 57 Completed: 51 Tx A: 23; M/F 17/6; 31.8±10.80 y (19-57) Tx B: 19; M/F 13/6; 35.8±11.16 y (18-56) Tx C: 15; M/F 13/2; 33.7±12.67 y (19-62)	Treatment A: retapamulin ointment, 1% 200 mg BID 3 days + placebo 2 days Treatment B: retapamulin ointment, 1% 200 mg BID 5 days Treatment C: placebo 200 mg BID 5 days	Complete, full

Table 1 continued: Complete Summary of Studies – Design and Methodology

Protocol No. Document No. Location of CSR	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects: Gender M/F: Mean Age (Range) (ITTC Population)	Treatment Details (Drug: Dose; Form; Route; Frequency; Duration)	Study Status: Type of Report
Completed Phase III Studies							
TOC103469 HM2005/00583/00 5.3.5.1.1	Efficacy and safety	Efficacy and safety for impetigo	Randomized, multicenter, double-blind, placebo-controlled, parallel-group, superiority study	Subjects ≥9 months with primary impetigo (bullous or non-bullous); SIRS ≥8	Retapamulin ointment, 1%: 139 M/F: 66/73 12.3 y (0-73) Placebo: 71 M/F: 37/34 8.9 y (0-44)	Retapamulin ointment, 1%: Topical application BID for 5 days Placebo ointment: Topical application BID for 5 days	Complete; Full
TOC100224 GM2005/00417/00 5.3.5.1.2	Efficacy and safety	Efficacy and safety for impetigo	Randomized, multicenter, observer-blind, active-controlled, parallel-group, noninferiority study	Subjects aged ≥9 months with primary impetigo (bullous or non-bullous); SIRS ≥8	Retapamulin ointment, 1%: 345 M/F: 178/167 17.8 y (0-84) Sodium fusidate ointment, 2%: 172 M/F: 100/72 14.4 y (0-66)	Retapamulin ointment, 1%: Topical application BID for 5 days Sodium fusidate ointment, 2%: Topical application TID for 7 days	Complete; Full
SB-275833/030A ZM2004/00080/00 m5.3.5.1.3	Efficacy and Safety	Evaluation of subjects with SITL	Randomized, double-blind, double-dummy, multicenter, noninferiority	Subjects ≥9 months old with SITL and high likelihood of *S. aureus* and/or *S. pyogenes* as causative agent.	662 (retapamulin) M/F: 390/272 37.5 y (1-98) 326 (cephalexin) M/F: 192/134 38.8 y (2-93)	Retapamulin (subjects ≥9 months): topical ointment, 1% concentration; topical application; BID;5 days Cephalexin (subjects ≥13 years of age): 2X250 mg capsules oral dosing; BID;10 days Cephalexin (subjects ≥9 months to <13 years): 250 mg/5 mL suspension, 12.5 mg/kg; oral dosing; BID;10 days	Complete; full
SB-275833/030B ZM2005/00069/00 m5.3.5.1.4	Efficacy and Safety	Evaluation of subjects SITL	Randomized, double-blind, double-dummy, multicenter, noninferiority	Subjects ≥9 months old with SITL and high likelihood of *S. aureus* and/or *S. pyogenes* as causative agent.	606 (retapamulin) M/F: 324/282; 44.2 y (2-90) 310 (cephalexin) M/F: 165/145; 43.2 (2-91)	Retapamulin (subjects ≥9 months): topical ointment, 1% concentration; topical application, BID, 5 days Cephalexin (subjects ≥13 years of age): 2X250 mg capsules oral dosing, BID, 10 days Cephalexin (subjects ≥9 months to <13 years): 250 mg/5 mL suspension, 12.5 mg/kg, oral dosing, BID, 10 days	Complete; full

Table 1 continued: Complete Summary of Studies – Design and Methodology

Protocol No. Document No. Location of CSR	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects: Gender M/F: Mean Age (Range) (ITTC Population)	Treatment Details (Drug: Dose; Form; Route; Frequency; Duration)	Study Status: Type of Report
SB-275833/032 UM2005/00008/00 m5.3.5.1.5	Efficacy and Safety	Evaluation of subjects with SID	Randomized, double-blind, double-dummy, multicenter, noninferiority	Subjects ≥9 months old with SID	363 (retapamulin) M/F: 232/131 33.7 y (0-84) 183 (cephalexin) M/F: 105/78 34.8 y (0-91)	Retapamulin (subjects ≥9 months): topical ointment, 1% concentration; topical application, BID, 5 days Cephalexin (subjects ≥13 years of age): 2X250 mg capsules oral dosing; BID; 10 days Cephalexin (subjects ≥9 months to <13 years): 250 mg/5 mL suspension, 12.5 mg/kg; oral dosing; BID; 10 days	Complete; full
TOC110977 RM2009/00386/00 m5.3.5.1.6	Phase IIIb	Evaluation of subjects ≥2 months of age with SITL	Randomized, double-blind, multicenter, placebo-controlled	Subjects ≥2 months old with SITL.	246 (retapamulin ITTC Primary Efficacy Population [A+C]); M/F 142/104; 33.1 y (1-86) 113 (placebo ITTC Primary Efficacy Population [A+C]); M/F 77/36, 28.2 y (1-86)	Retapamulin topical ointment, 1% applied BID for 5 days Placebo ointment BID for 5 days.	Complete, full
TOC110978 2011N112109_00 m5.3.5.1.7	Phase IIIb	Evaluation of SITL and impetigo due to MRSA	Randomized, double-blind, double-dummy, comparative, multicenter	Subjects ≥2 months of age with SITL or impetigo; SIRS≥8; pus exudate score ≥3	267 (retapamulin); M/F 159/108; 34.6 y (0-85) 137 (linezolid); M/F 88/49; 33.8 y (1-92)	Retapamulin (subjects ≥2 months): topical ointment, 1% concentration; topical application, BID, 5 days Linezolid subjects ≥12 years of age: 1 600-mg tablet oral dosing, BID, 10 days Linezolid subjects 5-11 years of age: 10 mg/kg of 100 mg/5mL suspension, oral dosing, BID, 10 days Linezolid subjects <5 years of age: 10 mg/kg of 100 mg/5mL suspension, oral dosing, TID, 10 days	Complete, full
Completed Phase IV Studies							
TOC106489 UM2008/00302/00 m5.3.5.2	Phase IV PK, safety, and efficacy	PK in subjects aged 2 to 24 months with uncomplicated skin structure infections	Open-label, noncomparative	Subjects 2 to 24 months with SID, SITL, and impetigo	86 (retapamulin); M/F 54/32; 10.6 mo (2-23)	Retapamulin topical ointment, 1% applied BID for 5 days	Complete, full

Table 1 continued: Complete Summary of Studies – Design and Methodology

Protocol No. Document No. Location of CSR Investigator-Sponsored Study	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects: Gender M/F: Mean Age (Range) (ITTC Population)	Treatment Details (Drug: Dose; Form; Route; Frequency; Duration)	Study Status: Type of Report
ALT111065 N/A m5.3.5.4.1	ISS	Evaluation in subjects with *P. acnes* colonization of the forehead	Randomized, double-blind, placebo-controlled	Subjects 18 to 61 years with ≥10,000 colonies/cm^2 *P. acnes* on forehead.	30 (retapamulin); M/F 20/10 40.7 y (19-61) 30 (placebo) M/F16/14 32.8 y (18-51)	Retapamulin topical ointment, 1% once daily in the morning for 28 days Placebo ointment once daily in the morning for 28 days.	Complete, abbreviated

BD – twice a day, CSR – clinical study report, F – female, ITTC – intent-to-treat clinical population, M – male, MRSA – methicillin-resistant S. aureus, PK – pharmacokinetic(s), SID –secondarily infected dermatoses, SIRS – skin infection rating scale, SITL, secondarily infected traumatic lesions, TID – three times a day

3.2. Paediatric data

The submission includes paediatric pharmacokinetic / pharmacodynamic / efficacy / safety data.

3.3. Good clinical practice

All studies were undertaken in accordance with standard operating procedures of the GlaxoSmithKline Group of Companies, which comply with the principles of Good Clinical Practice. All studies were conducted with the approval of Ethics Committees or Institutional Review Boards. Informed consent (and assent from minors, as applicable) was obtained for all subjects, and the studies were performed in accordance with the version of the Declaration of Helsinki that applied at the time the studies were conducted.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

The clinical pharmacology development program for retapamulin ointment was designed to establish safety and tolerability (including assessment of the potential for local irritation and sensitisation) and to describe pharmacokinetic parameters in humans. Three Phase I studies (Study 025, Study 026, and Study 027) evaluated 3 concentrations of retapamulin ointment (0.5%, 1%, and 2%).

Study 025 and Study 026 evaluated the irritation potential and PK, respectively, on both intact and abraded skin. Study 027 evaluated the sensitisation potential on intact skin. Study TOC101825 evaluated the PK of retapamulin 1% applied to abraded skin with and without oral ketoconazole, a potent CYP3A4 and Pgp inhibitor. In addition, a study was conducted to evaluate retapamulin ointment applied to the anterior nares of healthy adult subjects nasally colonized with *Staphylococcus aureus* (Study ALB110247).

Pharmacokinetic results from Phase II, III, and IV studies are also summarized in this document. Study 029 assessed systemic exposure to retapamulin after topical application of retapamulin ointment, 1%, to the skin of subjects with uncomplicated bacterial skin infections. Study 030A and Study 030B compared the efficacy and safety of topical applications of retapamulin ointment, 1%, with oral cephalexin in the treatment of adult and paediatric (down to age 9 months) subjects with secondarily infected traumatic skin lesions (SITL). Study TOC106489 assessed topical retapamulin ointment, 1%, in the treatment of uncomplicated skin and skin structure infections in paediatric subjects aged 2 to 24 months. PK data were collected in the Phase II Study 029, Phase III Studies 030A and 030B, the Phase IV paediatric Study TOC106489.

Table 2: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	General PK Single dose	Study 026 Study 025
	General PK Multi dose	Study 026 Study 029 TO101825 Study 025 Study 027 Study 001 Study 034 ALB110247 Study 030A

PK topic	Subtopic	Study ID
		Study 030B TOC106489
PK in special populations	Target population§ - Single dose	
	Target population - Multi-dose	ALB110247
	Neonates/infants/ children/adolescents	Study 030A Study 030B TOC106489
PK interactions	ketoconazole	TO101825
Population PK analyses	Healthy subjects	Study 026 Study 029 TO101825 Study 025 Study 027 Study 001 Study 034
	Target population	ALB110247 Study 030A Study 030B TOC106489

† Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

Two studies involved formulations that were not pursued further: Study 001 examined single and multiple dose rising of a pilot retapamulin nasal spray solution to assess safety and tolerability of this formulation; Study 034 evaluated the irritation of an alternative succinate salt, retapamulin-AAA ointment. Because these studies exposed healthy subjects to retapamulin, the data are included in this section.

4.1.1. Pharmacokinetics in healthy subjects

4.1.1.1. Absorption

The systemic exposure of retapamulin after topical application was assessed in healthy adult subjects in Study 026, Study TOC101825, and to the nares in healthy adult subjects in Study ALB110247.

Systemic exposure in healthy adult subjects (Study 026 and Study TOC101825) was examined on intact skin and/or using an abraded skin model; in both instances, full occlusion after topical application of retapamulin ointment was employed (to enhance penetration), maximizing exposure. The abraded skin model with tape-stripping was utilized to simulate the clinical settings in which this ointment will be used (ie, impetigo, SITL, SID). Tape-stripping as a method of abrading skin removes the stratum corneum (the main environmental barrier) and also enhances skin penetration.[1, 2, 3]

Comparisons of PK parameters across healthy adult studies show similar systemic exposures to retapamulin at similar doses utilizing the proposed commercial formulation of retapamulin ointment, 1% on abraded skin. In Table 3, the PK parameters from Study 026 (single dose or Day 1 of repeated dose, abraded skin cohorts) are compared to the PK parameters in Study TOC101825 after application of retapamulin ointment, 1%, alone (Regimen A). Generally,

[1] Benfeldt E, Serup J, Menne T. Effect of barrier perturbation on cutaneous salicylic acid penetration in human skin: *in vivo* pharmacokinetics using microdialysis and noninvasive quantification of barrier function. *Br J Dermatol* 1999;140:739-48.
[2] Bashir SJ, Chew A-L, Anigbogu A, Dreher F, Maibach HI. Physical and physiological effects of stratum corneum tape stripping. *Skin Res Technol* 2001;7:40-8.
[3] Rosado C, Rodrigues LM. In vivo study of the physiological impact of stratum corneum sampling methods. *Int J Cosmet Sci* 2003;25:1-2, 37-44.

exposures were similar across healthy adult studies when normalized by ointment strength and surface area, particularly when comparing Cohorts 8 and 11 of Study 026 with those from Regimen A of Study TOC101825 as they both used the retapamulin ointment, 1%.

Upon single dose, the systemic exposure from intact skin (generally non-quantifiable, Study 026), was much lower than that from the abraded skin model (Table 3) in healthy adult subjects.

Table 3: Comparison of Pharmacokinetic Parameters in Study 026 and Study TOC101825

Cohort	Regimen	AUC(0-24) (ng·h/mL) Mean (Range)	Cmax (ng/mL) Mean (Range)
Study 026: Day 1, Single Dose, Abraded Skin			
7 (n=4)	0.5% 100 cm²	22.3 (14.0-35.4)	1.45 (0.89-2.39)
8 (n=6)	1% 200 cm²	152.6(97.4-238.4)	10.65 (5.62-22.12)
9 (n=4)	2% 100 cm²	72.0(46.1-90.4)	5.51 (3.19-8.90)
10 (n=6)	0.5% 100 cm²	44.1(39.2-49.0)	2.99 (2.54-3.82)
11 (n=6)	1% 200 cm²	142.0(79.2-195.4)	9.75 (5.84-14.55)
12 (n=6)	2% 100 cm²	77.8(47.5-96.1)	4.83 (2.76-7.17)
Study TOC101825: Single Dose, Regimen A, Abraded Skin			
(n=26)	1% 50 cm²	54.96 (26.15-106.36)	4.27 (2.11-10.51)

Source: Study 026, Attachment 2, Table 1; Study TOC101825, Attachment 3, Table 1, Table 2

Systemic exposure when retapamulin ointment, 1% 200 mg BD, was applied to the anterior nares of healthy subjects colonized with S. aureus was also evaluated (Study ALB110247). Due to low systemic exposures, $AUC_{(0\text{-}12)}$ was best represented by AUC(0-t) in evaluating the results from Study ALB110247. The highest $AUC_{(0\text{-}t)}$ and C_{max} were 24.1 ng·h/mL and 2.74 ng/mL, respectively.

Pharmacokinetic results in Study 026 revealed minimal systemic exposure when applied daily for up to 7 days to large surface areas (400 - 1600cm²) of intact skin. Systemic exposure from abraded skin was higher than that of intact skin but still very low. To maximize absorption in Study 026 and Study TOC101825, retapamulin ointment, 1%, was applied as 10 mg ointment/cm² with a fully occlusive dressing but was applied with predominantly semi-occlusive or no dressing in Study 029, Study 030A, Study 030B, and Study TOC106489. In Study 026, the mean plasma concentrations of retapamulin in subjects dosed with retapamulin ointment, 1%, to 200 cm² abraded skin as a single dose (N=12) were 6.325 ng/mL at 12 hours after dosing, 4.787 ng/mL at 22.5 hours after dosing and 3.736 ng/mL at 24 hours after dosing.

The geometric mean maximum exposure (C_{max}) after topical application of retapamulin ointment, 1%, to 200cm² of abraded skin was very low (9.75 ng/mL on Day 1 and 8.79 ng/mL on Day 7 of treatment. The highest exposures observed in humans with retapamulin 1% after abrasion of skin in Study 026 (highest C_{max} 22.1 ng/mL and area under the concentration-time curve from 0 to 24 hours [$AUC_{(0\text{-}24)}$] 238 ng·h/mL) were still below the steady state C_{max} (124 ng/mL) and (739 ng·h/mL) at the 'no observed adverse effect level' (NOAEL) for oral administration in monkeys (50 mg/kg/day).

4.1.1.2. Distribution

4.1.1.2.1. Volume of distribution

No *in vivo* distribution data in humans are available because human intravenous studies were not performed. Following single intravenous administration of retapamulin to the rat, dog, and monkey, plasma clearance was high and the volume of distribution was in excess of total body water, indicating significant tissue distribution. Appreciable concentrations of radioactivity were associated with melanin-containing tissues and were observed for up to 35 days in the uveal tract of the eye and in sporadically localized areas of skin.

4.1.1.2.2. Plasma protein binding

No human studies have been done. Retapamulin displayed moderate to high *in vitro* plasma protein binding in the rat (84%), monkey (77%) and human (94%). *In vitro*, retapamulin was evenly distributed between blood cells and plasma in the rat and monkey whereas in humans, the blood:plasma concentration ratio was 0.6 with approximately 11% associated with blood cells.

4.1.1.3. Metabolism

Concentrations were so low that the elimination half-life after topical application of retapamulin ointment could not be determined in Study 026 or Study TOC101825. In Study 026, retapamulin T1/2 following topical application of retapamulin ointment to intact or abraded skin could not be estimated due to the variability as well as the relatively flat PK profiles, even when blood samples were collected up to 36 hours after dosing in Cohort 6 (retapamulin ointment, 2%, on 1600 cm^2 intact skin) and Cohort 12 (retapamulin ointment, 2%, on 100 cm^2 abraded skin). The available data are from either animal models or '*in-vitro*' studies.

4.1.1.3.1. Sites of metabolism and mechanisms / enzyme systems involved

· **Non-clinical data**

In vitro metabolism studies indicated that the predominant routes of [^{14}C]retapamulin metabolism in human hepatocytes were mono-oxygenation and di-oxygenation. Mono and di-oxygenation in combination with N-demethylation was also observed. The *in vitro* oxidative metabolism of [^{14}C]retapamulin in human liver microsomes is primarily mediated by CYP3A4.

In vitro metabolism of [^{14}C]retapamulin by human skin occurred to a very limited extent. In rats and monkeys following oral administration of [^{14}C]retapamulin, the predominant route of metabolism involved multiple mono-oxygenations. Parent retapamulin was a predominant component in rat plasma; however, it was present at relatively low concentrations in monkey plasma. Other notable pathways in the rat and monkey included combinations of mono-oxygenation with demethylation, or ketone formation, 0r glucuronidation or glucuronidation and demethylation. In the rat, mono-oxygenation with sulfation and di-oxygenation with demethylation was also detected. Hepatic microsomal clearance of retapamulin was rapid in the rat, dog, monkey and human, and was nicotinamide adenine dinucleotide phosphate (NADPH)-dependent.

Study CD2004/01478/02 was conducted to obtain qualitative information about the biotransformation of non-radiolabelled retapamulin in humans using samples from Study 026. Plasma and 24-hour urine samples collected on Day 1 and Day 7 for Cohorts 6 and 11 were analysed by LC/MS. The parent drug (retapamulin) was the only compound-related material detected by LC/MS in plasma samples obtained from Cohort 6. In plasma samples obtained from subjects following application of retapamulin ointment, 1%, to the abraded skin (Cohort 11), unchanged retapamulin was detected in both Day 1 and Day 7 plasma samples. One mono-oxygenated metabolite (P+16) was identified in Day 1 samples at 6, 12, and 24 hours, and in Day 7 samples at predose and 6 hours. An additional P+16 metabolite was detected only in the pre-dose Day 7 plasma sample. Metabolic profiles were similar in 24-hour urine samples collected from Cohorts 6 and 11. Because urinary excretion is a relatively minor pathway in rat and monkey, and systemic exposure in humans is very low, no attempt was made to quantify parent and metabolites in the urine samples of either cohort.

The *in vitro* oxidative metabolism of [^{14}C]retapamulin in human liver microsomes is primarily mediated by CYP3A4. Coincubation with the CYP3A4 inhibitors, ketoconazole or troleandomycin, resulted in complete or partial inhibition of the formation of retapamulin metabolites.

4.1.1.4. Excretion

4.1.1.4.1. Routes and mechanisms of excretion

· **Non-clinical data:**

Following oral administration of [^{14}C]retapamulin to intact male and female rats or monkeys, radioactivity was predominantly eliminated in the faeces. Following either an oral or intravenous dose of [^{14}C]retapamulin to male bile-duct-cannulated rats, bile was a major route of elimination of radioactivity indicating good oral absorption of radioactive material. In male intact monkeys, faecal and urinary elimination of radioactivity following an intravenous or oral dose was comparable, indicating good oral absorption of radioactive material.

· **Clinical data**

The elimination half-life after topical application of retapamulin ointment could not be determined in Study 026 or Study TOC101825. In Study 026, retapamulin $T_{½}$ following topical application of retapamulin ointment to intact or abraded skin could not be estimated, even when blood samples were collected up to 36 hours after dosing in Cohort 6 (retapamulin ointment, 2%, on 1600 cm^2 intact skin) and Cohort 12 (retapamulin ointment, 2%, on 100 cm^2 abraded skin).

4.1.2. Pharmacokinetics in the target population

In Study 029, full PK profiles were obtained in adult subjects after the first dose of retapamulin ointment, 1%, on Day 1 and Day 5. Only 9 out of 355 samples (total represents 11 samples per subject) taken in 7 subjects gave measurable concentrations (0.5 to approximately 4.3 ng/mL) and thus PK parameters (C_{max}, AUC, t_{max}, $T_{½}$) could not be derived. In Study 030A and Study 030B, a single PK sample was to be collected prior to the first dose of retapamulin ointment, 1%, or placebo on Day 3 or Day 4 from the first 500 enrolled adult subjects (≥18 years of age), to confirm the PK results observed in Study 029. Only 47 out of 380 samples (1 plasma sample per subject receiving retapamulin ointment, 1%) collected from adult subjects had measurable retapamulin concentrations. The limited number of measurable concentrations in adults across subject studies (Studies 029, 030A, and 030B) demonstrated either minimal or no systemic retapamulin exposures following repeat topical application of retapamulin ointment 1%, BD to wound surface areas up to 100 cm2 in subjects with SITL or other uncomplicated bacterial skin infections. No pharmacokinetic data are available in adult subjects with impetigo and SID. Wound sizes for adult subjects in the SITL studies (Study 030A and 030B) were comparable to those observed in the impetigo (Study TOC100224 and Study TOC103469) and SID (Study 032) studies. Of the measurable concentrations in subjects ≥2 years of age in Study 030A and 030B, the vast majority (52/56, 93%) were <2.5 ng/mL. This minimal exposure was comparable in adult and paediatric subjects. Although there appeared to be a positive correlation between wound size and detectable retapamulin, there was no apparent relationship between the magnitude of the observed plasma concentration and wound size. There was a progressive increase in the proportion of subjects with a detectable retapamulin with no dressing, semi occlusive, and occlusive dressings, respectively; the majority of subjects did not use an occlusive dressing.

Pharmacokinetic results from the Phase IV study, TOC106489, which assessed retapamulin exposure in children ≤2 years of age, showed that 46% of 79 PK samples had measurable levels of retapamulin. The plasma concentrations ranged from 0.52 ng/mL to 177.3 ng/mL, with 75% of the measurable samples <5.0ng/mL. The majority of the measurable samples (27/36, 75%) were <5.0 ng/mL; when including the non-measurable samples (n=43), 89% (70/79) were <5.0 ng/mL. A higher proportion of paediatric subjects ≥2 months to ≤6 months of age had measurable plasma concentrations of retapamulin compared with subjects >6 months of age. Three of the 4 highest plasma concentrations were seen in subjects ≤6 months of age; however, the majority of the measurable retapamulin concentrations were similar across the age ranges.

In Study TOC106489, 5 of the 36 measurable samples had retapamulin concentrations greater than the highest concentration seen in Studies 030A and 030B (18.5 ng/mL) or the highest C_{max} achieved in Phase I Study 026 (22.1 ng/mL). Review of the demographic, underlying disease, and treatment characteristics of these 5 subjects did not reveal any factors that would be predictive of the elevated exposures. There were also no clinically significant laboratory test abnormalities or AEs in these subjects. Wound sizes in the paediatric subjects were generally comparable. Similar to Study 030A and 030B, the percentage of subjects with measurable concentrations appeared to increase with increasing wound size, presumably due to the larger total dose administered, but a direct correlation between wound size and systemic concentration was not observed. In Study TOC106489 (conducted in paediatric subjects), the percentage of measurable samples were highest in SID subjects as compared to SITL and impetigo subjects; however these data need to be interpreted cautiously due to the small number of SITL subjects (n=9) enrolled in the study.

4.1.3. Pharmacokinetics in other special populations

4.1.3.1. Pharmacokinetics in subjects with impaired hepatic function

The primary route of elimination of retapamulin was via hepatic metabolism, as demonstrated in nonclinical studies. Although elimination is predominantly via hepatic metabolism, the systemic exposures to retapamulin are predominantly non-measurable in subjects. No dosage adjustment would be required in hepatic impairment.

Therefore, no studies to assess the PK of retapamulin after topical application of retapamulin ointment, 1%, in subjects with hepatic or renal impairment were performed.

4.1.3.2. Pharmacokinetics in paediatrics

Paediatric studies are discussed in section 4.1.2.

4.1.4. Pharmacokinetic interactions

4.1.4.1. Pharmacokinetic interactions demonstrated in human studies

One clinical drug interaction study was performed to determine the effect of co-administration of oral ketoconazole, a potent CYP3A4 and Pgp inhibitor, on the pharmacokinetics of retapamulin after topical application of retapamulin ointment, 1%. An approximate 80% increase in retapamulin plasma $AUC_{(0-24)}$ and C_{max} was observed with co-administration of oral ketoconazole with topical application of retapamulin ointment, 1%. The maximum individual systemic exposure in healthy subjects and adult subjects following topical application of retapamulin ointment, 1%, on 200 cm^2 of abraded skin (C_{max}= 22 ng/mL; $AUC_{(0-24)}$ = 238 ng·h/mL; Study 026) was 10-fold lower than the lowest Ki for CYP 3A4 inhibition by retapamulin and 660-fold lower than the IC_{50} for Pgp inhibition by retapamulin. No dosing modification is recommended due to the low overall exposure of retapamulin that has been observed in subject studies.

4.1.4.2. Clinical implications of in vitro findings

In human liver microsomes, retapamulin was a potent inhibitor of CYP3A4 when midazolam, nifedipine and atorvastatin were used as substrates. *In vitro*, retapamulin was shown to be a Pgp substrate and inhibited Pgp transport of digoxin with a 50% inhibitory concentration (IC_{50}) of 28.2 µM or 14601.3 ng/mL. Given that the concentrations are still so low (see previous section), topical application of retapamulin ointment, 1%, is unlikely to cause clinically relevant CYP 3A4 inhibition in subjects. In general, systemic exposures to retapamulin in most subjects with SITL, SID, impetigo, and other uncomplicated bacterial skin infections were <0.5 ng/mL. Although not demonstrated, in babies <6 months, with large areas being treated using retapamulin, there is potential for inhibition of drugs metabolised by the CYP34A pathway.

4.2. Evaluator's overall conclusions on pharmacokinetics

In the studies summarised above, both in healthy and target population studies, there were a limited number of measurable concentrations in adult and paediatric subjects (99/630 subjects or 16%). The findings demonstrated that in general there will be either minimal or no systemic retapamulin exposures following repeat topical application of retapamulin ointment, 1%, BD to wound surface areas up to 100 cm2 in subjects with SITL, SID, impetigo, or other uncomplicated bacterial skin infections (Study 029, Study 030A, Study 030B, and Study TOC106489). Additionally, the systemic exposure to retapamulin in the majority of adult and paediatric subjects with measurable concentrations (80/99 or 81% of subjects, Study 029, Study 30A, Study 030B, and Study TOC106489) following repeat topical applications of retapamulin ointment, 1%, was ≤2.5 ng/mL. For all but 2 subjects with measurable retapamulin concentrations, this was below the NOAEL level in monkeys after oral dosing (oral dose of 50 mg/kg/day). There is however, limited PK data available in impetigo or SID subjects. The retapamulin systemic exposures in subjects with impetigo or SID are likely comparable to or less than those observed in subjects with SITL and other uncomplicated bacterial skin infections based on depth and size of wounds. So in general, systemic retapamulin exposures are expected to be minimal after topical application of [the proposed dose].

Oral administration of ketoconazole, a potent CYP3A4 and Pgp inhibitor, increased the retapamulin $AUC_{(0\text{-}24)}$ and C_{max} by approximately 80% after topical application of retapamulin ointment, 1%, on abraded skin of healthy adult subjects (Study TOC101825). Due however, to minimal systemic exposure to retapamulin after topical application of retapamulin ointment, 1%, in subjects, the magnitude of these increases, which were within those seen in previous studies in healthy adult subjects, is unlikely to increase the incidence of adverse events or to require dosage adjustments for retapamulin ointment, 1%, when coadministered with oral CYP3A4/Pgp inhibitors in patients (Study TOC101825, Study 029, Study 030A and Study 030B).

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

Table 4 shows the studies relating to each pharmacodynamic topic.

Table 4. Submitted pharmacodynamic studies.

PD topic	Subtopic	Study ID
Primary Pharmacology	MIC of MSSA isolates	Study 030A, Study 030B, Study 032, TOC100224, TOC103469, TOC110977, and TOC110978
	MIC of MRSA isolates	ALB110247 TOC106489
Secondary Pharmacology	Irritation potential	Study 025 Study 034
	Sensitisation	Study 027
	Effect on QT interval	Study 026 and TOC101825

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

5.2.1. Mechanism of action

Pleuromutilins selectively inhibit the elongation phase of bacterial protein synthesis by interacting at a unique site on the prokaryotic ribosome. Retapamulin selectively inhibits multiple aspects of bacterial protein synthesis. Cross-resistance within the pleuromutilin class occurs for retapamulin; however, because of the specific mode of action, target-specific cross-resistance with currently available agents is infrequently observed. Retapamulin is fully active *in vitro* against Gram-positive isolates associated with skin infections, including S. aureus, S. pyogenes, S. epidermidis and anaerobic bacteria, including isolates that are resistant to currently available agents including β-lactams, macrolides, quinolones, fusidic acid, and mupirocin. Nineteen isolates with elevated retapamulin MICs of ≥2 μg/mL were identified; these isolates are considered resistant to retapamulin based on recently published microbiological cut-offs[4]. Of these 19 isolates, the mechanism of resistance was determined to be efflux for 9 isolates and methyltransferase for 1 isolate; the mechanism of resistance has not been characterized for 9 isolates. The low potential for development of resistance to retapamulin is also supported by the finding that based on outcomes of presumed eradication of pathogens and laboratory investigation of the limited number of subjects with post therapy isolates, no isolates demonstrated a reduction in susceptibility to retapamulin during treatment with retapamulin in the Phase III clinical program.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

The proposed indications for retapamulin are impetigo, SITL and SID. The primary pathogens are usually *Staphylococcus aureus*, methicillin-resistant *S. aureus* and *Streptococcus pyogenes*.

· *Staphylococcus aureus: In vitro profile studies*

There are 11 *in vitro* profile studies conducted to characterize the activity of retapamulin and comparator antibacterial agents against *S. aureus*. The results essentially demonstrated that retapamulin has excellent *in vitro* activity against *S. aureus* (over 1200 isolates tested). In the initial profiling studies, the MIC_{90} for retapamulin against *S. aureus* (31, 51, and 13 isolates) in three separate studies ranged from 0.06 to 0.125 μg/mL. There were then some more extensive studies to provide additional *in vitro* activity data for retapamulin with emphasis on geographically diverse, recently obtained clinical isolates. The *in vitro* activity of retapamulin along with various comparators was assessed against *S. aureus* in 8 expanded studies. In these studies, the MICs for retapamulin ranged from ≤0.008 to 64 μg/mL. All isolates chosen for testing were from skin and skin structure specimen sources. Against *S. aureus*, retapamulin and mupirocin were the most active agents tested, each with a MIC_{90} of 0.25 μg/mL. The MIC distribution for retapamulin demonstrates that 100% of the *S. aureus* isolates tested were inhibited at a retapamulin concentration of ≤1 μg/mL.

Retapamulin activity was also assessed against MRSA isolates from the GSK isolate collection that were characterized based on their staphylococcal chromosome cassette mec (SCCmec) element type and the presence or absence of the PVL genes as a biomarkers of community-associated MRSA (CA-MRSA). Of the 86 MRSA, 10 isolates were found to possess the PVL genes (lukS-PV – lukF-PV) and the type IV SCCmec element. Retapamulin demonstrated excellent activity against these isolates with 10/10 (100%) of the PVL-positive isolates inhibited by a retapamulin concentration of ≤0.12 μg/mL.

· *Global surveillance study*

This examined the in vitro the MIC_{50} and MIC_{90} for retapamulin against the 975 global isolates (442 from North America, 339 from Europe and 194 from International) of coagulase-negative staphylococci. Retapamulin demonstrated excellent activity against isolates of coagulase-negative staphylococci, *S. agalactiae* and viridans streptococci. All isolates of coagulase-negative staphylococci were inhibited by ≤0.5 µg/mL of retapamulin. The MIC_{50} and MIC_{90} values for retapamulin were 0.06 and 0.25 µg/mL, respectively, against the 930 isolates (471 from North America, 286 from Europe and 173 from International) of viridans streptococci. Retapamulin inhibited all isolates of viridans streptococci at ≤ 0.5 µg/mL. The percentage of MRSA recovered in the global surveillance study was 32.8% globally, 36.9% in North America, 29.8% in Europe, and 18.4% in International. Regardless of resistance phenotype (MRSA, macrolide-resistant, mupirocin-resistant and fusidic acid-resistant S. aureus) or geographic region from which isolates were collected, retapamulin had MIC50 and MIC90 values of 0.06 and 0.12 µg/mL, respectively, and was the most active compound tested

Table 5 contains frequency distributions of the retapamulin MICs for *S.aureus* that were isolated from the Intent-to-Treat, Bacteriological (ITTB) population for all subject visits during the Phase III clinical studies. The retapamulin MIC_{90} for *S. aureus* isolates recovered in all geographic regions was 0.12 µg/mL. As shown in Table 5, retapamulin inhibited 99.9% of *S. aureus* isolates tested at a concentration of ≤0.5 µg/mL, representing the cut-off MIC for susceptible isolates[4]. There was a single isolate from a subject in the ITTB population from Study TOC110978 (North America) with a retapamulin MIC of 2 µg/mL.

Table 5: Frequency Distribution of retapamulin MICs (mcg/mL) for *S.aureus* (Studies 030A, 030B, 032, TOC100224, TOC103469, TOC110977, and TOC110978

Geographic Region[a]	Number and Cumulative % of Isolates at Each MIC MIC (µg/mL)									
	0.008	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	Total
Global	1	1	14	844	1220	44	1	1	1	2129
	<0.1%	0.1%	0.8%	40.4%	97.7%	99.8%	99.9%	99.9%	100%	
North America	-	-	4	195	454	24	-	1	1	679
			0.6%	29.3%	96.2%	99.7%		99.9%	100%	
Central/South America	-	-	1	62	122	7	-	-	-	192
			0.5%	32.8%	96.4%	100%				
Europe	1	1	5	272	149	3	1	-	-	432
	0.2%	0.5%	1.6%	64.6%	99.1%	99.8%	100%			
International[a]	-	-	4	315	495	10	2	-	-	826
			0.5%	38.6%	98.5%	99.8%	100%			

Source: Table 7.01

a Geographic regions were as follows:
North America: United States and Canada;
Central/South America: Mexico, Costa Rica, Peru, Argentina, Brazil;
Europe: Austria, France, Germany, Greece, Italy, Netherlands, Poland, Russian Federation, Spain, United Kingdom;
International: South Africa and India.

Of the 1260 *S. aureus* isolates collected globally in Studies 030A, 030B, 032, and TOC110977, 1100 (87.3%) isolates were determined to be MSSA. Data were provided on the frequency distribution of retapamulin MICs for MSSA that were isolated at baseline by PVL genotype for the ITTB population for Studies 030A, 030B, 032, and TOC110977 combined. The retapamulin MIC_{90} for MSSA was 0.12 µg/mL. The *in vitro* activity of retapamulin was not affected by the presence or absence of the PVL genes. Retapamulin demonstrated similar *in vitro* activity against PVL-positive, PVL-negative, and all MSSA isolates with a MIC_{90} of 0.12 µg/mL against both sub-groups.

[4] Traczewski MM, Brown SD. Proposed MIC and disk diffusion microbiological cutoffs and spectrum of activity of retapamulin, a novel topical antimicrobial agent. *Antimicrob Agents Chemother* 2008;52:3863-7

Analysis of MRSA results includes data from clinical trials other than Phase III (Phase I, II, and IV) in which microbiology specimens were collected. In the Phase I/IIa clinical study ALB110247, 394 *S. aureus* nasal isolates were collected from the screening population at all visits during the study, including 298 isolates collected during screening and 96 collected during treatment and follow-up. All 394 *S. aureus* nasal isolates had retapamulin MICs ≤2 µg/mL; the MIC_{90} was 0.12 µg/mL. Of the 394 *S. aureus* nasal isolates, 28 (7%) were methicillin-resistant, including 24 MRSA isolates collected during screening and 4 MRSA isolates collected during treatment and follow-up.

In the Phase IV clinical study, TOC106489 in paediatric subjects aged 2 to 24 months, 44 *S. aureus* isolates were collected at baseline in the ITT population, including 3 MRSA isolates. Retapamulin exhibited MIC_{50}, MIC_{90}, and MIC range values of 0.12, 0.25 and 0.06–0.25 µg/mL, respectively. In addition, 3 *S. aureus* isolates were collected at post-baseline visits; the post-baseline MIC range for retapamulin was within the baseline MIC range, therefore demonstrating that no isolates developed reduced susceptibility to retapamulin during treatment.

5.2.2.2. Secondary pharmacodynamic effects

· *Irritation potential*

Assessment of irritation on abraded (tape-stripped) skin is considered to predict chemical irritation with exaggerated sensitivity[5], and the abraded skin model appropriately simulates the clinical setting in which retapamulin ointment will be used. Given this, the irritation potential of retapamulin ointment was assessed on both intact and abraded skin of healthy adult subjects in Phase I Study 025 and Phase I Study 034. On intact skin, retapamulin ointment, 0.5%, 1%, and 2%, and retapamulin-AAA ointment, 0.5%, 1%, and 2%, were not primary (single-dose) or cumulative (repeat-dose) irritants. Additionally, retapamulin-AAA ointment, 0.5%, 1%, and 2%, showed similar irritation to marketed products for treatment of uSSSI (0.1% gentamicin ointment and bacitracin/neomycin/polymyxin B) after single and repeat applications on intact skin under full occlusion. Because retapamulin-AAA ointment contains retapamulin (free base), the results from Study 034 (succinate salt ointment) are consistent with irritation results from Study 025 (free base ointment) on intact skin. In all studies in which the irritation potential of retapamulin ointment, 1%, was assessed following repeated application on intact or abraded skin, the formulation was well tolerated. These results supported the conclusion that the 1% ointment was the most appropriate for progression into the Phase II and Phase III studies. In Study 034, no clinically significant differences were observed in retapamulin-AAA ointment 0.5%, 1%, and 2%, retapamulin ointment, 1%, vehicle, gentamicin ointment, and Neosporin irritation scoring across occlusion conditions. Because retapamulin ointment, 2%, was more irritating and the succinate salt formulations were not progressed due to the safety and efficacy of the free base formulations, retapamulin ointment, 1%, was progressed for further clinical development.

· *Sensitisation*

The potential of retapamulin ointment in 0.5%, 1%, and 2% concentrations to induce contact sensitisation following repeated topical applications to intact skin in healthy subjects was evaluated in Phase I Study 027. Of 206 evaluable subjects, only 1 subject demonstrated definitive sensitisation upon challenge and rechallenge to the 1% and 2% concentrations of retapamulin. These results demonstrate that the potential for contact sensitisation after topical application of retapamulin ointment, 1%, was low and comparable to currently marketed topical products. No subjects in the Phase II/III studies had evidence of sensitisation to retapamulin ointment, 1%.

[5] Zhai H, Poblete N, Maibach HI. Stripped skin model to predict irritation potential of topical agents *in vivo* in humans. *Int J Dermatol* 1998;37:386-9.

· *QT effects*

The effects of topical application of retapamulin ointment, 0.5%, 1%, and 2%, on QT/QTc interval were assessed in post-hoc analyses of manually over-read ECG data collected in Study 026 (paper 12-lead ECGs) and Study TOC101825 (digitally-acquired 12-lead ECGs).

Study 026 was not designed as a thorough QT study, and the sample sizes were too small to meet the statistical requirements of a "negative" QT study6. Instead, statistically significant evidence for QTc prolongation was assessed. Wide confidence intervals reflect the small sample size associated with the comparisons of interest. Estimates of the time-matched mean differences in baseline-subtracted (after dosing minus baseline) QT, QTcF and QTcB between each retapamulin concentration and placebo, analysed by day and skin-type are provided in the CSR. No statistically significant evidence of QTc prolongation hazard (ie, 95% confidence interval [CI] of mean QTc changes completely above 0 msec) was identified for QTcF. Five likely false statistical decreases were observed (ie, 95% confidence interval of mean QTc changes completely below 0 msec). No subjects had a QTcF or QTcB >500 msec or a change from baseline in QT, QTcF or QTcB >60 msec.

Study TOC101825 was also not designed as a thorough QT study, and the ECG analysis outlined in the ICH E14 guidance[6] could not be performed on the ECG results from this study. Specifically, there was no active control or placebo in this study, and a single 12-lead ECG was obtained at each post-dosing evaluation time point, and the baseline ECG evaluation for Regimen B (oral ketoconazole + retapamulin ointment, 1%) was obtained after 3 days of oral ketoconazole dosing alone. Therefore, summary statistics are presented for ECG data obtained in Study TOC101825. Mean values did not change significantly over the course of Day 1, Regimen A or Day 4, Regimen B.

The change from baseline in QT, QTcB, and QTcF did not exceed 60 msec for any subject at any time point based on manually-read ECG values. An increase from baseline in QT between 31-60 msec was observed for one subject (Regimen B). Increase from baseline in QTcF between 31 and 60 msec was observed for 2 subjects, 1 in Regimen A and 1 in Regimen B. Increases from baseline in QTcB between 31-60 msec were observed more frequently (5 subjects in Regimen A and 5 subjects in Regimen B). For Regimen A, baseline QT, QTcB and QTcF intervals were determined from the average of 3 predose ECG values on Day 1. For Regimen B, baseline QT, QTcB and QTcF intervals were determined from the average of 3 predose (with respect to retapamulin ointment) ECG values on Day 4, after ketoconazole dosing had commenced.

5.2.3. Time course of pharmacodynamic effects

In Study 034, 2% retapamulin was found to be a cumulative irritant. Concentrations less than this did not cause irritation or sensitisation (as discussed in 5.2.2.2).

In Study 026, the mean/SE QTcF/QTcB/QT interval and the mean/SE plasma concentration were plotted versus time to evaluate the time course of potential QTcF/QTcB/QT interval prolongation in relation to retapamulin plasma levels. All subjects were grouped by study day (Day 1 or Day 7) and skin type (intact or abraded). It is shown that as retapamulin plasma concentration changed (increased or decreased), QTcF/QTcB/QT interval did not follow the changes, indicating that there is no relationship between retapamulin plasma concentration and QTcF/QTcB/QT interval. Also, as retapamulin plasma level increased from Regimen A to Regimen B, there was no apparent increase in QTcF/QTcB/QT interval from Regimen A to Regimen B. These indicate that there was no relationship between retapamulin plasma concentration and QTcF/QTcB/QT interval.

[6] <http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Guideline.pdf>

5.2.4. Relationship between drug concentration and pharmacodynamic effects

Retapamulin ointment, 2% was not a primary irritant on abraded skin but had similar irritation scores to 0.1% SLS in distilled water (positive control) after repeat applications. Retapamulin ointment, 2%, was considered a cumulative irritant on abraded skin. The results for the 2%, formulation trended higher than, but still overlapped with, the comparison treatments and were not consistent with the positive control.

In Study 026, the relationship between maximum change from baseline QTcF/QTcB/QT interval and retapamulin C_{max} was examined graphically for all subjects, regardless of study day (Day 1 or Day 7), cohort (Cohorts 1-12), regimen (active or placebo), and skin type (intact or abraded). Linear regression was performed and the associated p value of the slope was obtained to evaluate if a relationship exists. The graphs for QTcB and QT were similar. The p values were all >0.05, indicating no relationship between maximum change from baseline QTcF/QTcB/QT interval and retapamulin Cmax.

5.3. Evaluator's overall conclusions on pharmacodynamics

Overall, retapamulin ointment, 1%, was well-tolerated (Study 025, Study 026, Study 027, and Study TOC101825). The studies examining local irritation, sensitisation and effects on QTc indicated that these were not likely to be issues (even in combination with CYP3A4 inhibitors). In summary:

- On intact and abraded skin, retapamulin ointment, 1%, was not a primary or cumulative irritant after daily 24 hour applications for 2 days and 21/14 days (Study 025).
- One of 206 subjects demonstrated sensitisation upon challenge and re-challenge to retapamulin ointment, 1% and 2% (Study 027).

In post-hoc analyses of manually over-read 12-lead ECGs from healthy adult subjects from studies 026 and TOC101825 (N=103), no significant effects on QT/QTc were observed after topical application of retapamulin ointment on intact and abraded skin. Due to low systemic exposure to retapamulin with topical application, QTc interval prolongation is unlikely in the patient population, with or without co-administration of CYP3A4 or Pgp inhibitors (Study 026, Study TOC101825, Study 029, Study 030A, and Study 030B).

6. Dosage selection for the pivotal studies

Phase I studies of irritation and tolerance that indicated the 1% formulation was the maximal tolerated concentration when used under proposed therapeutic conditions. Twice-daily (BD) dosing was proposed based on studies done in animal models. The findings of preclinical studies were evaluated in a Phase I study (029) that evaluated PK and proof-of- concept for administration of retapamulin ointment topically for treatment of uSSSI.

7. Clinical efficacy

This application contains efficacy data from 7 multi-national Phase III clinical studies (Table 1):

- 1 active-comparator study (Study 100224) and 1 placebo-controlled study (Study 103469) for the treatment of impetigo.
- 2 identical active-comparator studies (Study 030A, Study 030B) and 1 placebo controlled study (TOC110977) for the treatment of SITL.
- 1 active-comparator study (TOC110978) for the treatment of SITL and impetigo due to MRSA.

· 1 active-comparator study (Study 032) for the treatment of SID.

Adult and paediatric subjects were enrolled in all 7 studies; subjects had skin infections that were suspected to be caused by *S. aureus* (methicillin susceptible and methicillin resistant) and/or *S. pyogenes*. The total number enrolled is summarised in Table 6.

Table 6: Summary of subject numbers in the Phase III Primary Efficacy studies

	SB-275833	Comparator
Indication	N	N[1]
Impetigo (103469, vs. placebo)	139	71
Impetigo (100224, vs. fusidic acid)	317	150
SITL (030A, vs cephalexin)	592	260
SITL (030B, vs. cephalexin)	540	249
SID (032, vs. cephalexin)	320	156
SITL (977, vs. placebo)	246	113
SITL / Impetigo Due to MRSA (978, vs. linezolid)	61	32
TOTAL	1908	886

The primary efficacy populations were Per-Protocol Clinical for Studies 100224, 030A, 030B, and 032; Intent-to-Treat Clinical for Study 103469, and Intent-to-Treat Clinical Primary Analysis for Study 977; and Per-Protocol MRSA for Study 978.

7.1. Impetigo

7.1.1. Pivotal efficacy studies

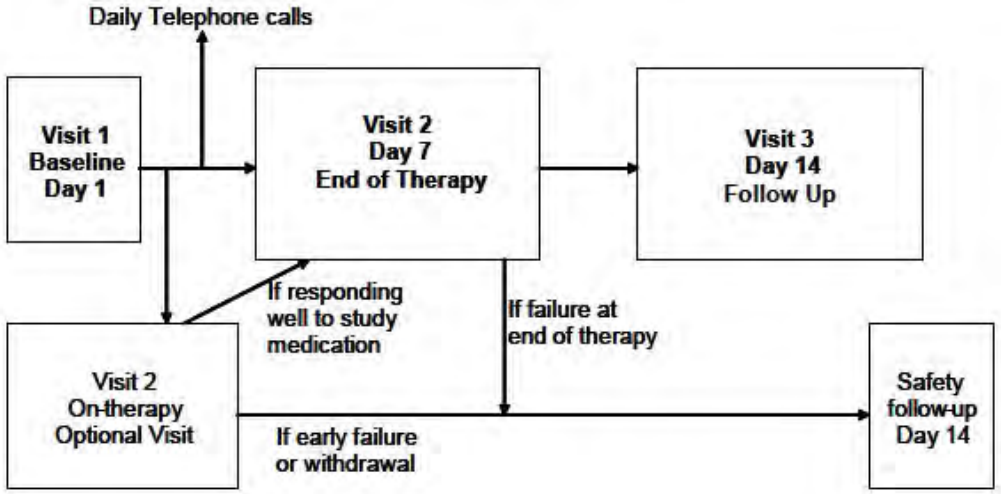
There are two phase 3 studies to support this indication, in one, retapamulin is compared to in the other it is compared to placebo. Both enrolled adults and children.

7.1.1.1. Study TOC103469

7.1.1.1.1. Study design, objectives, locations and dates

This study was conducted in 17 centres in four countries (Netherlands, India, Peru and Mexico) between 27 April 2005 - 02 January 2006. It was designed to compare the efficacy and safety of topical application of retapamulin Ointment, 1%, with topical placebo ointment given twice daily for 5 days, in the treatment of adult and paediatric subjects with primary impetigo. This was a randomised, double-blind, multicentre, placebo-controlled study to evaluate the efficacy and safety of topical retapamulin Ointment, 1%, versus placebo ointment in the treatment of paediatric (≥9 months old) and adult subjects with impetigo. Enrolled subjects were randomised (2:1 ratio) in a double-blind manner to receive either topical retapamulin Ointment, 1%, twice daily for 5 days or topical placebo ointment, twice daily for 5 days. The primary objective was to demonstrate that topical retapamulin Ointment, 1%, was clinically superior to placebo, with secondary objectives to evaluate the bacteriological efficacy and safety of retapamulin Ointment, 1%, and placebo in the treatment of impetigo. A schematic of the design of this study is shown in Figure 1.

Figure 1. Study Schematic Diagram: Study TOC103469



7.1.1.1.2. Inclusion and exclusion criteria

Diagnosis and main criteria for inclusion:

Inclusion criteria

- Diagnosis consistent with Study indication and study criteria.
- If childbearing age, and female, the subject had a negative urine pregnancy test prior to enrolment (if of childbearing potential).
- Subject was to comply with the two barrier methods of contraception (if of childbearing potential) or be of non-childbearing potential (post-menopausal or surgically sterile).
- The subject was willing and able to comply with the study protocol.
- The subject and guardian, if applicable, gave written informed, dated consent, and written assent, if applicable, to participate in the study.

A paediatric subject under the legal age of consent (dependent on local country practice) was included if the following applied:

- The subject had study appropriate age.
- The parent/legal guardian was willing to comply with the protocol.
- The child had given their assent to participate in the study (this was only required if the child was of an age to assent to enrol in the study – the age of assent was determined by IRB/IEC or was consistent with local legal requirements).
- The parent/legal guardian had given written informed, dated consent for the subject to participate in the study.

Exclusion criteria

- A subject was not eligible for inclusion in this study if any of the following criteria applied:
- The subject demonstrated a previous hypersensitivity reaction to retapamulin or any component of the ointment (refer to the Investigator Brochure for composition of retapamulin Ointment).
- The subject had an underlying skin disease (e.g., pre-existing eczematous dermatitis) or skin trauma, with clinical evidence of secondary infection.

- The subject had signs and symptoms of systemic infection (such as fever; defined an oral temperature greater than 101°F or 38.3°C).
- The subject had a bacterial skin infection, which, due to depth or severity, in the opinion of the investigator, could not be appropriately treated by a topical antibiotic (e.g., extensive cellulitis, furunculosis and abscess).
- The subject received a systemic antibacterial, steroid, or had applied any topical therapeutic agent (including glucocorticoid steroids, antibacterials and antifungals) directly to the impetigo lesion(s), less than 24 hours prior to study entry.
- The subject had a serious underlying disease that could be imminently life threatening.
- The subject was pregnant, breast-feeding or planning a pregnancy during the study.
- The subject used an investigational drug within 30 days prior to entering the study.
- The subject was previously enrolled in this study or in any other study involving retapamulin.

Subjects aged ≥9 months (or ≥18 months in The Netherlands) with a clinical diagnosis of primary impetigo (bullous or non-bullous), defined as a lesion or a group of lesions characterised by red spots or blisters without crusts, which later progress to lesions that ooze and form yellow or honey-coloured crusts surrounded by an erythematous margin; no more than 10 discrete localised impetigo lesions (lesion(s) not exceeding 100 cm^2 in total area) suitable for topical treatment; with a minimum of a Skin Infection Rating Scale Score (SIRS) of at least 8.

7.1.1.1.3. Study treatments

Subjects received one of two treatments: topical retapamulin Ointment, 1%, twice daily for 5 days or placebo ointment twice daily for 5 days. Subjects were randomised to treatment in a ratio of 2:1 (active:placebo).

7.1.1.1.4. Efficacy variables and outcomes

Primary and secondary efficacy endpoints were evaluated based on clinical and microbiological responses (success or failure) to study medication. The response was derived from clinical and microbiological outcomes. Clinical outcomes were determined by the investigator. Microbiological outcomes were derived by comparing pathogens isolated at baseline to those collected at later visits (samples were only collected at the later visits if the subject was a treatment failure. In the absence of any pathogens being isolated microbiological outcome was derived from the clinical outcome). AEs, serious AEs (SAEs) and clinical laboratory findings were evaluated for safety.

The primary efficacy endpoint was the clinical response (clinical success or clinical failure) to study medication at End of Therapy, 2 days after treatment (Day 7; Visit 2) in the ITTC population.

The hypothesis to be tested by the primary endpoint was that the clinical efficacy of retapamulin Ointment, 1%, at EOT was superior to that of placebo in the treatment of adult and paediatric subjects with impetigo.

The secondary efficacy endpoints included:

- Clinical endpoints:
  - Clinical response at End of Therapy - Day 7; Visit 2 (2 days after study treatment)
  - Clinical response at Follow-Up - Day 14; Visit 3 (9 days after study treatment)
  - Assessment of lesion(s) area at each visit

- Microbiological endpoints:
  - Microbiological response at End of Therapy - Day 7; Visit 2 (2 days after study treatment)
  - Microbiological response at Follow-Up - Day 14; Visit 3 (9 days after study treatment)

7.1.1.1.5. Randomisation and blinding methods

As this was a double-blind study the packaging and labelling of study medication was identical for the active medication and its placebo counterpart. All efforts were made to make the study medication and placebo identical with respect to appearance and smell. In an emergency, the investigator could unblind a subject's treatment assignment.

Subjects were assigned to study treatment using a predetermined 2:1 randomisation schedule (retapamulin Ointment, 1%: placebo). Randomisation was centre-based and performed using an automated telephone system. Subject randomisation was additionally stratified by age (9 months to ≤6 years, 6 years to <13 years and ≥13 years). The block size of 6 remained confidential until the code was unblinded and the data analysed.

7.1.1.1.6. Analysis populations

Four subject populations were defined for the analysis of clinical efficacy and bacteriology data, and one population was defined for the safety analyses, as follows:

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

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

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

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

Safety Population: All subjects who took at least one dose of study medication (i.e., the ITTC population).

As this is a superiority study, the ITT population is the most conservative approach to statistical analysis; hence the ITTC population is of primary interest.

7.1.1.1.7. Sample size

The planned sample size was 140 evaluable subjects in the retapamulin Ointment, 1%, group and 70 in the placebo group.

7.1.1.1.8. Statistical methods

This was a superiority study, with 90% power and a one-sided alpha of 2.5%. A 2:1 randomisation scheme of retapamulin Ointment, 1%: placebo ointment was employed. The comparison of primary interest in this study was the clinical response rate at End of Therapy (Day 7; Visit 2) for the Intent to Treat Clinical (ITTC) population. The hypothesis tested for the primary endpoint was that the clinical success rate for retapamulin Ointment, 1%, was superior to placebo. A conclusion of superior efficacy of retapamulin Ointment, 1%, was to be drawn if

the lower limit of the 95% confidence interval for the treatment difference was greater than zero. Conclusions of superiority were also confirmed with Fisher's Exact Tests.

7.1.1.1.9. Participant flow

See Table 7 and Table 8

Table 7: Subject Disposition

Subject Disposition	Treatment Group		
	SB-275833	Placebo	Total
Randomised	140	73	213
Randomised but not treated	1	2	3
Completed Study	122	40	162

Table 8: Number (%) of Subjects Present at Each Visit

Study Phase	Number (%) of Subjects		Total N=210
	SB-275833 N=139	Placebo N=71	
Visit 1 (Baseline; Day 1)	139	71	210
Optional visit	5 (3.6)	13 (18.3)	18 (8.6)
Visit 2 (Day 7)	131 (94.2)	58 (81.7)	189 (90.0)
Visit 3 (Day 14)	134 (96.4)	67 (94.4)	201 (95.7)

7.1.1.1.10. Major protocol violations/deviations

The number of subjects excluded due to protocol violations is shown in Table 9:

Table 9: Number (%) of Subjects Excluded from the Per Protocol Clinical Population, by Reason (ITTC Population)

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

UTD = unable to determine; 1 = Source Table states exposure to topical treatment, but also includes systemic treatment.

The most common protocol violation was exposure to other treatment.

7.1.1.1.11. Baseline data

Overall, 210 subjects were enrolled in the study and took at least one dose of study medication. Of these, 139 subjects were in the retapamulin Ointment, 1%, group and 71 were in the placebo group; these formed the ITTC population. The groups are summarised in Table 10 and Table 11.

Table 10: Number of Subjects in analysis groups

Population	Number of Subjects		
	SB-275833	Placebo	Total
ITTC	139	71	210
PPC at End of Therapy	124	62	186
PPC at Follow-Up	119	58	177
ITTB	114	57	171
PPB at End of Therapy	107	52	159
PPB at Follow-Up	102	48	150

Table 11: Number of Subjects by Age Strata (ITTC Population)

Population	Number of Subjects		
	SB-275833 N=139	Placebo N=71	Total N=210
9 months - <2 years	12	6	18
2 years - <6 years	38	24	62
6 years - <13 years	56	28	84
13 years - <18 years	5	6	11
18 years - <65 years	25	7	32
≥65 years	3	0	3

Overall, 175/210 (83.3%) subjects were paediatric (<18 years) of whom 111 received retapamulin Ointment, 1%, and 64 received placebo. Most were in the 6 years to <13 years and 2 years to <6 years strata. Similar trends were observed for the PPC population The subjects enrolled in this study were predominately <65 years of age; however, only three subjects (all in the retapamulin Ointment, 1%, group) were ≥65 years of age In all populations and in both treatment groups, the majority of subjects had the non-bullous form of impetigo.

The majority of subjects in the study had one or more pathogens identified at baseline *S. aureus* was the most frequently isolated pathogen in the study (64.6% of isolates from subjects in the retapamulin Ointment, 1%, group and 77.3% of isolates from the placebo group. All the isolates of *S. aureus* were methicillin-susceptible and all were susceptible to mupirocin. Pathogens were generally isolated with similar frequency in the two treatment groups, although slightly more *S. pyogenes* were isolated in the retapamulin Ointment, 1%, group (23% compared to 12% in the placebo group). The majority of subjects with two or more pathogens had *S. aureus* and *S. pyogenes* isolated from the same baseline sample. The MIC_{50}, MIC_{90} and MIC range for retapamulin against all *S. aureus* isolates were 0.12, 0.12 and 0.06-0.25µg/mL, respectively, indicating excellent in vitro activity of retapamulin against *S. aureus* isolates recovered from subjects at baseline. MIC values were similar between the two treatment groups.

7.1.1.1.12. Results for the primary efficacy outcome

In this study, retapamulin was found to superior to placebo, applied twice daily for 5 days, in the treatment of impetigo, based on the primary efficacy endpoint of clinical response at End of Therapy in the ITTC population. Superiority was also achieved in the Per Protocol Clinical (PPC) population. The lower limit of the 95% confidence interval for the treatment difference was substantially greater than the superiority margin of 0%, as shown in the Table below. The p-values from the Fisher's Exact Tests were <0.0001 for each analysis population.

Table 12: Clinical Response at End of Therapy by Analysis Population

Analysis Population	SB-275833		Placebo		Difference in Success Rates (%)	95% CI (%)
	n/N	Success Rate (%)	n/N	Success Rate (%)		
ITTC	119/139	85.6	37/71	52.1	33.5	(20.5, 46.5)
PPC	111/124	89.5	33/62	53.2	36.3	(22.8, 49.8)

CI = Confidence interval ITTC = Intent to Treat Clinical PPC = Per Protocol Clinical

A clinical response of 'success' was achieved by 85.6% (119/139) of the ITTC population at End of Therapy for the retapamulin Ointment, 1%, group compared to 52.1% (37/71) of the ITTC population for the placebo group. The lower limit of the confidence interval for the treatment difference was greater than zero, thus indicating that retapamulin Ointment, 1%, was superior to placebo ointment. Superiority was also achieved in all the analysis populations.

7.1.1.1.13. Results for other efficacy outcomes

Selected secondary efficacy results are presented in Table 13 below. The clinical success rate at Follow-Up was superior in the retapamulin Ointment, 1% group compared with the placebo group in all four analysis populations. The microbiological response rate observed was higher for retapamulin at both end of therapy and follow-up in comparison to placebo.

Table 13: Results for Secondary efficacy outcomes

Analysis Population	SB-275833		Placebo		Difference in Success Rates (%)	95% CI (%)
	n/N	Success Rate (%)	n/N	Success Rate (%)		
Clinical Response at Follow-Up						
ITTC	105/139	75.5	28/71	39.4	36.1	(22.7, 49.5)
Per-subject Microbiological Response at End of Therapy						
ITTB	104/114	91.2	29/57	50.9	40.4	NA
Per-subject Microbiological Response at Follow-Up						
ITTB	92/114	80.7	21/57	36.8	43.9	NA

CI = Confidence interval ITTC = Intent to Treat Clinical PPC = Per Protocol Clinical

The retapamulin Ointment, 1%, group was superior to the placebo group in all four analysis populations. On the whole, success rates at Follow-Up were slightly lower than those seen at End of Therapy. This was expected as subjects who were 'clinical failures' at End of Therapy were also classified as 'clinical failures' at Follow-Up.

7.1.1.2. Study TOC100224

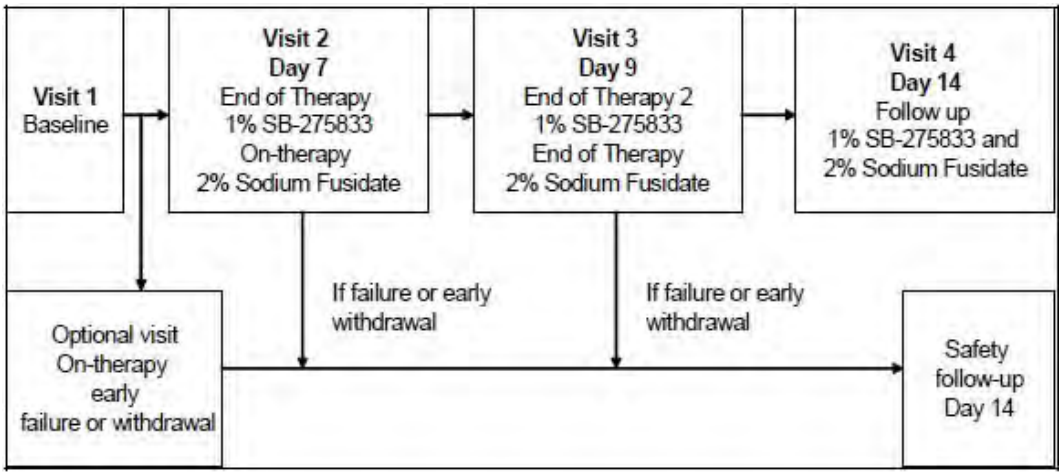
7.1.1.2.1. Study design, objectives, locations and dates

Study TOC100224 was a randomised, observer-blind, multicentre, noninferiority, comparative study. The primary objective of this study was to compare the efficacy and safety of topical applications of retapamulin ointment BD for 5 days, with topical 2% sodium fusidate ointment three times daily (TID) for 7 days in the treatment of primary impetigo in adult and paediatric (≥9 months of age) subjects. This study was conducted between 23 April 2005 and 07 September 2005 and was conducted in 42 centres in nine countries. Subjects with up to 10 lesions were enrolled (with a maximum area of 100 cm2 for either a single lesion or multiple lesions). The infected lesions had to be suitable for topical antibiotic therapy. In addition, the infections were to be those with a high likelihood of having *S. aureus* and/or *S.pyogenes* as the causative infectious agent.

Enrolled subjects were randomised in a 2:1 ratio in an observer-blind manner to receive either topical retapamulin Ointment, 1%, twice daily for 5 days or topical sodium fusidate ointment, 2%, three times daily for 7 days. During these visits, clinical evaluations were performed, bacteriology samples were collected for culture, Gram stain and susceptibility testing, and blood

samples were drawn for clinical laboratory (safety) evaluations, and AEs were monitored. The schematic for the design of this study is shown in Figure 2.

Figure 2. Study Schematic Diagram Study TOC100224



7.1.1.2.2. Inclusion and exclusion criteria

As described under 7.1.1.1.2.

Subjects aged ≥9 months with a clinical diagnosis of primary impetigo (bullous or non-bullous) defined as a lesion or a group of lesions characterized by red spots or blisters without crusts, which later progress to lesions that ooze and form yellow or honey-coloured crusts surrounded by an erythematous margin; no more than 10 discrete localized impetigo lesions (lesion(s) not exceeding 100 cm^2 in total area) suitable for topical treatment; Skin Infection Rating Scale Score (SIRS) of at least 8.

7.1.1.2.3. Study treatments

Subjects received one of two treatment regimens: topical retapamulin Ointment, 1%, twice daily for 5 days or topical sodium fusidate ointment, 2%, three times daily for 7. Subjects were required to attend the clinic for up to 4 visits over a 14-day period, with a further optional On-therapy visit for subjects who were considered not to be improving while on therapy and as a consequence had been withdrawn from the study.

7.1.1.2.4. Efficacy variables and outcomes

The primary efficacy endpoint was the clinical response (clinical success or clinical failure) to study medication at End of Therapy, two days after treatment (Day 7 [Visit 2] for retapamulin Ointment, 1%, and Day 9 [Visit 3] for sodium fusidate ointment, 2%) in the Per Protocol Clinical (PPC) population.

The hypothesis to be tested by the primary endpoint was that the clinical efficacy of retapamulin Ointment, 1%, at End of Therapy was non-inferior to that of sodium fusidate ointment, 2%, in the treatment of subjects with impetigo.

Secondary efficacy outcomes were:

- Clinical endpoints
  - Clinical response at Day 7; Visit 2 (2 days after treatment for retapamulin Ointment, 1%, and on-therapy for sodium fusidate ointment, 2%).
  - Clinical response at Day 9; Visit 3 (4 days after treatment for retapamulin Ointment, 1%, and 2 days after treatment for sodium fusidate ointment, 2%).
  - Clinical response at Follow-Up (Day 14; Visit 4).

- Assessment of lesion(s) area at End of Therapy (Day 7 [Visit 2] for retapamulin Ointment, 1%, Day 9 [Visit 3] for sodium fusidate ointment, 2%) and Follow-Up (Day 14; Visit 4).

· Microbiological endpoints

- Microbiological response at End of Therapy (Day 7 [Visit 2] for retapamulin Ointment, 1%, Day 9 [Visit 3] for sodium fusidate ointment, 2%).
- Microbiological response at Follow-Up (Day 14; Visit 4).
- Number and percent of subjects who had methicillin resistant S. aureus (MRSA), mupirocin resistant S. aureus (mupRSA) or fusidic acid resistant S. aureus (fusRSA) isolated at baseline and by clinical response at End of Therapy (Day 7 [Visit 2] for retapamulin Ointment, 1%, Day 9 [Visit 3] for sodium fusidate ointment, 2%).
- Number and percent of subjects who had various pathogens including MRSA, mupRSA and fusRSA isolated at baseline by clinical response at Follow-Up.

The tertiary efficacy endpoints were:

· Descriptive analysis (number and percent) of primary and secondary endpoints, as defined earlier, in the paediatric sub-population.

· Clinical and microbiological response at End of Therapy (Day 7 [Visit 2] for retapamulin Ointment, 1%, Day 9 [Visit 3] for sodium fusidate ointment, 2%) by subgroup factors.

· Clinical response at Follow-Up (Day 7 [Visit 2] for retapamulin Ointment, 1%, Day 9 [Visit 3] for sodium fusidate ointment, 2%) by presence of S. aureus nasal carriage at baseline.

· Time to resolution for paediatrics as defined by diary response.

· Extent of impact of child's illness upon parent/guardian as defined by diary response.

7.1.1.2.5. Randomisation and blinding methods

This was an observer-blind study. Observer blinding was utilized in this study because the study treatments differed in colour and application frequency. In this study, a blinded assessor was responsible for performing all clinical activities in assessing the lesion(s) following treatment. In order to maintain observer blinding, an unblinded study site member was responsible for dispensing the study medication and to maintain investigational product accountability records throughout the course of the study. This person ensured that the investigator/clinical assessor remained blinded and had no access to the product accountability records throughout the study. Furthermore, the subject or the subject's parent/legal guardian was instructed not to discuss aspects of the study medication or medication administration (i.e., dosing frequency, size/shape of tubes, colour of ointment administered) with the investigator.

Subjects were assigned to study treatment using a predetermined 2:1 randomization schedule of retapamulin Ointment, 1%: sodium fusidate ointment, 2%. Randomization was centre-based and performed using RAMOS. Subject randomization was additionally stratified by age (9 months to 5 years; 6 years to 12 years; and ≥13 years). The block size of 6 remained confidential. Once a treatment number had been assigned to a subject, if the subject was withdrawn, the number could not be reassigned to any other subject.

7.1.1.2.6. Analysis populations

Four subject populations were defined for the analysis of clinical efficacy and bacteriology data, and one population was defined for the safety analyses, as in Section 7.1.1.1.6.

7.1.1.2.7. Sample size

The planned sample size was 520 subjects. A total of 519 subjects were randomised: 346 to retapamulin Ointment, 1%, and 173 to sodium fusidate ointment, 2%.

7.1.1.2.8. Statistical methods

This was a non-inferiority trial with 90% power, a non-inferiority margin of 10% and a one-sided type 1 error rate of 2.5%. A 2:1 randomisation scheme of retapamulin Ointment, 1%: sodium fusidate, 2%, ointment was employed. The comparison of primary interest in this study was the clinical response rate at End of Therapy (Day 7; Visit 2) for retapamulin Ointment, 1%, versus End of Therapy (Day 9; Visit 3) sodium fusidate ointment, 2%, for the Per Protocol Clinical (PPC) population. A conclusion of non-inferior efficacy of retapamulin Ointment, 1%, was drawn if the lower limit of the 95% confidence interval for the treatment difference was greater than or equal to –10%.

7.1.1.2.9. Participant flow

See Table 14.

Table 14: Subject Disposition (ITTC Population)

Subject Disposition	Treatment Group		Total
	SB-275833	Sodium fusidate	
Randomized	346	173	519
Randomized but not treated	1	1	2
Completed Study	319	157	476

A total of 519 subjects were randomised into the study. Of the 519 randomised subjects, 517 had documented evidence of receiving study medication and 476 completed the study. The number (%) of subjects present at each visit is shown in Table 15 and the number completing study shown in Table 16.

Table 15: Number (%) of Subjects Present at Each Visit

Study Phase	Number (%) of Subjects		Total N=517
	SB-275833 N=345	Sodium fusidate N=172	
Visit 1 (Baseline; Day 1)	345	172	517
Optional visit	10 (2.9)	3 (1.7)	13 (2.5)
Visit 2 (Day 7)	333 (96.5)	171 (99.4)	504 (97.5)
Visit 3 (Day 9)	329 (95.4)	167 (97.1)	496 (95.9)
Visit 4 (Day 14)	333 (96.5)	171 (99.4)	504 (97.5)

Table 16: Number (%) of Subjects Withdrawn from the Study by Reason for Withdrawal (ITTC Population)

Reason For Withdrawal	Treatment Group		
	SB-275833 N=345	Sodium fusidate N=172	Total N=517
	n (%)	n (%)	n (%)
Completed Study	319 (92)	157 (91)	476 (92)
Prematurely Withdrawn	26 (8)	15 (9)	41 (8)
Disease progression	8 (2)	6 (3)	14 (3)
Lost to Follow-Up	8 (2)	1 (<1)	9 (2)
Other	3 (<1)	3 (2)	6 (1)
Subject decided to withdraw from study	3 (<1)	1 (<1)	4 (<1)
AE	1 (<1)	3 (2)	4 (<1)
Lack of Efficacy	1 (<1)	1 (<1)	2 (<1)
Protocol violation	1 (<1)	0	1 (<1)
Sponsor terminated study	1 (<1)	0	1(<1)

A total of 8% (41/517) of subjects were prematurely withdrawn from the study. A similar proportion was withdrawn from both treatment groups (8% [26/345] subjects and 9% [15/172] subjects in the retapamulin Ointment, 1%, and sodium fusidate ointment, 2%, groups, respectively). The most common reasons for withdrawal in the retapamulin Ointment, 1%, group were disease progression and lost to Follow-Up. While in the sodium fusidate ointment, 2%, group, the most common reason for withdrawal was disease progression.

7.1.1.2.10. Major protocol violations/deviations

The number of subjects excluded due to protocol violations is shown in Table 17.

Table 17: Number (%) of Subjects Excluded from the Per Protocol Clinical Population, by Reason (ITTC Population)

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

The PPC population at Follow-Up consisted of 87% (451/517) of subjects. The most common reasons that led to exclusion from the PPC population in the retapamulin Ointment, 1%, group were (i) a clinical response of UTD and (ii) subjects being exposed to other topical treatment. The most common reasons for exclusion in the sodium fusidate ointment, 2%, group, were (i) subjects' visit day not being in a specified visit window, (ii) subjects being less than 80% compliant with study medication and (iii) subjects being exposed to other topical treatment. The summary of analysis population is provided in Table 18.

Table 18: Summary of Analysis Populations

Population	Number of Subjects		
	SB-275833	Sodium fusidate	Total
ITTC	345	172	517
PPC at End of Therapy	317	150	467
PPC at Follow-Up	308	143	451
ITTB	263	131	394
PPB at End of Therapy	242	114	356
PPB at Follow-Up	235	107	342

Overall, 517 subjects in total were enrolled in the study and took at least one dose of study medication. Of these, 345 subjects were in the retapamulin Ointment, 1%, group and 172 were in the sodium fusidate ointment, 2%, group and formed the ITTC population. The treatment groups were balanced with respect to gender, race and ethnicity. Overall, 359/517 (69.4%) were paediatric subjects (<18 years) of whom 233 received retapamulin Ointment, 1%, and 126 received sodium fusidate ointment, 2%. Most were in the 2 years to <6 years and 6 years to <13 years strata; these age groups are known to have relatively high rates of impetigo. The subjects enrolled in this study were predominately <65 years of age. The majority of subjects in the

study had one or more pathogen identified at baseline. Of the subjects with a pathogen, most had a single pathogen isolated.

S. aureus was the most frequently isolated pathogen in the study (65.3% of isolates from subjects in the retapamulin Ointment, 1%, group and 63.8% of isolates from the sodium fusidate ointment, 2%, group). Of all the isolates of *S. aureus*, most were methicillin-susceptible while only 10 (1.9% of all *S. aureus* isolates) were methicillin resistant. The MIC_{50}, MIC_{90} and MIC range for retapamulin against all *S. aureus* isolates were 0.12, 0.12 and 0.03-0.25 µg/mL, respectively, indicating excellent in vitro activity of SB- 275833 against *S. aureus* isolates recovered from subjects at baseline. In general, all of the MIC values were similar between the two treatment groups.

7.1.1.2.11. Results for the primary efficacy outcome

Retapamulin Ointment, 1%, twice daily for 5 days was shown to be non-inferior to sodium fusidate ointment, 2%, three times daily for 7 days in the treatment of impetigo based on the primary efficacy endpoint of clinical response at End of Therapy in the PPC population (Table 19). The lower limit of the confidence interval for the treatment difference was substantially greater than the non-inferiority margin of -10%. Results suggested superior efficacy over sodium fusidate ointment, 2%.

Table 19: Results for the primary efficacy outcome (clinical response at EOT)

Analysis Population	SB-275833		Sodium fusidate		Difference in Success Rates (%)	95% CI (%)
	n/N	Success Rate (%)	n/N	Success Rate (%)		
PPC	**314/317**	**99.1**	**141/150**	**94.0**	**5.1**	**(1.1, 9.0)[1]**
ITTC	327/345	94.8	155/172	90.1	4.7	(-0.4, 9.7)
PPB	240/242	99.2	106/114	93.0	6.2	(1.4, 11.0)[1]
ITTB	250/263	95.1	116/131	88.5	6.5	(0.5, 12.6)

1. Due to high efficacy rate, the normality assumption may not have been valid. CI = Confidence interval

Selected secondary efficacy results are presented in the table below. Overall, the clinical success rate at Follow-Up was higher in the retapamulin Ointment, 1%, group compared with the sodium fusidate ointment, 2%, group. The findings were similar for microbiological endpoints. A clinical response of 'success' was achieved by 99.1% (314/317) of the PPC population at End of Therapy for the retapamulin Ointment, 1%, group compared to 94.0% (141/150) of the PPC population for the sodium fusidate ointment, 2%, group. The lower limit of the confidence interval for the treatment difference was greater than the non-inferiority margin of -10%, thus indicating that retapamulin Ointment, 1%, was non-inferior to sodium fusidate ointment, 2%. Indeed the lower limit of the confidence interval was greater than zero indicating superiority in the PPC population. Non-inferiority was achieved in all analysis populations and statistical superiority was additionally achieved in the PPB, and ITTB populations.

7.1.1.2.12. Results for other efficacy outcomes

Success rates for all analysis populations were slightly higher for the retapamulin Ointment, 1%, group compared with the sodium fusidate ointment, 2%, group (Table 20).

Table 20: Results for secondary outcomes

Analysis Population	SB-275833		Sodium fusidate		Difference in Success Rates (%)	95% CI (%)[1]
	n/N	Success Rate (%)	n/N	Success Rate (%)		
Clinical Response at Follow-up						
PPC	297/308	96.4	134/143	93.7	2.7	(-1.8, 7.2)
Per-subject Microbiological Response at End of Therapy						
PPB	238/242	98.3	107/114	93.9	4.2	NA
Per-subject Microbiological Response at Follow-up						
PPB	227/235	96.6	100/107	93.5	3.1	NA

1. Confidence intervals were not adjusted for multiplicity. Note: CI = Confidence interval; PPB = Per Protocol Bacteriology; NA = not applicable

On the whole, success rates at Follow-Up were slightly lower than those seen at End of Therapy. This was as expected as subjects who were 'clinical failures' at End of Therapy were also classified as 'clinical failures' at Follow-Up. In general, the proportion of subjects who were classified as clinical failures was low in both treatment groups. In the ITTC population, 10.1%. Seventy seven percent [35/345] of subjects in the retapamulin Ointment, 1%, group and 12.8% [22/172] in the sodium fusidate ointment, 2%, group were classed as clinical failures at Follow-Up. The findings for the PPC population were supportive of those for the ITTC population. Of these subjects classed as clinical failures, a small number in each treatment group were the result of clinical recurrences (11 subjects in the retapamulin Ointment, 1%, group and eight in the sodium fusidate ointment, 2%, group; ITTC population.

7.1.2. Evaluator's conclusions on clinical efficacy for impetigo

Retapamulin was compared with topical placebo in Study TOC103469 for the treatment of impetigo. Based on the primary efficacy endpoint of clinical response at End of Therapy in the ITTC population, retapamulin was superior with an 85% versus 52% response (statistically significant). Superiority was also achieved in the Per Protocol Clinical group (89% versus 53% clinical response), also in the follow-up as well as the EOT group. The other major study assessing this indication was Study TOC100224, in which retapamulin with compared to topical Sodium Fusidate ointment. Based on the primary efficacy endpoint of clinical response at End of Therapy in the PPC population, retapamulin was found to be non-inferior to topical sodium fusidate (94% versus 91% clinical response). Both the above studies appear to be well conducted with valid conclusions.

7.2. SITL

7.2.1. Pivotal efficacy studies

7.2.1.1. Study 030A and Study 030B

Two pivotal studies, Study 030A and Study 030B, examined the use of retapamulin ointment in adult and paediatric (≥9 months of age) subjects for the indication of SITL. These studies were to be run concurrently with identical designs. They will be discussed together other than results.

7.2.1.1.1. Study design, objectives, locations and dates

Both studies commenced in May 2004 and were completed in April 2005. Study 030A was conducted in 117 centers in 10 countries. These studies were identical in design, objectives and dates, just different locations. They were randomised, double-blind, double-dummy, multi-centre, comparative studies, comparing the efficacy and safety of topical retapamulin Ointment, 1% and oral cephalexin in the treatment of subjects with SITL, such as small lacerations, sutured wounds or abrasions. The infected area of the lesions was to be no larger than 10 cm in length, or 100 cm^2 in area, not require surgical intervention and must be able to be appropriately treated with a topical antibiotic. In addition, the infections were to be those with a high likelihood of having *S. aureus* and/or *S. pyogenes* as the causative infectious agent. An Independent Data Monitoring Committee (IDMC) then reviewed unblinded safety data from the Primary 600 subjects enrolled into the two SITL studies, which were originally limited to subjects aged ≥13 years of age. Following the data review, the IDMC recommended that it was safe to reduce the minimum age of subjects enrolled to 9 months. Samples for pharmacokinetic (PK) analysis were to be taken from the first 500 adult subjects enrolled across Studies 030A and 030B, as well as from all paediatric subjects (<13 years of age) who were enrolled. This was for the purpose of population pharmacokinetic analysis and further to characterize the systemic exposure of subjects to retapamulin ointment when applied topically to the skin.

Pharmacokinetic (PK) methods: PK assessments included the collection of a plasma sample at the on-therapy visit, Visit 2 (Day 3-4), for the first 500 subjects ≥18years of age, across both

studies, and for all paediatric subjects, ≥9 months and <18 years old for bioanalysis of retapamulin concentrations.

7.2.1.1.2. Inclusion and exclusion criteria

As described under 7.1.1.1.2.

Initially, subjects ≥13 years of age were enrolled, regardless of race or gender. Once the safety review of an Independent Data Monitoring Committee (IDMC) for retapamulin studies Study 030A and Study 030B was completed regulatory authorities, IRBs and IECs, were notified the age range was extended to include infants and children ≥9 months of age. All subjects had to have a secondarily infected traumatic lesion such as a small laceration, sutured wound or abrasion with the infected portion not exceeding 10cm in length and surrounding erythema not extending more than 2cm from the edge of the lesion. Abrasions were not to exceed 100cm^2 in total area. All subjects had to have a total SIRS score of at least 8 and be suitable for treatment with topical or oral antibacterial therapy.

7.2.1.1.3. Study treatments

This was a double-dummy study: hence, adult subjects received either retapamulin ointment BD for 5 days and oral cephalexin placebo capsules BD for 10 days; or retapamulin matching placebo ointment BD for 5 days and oral cephalexin BD for 10 days. Paediatric subjects received an oral suspension of cephalexin or a cephalexin placebo suspension, rather than cephalexin in capsule form.

7.2.1.1.4. Efficacy variables and outcomes

Primary and secondary efficacy endpoints were evaluated based on pre-defined clinical and microbiological responses (success or failure) to the study medication. Clinical outcomes were determined by the investigator. Microbiological outcomes were determined programmatically using prospectively defined algorithms. Adverse events (AEs), serious AEs and clinical laboratory findings were evaluated for safety. Due to the limited number of measurable concentrations observed in this study, no formal population PK analysis was conducted.

Primary efficacy endpoint

The primary efficacy endpoint was clinical response at follow-up (7-9 days post-therapy; Day 12-14 and Day 17-19) in the Clinical Per Protocol (PPC) population.

Secondary and tertiary efficacy endpoints

- 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 (ITTC) population
  - 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 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 ITTC, and PPC populations.
- 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 Bacteriology (ITTB), and Bacteriology Per Protocol (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 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).

· Therapeutic response endpoint

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

· Tertiary 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.

7.2.1.1.5. Randomisation and blinding methods

This was a double-blind, double-dummy study. All subjects received active medication and placebo. The packaging and labelling of study medication was identical for the active medication and its placebo counterpart. Subjects were randomised to 1 or other of the treatment arms from a single randomization schedule, stratified by site and age. Once enrolment was completed with enough subjects for both studies, centers were size-ranked and randomised accordingly to either Study 030A or Study 030B, using a block size of 4 and stratifying by region. The site to study randomization scheme was constructed via GSK's randomization software system (RANDALL) and was unblinded prior to unblinding the subjects' treatment information.

7.2.1.1.6. Analysis populations

As described under 7.1.1.1.6.

7.2.1.1.7. Sample size

The original target enrolment of approximately 870 subjects was subsequently increased in order to provide a sufficient number of younger paediatric subjects. The 2:1 randomization and larger number of subjects than required for 90% power was intended to ensure sufficient numbers of subjects for the safety database.

7.2.1.1.8. Statistical methods

This study was a non-inferiority trial, with at least 90% power to detect a treatment difference greater than 10% (delta=10%), with 2.5% one-sided alpha. A 2:1 randomization scheme was employed. The original target enrolment of approximately 870 subjects (1740 across both studies) enrolled and allocated to study 030B was increased in order to provide a superior number of paediatric subjects. The 2:1 randomization and larger number of subjects than required for 90% power was intended to ensure sufficient numbers of subjects for the safety database. An interim safety analysis was performed when approximately 600 adult subjects were enrolled (400 on 1% retapamulin ointment), across studies 030A and 030B. An IDMC then convened to review the safety data and to determine if there were any significant safety issues that would preclude enrolment of ≥9 months of age and older. Once the review was complete, and a positive recommendation made to the sponsor, enrolment of children ≥9 months of age commenced.

7.2.1.1.9. Participant flow

A total of 996 subjects were randomised into the study. Subjects were randomised in a 2:1 ratio (retapamulin Ointment, 1%: cephalexin), 988 received study medication and 861 subjects completed the study. One hundred twenty-seven subjects were prematurely withdrawn.

A total of 13% (127/988) of subjects were prematurely withdrawn from the study. A similar proportion of subjects were withdrawn from both treatment groups (12% [82/662] subjects and 14% [45/326] subjects in the retapamulin and cephalexin groups, respectively). The most frequent reason for withdrawal in both groups was subjects being lost to follow-up (Table 21).

Table 21: Number (%) of Subjects Withdrawn from the Study by Reason for Withdrawal (ITTC Population)

	Number (%) of Subjects		
Reason For Withdrawal	SB-275833 N=662	Cephalexin N=326	Total N=988
Completed Study	580 (88)	281 (86)	861 (87)
Prematurely Withdrawn	82 (12)	45 (14)	127 (13)
Lost to Follow-Up	32 (5)	19 (6)	51 (5)
Lack of Efficacy	22 (3)	10 ((3)	32 (3)
Withdrawal of Consent	11 (2)	7 (2)	18 (2)
AE	10 (2)	6 (2)	16 (2)
Deviation from Protocol	1 (<1)	1 (<1)	2 (<1)
Other	6 (<1)	2 (<1)	8 (<1)

7.2.1.1.10. Major protocol violations/deviations

The PPC population consisted of 83.6% (826/988) subjects of the ITTC population. The most frequent protocol violation leading to exclusion from the PPC population for both treatment groups was due to the day of the subject visit being outside of the specified visit window (8.31%, [55/662] of subjects in the retapamulin treatment group and 8.90%, [29/326] of subjects in the cephalexin group).

Four hundred eighty subjects did not have a pathogen isolated at baseline and thus were not included in the ITTB population (315 subjects and 165 subjects in the retapamulin and cephalexin treatment groups, respectively). Most subjects were excluded from the PPB population as a result of one of their study visits being outside of the specified visit window (33 subjects and 12 subjects in the retapamulin and cephalexin treatment groups, respectively.

7.2.1.1.11. Baseline data

Six hundred sixty-two subjects received retapamulin and 326 subjects received cephalexin according to the 2:1 randomization scheme. Since protocol violations are visit based, the number of evaluable subjects decreased from end-of-therapy to follow-up in both the PPC and PPB populations, but the 2:1 ratio of retapamulin:cephalexin treated subjects was maintained (Table 22).

Table 22: Summary of Analysis Populations

Population	Number of Subjects		
	SB-275833	Cephalexin	Total
ITTC	662	326	988
PPC at EOT	629	285	914
PPC at FU	592	260	852
ITTB	338	159	497
PPB at EOT	319	142	461
PPB at FU	302	132	434

The treatment groups were balanced with respect to age, gender, race and ethnicity. The majority of subjects were male (59%). Most subjects reported their race as Caucasian (55%), however a large percentage of subjects were African American/African heritage (24%) or South Asian (19%) Demographic characteristics for the PPC population were similar to that of the

ITTC population. The majority of subjects treated (866/988) were less than 65 years of age, with most subjects being between the ages of 18 and 64. One hundred sixty-four subjects treated were less than 18 years of age. The treatment groups were well balanced with respect to age strata. The distribution of wound sites was similar in each treatment group. Approximately half of the subjects in each treatment group had pathogens isolated from a wound sample taken at baseline (51.06% [338/662] and 48.77% [159/326] of subjects in the retapamulin and cephalexin treatment groups, respectively. The majority of these subjects had only one pathogen identified in the sample. *S. aureus* was the most frequently isolated pathogen in the study (242 isolates from subjects in the retapamulin group and 110 isolates from subjects in the cephalexin treatment group). The proportion of isolates of *S. aureus* (including MRSA) and *S. pyogenes* at baseline was similar between the treatment groups. Most *S. aureus* isolates were methicillin-susceptible *S. aureus* (MSSA). There were 27 MRSA isolates from subjects in the retapamulin treatment group and 13 MRSA isolates from subjects in the cephalexin group.

7.2.1.1.12. Results for the primary efficacy outcome

Clinical response at follow-up for the PPC population was the primary efficacy endpoint. A clinical response of success was achieved by 88.7% (525/592) of the PPC population at follow-up for the retapamulin treatment group compared to 91.9% (239/260) of the PPC population for the cephalexin group (Table 23). The lower limit of the confidence interval for the treatment difference was greater than the non-inferiority margin, -10%, with the upper limit crossing zero. Success rates were comparable between the treatment groups for the ITTC and bacteriology populations.

Table 23: Clinical Response at Follow-Up by Analysis Population

Analysis Population	SB-275833		Cephalexin		Difference in Success Rates (%)	95% CI[1] (%)
	n/N	Success Rate (%)	n/N	Success Rate (%)		
PPC	525/592	88.7	239/260	91.9	-3.2	(-7.4, 0.9)
ITTC	564/662	85.2	274/ 326	84.0	1.1	(-3.7, 6.0)
PPB	264/302	87.4	119/132	90.2	-2.7	(-9.0, 3.6)
ITTB	286/338	84.6	134/159	84.3	0.3	(-6.5, 7.2)

In the ITTC population, 4.68% of subjects in the retapamulin treatment group and 7.36% of subjects in the cephalexin group had a clinical outcome of "unable to determine" that was counted as a clinical failure. A similar percentage of subjects in the two treatment groups had clinical responses of failure at the end of therapy visit resulting in a clinical response of failure at follow-up (9.67% and 8.28% of subjects for the retapamulin and cephalexin groups, respectively). A small number of clinical failures in each treatment group were the result of clinical recurrences of the wound infection (0.45% and 0.31% of subjects in the retapamulin and cephalexin treatment groups, respectively). Based on the primary efficacy endpoint of clinical response at follow up retapamulin Ointment, 1%, was shown to be non-inferior to cephalexin in the treatment of SITL. Subgroup analysis showed no significant association between subject age groups and clinical response.

7.2.1.1.13. Results for other efficacy outcomes

Although the study was not designed to demonstrate non-inferiority for secondary endpoints, the clinical efficacy of retapamulin Ointment, 1%, at the end of therapy (EOT), was non-inferior to cephalexin. For MRSA the success rates were 72.0% and 81.8% for the retapamulin and cephalexin treatment groups, respectively. Success rates for *S. pyogenes* were 92.3% and 88.9% in the retapamulin and cephalexin treatment groups, respectively. For the PPC population, the clinical success rate at end of therapy was 90.6% (570/ 629) of the subjects in the retapamulin treatment group and 93.0% (265/285) of subjects in the cephalexin treatment group. Results at end of therapy were comparable for the ITTC, ITTB and PPB populations.

7.2.1.2. Study 30B

7.2.1.2.1. Study design, objectives, locations and dates

Same design and dates as 30A, conducted at 36 centers in North America, 23 centers in Europe, and 5 centers internationally.

7.2.1.2.2. Inclusion and exclusion criteria

Same as 30A

7.2.1.2.3. Study treatments

Same as 30A

7.2.1.2.4. Efficacy variables and outcomes

Same as 30A

7.2.1.2.5. Randomisation and blinding methods

Same as 30A

7.2.1.2.6. Analysis populations

Same as 30A

7.2.1.2.7. Sample size

Same as 30A, initially planned to enrol 870 participants, but this number increased to provide sufficient numbers of young paediatric patients.

7.2.1.2.8. Statistical methods

Same as 30A

7.2.1.2.9. Participant flow

A total of 922 subjects were randomised in the study. Subjects were randomised in a 2:1 ratio (retapamulin Ointment, 1%: cephalexin), 916 received study medication and 824 subjects completed the study. Ninety-two subjects were prematurely withdrawn.

A total of 92/916 subjects (10%) withdrew from the study, 64/310 subjects (11%) in the retapamulin group and 28/606 subjects (9%) in the cephalexin group, respectively. The most common reasons for withdrawal were lack of efficacy (4%, 34/916 subjects) and subject lost to follow-up (3%, 23/916 subjects). Reasons for subject withdrawal were generally similar for both treatment groups with a slightly higher rate of withdrawal due to an AE in the cephalexin treatment group and more subjects being lost to follow-up for the retapamulin treatment group.

7.2.1.2.10. Major protocol violations/deviations

The PPC population consisted of 83.6%, [766/916 subjects] of the ITTC population. The most common reason for exclusion from the PPC population occurring in a total of 88/916 subjects (9.61%) was due to the day of the subject visit not being in a specified visit window. Other reasons for exclusions were similar between the two treatment groups with the exception of more subjects in the cephalexin group (10%, 31/310 subjects) having less than 80% compliance compared to only 3/606 subjects (0.50%) in the retapamulin group. Reasons of exclusion for ITTB and PPB populations were similar for both treatment groups.

Subjects were excluded from the ITTB population if no pathogen was isolated from the subject's wound sample at baseline (297 subjects, 49.01% and 149 subjects 48.06% in the retapamulin and cephalexin treatment groups, respectively). For 8 subjects, 1.32% in the retapamulin group and 5 subjects, 1.61% in the cephalexin group, isolates were sent to the local lab but not sent to the central laboratory resulting in exclusion of these subjects from the ITTB population. The PPB population was a subset of the ITTB population. As for the PPC population, most subjects

were excluded from the PPB population as a result of one of their study visits being outside of the specified visit window (33 subjects, 5.45% and 16 subjects, 5.16% in the retapamulin and cephalexin treatment groups, respectively).

7.2.1.2.11. Baseline data

Six hundred and six subjects received retapamulin and 310 subjects received cephalexin according to the 2:1 randomization scheme. Since protocol violations are visit based, the number of evaluable subjects decreased from EOT to FU in both the PPC and PPB populations, but the 2:1 ratio of retapamulin:cephalexin treated subjects was maintained (Table 24).

Table 24: Summary of Analysis Populations Population

Population	Number of Subjects		
	SB-275833	Cephalexin	Total
ITTC	606	310	916
PPC at EOT	573	259	832
PPC at FU	540	249	789
ITTB	301	156	457
PPB at EOT	301	128	410
PPB at FU	282	123	387

The treatment groups were balanced with respect to age, gender, race, and ethnicity. The majority of subjects were male (53%) with a mean age of 44 years, and of Caucasian race (72%). Demographic characteristics for the PPC, ITTB and PPB populations were generally similar to that of the ITTC population. The majority of subjects (81.4%, 746/916 subjects) were <65 years of age, with most subjects being between the ages of 18 and 64. Seventy-seven subjects treated (8.4%) were less than 18 years of age. Both treatment groups were well balanced with respect to age strata. In all populations, the majority of samples obtained were from secondarily infected open wounds. Wounds were located in a variety of sites on subjects' bodies. Approximately half of the subjects in each treatment group had pathogens isolated from a wound sample taken at baseline (49.67%, [301/606 subjects] in the retapamulin group and 50.32%, [156/310 subjects] in the cephalexin group). The majority of these subjects only had one pathogen identified in the sample. *S. aureus* was the most frequently isolated pathogen in the study with 217 isolates in the retapamulin group and 109 isolates in the cephalexin group. The percentage of isolates of *S. aureus* at baseline was proportional between the treatment groups. Most *S. aureus* isolates were susceptible to methicillin. There were 30 MRSA isolates (8.5%) from subjects in the retapamulin group and 20 MRSA isolates (12.6%) from the cephalexin group at baseline.

7.2.1.2.12. Results for the primary efficacy outcome

A clinical response of success was achieved by 90.4%, [488/540 subjects] of the PPC population at follow-up for the retapamulin treatment group compared to 92.0%, [229/249 subjects] in the cephalexin group (Table 25). Based upon the results obtained with the PPC population, retapamulin Ointment, 1%, demonstrated non-inferiority (lower limit of the confidence interval for the treatment difference was greater than -10%, with the upper limit crossing zero) to cephalexin in the treatment of subjects with SITL.

Table 25: Clinical Response Rate at Follow-Up by Analysis Population

Analysis Population	SB-275833		Cephalexin		Difference in Success Rates (%)	95% CI[1] (%)
	n/N	Success Rate (%)	n/N	Success Rate (%)		
PPC	488/540	90.4	229/249	92.0	-1.6	(-5.8, 2.6)
ITTC	530/606	87.5	271/310	87.4	0.0	(-4.5, 4.6)
PPB	240/264	90.9	111/123	90.2	0.7	(-5.6, 7.0)
ITTB	264/301	87.7	132/156	84.6	3.1	(-3.7, 9.9)

1. Confidence intervals not adjusted for multiplicity

In the ITTC population 2.31% of subjects in the retapamulin group and 2.90% of subjects in the cephalexin group had a clinical outcome of "unable to determine" that, by definition, resulted in a response of clinical failure. A similar percentage of subjects in the two treatment groups had responses of failure at the end of therapy visit resulting in a clinical response of failure at follow-up (4.46% and 4.52%) of subjects for the retapamulin and cephalexin groups, respectively). A small number of clinical failures in each treatment group were the result of clinical recurrences of the wound infection (1.49% and 0.65% of subjects in the retapamulin and cephalexin groups, respectively).

7.2.1.2.13. Results for other efficacy outcomes

The clinical success rate at the end of therapy for the PPC population was 92.7%, [531/573 subjects] for the retapamulin group and 91.5%, [237/259 subjects] for the cephalexin group with a difference in success rates of 1.2% (95% C.I: -2.8%, 5.2%). Similar results were observed for the ITTC, ITTB, and PPB populations. Although the study was not designed to demonstrate non-inferiority for secondary endpoints, the clinical efficacy of retapamulin Ointment, 1%, at the end of therapy (EOT), was indicated to be non-inferior to cephalexin. For *S. aureus* overall, the microbiological success rate at follow-up was 90.7% for the retapamulin treatment group and 92.9% for the cephalexin group. For MRSA the success rates were 70.4% and 93.3% for the retapamulin and cephalexin treatment groups, respectively. Success rates for *S. pyogenes* were 96.6% and 100.0% for the retapamulin and cephalexin treatment groups, respectively.

7.2.2. Other efficacy studies

7.2.2.1. Study TOC110977

7.2.2.1.1. Study design, objectives, locations and dates

Study TOC110977 was a randomised prospective, multicentre, double-blind, placebo-controlled parallel group phase III superiority study to assess the safety and efficacy of topical retapamulin ointment, 1%, versus placebo ointment applied twice daily for 5 days in the treatment of adult and paediatric subjects aged 2 months and older with SITL, which included secondarily infected lacerations, sutured wounds or abrasions.

A total of 357 subjects were originally planned for enrolment.

The study was required by the US FDA as the primary basis of approval for a SITL indication. The existing two non-inferiority studies (Study 030A and Study 030B, wherein retapamulin was shown to be non-inferior to oral cephalexin, were deemed by the FDA to be insufficient evidence for the basis of approval of a SITL indication. Study TOC110977 was also intended to estimate the treatment effect to justify the noninferiority margins used in the previous phase III SITL studies (030A and 030B); but changes to the outcome definitions in Amendment No. 1 precluded this.

All subjects attended up to four study clinic visits which occurred over a 12-14 day. At the Baseline visit (Visit 1, Day 1), subjects were randomised to receive retapamulin or placebo in a 2:1 ratio. The 2:1 randomization scheme was utilized to reduce the number of subjects exposed to placebo ointment. Both retapamulin and placebo were dosed topically twice daily (BD) for 5 days.

This study began on 21 May 2008 and was completed on 02 Oct2009. There were 39 enrolling centers in TOC110977 among five countries with four enrolling centers in Argentina, one centre in Brazil, four centers in India, nine centers in South Africa, and twenty-one centers in the US.

7.2.2.1.2. Inclusion and exclusion criteria

Diagnosis and main criteria for inclusion are as described under 7.1.1.1.2.

The subject had to be 2 months or older. The subject had 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. The infected portion of the abrasion should not exceed 100 cm^2 in total area, or up to a maximum of 2% total body surface area for subjects <18 years of age, with surrounding erythema not extending more than 2 cm from the edge of the abrasion.

7.2.2.1.3. Study treatments

Subjects were treated with retapamulin ointment or placebo ointment BD for 5 days. Retapamulin and placebo were provided as approximately 10 grams of an off-white smooth ointment in collapsible aluminium tubes with reverse taper puncture tip caps. At the Baseline visit (Visit 1), each randomised subject received one carton containing a single 10 gram tube of retapamulin ointment or matched placebo ointment. The contents of the label were defined in accordance with all applicable regulatory requirements.

7.2.2.1.4. Efficacy variables and outcomes

The primary objective of this study was to evaluate topical retapamulin ointment, 1%, compared with placebo ointment in the treatment of subjects with SITL that included secondarily-infected lacerations, abrasions, and sutured wounds. The primary endpoint of this study was the clinical response at FU (Day 12 to 14; 7 to 9 days after the EoT) in the Intent-to-Treat Clinical (ITTC) population.

The secondary objectives of this study were to evaluate the bacteriological efficacy and safety of retapamulin versus placebo in the treatment of SITL.

7.2.2.1.5. Randomisation and blinding methods

Subjects were randomly assigned to study treatment in accordance with the predetermined allocation ratio of 2:1 (retapamulin: placebo). Randomization was centre based and performed using the registration and medication ordering system (RAMOS), IVRS system. Study drug, both retapamulin and placebo, were presented with labelling and packaging consistent with the blinded study design as well as any local requirements. The blinding of the study was appropriately maintained throughout the study until after all subject data was collected, cleaned and the database was "frozen". Randomization was performed in a 2:1 fashion utilizing individual site block sizes of 6 subjects (4 actives, 2 placebos). The 2:1 randomization was utilized to minimize the number of subjects exposed to treatment with placebo.

7.2.2.1.6. Analysis populations

Populations for analysis were defined as in 7.1.1.1.6.

Table 26: Population Subsets

Subjects enrolled under the original protocol	Subjects enrolled under the amended protocol
A: subjects with baseline pus/exudate score >=3 and data captured under eCRF V1	C: subjects with baseline pus/exudate score >=3 and data captured under eCRF V2
B: subjects with baseline pus/exudate score <3 and data captured under eCRF V1	D: subjects with baseline pus/exudate score >=3 and data captured under eCRF V1

Efficacy analyses were conducted for the following analysis subpopulations (as in Table 26).

- Subjects from A+C;
- Subjects from A+C+D;
- Subjects from A+B and C+D separately;
- Subjects from A+B+D and C separately;
- Subjects from A+B+C+D altogether.

The first analysis population comprised of subjects from A + C using the new definition of clinical response in the protocol amendments and was designated as the primary efficacy analysis population. Subjects from the subset B were not included in the primary analysis since they did not meet the inclusion criterion as defined in the protocol amendments. Subjects from the subset D were not included in the primary analysis since the improper use of eCRF V1 may have impacted the investigator's evaluations. However, sensitivity analyses were conducted for these two subsets.

Subjects recruited under the original protocol (Groups A+B) did not have 'Improvement' as an option for the clinical outcome at End of therapy visit or as an option for both the clinical outcome and clinical response at Follow-up.

7.2.2.1.7. Sample size

A total of 357 subjects were originally planned for enrolment. Under the original protocol, 357 subjects (238 in the retapamulin arm and 119 in placebo arm) were required to provide at least 90% power to detect a minimum clinically meaningful difference of 15% with an assumption of a clinical success rate of 85% for retapamulin and 70% for placebo and one-sided type I error of 2.5%. Due to the protocol amendments, the actual number of enrolled subjects was 508. With the amended definition of clinical outcome/response under the protocol amendment 1, the clinical success rate was expected to be lower for both treatment groups. With the planned sample size of 357, a sample size sensitivity analysis showed that the statistical power was maintained at ≥ 80% for most scenarios when the assumed success rates drop for both treatment groups. The amendment 1 changes in inclusion criterion 4 (minimum entry pus score was higher) required that an additional 78 subjects be enrolled into the study. Amendment 2 changes (see below) necessitated an additional 70 subjects be enrolled into the study. Therefore, a total of 505 subjects were required to ensure that 357 subjects who fulfil all requirements of the protocol and subsequent amendments would be enrolled.

7.2.2.1.8. Statistical methods

The study was amended twice during study conduct. Amendment 1 changed the definition of a clinical response of 'success' and increased the minimum entry pus score (SIRS component) of ≥ 3.

Amendment 2 was implemented to allow the recruitment of 70 additional subjects to replace subjects that were enrolled and had data captured in an incorrect version of the eCRF. Both amendments required adaptations to the Reporting and Analysis Plan (RAP) which were incorporated and finalized before the final Database Freeze (DBF). There was no change in the planned analyses specified in the RAP after DBF.

Under the original protocol, 357 subjects (238 in the retapamulin arm and 119 in placebo arm) were required to provide at least 90% power to detect a minimum clinically meaningful difference of 15% with an assumption of a clinical success rate of 85% for retapamulin and 70% for placebo and one-sided type I error of 2.5%. Due to the protocol amendments, the actual number of enrolled subjects was 508.

With the amended definition of clinical outcome/response under the protocol amendment 1, the clinical success rate was expected to be lower for both treatment groups. With the planned sample size of 357, a sample size sensitivity analysis showed that the statistical power was maintained at ≥ 80% for most scenarios when the assumed success rates drop for both treatment groups.

7.2.2.1.9. Participant flow

A total of 508 subjects were enrolled into the study. Of these, 343 subjects were treated with retapamulin and 165 subjects with placebo ointment. One subject in the placebo ointment arm did not start study medication. Therefore, 507 subjects make up the ITTC population (Groups A+B+C+D). More than 91% of subjects in the ITTC completed the study with a higher proportion

completing in the retapamulin arm (93.9%) than in the placebo ointment arm (85.5%). A higher proportion of subjects were prematurely withdrawn from the study in the placebo ointment arm (14.0%) compared with retapamulin ointment (6.1%). 'Lack of Efficacy' was the most frequent reason for early withdrawal and demonstrated a higher proportion with placebo ointment (9.1%) than with retapamulin (2.9%), although actual numbers were very small. Three hundred and sixty (360) subjects were enrolled in the study in the ITTC Primary Efficacy Population (Groups A+C) and 326 subjects (90.6%) of these subjects completed the study. A higher proportion of subjects on the retapamulin arm (93.5%) completed the study compared with the placebo ointment arm (84.2%). One of the 360 enrolled subjects was not exposed to study treatment; thus, 359 subjects were included in the ITTC Primary Efficacy Population. The ITTB population included 266 subjects Thirty three of 359 (9.2%) subjects were withdrawn from study treatment prior to completing the study. The frequency of withdrawal for the placebo group was twice that of the retapamulin group. Of note, withdrawals attributed to Lack of Efficacy were proportionally higher in the placebo (8.8%) ointment arm when compared to the retapamulin arm (2.8%). The remaining withdrawals were attributed in similar proportions to the categories shown in Table 27.

Table 27: Disposition of Subjects

	Retapamulin n (%)	Placebo n (%)	Total n (%)
Enrolled	246	114	360
Enrolled but not Treated	0	1 (0.9)	1 (0.3)
Completed Study	230 (93.5)	96 (84.2)	326 (90.6)
Analysis Populations			
ITTC	246 (100.0)	113 (99.1)	359 (99.7)
PPC at follow-up	215 (87.4)	97 (85.1)	312 (86.7)
ITTB	182 (74.0)	84 (73.7)	266 (73.9)
PPB	158 (64.2)	69 (60.5)	227 (63.1)
Withdrawn from Study	16 (6.5)	17 (15.0)	33 (9.2)
Primary Reason for Withdrawal			
Adverse Event	4 (1.6)	3 (2.7)	7 (1.9)
Lack of Efficacy	7 (2.8)	10 (8.8)	17 (4.7)
Protocol Deviation	1 (0.4)	0	1 (0.3)
Lost to Follow-up	2 (0.8)	1 (0.9)	3 (0.8)
Investigator Discretion	2 (0.8)	0	2 (0.6)
Withdrawal of Consent	0	2 (1.8)	2 (0.6)
Other	0	1 (0.9)	1 (0.3)

7.2.2.1.10. Major protocol violations/deviations

There were no deviations from the protocol with respect to inclusion/exclusion criteria. One subject received incorrect study medication but the subject was not withdrawn from the study. With respect to this single subject, for the efficacy analysis the randomised treatment group was used and for the safety analysis the actual treatment group was used.

7.2.2.1.11. Baseline data

For the ITTC primary efficacy population, the median age of the study subjects was 30.0 years old, with a range of 1 to 86 years old. Demographic characteristics were largely similar between study arms. Demographic characteristics were similar for the ITTB. Of the 359 subjects that were enrolled in the ITTC primary efficacy population, the majority of the subjects were recruited in the 18 to <65 strata (74%) with the remaining subjects distributed similarly across the remaining age categories Across both arms, secondarily-infected abrasions was the most common type of wound among the subjects randomised into the study, accounting for more than half (59.2%) of all skin infections. More than one-third (35.3%) of the skin infections were secondarily infected lacerations and 5.5% were due to secondarily infected sutured wounds.

The clinical diagnoses for the ITTB population were generally similar to that of the ITTC population. In 76.5% of the subjects, the treated lesions were on the front side of the body, with almost one-third of the lesions on the legs, face or neck (29%). Overall, the majority (74.1%) of subjects had at least one pathogen isolated from their wound sample at Baseline. *Staphylococcus aureus* was the most frequently-isolated pathogen (212 of 353 isolates; 60.1%) at Baseline. Of the 212 isolates of *S. aureus*, all were susceptible to fusidic acid, 32 (9.1% overall) were methicillin-resistant, and 4 (1.1% overall) were mupirocin-resistant. *Streptococcus pyogenes* isolates were recovered from 14.4% of the baseline wound specimens. Approximately twenty percent of the Baseline pathogens were Gram-negative organisms. Pathogens were generally isolated with similar frequency in the two treatment groups.

7.2.2.1.12. Results for the primary efficacy outcome

Subjects who met all criteria for inclusion in our ITTC primary efficacy population (Groups A+C) were included in the analyses of efficacy. Sensitivity analyses were completed with the other populations as described in Section 7.2.2.1.6. The primary efficacy endpoint was the clinical response to study medication assessed as 'success' or 'failure' was based on the investigator's determination of the clinical outcome at the Follow-up visit (Day 12 -14). A status of 'unable to determine' was due to a subject's failure to attend the Follow-up visit and in such a case, the subject was categorized as a clinical failure.

In the primary efficacy analysis population (ITTC), the observed clinical success rate for retapamulin (74.8%) was higher than for placebo (66.4%), however, the difference of 8.4% in clinical success rates was not statistically significant. The observed clinical success rate for the retapamulin in the ITTB (76.4%) population was also higher than that for the placebo (64.3%). The difference of 12.1% in clinical success rates in this bacteriologically evaluable population and the corresponding 95% confidence interval (0.6, 23.6) suggest that retapamulin has a statistically significant clinical benefit in the treatment of bacteriologically confirmed SITL patients. The data for this endpoint are summarized in Table 28. The differences in clinical success rates at follow-up by analysis population are presented graphically in Figure 3. The difference of 8.1% between clinical success rates at follow-up for all subjects enrolled into the study (Groups A+B+C+D) was similar to that seen in the ITTC primary efficacy population (Groups A+C).

Figure 3: Difference in Clinical Success Rates at Follow-up With 95% CI, by Analysis Population) Study TOC110977

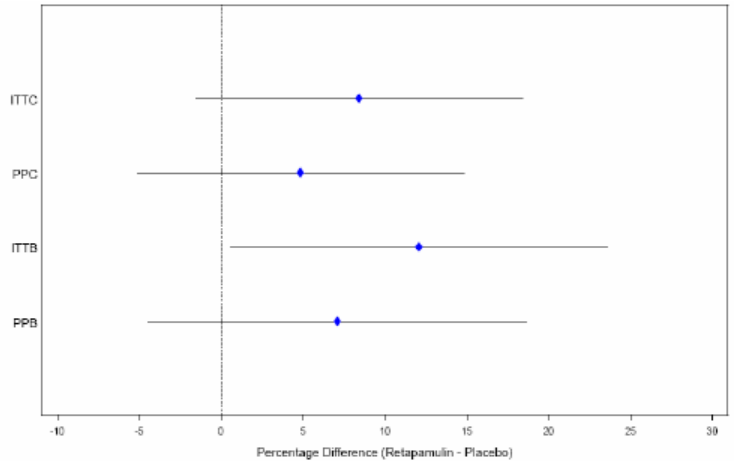


Table 28: Clinical Response at Follow-up, by Analysis Population

	Retapamulin		Placebo		Diff. in Success Rates (%)	95% CI [1] (%)
Analysis Population	n / N	Success Rate (%)	n / N	Success Rate (%)		
ITTC	184/246	74.8	75/113	66.4	8.4	(-1.6, 18.4)
PPC	170/215	79.1	72/97	74.2	4.8	(-5.2, 14.8)
ITTB	139/182	76.4	54/ 84	64.3	12.1	(0.6, 23.6)
PPB	128/158	81.0	51/69	73.9	7.1	(-4.4, 18.6)

ITTC = Intent to Treat Clinical Primary Efficacy Population (A +C); PPC = Per Protocol Clinical Primary Efficacy Population (A +C); ITTB = Intent to Treat Bacteriogically evaluable, Primary Efficacy Population (A +C); PPB = Per Protocol Bacteriogically evaluable, Primary Efficacy Population (A +C)

Using logistic regression analysis to adjust for the differences in baseline wound characteristics, for the primary endpoint, the retapamulin treatment was found to be superior to placebo (p=0.0336) with an odds ratio estimate of 1.73 and 95% CI of (1.04, 2.87).

In the primary efficacy population the overall per pathogen clinical success rates at follow-up were 76.5% and 62.7% in the retapamulin and placebo arms, respectively. Similar success rates were observed for subjects enrolled with *S. aureus* as the baseline pathogen. However, a much higher proportion of subjects enrolled with MRSA as their baseline pathogen were deemed a clinical success on retapamulin (62.5%) compared to placebo (25%). For patients treated with retapamulin, the clinical success rate for subjects with MRSA (62.5%) was lower than that seen for subjects with MSSA (82.9%) as their baseline pathogen. For subjects with *S. pyogenes* as their baseline pathogen, the clinical success rates at follow-up were similar for the retapamulin and placebo arms (80.6 and 80%). Observed success rates for all subjects enrolled in the study (Groups A+B+C+D) with *S. aureus* as the baseline pathogen were also higher in the retapamulin arm (78.4%) compared with the placebo arm (70.7%). Subjects with *S. pyogenes* as the baseline pathogen from Groups A+B+C+D had similar success rates on the retapamulin and placebo arms (80.8% and 78.3%, respectively). In the ITTC population, subjects on the retapamulin arm had a 'Clinical Success' rate of 52.8% at the End of Therapy Visit compared to 46% in the placebo ointment arm. For subjects in the ITTB population, a higher proportion of retapamulin subjects (56.6%) were 'Clinical Successes' compared to subjects on placebo (45.2%) arm (Table 29).

Table 29: Clinical Outcome at End of Therapy

	Retapamulin		Placebo		Difference in Success Rate (%)
	N	Success Rate (%)	N	Success Rate (%)	
ITTC	**N=246**		**N=113**		
Clinical Success	130	52.8	52	46.0	6.8
Clinical Improvement	102	41.5	45	39.8	1.7
Clinical Failure	11	4.5	14	12.4	- 7.9
Unable to Determine	3	1.2	2	1.8	- 1.6
ITTB	**N=182**		**N=84**		
Clinical Success	103	56.6	38	45.2	11.4
Clinical Improvement	70	38.5	34	40.5	- 1.5
Clinical Failure	8	4.4	10	11.9	- 7.5
Unable to Determine	1	0.5	2	2.4	- 1.9

ITTC = Intent to Treat Clinical Primary Efficacy Population (A+C); ITTB = Intent to Treat Bacteriological (A+C)

7.2.2.1.13. Results for other efficacy outcomes

Bacteriological samples were obtained for culture, Gram stain and susceptibility testing at the baseline visit for all subjects. Samples were only to be collected at the 'on therapy', defined End of Therapy and Follow-Up visits if the subject was a 'clinical failure' and material for culture was present. In the ITTB primary efficacy population, subjects treated with retapamulin had higher

levels of 'Eradication' and 'Presumed Eradication' rates at the End of Therapy visit (Day 7 – 9) when compared to placebo for subjects with baseline isolates of *S. aureus* (63.2% to 47.7%). Similar rates were observed in the subgroups including MSSA, mupRSA, mupSSA, and fusSSA. 'Eradication' and 'Presumed Eradication' was achieved at end of therapy against approximately 33% of MRSA isolates in subjects within the retapamulin arm and in 0% of the subjects in the placebo arm. Rates of 'Eradication' and 'Presumed Eradication' at End of Therapy were similar between arms for subjects entering the study with *S. pyogenes* isolates at baseline (63.9% to 66.7%, respectively.

7.2.2.2. Study TOC110978 SITL or Impetigo due to MRSA

7.2.2.2.1. Study design, objectives, locations and dates

Study TOC110978 was a randomised, double-blind, double dummy, multicentre, comparative study to assess the safety and efficacy of topical retapamulin ointment 1%, versus oral linezolid in subjects 2 months of age and older with SITL (including secondarily-infected lacerations, sutured wounds and abrasions) or impetigo (bullous and non-bullous) due to MRSA. There were 5 study visits occurring over a 17- to 19-day period. At the Baseline visit (Visit 1, Day 1), subjects were randomised to receive either retapamulin ointment (plus oral placebo) or oral linezolid (plus placebo ointment) in a 2:1 ratio. Retapamulin was applied BD for 5 days, and linezolid was dosed, depending on subject age, either BD or TID for 10 days. The On-therapy, EoT, and FU visits were therefore staggered due to the difference in duration of the treatment regimens. The study was conducted between 27 April 2009 and 27 September 2010.

7.2.2.2.2. Inclusion and exclusion criteria

As described under 7.1.1.1.2.

In this study subjects aged 2 months or older, who had a SITL no longer than 10 cm or no larger than 100 cm^2 in total area (or no more than 2% of total body surface area for subjects <18 years of age) or had impetigo consisting of ≤10 discrete localized lesions on otherwise healthy skin not to exceed 100 cm^2 in area with surrounding erythema not extending more than 2 cm from the edge of any lesion or up to a maximum of 2% body surface area for subjects <18 years of age, a total SIRS score of at least 8 which included a pus/exudate score of at least 3 could be enrolled.

7.2.2.2.3. Study treatments

Retapamulin or placebo ointment was to have been applied twice daily for 5 days. Subjects receiving linezolid were to have been dosed, according to age, as presented in the following table:

Table 30: Linezolid Dosing Information

Age Group	Formulation	Dose
Adolescent and Adult (≥12 years of age)	600 mg tablet	600 mg q12h for 10 days
Pediatric (5 – 11 years of age)	100 mg/5 mL oral suspension	10 mg/kg q12h for 10 days
Pediatric (<5 years of age)	100 mg/5 mL oral suspension	10 mg/kg q8h for 10 days

7.2.2.2.4. Efficacy variables and outcomes

The primary objective of this study was to evaluate the clinical and bacteriological efficacy of topical retapamulin ointment, 1%, versus oral linezolid, in the treatment of subjects with SITL (excluding abscesses) or impetigo due to MRSA.

There were 2 secondary objectives: 1) to evaluate the safety of topical retapamulin ointment, 1%, versus linezolid, in the treatment of subjects with SITL (excluding abscesses) or impetigo due to MRSA, and 2) to evaluate the efficacy and safety of topical retapamulin ointment, 1%, versus linezolid, in the treatment of subjects with SITL (excluding abscesses) or impetigo, without regard to baseline pathogen.

7.2.2.2.5. Randomisation and blinding methods

Randomization was centre-based and stratified by age (<5 years, ≥5 to <12 years, ≥12 years), and performed using an appropriate Interactive Voice Response System (IVRS), an automated telephone system. The block size remained confidential during conduct of the study.

7.2.2.2.6. Analysis populations

Six analysis populations were described in this study – As in 7.1.1.1.6 plus:

- Intent to Treat MRSA (ITTMRSA): All randomised subjects who took at least one dose of study.
- Per Protocol MRSA (PPMRSA): Subjects from the ITTMRSA population who adhered to the protocol (did not violate the protocol). Subjects who did not adhere to the inclusion/exclusion criteria were excluded from any Per Protocol (PP) population.

7.2.2.2.7. Sample size

The proposed size was 500 subjects. The actual enrolment number was 410 (270 in retapamulin arm, 140 in the linezolid arm. Because no formal hypothesis was tested, no formal power calculations were performed. The choice of sample size was based on feasibility and predicted number needed to determine efficacy against a resistant pathogen. It was estimated that 70 subjects on retapamulin and 35 subjects on linezolid with MRSA pathogen confirmed at baseline would be enrolled into this study.

7.2.2.2.8. Statistical methods

The primary efficacy endpoint was the clinical response at follow-up (7 to 9 days post therapy; Day 12 to 14 for retapamulin and Day 17 to 19 for linezolid) in subjects with MRSA as the baseline pathogen.

Secondary efficacy endpoints included the following:

- Microbiological response at follow-up in subjects with MRSA as the baseline pathogen.
- Clinical response and outcome at follow-up in all subjects.
- Microbiological response and outcome at follow-up in all subjects with a baseline pathogen.
- Clinical outcome at end of therapy (2 to 4 days post-therapy; Day 7 to 9 for retapamulin and Day 12 to14 for linezolid) in subjects with MRSA as the baseline pathogen.
- Microbiological outcome at end of therapy in subjects with MRSA as the baseline pathogen.
- Therapeutic response (combined clinical and microbiological response) at follow-up. Other endpoints included the following:
- Comparison of percent decrease in wound size from baseline (Day 1) to follow up.
- Comparison of SIRS scores from baseline to follow-up
- Descriptive analysis (number and percent) of primary and secondary endpoints, as defined above, in the paediatric subpopulation.

Safety criteria included concomitant medications, adverse events, and serious adverse events. For comparisons of interest, the number and percent success rate for each treatment in each analysis population was to be presented. The 95% CIs of the difference in success rates between the treatment groups were to be constructed. An exploratory evaluation of the effect of covariates such as diagnosis of infection, compliance, etc on clinical response was performed with the use of logistic regression and/or Mantel-Haenszel tests, when sufficient numbers of subjects were available within the subgroups. An analysis of subjects who were nasal carriers of *S. aureus* at baseline was to be provided using the Chi Square test.

7.2.2.2.9. Participant flow

Table 31 summarizes the subject disposition in Study TOC110978.

Table 31: Summary of Subject Disposition

Population	Retapamulin	Linezolid	Total
Randomized	270	140	410
Randomized but not treated	3 (1.1%)	3 (2.1%)	6 (1.5%)
Completed study	234 (86.7%)	122 (87.1%)	356 (86.8%)

In total, 410 subjects were enrolled in the study, 267 received at least 1 dose of retapamulin arm and 137 received at least 1 dose of linezolid. Of these subjects, 234 retapamulin subjects and 122 linezolid subjects completed the study, which is approximately 87% of randomised subjects in either group. Table 32 summarizes the end-of-study status for subjects in the ITTC population.

Table 32: Summary of Subject Status (ITTC Population)

Completion Status	Retapamulin (N=267)	Linezolid (N=137)	Total (N=404)
Completed	234 (87.6%)	122 (89.1%)	356 (88.1%)
Prematurely withdrawn	33 (12.4%)	15 (10.9%)	48 (11.9%)
Primary reason for withdrawal[a]			
Adverse event	10 (3.7%)	3 (2.2%)	13 (3.2%)
Lack of efficacy	15 (5.6%)	3 (2.2%)	18 (4.5%)
Protocol deviation	1 (0.4%)	2 (1.5%)	3 (0.7%)
Lost to follow-up	2 (0.7%)	3 (2.2%)	5 (1.2%)
Investigator discretion	2 (0.7%)	3 (2.2%)	5 (1.2%)
Withdrawal of consent	3 (1.1%)	1 (0.7%)	4 (1.0%)

A similar proportion of subjects withdrew prematurely from the study (12.4% in the retapamulin group and 10.9% in the linezolid group). The most frequently reported reason for early withdrawal was lack of efficacy (4.5% overall), 5.6% of the retapamulin group and 2.2% of the linezolid group reported this as the reason for withdrawal.

7.2.2.2.10. Major protocol violations/deviations

The most common reason for subjects to be excluded from the ITTB and ITTMRSA population was “no baseline pathogen noted,” which was noted in an overall total of approximately 34% in the ITTB population and 69% in the ITTMRSA population. In approximately 3% of the total population for both the ITTB and ITTMRSA population, no sample was provided to the central laboratory. In general, the most common reason for a subject to be excluded from the PP group was that they were out of range of dosing compliance (<80% or >120%). For the PPC population, 8.0% of the total subjects were in this category for both the end-of-therapy (EOT) and follow-up (FU) visits; 5.4% of total subjects in the PPB, and 2.4% of the PPMRSA. There was no notable difference between treatment groups in the proportion of subjects who met this protocol deviation criterion.

For the deviation of ‘did not attend FU visit and clinical evaluation at FU was not EOT failure and clinical outcome at final FU was not FU failure,’ approximately 6% of subjects in the PPC FU group, 4% of subjects in the PPB FU group, and 2% of subjects in the PPMRSA FU group met this criterion. There was no pattern of a greater proportion of subjects meeting this criterion in 1 treatment group than another across all PP FU subsets.

One subject received the wrong study medication. This subject was randomised to retapamulin but received linezolid and one received an incorrect tube of ointment; placebo was dispensed instead of retapamulin.

7.2.2.2.11. Baseline data

Table 33 summarised the populations analysed.

Table 33: Populations Analysed

Population	Retapamulin	Linezolid	Total
Randomized	270	140	410
Randomized but not treated	3 (1.1%)	3 (2.1%)	6 (1.5%)
Completed study	234 (86.7%)	122 (87.1%)	356 (86.8%)
Analysis populations			
Intent to Treat Clinical (ITTC)	267 (98.9%)	137 (97.9%)	404 (98.5%)
Per Protocol Clinical (PPC) at EOT	242 (89.6%)	118 (84.3%)	360 (87.8%)
Per Protocol Clinical (PPC) at FU	235 (87.0%)	112 (80.0%)	347 (84.6%)
Intent to Treat Bacteriological (ITTB)	176 (65.2%)	79 (56.4%)	255 (62.2%)
Per Protocol Bacteriological (PPB) at EOT	156 (57.8%)	68 (48.6%)	224 (54.6%)
Per Protocol Bacteriological (PPB) at FU	152 (56.3%)	65 (46.4%)	217 (52.9%)
Intent to Treat MRSA (ITTMRSA)	72 (26.7%)	38 (27.1%)	110 (26.8%)
Per Protocol MRSA (PPMRSA) at EOT	63 (23.3%)	32 (22.9%)	95 (23.2%)
Per Protocol MRSA (PPMRSA) at FU	61 (22.6%)	32 (22.9%)	93 (22.7%)

A slightly larger proportion of subjects in the retapamulin arm met criteria for efficacy subset inclusion. For example, PPC at FU was 87% in the retapamulin group and 80% in the linezolid group. However, the primary endpoint is measured for the PPMRSA analysis set, for which an approximately equivalent proportion of subjects in both groups (22.6% and 22.9% of the randomised subjects in the retapamulin and linezolid treatment groups, respectively) were included at FU.

Overall, in the ITTC population the demographic characteristics were similar between groups. Median age was 35 years for both treatment groups (range: 0 [less than 1 year] to 92.

The majority of isolates were *S. aureus* (74% of total isolated pathogens in the retapamulin group, 71% in the linezolid group). In the linezolid group, 40% of isolates were MRSA and 31% were methicillin-susceptible Staphylococcus aureus (MSSA); in the retapamulin group 36% were MRSA and 38% were MSSA. There were no susceptibility differences between the two groups. Approximately 10% of isolates were *S. pyogenes*, approximately 13% of isolates were Gram-negative pathogens.

7.2.2.2.12. Results for the primary efficacy outcome

The comparison of primary interest in this study was the clinical success rate at follow-up in subjects with MRSA as the baseline pathogen. An analysis was performed using a definition of clinical success as both clinical success and clinical improvement at follow-up. Because there were approximately 2-fold the number of subjects in the retapamulin group who were considered to have improved vs subjects in the linezolid group, adding subjects with clinical improvement increased the success rate in PPMRSA retapamulin-treated subjects to 91.8% and to 100% in the linezolid group. The difference was not considered to be significant.

When subgroup factors are considered, tests for association between factors and possible significant effect on clinical response were restricted to compliance in the ITTC and ITTMRSA populations. When the clinical response in paediatric subjects (<18 years of age) and adults (≥18 years) were compared, it appears that significant differences between retapamulin and linezolid occurred in adult subjects with SITL in all but the ITTMRSA populations. There were no apparent differences in paediatric response rates when comparing 95% CI for SITL or impetigo. Table 34 summarizes the results for the primary comparison of interest.

Table 34: Clinical Success Rate at Follow-up by Treatment for Subjects with Baseline MRSA

	Retapamulin			Linezolid		
Analysis Population	Successes/N	Success Rate	95% CI[a]	Successes/N	Success Rate	95% CI[a]
ITTMRSA	41/ 72	56.9%	(45.5%, 68.4%)	32/ 38	84.2%	(72.6%, 95.8%)
PPMRSA	39/ 61	63.9%	(51.9%, 76.0%)	29/ 32	90.6%	(80.5%, 100.7%)

a. Confidence intervals are not adjusted for multiplicity.

For subjects in the PP population with baseline MRSA, the success rate in retapamulin treated subjects was significantly different (ie, 95% CI did not overlap) from the linezolid-treated

subjects. For the retapamulin-treated subjects, the success rate was approximately 64% whereas the success rate in linezolid-treated subjects was approximately 91%.

Clinical success rate at follow-up by Baseline pathogen indicates that the linezolid group had approximately 30% greater success that the retapamulin group for all pathogens identified except for Gram-negative pathogens, for which linezolid had a success rate of 100% and retapamulin 42.9%. In no population did the retapamulin treated group have a higher clinical success rate than linezolid. Table 35 summarizes the clinical success at follow-up by analysis population.

Table 35: Clinical Success at Follow-up by Analysis Population

	Retapamulin		Linezolid			
Analysis Pop	Successes/N	Success Rate	Successes/N	Success Rate	Diff in Success Rates[a]	95% CI[b]
ITTC	161/268	60.1%	112/136	82.4%	-22.3%	(-31.9%,-12.6%)
PPC	152/235	64.7%	102/112	91.1%	-26.4%	(-36.4%,-16.4%)
ITTB	100/177	56.5%	65/ 78	83.3%	-26.8%	(-39.6%,-14.1%)
PPB	93/152	61.2%	58/ 65	89.2%	-28.0%	(-41.4%,-14.7%)
ITTMRSA	41/ 72	56.9%	32/ 38	84.2%	-27.3%	(-45.8%, -8.7%)
PPMRSA	39/ 61	63.9%	29/ 32	90.6%	-26.7%	(-45.7%, -7.7%)

a. Difference in Success Rates = retapamulin - Linezolid. b. The confidence intervals are not adjusted for multiplicity.

7.2.2.2.13. Results for other efficacy outcomes

Microbiological success rates at follow-up in the retapamulin group were significantly (approximately 27%) lower than the linezolid group; for both treatment groups the PP populations had approximately 6% better microbiological success rates than the corresponding ITT populations. Results of a therapeutic response evaluation, where therapeutic success is defined to be clinical and microbiological successes, indicate that the number of subjects who achieve therapeutic success is the same as the number of subjects achieving microbiological success. The response rate (considered to be presumed eradication) at follow-up in non-*S. pyogenes* streptococcal species was about the same for retapamulin and linezolid (approximately 63%); for all other pathogens with a sample size >2, linezolid had an approximately 30% greater pathogen eradication rate than retapamulin.

7.2.3. Evaluator's conclusions on clinical efficacy for SITL

Study 30A and 30B showed non-inferiority when retapamulin 1% was compared to oral Cephalexin for this indication. This study appeared to be well conducted and groups were well balanced overall with respect to retapamulin and control groups. Based on the results presented for this study, conservative estimates in the PPC group suggest that retapamulin is as good as Cephalexin for mild SITL overall (likely to be caused by *S.aureus* or *S. pyogenes*). Retapamulin was better than Cephalexin for wounds infected with MRSA (not surprising as this antibiotic would not be expected to have effect).

In Study TOC110977, retapamulin was compared to placebo for SITL and the differences in the primary efficacy ITTC group (clinical response) did not reach statistical significance for superiority (74% versus 66% for placebo). Response rates were slightly higher (and reached significance) with retapamulin for other groups (those that included clinical improvement or bacteriological cure). When a logistic regression analysis was used to adjust for the differences in baseline wound characteristics, for the primary endpoint, the retapamulin treatment was found to be superior to placebo (p=0.0336) with an odds ratio estimate of 1.73 and 95% CI of (1.04, 2.87). In the bacteriologically assessable group (ITTB group) outcome of clinical cure was for statistically higher in the retapamulin group. It was also higher for retapamulin in the group with MRSA. It is interesting that in the dossier, the sponsors also point to the fact that concerns about the placebo-controlled studies may have generated a study population in the mild range of the SITL indication and that there was lack of consistency in the population at entry and subject evaluation between countries contributed to highly variable study results.

In Study TOC110978 retapamulin was compared to oral linezolid (an antibiotic effective for MRSA), for SITL (or impetigo) secondarily infected with MRSA. The results of this study, suggest that topical retapamulin is an inferior treatment in terms of efficacy. It is important to note that oral linezolid would not be first line systemic treatment for MRSA infections (at this point in time), but is highly efficacious. Topical treatment with retapamulin could not be recommended for SITL or impetigo known to be infected with SITL as there is a proven superior treatment.

So, in one summary, in the two pivotal efficacy studies, efficacy for retapamulin ointment (compared to Cephalexin) was shown for SITL, but not in the placebo controlled study or in the study specifically examining efficacy in MRSA infected wounds. I think one can conclude from this, that retapamulin probably has some effect for MRSA infected wounds, but linezolid is better. It is hard to know how to interpret the findings of the other studies. The likelihood is that for many mildly infected wounds, there would be clinical cure with or without specific treatment (as shown in Study TOC110977). There may be some benefit from topical retapamulin (as shown in a number of secondary endpoints) and also in Studies 30A and 30B for mild wounds, and obviously one of the major advantages is the avoidance of a systemic antibiotic.

7.3. SID

7.3.1. Pivotal efficacy study

There is one active-comparator study for retapamulin in the treatment of SID

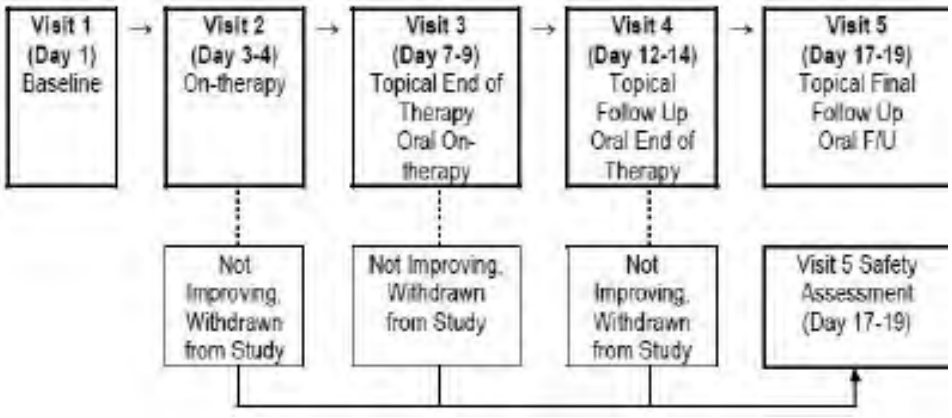
7.3.1.1. Study 032

7.3.1.1.1. Study design, objectives, locations and dates

This was a randomised, double-blind, double-dummy, multicentre, comparative study, comparing the efficacy and safety of topical retapamulin Ointment, 1% and oral cephalexin in the treatment of paediatric and adult subjects (≥9 months) with secondarily infected dermatoses (SID). Subjects with SID had a diagnosis of atopic dermatitis, psoriasis or allergic contact dermatitis that had a secondary bacterial infection. It was conducted between 24 September 2004 and 12 April 2005. This study was conducted in 109 centers in 11 countries.

All subjects who met the inclusion and exclusion were randomised in a 2:1 ratio to treatment with either retapamulin ointment BD for 5 days and oral cephalexin placebo BD for 10 days; or retapamulin matching placebo ointment BD for 5 days and oral cephalexin BD for 10 days. Paediatric subjects received an oral suspension of cephalexin or a cephalexin placebo suspension, rather than cephalexin in capsule form. A schematic diagram of the visit schedule is presented in Figure 4.

Figure 4: Study Schematic Diagram (Study 032)



7.3.1.1.2. Inclusion and exclusion criteria

As described under 7.1.1.1.2.

To be enrolled, subjects with SID had to have one or more clinical signs and symptoms of infection, The area of the infected lesion receiving topical treatment was to be no larger than 100 cm^2, or up to a maximum of 2% body surface area for subjects <18 years of age. Initially, subjects ≥13 years of age were enrolled, regardless of race or gender. Once the safety review of an IDMC for retapamulin studies Study 030A and Study 030B was completed and approved by regulatory authorities, IRBs and IECs, the age range was extended to include infants and children ≥9 months of age. In addition, subjects had a diagnosis of atopic dermatitis, psoriasis or allergic contact dermatitis with clinical signs and symptoms of secondary infection, suitable for treatment with topical or oral antibacterial therapy.

7.3.1.1.3. Study treatments

Subjects received one of two treatment regimens, either A: retapamulin Ointment, 1% and cephalexin placebo capsules or placebo suspension or B: cephalexin or cephalexin suspension and placebo ointment.

7.3.1.1.4. Efficacy variables and outcomes

The primary objective: to demonstrate that topical retapamulin Ointment, 1%, applied twice daily for 5 days, was at least as effective clinically as oral cephalexin, 500mg in adults, or 12.5mg/kg in children, twice daily for 10 days, in the treatment of SID, including atopic dermatitis, psoriasis and allergic contact dermatitis.

The secondary objective: to evaluate the bacteriological efficacy and safety of topical retapamulin Ointment, 1%, applied twice daily for 5 days and oral cephalexin, 500mg in adults, or 12.5mg/kg in children, twice daily for 10 days, in the treatment of SID.

7.3.1.1.5. Randomisation and blinding methods

Subjects were assigned to study treatment using a 2:1 (retapamulin Ointment 1%: Cephalexin), predetermined randomization schedule. Randomization was performed centrally by RAMOS. The block size remained confidential until the code was unblinded and the data analysed. Once a treatment number had been assigned to a subject, if the subject was withdrawn, the number could not be reassigned to any other subject. Ointments and oral medications were matched.

7.3.1.1.6. Analysis populations

As in 7.1.1.1.6.

7.3.1.1.7. Sample size

The planned sample size was 532 subjects. A total of 546 subjects were randomised: 363 to retapamulin Ointment, 1%, and 183 to cephalexin.

7.3.1.1.8. Statistical methods

This was a non-inferiority trial, with at least 90% power to detect a treatment difference greater than 10% (i.e., a non-inferiority test with delta = 10%), and with a 2.5% one-sided type 1 error rate. Sample size estimates were based upon assumed clinical success rates for retapamulin Ointment, 1%, and cephalexin of 90%, and an assumed 20% nonevaluability rate. These assumptions and the study design lead to an estimated required sample size of 426 evaluable subjects (532 total subjects). The claim of non-inferiority was achieved if the lower limit of the 95% confidence interval was greater than -10%.

7.3.1.1.9. Participant flow

Of the 546 subjects who were randomised to the study, 496 subjects completed (Table 36).

Table 36: Subject Disposition

Subject Disposition	Number of Subjects		
	SB-275833	Cephalexin	Total
Randomized	363	183	546
Randomized but not treated	0	1	1
Completed Study	320	176	496

A total of 95.3% (346/363) of subjects in the retapamulin treatment group attended the EOT visit (Visit 3), and 96.2% (176/183) of subjects in the cephalexin treatment group attended.

The percentage of total subjects withdrawn was greater in the retapamulin treatment group than in the cephalexin treatment group (Table 37). The most common reason for withdrawal was 'lost to follow-up' in the retapamulin treatment group and 'lack of efficacy' in the cephalexin treatment group.

Table 37: Number (%) of Subjects Withdrawn from the Study by Reason for Withdrawal (ITTC Population)

Reason For Withdrawal	Number (%) of Subjects		
	SB-275833 N=363	Cephalexin N=183	Total N=546
Completed Study	320 (88)	176 (96)	496 (91)
Prematurely Withdrawn	43 (12)	7 (4)	50 (9)
AE	5 (1)	0	5 (<1)
Lost to Follow-Up	15 (4)	1 (<1)	16 (3)
Deviation from Protocol	1 (<1)	1 (<1)	2 (<1)
Subject withdrew	5 (1)	1 (<1)	6 (1)
Lack of Efficacy	14 (4)	4 (2)	18 (3)
Other	3 (<1)	0	3 (<1)

7.3.1.1.10. Major protocol violations/deviations

The proportion of subjects excluded from the PPC population was very similar between the two treatment groups. The most common reason for exclusion in both treatment groups was attendance of a study visit outside the specified visit window. In the retapamulin treatment group, a greater proportion of subjects were excluded for being exposed to other topical treatment and for not returning to the scheduled FU visit than in the cephalexin treatment group.

Subjects were excluded from the ITTB population if no baseline pathogen was isolated by the central laboratory. For subjects receiving retapamulin Ointment, 1%, 41.3% (150/363) were excluded from the ITTB population, while for subjects receiving cephalexin, 36.6% (67/183) were excluded. A total of 10.2% (37/363) and 10.4% (19/183) of subjects from the retapamulin and cephalexin treatment groups, respectively, were excluded from the PPB population. The primary reasons for exclusion were similar to those observed for the PPC population.

7.3.1.1.11. Baseline data

The analysis populations are shown below (Table 38). End of Therapy and FU are based on days post-therapy, and because of the difference in duration of the two treatments, the EOT and FU endpoints are staggered over two visits (e.g., EOT is Visit 3 for retapamulin Ointment, 1%, and Visit 4 for cephalexin).

Table 38: Summary of Analysis Populations

Population	Number of Subjects		
	SB-275833	Cephalexin	Total
ITT Clinical	363	183	546
PP Clinical at EOT	339	162	501
PP Clinical at FU	320	156	476
ITT Bacteriological	212	115	327
PP Bacteriological at EOT	199	101	300
PP Bacteriological at FU	187	98	285

The demographic characteristics in the ITTC population were similar across the two treatment groups. The median age of the subjects was 33 years. The subjects in the study were predominantly <65 years of age. Overall, 124 paediatric subjects (<18 years) were enrolled, of which 81 received retapamulin Ointment, 1%, and 43 received cephalexin. A representative number of subjects were enrolled in each of the three paediatric age strata. Most were enrolled in the 9 months - <6 years stratum, as this age group has relatively high rates of atopic dermatitis. The majority of subjects had a clinical diagnosis of atopic dermatitis for the primary infected lesion at baseline, with the percentages and rank order of inflammatory skin disease type being similar between treatment groups. The majority of subjects in the study had one or more pathogen at baseline, most had a single pathogen isolated.

7.3.1.1.12. Results for the primary efficacy outcome

The primary efficacy results were based upon a 95% normal approximation confidence interval (without continuity correction) for the difference of clinical response rates at FU within the PPC population. Therefore, retapamulin Ointment, 1%, was shown to be noninferior to cephalexin in the treatment of subjects with SID (Table 39). The lower limit of the confidence interval for the treatment difference was greater than the non-inferiority margin, -10%, with the upper limit crossing zero. The results for the ITTC population were supportive of the primary study population (Table 39). The magnitude of the differences in success rates between treatment groups was greater for the ITTB and PPB populations. However, this study was not designed or powered to assess non-inferiority in these study populations.

Table 39: Clinical Response at Follow-Up by Analysis Population

Analysis Population	SB-275833		Cephalexin		Difference in Success Rates (%)	95% CI[2] (%)
	n/N[1]	Success Rate (%)	n/N[1]	Success Rate (%)		
PPC	**275/320**	**85.9**	**140/156**	**89.7**	**-3.8**	**(-9.9, 2.3)**
ITTC	301/363	82.9	158/183	86.3	-3.4	(-9.7, 2.9)
PPB	159/187	85.0	89/98	90.8	-5.8	(-13.5, 1.9)
ITTB	172/212	81.1	100/115	87.0	-5.8	(-13.9, 2.3)

7.3.1.1.13. Results for other efficacy outcomes

Selected secondary efficacy results are presented in the table below. Although the study was not designed to demonstrate non-inferiority for secondary endpoints, the clinical efficacy of retapamulin Ointment, 1%, at the end of therapy (EOT), was indicated to be non-inferior to cephalexin. Results were also favourable for both microbiological endpoints.

Table 40: Selected Secondary Efficacy Results

Analysis Population	SB-275833		Cephalexin		Difference in Success Rates (%)	95% CI[2] (%)
	n/N[1]	Success Rate (%)	n/N[1]	Success Rate (%)		
Clinical Response at EOT						
PP Clinical	312/339	92.0	152/162	93.8	-1.8	(-6.5, 2.9)
Per-Subject Microbiological Response at FU						
PP Bacteriological	163/187	87.2	90/98	91.8	-4.7	NA[3]
Per-Subject Microbiological Response at EOT						
PP Bacteriological	185/199	93.0	95/101	94.1	-1.1	NA[3]

1. n/N = number of successes / number of subjects that qualified for the respective analysis population in the respective treatment. 2. CIs were not adjusted for multiplicity. 3. NA = Not Applicable.

7.3.2. Evaluator's conclusions on clinical efficacy for SID

In the one study assessing efficacy for this indication, Study 032, retapamulin Ointment, 1%, was shown to be noninferior to cephalexin in the treatment of subjects with SID in the primary efficacy population. This study does not appear to have any major flaws.

8. Clinical safety

8.1. Studies providing evaluable safety data

This Safety Summary comprises safety data from 7 Phase III studies: 2 studies (TOC103469 and TOC100224) for the indication of primary impetigo, 2 identical comparator-controlled studies (Study 030A and Study 030B) and 1 placebo-controlled study (TOC110977) for the indication of SITL, 1 comparator-controlled study (TOC110978) for the indication of SITL and impetigo due to methicillin-resistant Staphylococcus aureus (MRSA), and 1 study (Study 032) for the indication of SID (Table 1 above). These studies are included in the safety integrated analysis set and the results are presented.

Overall, there were 4088 subjects in the integrated analysis set: 2724 treated with retapamulin, 137 treated with linezolid, 819 treated with cephalexin, 172 treated with fusidic acid, and 236 given placebo.

- **Pivotal efficacy studies**

The integrated analysis set presented in this summary contains information for the following 7 studies: TOC103469, TOC100224, 030A, 030B, 032, TOC110977, and TOC110978. In the Phase III studies, safety was evaluated using adverse event (AE) reports and clinical laboratory evaluations. AEs of particular interest (such as Q-T prolongation) were assessed by ECGs in two studies. These studies are summarised in Table 1, above. Age ranges of the subjects who participated in the studies are summarized in Table 41. There were 3 subjects in the retapamulin ointment group and 1 subject in the fusidic acid group who were ≥2 and <9 months of age.

Table 41: Summary of Age Group (Integrated Analysis Set, ITTC Population)

Age Range	Retapamulin (N=2724)	Linezolid (N=137)	Cephalexin (N=819)	Fusidic Acid (N=172)	Placebo (N=236)	Total (N=4088)
≥9 months to <6 years	290 (10.66)	19 (13.87)	34 (4.15)	64 (37.43)	47 (19.92)	454 (11.12)
≥6 years to<13 years	308 (11.32)	12 (8.76)	53 (6.47)	47 (27.49)	47 (19.92)	467 (11.43)
≥13 years to <18 years	139 (5.11)	11 (8.03)	34 (4.15)	14 (8.19)	18 (7.63)	216 (5.29)
≥18 years to <65 years	1715 (63.03)	85 (62.04)	584 (71.31)	45 (26.32)	118 (50.00)	2547 (62.37)
≥65 years	269 (9.89)	10 (7.30)	114 (13.92)	1 (0.58)	6 (2.54)	400 (9.79)

Table 42 summarizes the end-of-study records for the subjects in the integrated analysis set. Approximately 90% of all subjects completed the studies in which they were enrolled. In general, the proportion of subjects in each treatment group was similar in regard to reason for early withdrawal; except that the placebo group has higher proportions of subjects withdrawing early due to lack of efficacy and lost to follow-up than the other groups.

Table 42: Summary of End of Study Record (Integrated Analysis Set)

	Retapamulin (N=2724)	Linezolid (N=137)	Cephalexin (N=819)	Fusidic Acid (N=172)	Placebo (N=236)	Total (N=4088)
Completion Status						
Completed	2438 (89.50)	122 (89.05)	739 (90.23)	157 (91.28)	182 (77.12)	3638 (88.99)
Early Withdrawal	286 (10.50)	15 (10.95)	80 (9.77)	15 (8.72)	54 (22.88)	450 (11.01)
Reason for Early Withdrawal						
Adverse Event	39 (1.43)	3 (2.19)	14 (1.71)	3 (1.74)	2 (0.85)	61 (1.49)
Lost to follow-up	104 (3.82)	3 (2.19)	24 (2.93)	1 (0.58)	18 (7.63)	150 (3.67)
Protocol violation	8 (0.29)	2 (1.46)	3 (0.37)	0	0	13 (0.32)
Subject decided to withdraw	27 (0.99)	0	14 (1.71)	1 (0.58)	0	42 (1.03)
Lack of efficacy	68 (2.50)	0	22 (2.69)	1 (0.58)	18 (7.63)	109 (2.67)
Sponsor terminated study	5 (0.18)	3 (2.19)	0	0	1 (0.42)	9 (0.22)
Disease progression	15 (0.55)	3 (2.19)	0	6 (3.49)	10 (4.24)	34 (0.83)
Investigator discretion	4 (0.15)	1 (0.73)	0	0	2 (0.85)	7 (0.17)
Other	15 (0.55)	0	3 (0.37)	3 (1.74)	0	21 (0.51)
Missing	1 (0.04)	0	0	0	3 (1.27)	4 (0.10)

- **Pivotal studies that assessed safety as a primary outcome**

There were no pivotal studies that assessed safety as a primary outcome.

- **Dose-response and non-pivotal efficacy studies**

The following studies are not included in the Integrated safety as they are either different design or type of usage, but contribute to the safety data.

- Study 029 was a non-comparative Phase II study conducted in 35 subjects with uncomplicated bacterial skin infections;
- Study ALB110247 was a placebo controlled Phase I/IIA evaluation in 57 subjects nasally colonized with S. aureus; and
- Study TOC106489 was a Phase IV open-label pharmacokinetic (PK) study in 86 treated subjects between 2 and 24 months of age with uncomplicated skin and skin structure infections.

8.2. Pivotal studies that assessed safety as a primary outcome

All the studies in the current submission had safety as a secondary outcome.

8.3. Adverse events

8.3.1. All adverse events (irrespective of relationship to study treatment)

8.3.1.1. Pivotal studies

Although this safety summary is based on analysis of integrated safety data from all 7 studies within the Phase III program, data from 2 of the comparator treatment arms (sodium fusidate ointment and linezolid) are from single studies (Table 43).

Table 43: Number of Subjects (%) with Any Adverse Event (ITTC Population)

	n/N (%) of Subjects				
Study	Retapamulin	Linezolid	Cephalexin	Sodium Fusidate	Placebo
TOC103469	34/139 (25)	NA	NA	NA	18/71 (25)
TOC100224	56/345 (16)	NA	NA	25/172 (15)	NA
030A	130/662 (20)	NA	64/326 (20)	NA	NA
030B	159/606 (26)	NA	101/310 (33)	NA	NA
032	79/363 (22)	NA	40/183 (22)	NA	NA
TOC110977	19/342 (6)	NA	NA	NA	8/165 (5)
TOC110978	70/267 (26)	42/137 (31)	NA	NA	NA

In the integrated analysis set (all ages), a greater proportion of subjects in the linezolid and cephalexin groups experienced AEs than in the retapamulin group (Table 44). The most commonly occurring AEs in the retapamulin group were application site pain (1.54%), headache (1.51%), diarrhoea (1.43%), and nasopharyngitis (1.14%). No other AEs were reported in >1% of subjects in the retapamulin group. In the linezolid group, the most commonly occurring AEs were diarrhoea (11.68%), nausea (7.30%), and headache (4.38%). In the cephalexin group the most commonly reported AEs were diarrhoea (2.69%), headache (1.95%), and nausea (1.83%). The most commonly reported AEs in the fusidic acid group were urinary tract infection (2.33%), excoriation (2.33%), diarrhoea (1.16%), and arthropod bite (1.16%). In the placebo group, the most commonly reported AEs was pyrexia (1.69%).

Table 44: Summary of Most Frequently Reported Adverse Events (Greater Than or Equal to 1% and in 2 or More Subjects) in Any Treatment Group in Decreasing Frequency (Integrated Analysis Set, ITTC Population)

Preferred Term	Retapamulin (N=2724)	Linezolid (N=137)	Cephalexin (N=819)	Fusidic Acid (N=172)	Placebo (N=236)
Any event	547 (20.08)	42 (30.66)	205 (25.03)	25 (14.53)	26 (11.02)
Application site pain	43 (1.54)	0	4 (0.49)	0	0
Headache	41 (1.51)	6 (4.38)	16 (1.95)	0	0
Diarrhoea	39 (1.43)	16 (11.68)	22 (2.69)	2 (1.16)	0
Nasopharyngitis	31 (1.14)	0	7 (0.85)	0	0
Application site pruritus	26 (0.95)	1 (0.73)	3 (0.37)	0	1 (0.42)
Nausea	25 (0.92)	10 (7.30)	15 (1.83)	0	1 (0.42)
Pyrexia	15 (0.55)	1 (0.73)	3 (0.37)	0	4 (1.69)
Oropharyngeal pain	7 (0.26)	2 (1.46)	2 (0.24)	0	0
Abdominal discomfort	6 (0.22)	2 (1.46)	3 (0.37)	0	0
Urinary tract infection	5 (0.18%)	0	2 (0.24%)	4 (2.33)	0
Excoriation	4 (0.15)	0	1 (0.12)	4 (2.33)	0
Dysgeusia	0	2 (1.46)	0	0	0
Abdominal distension	0	2 (1.46)	1 (0.12)	0	0
Arthropod bite	0	0	1 (0.12)	2 (1.16)	0

8.3.1.2. Other studies

Integrated safety data from 4 Phase I studies (Study 025, Study 026, Study 027, and Study TOC101825) that assessed retapamulin ointment, 0.5%, 1%, or 2%, applied to the skin of healthy volunteers are summarized in this Section. Study 001 and Study 0034 safety were not integrated because those studies used different forms and formulations of retapamulin and are not for the indications or formulations being sought in the application. In addition, safety data from Study ALB110247 were not integrated with safety data from other Phase 1 studies because that study addressed nasal colonization and not skin structure infections (an indication not being sought in this application).

A total of 456 healthy adult subjects were exposed to retapamulin ointment or placebo ointment in the Phase I studies. Approximately equal numbers of men and women received retapamulin in the 4 Phase I studies (56% men and 44% women); subjects had a mean age of 38.2 years (range 18-66 years) and were predominantly White. In Study 025 and Study 027, retapamulin ointment, 0.5%, 1%, and 2%, was concomitantly applied along with controls to intact or abraded skin for various lengths of time. The AEs reported by these subjects were combined into the group labelled retapamulin patch.

In Study 026 and Study TOC101825, subjects received single concentrations of retapamulin ointment or placebo on intact or abraded skin for various lengths of time. The AEs reported by these subjects are grouped by concentration of retapamulin ointment (0.5%, 1% and 2%), AEs reported by all placebo subjects in Subjects in study 026, regardless of whether on intact or abraded skin, were grouped together, and AEs reported by subjects in Study TOC101825 after receiving retapamulin ointment along with ketoconazole were grouped together. A total of 484 subject sessions are summarized for adverse events; the subject sessions reflect each subject who received at least 1 dose of the corresponding treatment (eg, placebo, retapamulin patch, etc.). Therefore, subjects in Study TOC101825 are included twice in the subject sessions, once for retapamulin ointment, 1%, and again for retapamulin + ketoconazole.

The occurrence of overall AEs in healthy adults was low. The most frequent AE was headache, reported in 13.4% (65/484) subject-sessions. AEs related to the application site of the ointment occurred most frequently in subjects receiving retapamulin ointment, 2%. The most common AEs considered related ("probably," "suspected," or "unlikely") by the investigator to study drug, besides headache, were predominantly associated with the site of ointment application. Application site drug-related AEs occurred most frequently in the retapamulin 2% group.

8.3.2. Treatment-related adverse events (adverse drug reactions)

8.3.2.1. Pivotal studies

Drug-related AEs were infrequent, with only diarrhoea, nausea, and application site irritation reported in >1% of any treatment group (Table 45). Application site pain was the most frequently reported related AE in the retapamulin group (1.54% of subjects). Proportionally more subjects in the linezolid and cephalexin groups experienced diarrhoea and nausea than retapamulin group.

Table 45: Summary of Most Frequently Reported (Greater than or Equal to 1% and in 2 or more Subjects) Drug-related Adverse Events in Decreasing Frequency (Integrated Analysis Set, ITTC Population)

Preferred Term	Retapamulin (N=2724)	Linezolid (N=137)	Cephalexin (N=819)	Fusidic Acid (N=172)	Placebo (N=236)
Any event	146 (5.36)	25 (18.25)	54 (6.59)	1 (0.58)	2 (0.85)
Diarrhoea	24 (0.88)	11 (8.03)	14 (1.71)	0	0
Application site pain	42 (1.54)	0	4 (0.49)	0	0
Nausea	16 (0.59)	8 (5.84)	10 (1.22)	0	0
Application site pruritus	23 (0.84)	1 (0.73)	3 (0.37)	0	1 (0.42)
Headache	7 (0.26)	3 (2.19)	2 (0.24)	0	0
Abdominal discomfort	5 (0.18)	2 (1.46)	0	0	0
Dysgeusia	0	2 (1.46)	0	0	0

In the integrated analysis set, application site reactions occurred more frequently in the retapamulin group than in the placebo group (formulation comparator) or the active comparator groups (which used a placebo ointment in the double-dummy designed studies) (Table 46). There were no subjects in the fusidic acid group that experienced application site reactions. There was only 1 preferred term, application site pain, that was reported in >1% of subjects in any group (1.54% in the retapamulin group).

Table 46: Application Site Reactions (Integrated Analysis Set, ITTC Population)

Preferred Term	Retapamulin (N=2724)	Linezolid (N=137)	Cephalexin (N=819)	Fusidic Acid (N=172)	Placebo (N=236)
Application site pain	42 (1.54)	0	4 (0.49)	0	0
Application site pruritus	26 (0.95)	1 (0.73)	3 (0.37)	0	1 (0.42)
Application site paraesthesia	5 (0.18)	0	0	0	1 (0.42)
Application site irritation	3 (0.11)	0	0	0	1 (0.42)
Application site erythema	2 (0.07)	0	0	0	0
Application site bleeding	1 (0.04)	0	0	0	0
Application site discomfort	1 (0.04)	0	0	0	0
Application site hypersensitivity	0	0	1 (0.12)	0	0

8.3.2.2. Other studies

In Study 029, one subject had two episodes of pruritis (not severe). In Study TOC106489, one child developed a mild allergic reaction on the face (hypersensitivity) on Day 2 of study treatment for SID, following the third application of retapamulin. There were no AEs reported in Study ALT111065. In Study ALB110247, there were several reports of AEs occurring at the site of application (the anterior nares) that can be considered to be application site reactions (Table 47). The nasal symptom AEs, nasal discomfort and rhinorrhoea, occurred at similar rates in retapamulin ointment, 1% 200 mg and placebo groups.

Table 47: Adverse Events Occurring at the Application Site (Study ALB110247, Safety Population)

Preferred Term	Treatment A N=23	Treatment B N=19	Treatment C N=15
Nasal discomfort	2 (9)	1 (5)	1 (7)
Rhinorrhea	1 (4)	1 (5)	1 (7)
Sneezing	0	2 (11)	1 (7)
Epistaxis	0	2 (11)	0

Treatment A = retapamulin ointment, 1% 200 mg BD 3 Days and Placebo 2 Days Treatment B = retapamulin ointment, 1% 200 mg BD 5 Days Treatment C = Placebo 200mg BD for 5 days.

In Study TOC106489, 2 AEs were attributed to study treatment by the investigator: hypersensitivity and impetigo, each reported in 1 subject (both not severe).

No adverse experiences or unanticipated reactions were encountered or reported by any of the subjects during the course of the Study ALT111065.

8.3.3. Deaths and other serious adverse events

8.3.3.1. Pivotal studies

There were no deaths in Study TOC100224, Study TOC103469, Study 030B, Study 032, or Study TOC110978. In Study 030A, there were 2 deaths (SAEs of diabetic mellitus and diabetic coma; SAEs of cardiopulmonary arrest and septic shock) reported in the retapamulin ointment group. Neither of the deaths was attributed to study medication. Overall, severe AEs were reported in approximately 1% to 2% of subjects receiving active treatment, and in <1% in subjects who received placebo. Overall, incidence of SAEs was low in the integrated analysis set (26 subjects with events in 4088 subjects), with only linezolid having more than 1% of all subjects experiencing an SAE . No subjects experienced an SAE in the fusidic acid group, and only 1 subject experienced an SAE in the placebo group. In the retapamulin group, 4 reports of cellulitis considered to be serious were made, the remaining SAEs in the retapamulin, linezolid, and cephalexin groups were reported only once. None of the SAEs reported were considered by the investigator to be related to study product.

In general, withdrawal due to AEs was low (typically <3% of subjects per group) with few AEs reported as cause for withdrawal in >1 subject. The most frequently reported AEs leading to withdrawal in the retapamulin group were cellulitis (0.18%), abscess (0.11%), and 2 instances (0.07%) each of diarrhoea, application site irritation, application site pain, skin infection, and staphylococcal infection. In comparison, the most common AEs leading to withdrawal in the cephalexin groups were 4 instances of vomiting (0.49%), and 2 instances each of cellulitis, diarrhoea, bronchitis, nausea, and dizziness (0.24%). No other AEs leading to withdrawal in any group were reported more than once per group.

8.3.3.2. Other studies

There was one death in one of the studies not included in the integrated analysis set. In Study TOC106489, 1 SAE (cough) was reported; this subject later died. This was a 3-month old [**Information redacted**] who received retapamulin BD for 4 days, was reported to have had a severe cough and died on Day 6 of the study, 1 day after the last dose of retapamulin for the treatment of impetigo. The subject had a retapamulin plasma concentration of 2.09 ng/mL 4 hours after the first application of treatment at the On Therapy visit. The investigator considered the event and resulting death to be unrelated to study treatment. No further information is available about the aetiology of the cough.

In Study ALB110247, 3 severe AEs were reported. One subject 470256 had severe abdominal pain, one had back pain, and one had nasal pruritis. None were withdrawn and none were considered drug related.

8.3.4. Discontinuation due to adverse events

8.3.4.1. Pivotal studies

A summary of the AEs that led to subject withdrawal from studies included in the integrated analysis set was provided. In general, withdrawal due to AEs was low (typically <3% of subjects per group) with few AEs reported as cause for withdrawal in >1 subject. The most frequently reported AEs leading to withdrawal in the retapamulin group were cellulitis (0.18%), abscess (0.11%), and 2 instances (0.07%) each of diarrhoea, application site irritation, application site pain, skin infection, and staphylococcal infection. In comparison, the most common AEs leading to withdrawal in the cephalexin groups were 4 instances of vomiting (0.49%), and 2 instances each of cellulitis, diarrhoea, bronchitis, nausea, and dizziness (0.24%). No other AEs leading to withdrawal in any group were reported more than once per group.

8.3.4.2. Other studies

No subjects were withdrawn from Study 029, ALB110247 or ALT111065. In study TOC106489, 3 (3.5%) subjects withdrew from study treatment or the study due to AEs. The events leading to withdrawal included hypersensitivity, impetigo, and cough.

8.4. Laboratory tests

Routine haematology and clinical chemistry tests were performed at the following visits:

- Study TOC103469: baseline visit and end of therapy visit (ie, Day 7, Visit 2).
- Study TOC100224: baseline visit and end of therapy visit (ie, Day 7, Visit 2 for retapamulin ointment and Day 9, Visit 3 for sodium fusidate ointment, 2%).
- Study 030A and Study 030B: baseline visit and at each clinical visit.
- Study 032: baseline visit, Visit 2 (in case of withdrawal; Days 3 to 4, topical and oral on therapy) and Visit 3 (Days 7 to 9, topical end of therapy and oral on therapy). No clinical laboratory evaluations were performed in the conduct of Studies TOC110977 and TOC110978.

Due to differences in visit structure for the 5 studies, laboratory values in the combined analysis are presented at Day 1 (baseline) and Days 7 to 9 (corresponding to Visit 2 for Study TOC103469 and Study TOC100224, and Visit 3 for Study 030A, Study 030B and Study 032).

For all the clinical laboratory values, there were no large mean changes from baseline during the study for the total population or for the individual age groups subjects <18 years of age, subjects 18 to <65 years of age, and subjects ≥65 years of age. The number of subjects with values outside the normal reference range was low throughout the study for all treatment groups and all age groups.

8.4.1. Liver function

8.4.1.1. Pivotal studies

There were few subjects (≤2%) in any treatment group with shifts from normal to high in GGT values, and no subjects had shifts from normal to low GGT values. The incidence of subjects with shifts from normal to high CPK values was similar in the retapamulin ointment and cephalexin groups for subjects <18 years of age and 18 to <65 years of age, but was slightly higher in the cephalexin group (5%) compared with the retapamulin ointment group (1%) for subjects aged ≥65 years.

8.4.1.2. Other studies

N/A

8.4.2. Kidney function

No abnormalities are reported.

8.4.3. Other clinical chemistry

8.4.3.1. Pivotal studies

A small number of subjects had elevations in blood glucose and CPK, not different between control and treatment groups.

8.4.3.2. Other studies

N/A

8.4.4. Haematology

8.4.4.1. Pivotal studies

The incidence of shifts from normal to high in eosinophil counts was greatest for subjects <18 years of age in the retapamulin ointment group (9%), compared with 5% and 3% in the cephalexin and sodium fusidate ointment groups, respectively. Shifts to high or low values for eosinophil counts were generally comparable across the treatment groups for subjects ≥18 years of age.

8.4.4.2. Other studies

N/A

8.4.5. Electrocardiograph

8.4.5.1. Pivotal studies

N/A

8.4.5.2. Other studies

Electrocardiograms taken during Phase I studies in healthy adult subjects exposed to retapamulin ointment (0.5%, 1%, and 2%; on intact and abraded skin), showed no significant effect on QT or QTc intervals. No significant effects on QT/QTc were observed in post-hoc analyses of manually over-read 12-lead ECGs from 2 Phase I studies with 103 healthy adult subjects receiving at least a single dose of retapamulin ointment (0.5%, 1%, and 2%). In Study ALB110247, 3 ECG measurements were taken at pre-dose at the Screening 2 visit and on Day 1, Day 3, and Day 5 approximately 5 min apart and recorded in the CRF. Changes from baseline in ECG values were small and not clinically significant. No subject receiving retapamulin had a QTc or QTcF >480 msec or a change from baseline in QTc and QTcF >30 msec.

In post-hoc analyses of manually over-read 12-lead ECGs from studies 026 and TOC101825 with 103 healthy adult subjects receiving at least a single dose of retapamulin ointment, the statistical analysis and summary statistics show that topical application of retapamulin ointment does not cause QT/QTc prolongation. In light of the statistical limitations due to small sample sizes for each dosing cohort and primary study designs, pharmacokinetic-pharmacodynamic (PK/PD) analyses were performed as an alternative approach to assess the potential QT effects of retapamulin ointment. The PK/PD analyses of the ECG data in Study 026 and Study TOC101825 showed no correlation between QTcF, QTcB, or QT absolute values or maximum change from baseline with retapamulin ointment strength (Study 026) or treatment regimen (TOC101825). Cmax. QTcF/QTcB/QT interval prolongation was not observed as retapamulin ointment strength, Cmax, or plasma concentration increased or after co-administration with oral ketoconazole.

8.4.6. Application site reactions

8.4.6.1. Pivotal studies

In the integrated analysis set, application site reactions occurred more frequently in the retapamulin group than in the placebo group (formulation comparator) or the active comparator groups (which used a placebo ointment in the double-dummy designed studies; Table 48):

Table 48: Application Site Reactions (Integrated Analysis Set, ITTC Population)

Preferred Term	Retapamulin (N=2724)	Linezolid (N=137)	Cephalexin (N=819)	Fusidic Acid (N=172)	Placebo (N=236)
Application site pain	42 (1.54)	0	4 (0.49)	0	0
Application site pruritus	26 (0.95)	1 (0.73)	3 (0.37)	0	1 (0.42)
Application site paresthesia	5 (0.18)	0	0	0	1 (0.42)
Application site irritation	3 (0.11)	0	0	0	1 (0.42)
Application site erythema	2 (0.07)	0	0	0	0
Application site bleeding	1 (0.04)	0	0	0	0
Application site discomfort	1 (0.04)	0	0	0	0
Application site hypersensitivity	0	0	1 (0.12)	0	0

8.4.6.2. Other studies

In Study TOC106489, a 2-month-old White female with primary lesions on the face and neck developed a mild allergic reaction on the face (hypersensitivity) on Day 2 of study treatment for SID, following the third application of retapamulin. Study treatment (retapamulin ointment) was discontinued by the subject's parent, no additional medical therapies were given, and the event was reported to have resolved after 2 days.

There were no local AEs reported in Study ALT111065. In Study ALB110247, the nasal symptom AEs, nasal discomfort and rhinorrhoea, occurred at similar rates in retapamulin ointment, 1% 200 mg and placebo groups.

8.4.7. Epistaxis

8.4.7.1. Pivotal studies

N/A

8.4.7.2. Other studies

In Study ALB110247, the AE profile following intranasal application of retapamulin was predominantly similar to that following topical application to the skin (eg, application site discomfort). However, 2 individuals in this study who received retapamulin ointment BD for 5 days experienced epistaxis. The event was not seen in the placebo arm or in those who received retapamulin for only 3 days.

8.5. Post-marketing experience

Retapamulin has been approved in 60 countries and currently is available in 27 countries. Trade names include Altargo and Altabax. Retapamulin ointment contains butylated hydroxytoluene and white soft paraffin. Retapamulin was approved on 12 April 2007 in the United States and is authorized as a centralized product in the EU. On 24 May 2007, retapamulin was first authorized in the European Economic Area. The dosing recommendation is BD application for 5 days intended for administration in adult and paediatric patients aged 9 months and older. From product launch through 01 December 2011, there have been approximately 2.58 million units of retapamulin distributed over the 27 countries where it is available. The number of reports received is summarised in Table 49.

Table 49: Post-marketing Reports Received For retapamulin From Product Launch through 01 December 2011

REPORTS FULFILLING ICH E2C CRITERIA	NUMBER OF CASES
Serious unlisted	33
Serious listed	1
Non-serious unlisted	370
Total (line listing)	**404**
Non-serious listed	152
Total (serious plus non-serious cases)	**556**
OTHER REPORTS	
Non-medically verified	212
Regulatory, non-serious	2
Total (other reports)	**214**
GRAND TOTAL (all reports)	**770**

Note: One case may have had multiple events.

Table 50 lists the most frequently reported events from spontaneous case reports from product launch through to 01-12-2011. Local application site reactions are by far the most common.

Table 50: Most Frequently Reported Events from Spontaneous Case Reports

Event PT	Number of Events Reported
Application site pain	**265**
Burning sensation	**154**
Pain	85
Drug ineffective	63
Pruritus	**59**
Application site irritation	**52**
Erythema	**51**
Application site erythema	**48**
Hypersensitivity	**46**
Rash	41
Dermatitis contact	**37**
Application site pruritus	**29**
Crying	29
Skin irritation	**26**
Blister	21
Drug administration error	18
Swelling	16
Skin burning sensation	**15**
Dermatitis	13
Screaming	14
Therapeutic response unexpected	14
Ill-defined disorder	10
Application site reaction	**9**
Condition aggravated	9
Paraesthesia	9
Thermal burn	8
Wound complication	9
Skin lesion	8
Cheilitis	8
Lip swelling	8

8.6. Safety issues with the potential for major regulatory impact

8.6.1. Cardiovascular safety

The incidence of AEs possibly related to QT prolongation or torsades de pointes in the integrated analysis set was low (<1%) in any treatment group. There were no seizures, ventricular tachycardia, torsades, or ventricular fibrillation/flutter reported in the integrated analysis set.

There were no AEs of concern possibly related to QT prolongation/torsades de pointes in Study 029, Study ALB110247, Study TOC106489, or Study ALT111065. The studies that included electrocardiograms are discussed in Section 8.4.5.

8.7. Other safety issues

8.7.1. Safety related to drug-drug interactions and other interactions

Study TOC101825 showed that ketoconazole increased the retapamulin area under the concentration-time curve from time zero to 24-hours ($AUC_{(0-24)}$) and maximum plasma concentration (C_{max}) by 81% after topical application of retapamulin ointment, 1%, on abraded skin of healthy adult subjects. Despite this increase, none of the PK parameters values exceeded those observed previously in healthy adult subjects (Study 026), and therefore did not pose a risk of exceeding the plasma concentration established as the no-observed-adverse-effect-level (NOAEL) in monkeys. No clinical impact was found.

8.8. Evaluator's overall conclusions on clinical safety

In the integrated analysis set, one or more AEs were reported in 20% of subjects in the retapamulin ointment group, 25% of subjects in the cephalexin group, 15% of subjects in the sodium fusidate ointment group, 31% of the linezolid group, and 11% of subjects in the placebo group. Most AEs were of mild to moderate intensity and relatively few AEs led to discontinuation (≤3% of subjects in any treatment group). Drug-related AEs were infrequent, with application site pain reported in >1% of the retapamulin group. Application site pain was the most frequently reported related AE in the retapamulin group (1.54% of subjects). Proportionally many more subjects in the linezolid and cephalexin groups experienced the systemic AEs of diarrhoea and nausea considered to be related to study treatment than the retapamulin group. The local skin reactions – pain, pruritis, burning and redness were more common in the retapamulin group. This has also been borne out in the post-marketing reports.

The incidence of SAEs was low (n/N = 26/4088 subjects); approximately 2% in the linezolid group and <1% of subjects in the retapamulin ointment, cephalexin treatment or placebo ointment groups, and no subjects in the sodium fusidate ointment group. Most of these SAEs were related to progression of the infectious condition (cellulitis, abscess formation). Cellulitis was reported by 4 subjects in the retapamulin ointment group, 1 subject in the linezolid group, and by 1 subject in the cephalexin group; all other SAEs were reported in no more than 1 subject. Five deaths occurred in the studies. None of the events were considered by the investigators to be related to study drug administration.

None of the commonly reported AEs in the retapamulin group occurred in >4% of subjects (application site pruritus in 6 to 12 years olds was 3.90%). In the integrated analysis set, application site reactions occurred more frequently in the retapamulin group than in the placebo group (formulation comparator) or the active comparator groups plus their placebo ointment. The incidence of AEs identified as possibly related to QT prolongation or torsades de pointes was low (<1%) in any treatment group. Moreover, ECGs taken in healthy adult subjects exposed to several different doses of retapamulin ointment (0.5%, 1%, and 2%) during Phase I studies showed no significant effect of topical administration of retapamulin ointment on QT or

QTc intervals. Overall, for all clinical laboratory values, there were no notable changes from Baseline to Days 7 to 9 in any treatment group.

Due to the very low systemic exposure and rapid clearance of retapamulin ointment, the only events likely to be drug-related are the non-serious reactions at the site of application.

Due to the low system exposure to retapamulin after topical application, the drug interaction observed between retapamulin ointment and oral CYP3A4 and Pgp inhibitors is unlikely to increase the incidence of AEs or require dosing adjustment.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of retapamulin in the proposed usage are:

- Retapamulin ointment is an effective alternative to topical sodium fusidate for the treatment of impetigo, and to oral cephalexin for the topical treatment of SITL and SID.
- Efficacy for impetigo comparable to oral cephalexin and topical sodium fusidate.
- Efficacy for SITL which is comparable to cephalexin and probably slightly better than placebo (for mild disease).
- Efficacy for SID appears to be non-inferior to Cephalexin (based only on one study)
- With retapamulin ointment, there is no need for dosage adjustments based on age or the use of concomitant medications.
- Minimal systemic absorption.
- Low incidence of side effects, and these tend to be only local reactions.
- Low incidence of microbial resistance (and not related to any oral antibiotics currently in use).
- Topical treatment, avoiding the need for oral antibiotic administration.

9.2. First round assessment of risks

The risks of retapamulin in the proposed usage are:

- Local side effects (pain, burning, itch and hypersensitivity)
- Ineffectiveness of treatment for severe infection (ie. Progression to abscess/cellulitis)
- Relative poor efficacy for MRSA infections (compared to linezolid).

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of retapamulin, given the proposed usage, is favourable.

10. First round recommendation regarding authorisation

Pending amendments to the PI, I would recommend approval.

Regarding the proposed Indications:

Altargo is indicated for the topical treatment of the following bacterial skin and skin structure infections (SSSI):

- primary impetigo
- secondarily infected traumatic lesions e.g. small lacerations, abrasions, sutured wounds
- secondarily infected dermatoses including infected psoriasis, infected atopic dermatitis and infected contact dermatitis

It should be adjusted to read:

Altargo is indicated for the topical treatment of the following bacterial skin and skin structure infections (SSSI) in the absence of systemic signs or symptoms:

- *primary impetigo*
- *secondarily infected traumatic lesions e.g. small lacerations, abrasions, sutured wounds*
- *secondarily infected dermatoses including infected psoriasis, infected atopic dermatitis and infected contact dermatitis*

In the absence of known or suspected infection due to MRSA.

Also under the heading 'PRECAUTIONS' in the PI, the first and second precaution points should be:

Patients should be frequently assessed for non-responsiveness or progression of infection. If this occurs, change to a systemic antimicrobial agent may be necessary.

This agent is less effective than appropriate oral agent for the treatment of SSSI's caused by MRSA.

11. Clinical questions

None

12. Second round evaluation of clinical data submitted in response to questions

Not applicable

13. Appendix

13.1. Antibiotic resistance risk assessment

The development of resistance to retapamulin appears to be low, from the information supplied in the *in vitro* studies. A number of studies have been done to assess the in vitro susceptibility of clinical isolates of staphylococci, *S. pyogenes*, and *Propionibacterium acnes* from within Australia.

The first study was conducted to assess current retapamulin *in vitro* activity and spectrum results tested against 1,166 *S. aureus*, 23 coagulase-negative staphylococcal (CoNS) and 111 *S. pyogenes* clinical isolates recovered from hospitalized patients with documented infection in Australia (TOC1165567). All organisms were collected as part of the SENTRY Antimicrobial Surveillance Program from 2009 to 2010 for Australia.

Retapamulin demonstrated very good activity against *S. aureus* isolates in Australia ($MIC_{50/90}$, 0.06/0.12 mg/L), regardless of susceptibility to oxacillin or mupirocin, and inhibited all strains at ≤0.25 mg/L (modal MIC, 0.06 mg/L), except for two strains with reproducible MIC values of 2 mg/L. MIC results for retapamulin tested against CoNS ($MIC_{50/90}$, 0.06/0.05 mg/L) strains were equivalent to those obtained against the *S. aureus* population ($MIC_{50/90}$, 0.06/0.12 mg/L). Higher MIC_{90} values were observed for retapamulin tested against CoNS due to a small sample size (23 isolates) and detection of 3 isolates with non-wildtype MIC results (0.5 to 32 mg/L). Retapamulin demonstrated very good $MIC_{50/90}$ results (≤0.015/≤0.015 mg/L) when tested against a collection of clinically relevant *S. pyogenes* isolates.

The second study evaluated the *in vitro* activity of retapamulin and seven comparative agents against 107 *Propionibacterium acnes* clinical isolates collected in Australia (TOC116556). Acne skin sources accounted for 86.9% of the isolates (all outpatients) and 13.1% were from blood (all inpatients). All *P. acnes* isolates tested were inhibited by retapamulin at concentrations of ≤1 µg/ml. Retapamulin demonstrated excellent activity against the 107 *P. acnes* isolates tested, including those highly resistant to clindamycin and erythromycin and those with high MICs to neomycin. The MIC_{50} value of retapamulin was 4-fold lower than clindamycin, doxycycline, erythromycin, and minocycline, 16-fold lower than bacitracin, and 128-fold lower than neomycin. The MIC_{90} value for retapamulin was equal to bacitracin.

In total, more than 16,000 recent, geographically diverse, clinical isolates of *S. aureus* and *S. pyogenes* from pre-clinical studies, global surveillance studies and the clinical program, the vast majority (>99%) of isolates were inhibited by retapamulin concentrations of <2 g/mL. Nineteen isolates with elevated retapamulin MICs of ≥2 µg/mL were identified. These isolates are considered resistant to retapamulin4. Of these 19 isolates, the mechanism of resistance was determined to be efflux for 9 isolates and the presence of methyltransferase for 1 isolate; the mechanism of resistance has not been characterized for 9 isolates.

At present, the very low *in vitro* resistance rates, combined with the fact that there is no oral agent in the same class as retapamulin, make the development of resistance unlikely to be an issue of major clinical importance.

The statement in the draft PI: "The prevalence of retapamulin resistance may vary geographically and with time for selected species. Local recommendations about antibiotic use and prevalence of resistance should be taken into consideration." is appropriate, given that the different regulations and patterns of usage of both for this drug and for the other pleuromutilin antibiotics in animals may vary immensely, and may exert different selection pressures on this antibiotic over time.

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