Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Retapamulin

Proprietary Product Name: Altargo

Sponsor: GlaxoSmithKline Australia Pty Ltd

November 2013

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 AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of submission:	New Chemical Entity
Decision:	Approved
Date of decision:	19 July 2013
Active ingredient:	Retapamulin
Product name:	Altargo
Sponsor's name and address:	GlaxoSmithKline Australia Pty Ltd Level 4, 436 Johnston Street Abbotsford VIC 3067
Dose form:	Topical ointment
Strength:	1% weight/weight
Container:	Tube
Pack sizes:	2.5, 5, 10 and 15 g
Approved therapeutic use:	Altargo is indicated for the short term treatment of superficial skin infections (including impetigo, infected small lacerations, abrasions, sutured wounds, and secondarily infected dermatoses) in adults, adolescents, children and infants aged from 9 months, in the absence of abscess formation and infections due to methicillin-resistant *Staphylococcus aureus* (MRSA). The *in vitro* susceptibility to antibiotics varies geographically and with time; the local situation must always be considered when selecting antibiotic therapy.
Route of administration:	Topical
Dosage (abbreviated):	A thin layer of ointment should be applied to the affected area twice daily for five days. The area treated may be covered with sterile bandage or gauze dressing if desired. Patients not showing a clinical response within three to four days should be re-evaluated. 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). For topical application only.
ARTG number:	198947

Product background

Retapamulin is an antibacterial agent with a novel structure and a distinct mode of action. It is a member of a new chemical class of antibacterial agents for human use known as pleuromutilins. Retapamulin is a semisynthetic derivative of the compound pleuromutilin, which is isolated through fermentation from *Clitopilus passeckerianus*.

Retapamulin selectively inhibits bacterial protein synthesis by interacting with the 50s subunit of the bacterial ribosome in a way that is distinct from that of other non-pleuromutilin antibiotics that interact with the ribosome.

This AusPAR describes the application by GlaxoSmithKline Australia Pty Ltd (the sponsor) to register retapamulin as a 1% weight/weight (w/w) topical ointment (Altargo) for the following indications in adults, children and infants aged nine months and over:

> *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*
>
> *The in vitro susceptibility to antibiotics varies geographically and with time; the local situation must always be considered when selecting antibiotic therapy.*
>
> *For a list of susceptible microorganisms (see Pharmacodynamics).*

The primary pathogens in impetigo, secondarily-infected traumatic lesions (SITL) and secondarily-infected dermatoses (SID) are usually *Staphylococcus aureus (S. aureus)*, methicillin-resistant *S. aureus* (MRSA) and *Streptococcus pyogenes* (*S. pyogenes*) in both adult and paediatric patients.

The proposed dosage instructions for Altargo state (in part) that a thin layer of ointment should be applied to the affected area twice daily for five days.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 24 July 2013.

At the time this application was considered by the TGA, a similar application has been approved in approximately 60 countries including Canada (March 2008), the USA (April 2007), the European Union (EU; May 2007) and Switzerland (August 2009).

Product Information

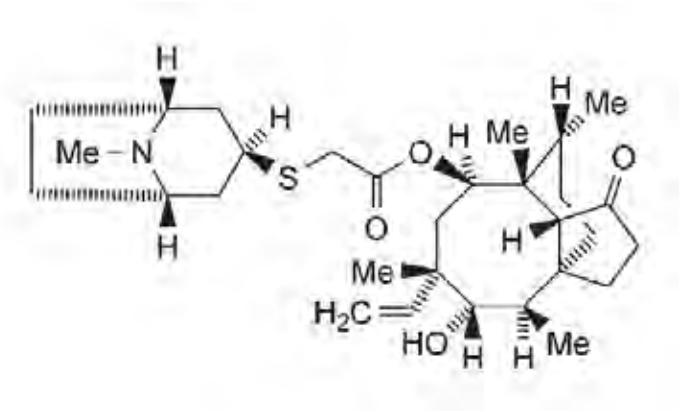
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

The drug substance, retapamulin, has the following structure:

Figure 1. Structure of retapamulin



Retapamulin is a semi-synthetic antibiotic derived from the fermentation of *Cliopilus passecterianus*. The product of the fermentation process is pleuromutalin which is synthetically transformed and coupled to produce retapamulin.

The stereochemistry of the pleuromutilin nucleus is fixed by biosynthesis and remains unchanged during the subsequent synthetic steps. Retapamulin is produced as a single stereoisomer.

Retapamulin drug substance is a white to pale yellow crystalline solid. Two polymorphic forms of retapamulin have been identified. The sponsor has adequately justified the selection of Form 1 for use in the drug product. It is controlled in the drug substance and no inter-conversion between Form 1 and 2 was observed in the drug product.

Retapamulin is soluble in acidic aqueous solutions and is practically insoluble in water and basic solutions.

The drug substance is milled and the particle size is controlled.

Limits for four impurities that exceed the qualification threshold according to the relevant International Conference of Harmonisation (ICH) guideline have been referred to the Toxicology Section for assessment.

Drug product

Altargo is an off-white, smooth ointment containing retapamulin 1% w/w. It contains the drug substance dispersed in solid form into white soft paraffin and may also contain traces of the antioxidant butylated hydroxytoluene. It is non-sterile, and typically for an ointment, contains no antimicrobial preservative.

The ointment is packaged into epoxy phenolic lacquered aluminium tubes with polyethylene or polypropylene caps in packs of 2.5 g, 5 g, 10 g and 15 g.

Adequate data was provided to show that the polymorphic form and particle size of the dispersed drug substance in the ointment does not change over 24 months. *In vitro* release rate testing data of stability batches and Phase I and Phase III clinical trial batches support the proposed drug substance particle size limits.

The finished product specifications include impurity limits within the relevant ICH *Guidance for Industry* Q3B (*Impurities in New Drug Products*) thresholds.

The ointment failed specification limits under accelerated conditions (40°C/75% relative humidity (RH)) due to the low melting point of the paraffin. However, satisfactory data generated at 30°C/65% RH and 25°C/60 RH support the claimed shelf-life of 24 months below 25°C.

Biopharmaceutics

No bioavailability data have been evaluated as the product is a topical ointment.

Advisory committee considerations

The submission was considered by the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) at its 149th meeting in January 2013. The subcommittee endorsed the issues raised by the TGA.

Quality summary and conclusions

All issues have been satisfactorily resolved by the sponsor.

There are no objections to the registration of retapamulin 1% w/w ointment from a pharmaceutical chemistry perspective.

III. Nonclinical findings

Introduction

General comments

Pleuromutilins were first discovered in 1950 and have been used orally in veterinary medicine since 1979 (tiamulin, valnemulin) in Europe. Retapamulin is the first pleuromutilin that was approved for human use (2007, Europe; and 2008, USA). To date, no pleuromutilin antibiotic is registered on the ARTG.

Nonclinical data consisted of primary (microbiology), secondary and safety pharmacology, dermal irritancy, repeat-dose and reproductive toxicity, skin sensitisation and genotoxicity studies. Repeat-dose oral studies up to 2-weeks duration were conducted in rats and monkeys at higher systemic exposures than those attained by dermal administration. Paediatric use was supported by studies in neonatal rats and juvenile minipigs. An Australian *Risk Assessment of Microbial Resistance* [for] *Altargo 1% Ointment* was provided. Pivotal toxicity studies were compliant with principles of good laboratory practice (GLP-compliant). Toxicokinetic data were provided for pivotal toxicity studies. A number of repeat dose toxicity studies investigating local toxicity after intranasal application were provided but were not considered relevant to the current intended use on infected skin and therefore were not evaluated.

Pharmacology

Primary pharmacology

Mechanism of action

Retapamulin is a semi synthetic pleuromutilin antibiotic. The mechanism of action of this drug class is the inhibition of protein synthesis by interaction with the 50S prokaryotic ribosomal unit. The site of retapamulin interaction is different from other antibiotics (Borrza 2008[1]). Pleuromutilins do not bind to eukaryotic ribosomes and do not inhibit mammalian protein

[1] Borrza, S, Philippi, E. (Editor). Physicians' Desk Reference (62 ed.); 2008;1318–20.

synthesis (Novak 2011[2], Tang and Liu 2012[3]). Retapamulin was shown to be bacteriostatic against *S. aureu*s and *S. pyogenes*. The minimum bactericidal concentration (MBC_{90}) against *S. aureu*s and *S. pyogene*s was 512 and 1024-fold the minimum inhibitory concentration (MIC) required to inhibit the growth of 90% of organisms (MIC_{90}). However, retapamulin demonstrated bactericidal activity against *Streptococcus pneumoniae*, *Haemophilus influenza* and *Moraxella catarrhalis* at concentrations 0.03 to 2 µg/mL.

Antibacterial activity

A range of *in vitro* studies investigated the antibacterial action of retapamulin against target Gram positive bacteria (focussing on S*. aureus*, drug resistant *S. aureus* and *S. pyogenes*) as well as other Gram positive aerobes, anaerobes, Gram negative aerobes and biothreat organisms. The activity of retapamulin was compared with antibiotics that are currently in use. Retapamulin was effective against skin and skin structure organisms including *S. aureus* and *S. pyogenes*. In >16,000 *S. aureus* or *S. pyogenes* isolates tested in *in vitro* studies and clinical trials, >99% were inhibited by a retapamulin concentration of <2 µg/mL. Retapamulin was also shown to be effective against most single or multi drug resistant isolates including resistance to β-lactams, macrolides, quinolones, fusidic-acid and mupirocin. All methicillin-resistant *S. aureus* (MRSA) isolates tested were inhibited by ≤0.25 µg/mL of retapamulin. A total of 19 *S. aureus* or *S. pyogenes* isolates with MICs of ≥ 2 µg/mL were identified. The mechanism of resistance for these isolates was shown to be efflux for 9 isolates, methyltransferase for 1 isolate, and is unknown for the remaining 9 isolates.

The sponsor's *Risk Assessment of Microbial Resistance* included 2 *in vitro* studies of Australian clinical isolates. The first study tested retapamulin activity against 1,166 *S. aureus*, 23 coagulase-negative staphylococcal (CoNS) and 111 *S. pyogenes* clinical isolates recovered from hospitalised patients with documented infection in Australia, collected as part of the SENTRY surveillance program for 2009-2010. Retapamulin was active against all *S. aureus* isolates ($MIC_{50/90}$ = 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 2 strains with reproducible MICs of 2 mg/L. $MIC_{50/90}$ values against CoNS strains were 0.06/0.12 mg/L. Higher MIC_{90} values were observed due to a small sample size (23 isolates) and detection of 3 isolates with non-wildtype MICs (0.5-32 mg/L). Retapamulin $MIC_{50/90}$ values against *S. pyogenes* were ≤0.015/≤0.015 mg/L (111 isolates). The second study showed that retapamulin at concentrations of ≤1 mg/L was active against all 111 *Propionibacterium (P.) acnes* clinical isolates collected in Australia from acne skin (86.9%) and blood (13.1%).

Retapamulin also showed *in vitro* activity against most strains of *Staphylococcus epidermidis*, *Streptococcus agalactiae*, *viridans* streptococci, *P. acnes*, *Peptostreptococcus* species, *Prevotella* species, *Fusobacterium* species, and *Porphyromonas* species, the clinical significance of these *in vitro* findings is not known.

In an *in vivo* experimental surgical wound infection model in mice, twice daily (BD) or three times daily (TID) application of retapamulin as a 1% w/w ointment for 4 days was effective against *S. aureus* methicillin-resistant and low or high level mupirocin-resistant isolates of *S. aureus* as well as *S. pyogenes 257*. The efficacy of 1% retapamulin was similar to or better than that obtained with TID application of mupirocin (1% or 2% w/w ointment) or fusidic acid (2% w/w cream). Local skin concentrations of retapamulin were not measured. Other animal models of skin infection were not assessed. These results were considered to support the proposed use in the treatment of patients with uncomplicated bacterial skin infections which are caused by infection with *S. aureus* or *S. pyogenes*.

[2] Novak R. Are pleuromutilin antibiotics finally fit for human use? *Ann N Y Acad Sci*. 2011;1241:71-81.
[3] Tang Y.-Z. , Liu Y.-H. and Chen J.-X. Pleuromutilin and its Derivatives-The Lead Compounds for Novel Antibiotics. *Mini-Reviews in Medicinal Chemistry*. 2001;12:53-61

Interaction with other antibiotics

The *in vitro* bactericidal activity of retapamulin alone and in combination with each of 8 antibiotics from different classes (bacitracin, clindamycin, ciprofloxacin, cephalothin, erythromycin, gentamicin, neomycin, and tetracycline) was evaluated using time-kill methods against one isolate each of MRSA and methicillin sensitive *S. aureus* (MSSA) and *S. pyogenes*. All compounds were tested over the range of concentrations (¼ times the MIC, 1 times the MIC, 4 times the MIC). Synergy and antagonism were defined as a decrease of ≥2 log10 or increase of ≥2 log10, in bacterial killing, assessed at 8 and 24 h for the combination of drugs compared with the more active of the two compounds alone. Antagonism was detected after combination of retapamulin with the cell wall synthesis inhibitor cephalexin or the deoxyribonucleic acid (DNA) gyrase inhibitor ciprofloxacin. Synergy was observed after combination of retapamulin with other antibiotics also interfering with protein synthesis, either by interaction with the 50s subunit (clindamycin, erythromycin) or the 30s subunit (gentamicin), as well as bacitracin whose antibacterial mechanism of action is inhibition of cell wall synthesis and alteration of membrane permeability.

Resistance development

Three mechanisms of resistance have been determined for retapamulin: mutations in the ribosomal protein L3, presence of the adenosine triphosphate (ATP) binding cassette (ABC) transporter *vgaAv*, and presence of Cfr methyltransferase. The presence of Cfr methyltransferase has been shown to confer resistance to phenicols, lincosamides, oxazolidinones, pleuromutilins and streptogramin A, through decreased drug binding to Cfr-methylated ribosomes. The sponsor reported that no clinical *S. aureus* or *S. pyogenes* isolates with mutations in ribosomal protein L3 were detected clinically and that isolates possessing the *vgaAv* or *cfr* genes appeared to be rare.

Retapamulin exhibited a low potential for spontaneous resistance development, including resistance of *S. aureus* and *S. pyogenes,* shown in serial passage and spontaneous resistance development studies. The highest MIC of clones subjected to serial passage in the presence of sub-MIC retapamulin concentrations was 2 µg/mL. The frequency of spontaneous resistance of *S. aureus* and *S. pyogenes* to retapamulin was lower than observed with cephalexin, erythromycin, mupirocin, quinupristin-dalfopristin, vancomycin. Treatment with fusidic acid also induced higher frequencies of resistance in *S. aureus* than retapamulin. Only linezolid exhibited a lower frequency of spontaneous resistance development. No clinical isolates of *S. aureus* or *S. pyogenes* with a mutation in ribosomal protein L3 were reported. Isolates carrying the *vgaAv* or *cfr* genes appear to be rare since >99% of the >16000 tested *S. aureus* or *S. pyogenes* isolates were inhibited by a retapamulin concentration of <2 µg/mL.

The percentage of MRSA determined in a global surveillance study was 32.8% globally, 36.9% in North America, 29.8% in Europe, and 18.4% in International (12 sites located in Australia, India, Singapore, and South Africa). Resistance to mupirocin ranged from 7.3% in Europe to 20.9% in the International regions. Rates of macrolide resistant *S. aureus* ranged from 25.7% in the International regions to 57.8% in North America. Fusidic acid resistance rates were 6.8% globally, 4.2% in North America, 12.6% in Europe, and 4.9% in international regions.

Cross resistance

The cross resistance of *S. aureus* isolates with elevated retapamulin MICs and the cross resistance of these isolates identified in *in vitro* profiling studies, surveillance studies and clinical trials with other antibiotic classes are listed in Table 1.

Table 1. Summary of cross resistance for *S. aureus* isolates with elevated retapamulin MICs

Report number	Strain	Isolate number	Retapamulin MIC (µg/mL)	Mechanism of resistance	Cross-resistance
UH2008/00143/00	S. aureus (MSSA)	440285	64	Efflux (vgaAv)	Mupirocin, clindamycin, erythromycin, trimeth-sulfa
	S. aureus (MRSA)	439700	16	Efflux (vgaAv)	Methicillin, clindamycin, erythromycin
UH2009/00005/00[a]	S. aureus	IV20204009	2	Efflux (vgaAv)	Fusidic acid
	S. aureus	IV20205004	2	Efflux (vgaAv)	Oxacillin
	S. aureus	IV20217008	4	Efflux (vgaAv)	Oxacillin
	S. aureus	IV20217033	64	Efflux (vgaA)	Fusidic acid, gentamycin
	S. aureus	IV20222009	4	Efflux (vgaAv)	Fusidic acid
	S. aureus	IHMA127277	2	Efflux (vgaAv)	Unknown
Harrington, 2010	S. aureus (MRSA)	#142	>16	Efflux (vgaA)	methicillin, clindamycin, erythromycin
UH2009/00185/00	S. aureus (MRSA)	553304	32	Methyltransferase (cfr)	methicillin (cefoxitin), clindamycin, erythromycin, gentamycin
UC2009/00010/00 (Woodford, 2008)	S. aureus (MRSA)	NA	2	Not characterized (Section 4.3.2.3)	methicillin (oxacillin) and mupirocin
UD2009/00186/00 (European surveillance study)	S. aureus (MRSA)	556146	4	Not characterized	methicillin, amoxi/clav, ceftriaxone, cefoxitin, penicillin, ciprofloxacin
	S. aureus (MRSA)	586628	4	Not characterized	methicillin, amoxi/clav, ceftriaxone, cefoxitin, penicillin, ciprofloxacin, macrolide
	S. aureus (MSSA)	560408	4	Not characterized	penicillin
	S. aureus (MSSA)	586476	4	Not characterized	penicillin
ALT111558 (Brown, 2009)	S. aureus (MRSA)	#005 045	2	Not characterized	methicillin (oxacillin), clindamycin, erythromycin, minocycline
TOC110978 (Phase III clinical study)	S. aureus	39457093558 667	2	Characterization ongoing[b]	ceftriaxone, clindamycin, erythromycin,
	S. aureus	39457085558 675	16	Characterization ongoing[b]	ceftriaxone
	S. aureus	39457065024 699	32	Characterization ongoing[b]	ceftriaxone, clindamycin (intermediate)

NA – Not available

a. When initially tested for *in vitro* susceptibility, S. aureus isolates IV20217008 and IV20222009 had retapamulin MICs of 2 µg/mL (UH2005/00086/00). Upon repeat testing, both isolates had retapamulin MICs of 4 µg/mL (UH2009/00005/00).

b. Mechanism of resistance is being characterized at the time of this report.

Post antibiotic effect

The post-antibiotic effect (PAE) of an antimicrobial is the persistent suppression of bacterial growth after short microbial exposure and removal of the antibiotic. The PAE was calculated as PAE = T-C, where T is the time in hours (h) taken for a treated culture to increase by 10-fold after removal of the antibiotic and C is the time for an untreated culture to increase by 10-fold. The post antibiotic effect against *S. aureus* at 4times the MIC was 3.1-3.4 h, and against *S. pyogenes* 3.5-4.2 h.

Secondary pharmacodynamics and safety pharmacology

Retapamulin was tested for secondary activity at 55 receptors ion channels and enzymes *in vitro*. Retapamulin inhibited the muscarinic M1 receptor with a concentration causing 50% inhibition (IC_{50}) of 131 nM (67.8 ng/mL). This concentration is about 3-fold the clinically anticipated maximum concentration (C_{max}) of 22.1 ng/mL.

Muscarinic M1 receptors are mainly found in the central and peripheral nervous system. More specifically, the M1 receptor has been identified in a number of brain regions including the hippocampus, cerebral cortex, and ganglion cells, and peripherally in lung, ovary, stomach, salivary glands, prostate, and duodenum (as reported in the sponsor's response to the TGA request for information). The sponsor reported that the M1 receptor and other muscarinic receptors are the cholinergic receptors correlated with increased cognition, control of vagally-induced bronchoconstriction, heart rate and gastric acid secretion. The rat brain penetration of retapamulin was shown to be low by whole body autoradiography. However the pituitary gland was among the tissues with the highest level of radioactivity after 0.5 h. Safety pharmacology studies in rats, dogs, and monkeys did not reveal any treatment-related effects at clinically

relevant concentrations on the central nervous system or cardiac function which could be attributed to M1 receptor inhibition.

Specialised safety pharmacology studies covered the core battery of systems (central nervous system (CNS), respiratory, cardiovascular renal and gastrointestinal systems). Dose ratios are rough estimates where doses administered by different routes are compared. CNS studies were conducted in mice. At 450 mg/kg (200 fold the clinically expected dermal dose on a mg/m^2 basis[4]), oral retapamulin induced decreases in motor activity as well as an analgesic activity in the mouse phenylquinone writhing assay. Retapamulin did not show proconvulsant effect at oral (PO) doses up to 450 mg/kg in mice. However, seizures and/or decreased body temperature were observed in monkeys at intravenous (IV) doses ≥ 15 mg/kg (≥27-fold the anticipated clinical dermal dose on a mg/m^2 basis).

In vivo cardiovascular studies were conducted in dogs and monkeys. A small increase (8 mmHg) in mean blood pressure (BP) due to increased systolic and diastolic pressure was observed with 450 mg/kg PO (1360-fold the anticipated clinical dermal dose on a mg/m^2 basis). Increases in blood pressure were also observed after IV administration of ≥ 10 mg/kg in dogs (exposure ratio based on area under the (plasma) concentration-time curve (AUC) 15). In monkeys IV administration of 10 and 30 mg/kg retapamulin (18 or 55 -fold the clinically expected dermal dose on a mg/m^2 basis) induced 16-60% decrease in blood pressure accompanied by transient reflex tachycardia and was followed by a further fatal decrease in blood pressure in the 30 mg/kg group. In the same study, the 15 mg/kg IV dose in monkeys induced a transient increase in BP and abolished diurnal fluctuation in blood pressure and heart rate for several days after dosing (18-fold the clinically expected dermal dose on a mg/m^2 basis).

Retapamulin was shown to inhibit human Ether-à-go-go-Related Gene (hERG) potassium channels *in vitro* with an IC_{50} of 3.3µg/mL (about 150-fold the clinically anticipated C_{max}). No changes in electrocardiogram (ECG) parameters were observed after IV doses of up to 3 mg/kg (plasma AUC ratio 3.6) in dogs and up to 30 mg/kg in monkeys (clinically expected dermal dose ratios on a mg/m^2 basis of 360). These cardiovascular effects are not expected to be induced by retapamulin treatment at clinically relevant exposures.

In rats, an increase in expiratory time was induced at 450 mg/kg PO (about 200-fold the clinically expected dermal dose on a mg/m^2 basis). In the absence of evidence for retapamulin changes to pulmonary resistance or peak expiratory flow this is thought to occur via a central mechanism. Retapamulin induced effects on respiration are not expected to occur at clinically relevant plasma concentrations.

A distribution study in pigmented rats after an IV dose showed levels of retapamulin related radioactivity were low in brain tissue after an IV dose. The low levels detected in brain tissue may have been due to retapamulin related radioactivity in circulating blood. Based on these results retapamulin is not expected to efficiently penetrate the blood brain barrier.

A renal safety pharmacology study in rats demonstrated increased water intake from retapamulin doses ≥ 150 mg/kg PO (70-fold the clinically expected dermal dose on a mg/m^2 basis) accompanied by increased urine volume and decreased osmolarity from 450 mg/kg PO. It is unlikely that increased water intake will occur at clinically relevant retapamulin plasma exposures.

Gastrointestinal safety was investigated in mice and guineapigs. Retapamulin inhibited agonist-induced guineapig ileal contraction from 10 µg/ml (450-fold the clinically anticipated C_{max}).

[4] The maximum amount of retapamulin ointment applied per dose to a subject was estimated to be 200 to 500 mg per 100 cm^2 by the sponsor in the clinical overview document. For BID dosing, the total daily dose applied is estimated to be 0.4 to 1 g of 1% retapamulin ointment per 100 cm^2. This corresponds to 4 to 10 mg of retapamulin. Conversion to mg/m^2 using a factor of 33 gives a dose of 6.6 mg/m^2 for a 50 kg human. Factors of 3 (mice) and 20 (dog), 12 (monkey) were used.

These findings were confirmed by reduced *in vivo* gastrointestinal motility in mice from 150 mg/kg PO (70-fold the clinically expected dermal dose on a mg/m^2 basis). These effects are expected to occur only at high doses that are unlikely to occur clinically.

Retapamulin induced complete or partial haemolysis of rat monkey and human whole blood at 10 mg/mL. As this is approximately 40,000-fold the anticipated clinical C_{max} after dermal application this finding is not expected to have clinical relevance.

Pharmacokinetics

Absorption: Following IV administration plasma clearance was moderate to high in rats, dogs and monkeys, but half-life was longer in dogs (2 h) than in rats and monkeys (about 1 h). Retapamulin was rapidly absorbed (time to achieve maximum concentration (T_{max}) 0.3-4.2 h) after a single oral administration in rats and monkeys. Retapamulin showed extensive biliary excretion and oral bioavailability was low (1-2% in rats). Based on total biliary and urinary excretion in rats the oral absorption was estimated to be 55% (fasted) and 83% (fed). Plasma levels in rats and monkeys were typically in the high ng/mL to low µg/mL range after oral administration of up to 450 mg/kg to rats and monkeys.

After single administration of topical doses (up to 5% over 25 cm^2), plasma levels were generally not detectable (< 0.5-1 ng/mL) in rabbits and minipigs. Systemic exposure increased with repeated topical dosing and measurable exposure (low ng/mL range) was achieved in some animals after repeated once daily (20 h) dermal application for 1-13 weeks. In general, measurable systemic exposure was more frequent and higher when retapamulin was applied to skin that was abraded to simulate non-intact skin or wounds. Due to variability and varying number of samples with detectable concentrations, no other dose comparisons were made. Maximum plasma concentrations were reached after 3-8 h. No consistent sex differences were observed in any of the preclinical studies, but again comparisons were compromised by high variability of the data or limited numbers of samples.

No bioavailability studies were conducted in humans since systemic exposure was low, as desired for a topical product. The exposure to retapamulin is expected to be low even when the skin barrier (integrity of the stratum corneum) is compromised.

Distribution: Extravascular distribution was rapid and extensive following IV administration of radiolabelled (^{14}C)-retapamulin to rats. Highest concentrations were generally detected after 0.5 h. The tissues with the highest concentration of radioactivity at 0.5 h were contents of small intestine and urinary bladder, as well as the uveal tract of the eye, the kidney, liver, lung and the pituitary gland. Radioactivity was detected in the meninges but was lower than blood (ratio 0.2) in the brain tissue itself. At 7 days post dose appreciable radioactivity was still detected in the uveal tract of the eye, the skin, liver, kidney, spleen, adrenal gland, pituitary gland thyroid, bone marrow and lymph nodes. Radioactivity persisted in pigmented skin, uveal tract of the eye, spleen, adrenal gland and lymph node, where measurable levels were still detected 35 days after the dose. Association of retapamulin related radioactivity with melanin containing tissue is considered likely.

Protein binding was moderate to high (75-94%) in the order human > rat > monkey *in vitro*. Protein binding was not concentration dependent. Only limited distribution of retapamulin into blood cells was seen in humans, whereas retapamulin was almost evenly distributed between blood cells and plasma in rats and monkeys.

Metabolism: Characterisation of the metabolic profile *in vitro* showed that retapamulin is rapidly and extensively metabolised. Clearance was more rapid in humans and monkeys than rat and dog. The main metabolic pathways were similar across species (rats, dogs, monkeys, humans) and consisted of mono and di-oxygenation and N-demethylation. One human specific metabolite, M15, a di-oxygenation product, was observed in hepatocytes. Cytochrome P450

(CYP) 3A4 was shown to be the main CYP isoform involved in retapamulin metabolism in human liver microsomes *in vitro*. Minor contribution of CYP2C8 and CYP2D6 to over all metabolism is expected. In the absence of nicotinamide adenine dinucleotide phosphate-oxidase (NADPH), retapamulin remained stable in aqueous solution over a 30 min period.

I*n vivo* a large number of metabolites (about 100 metabolites across matrices) were observed in plasma, urine, faeces and bile of rats and monkeys dosed orally. Discrete structural identification was not conducted. The highest levels of unchanged drug were detected in rat plasma after oral dosing (10-33%), levels were low in urine and the parent was not detected in faeces. In monkeys low levels of parent compound were only detected in faeces. Most of the metabolites measured in rat and monkey plasma, urine bile and faeces were < 5%. Only 3-4 metabolites/matrix were more prominent. Similar to the *in vitro* results the major pathways of metabolism in plasma were mono- and di-oxygenation. The main metabolites in bile/faeces were numerous monooxygenation products. Additional metabolic pathways in bile and faeces consisted of di-oxygenation with demethylation, mono-oxygenation with demethylation, monooxygenation with ketone formation, monooxygenation with sulfation, monooxygenation with glucuronidation, and monooxygenation with demethylation and glucuronidation. Metabolism in the other species used in the toxicity studies (rabbits and minipigs) was not investigated.

Retapamulin was metabolised to three minor mono-oxygenation products *in vitro* by human skin from which the stratum corneum had been removed. Only two circulating mono-oxygenated compounds were detected in plasma of subjects after topical administration of retapamulin ointment to abraded skin, both minor compared to the parent compound.

Excretion: Excretion was rapid in rats and monkeys after PO and IV administration, the largest fraction was excreted within 48 h. The predominant excretion route in rats and monkeys was faeces (80-90%). Urinary excretion was minor in rats (8-10%) and monkeys (13-17%). Substantial biliary excretion (about 70%) occurred after IV or PO administration in rats. No sex differences were observed.

Conclusion: In vitro studies suggest that the metabolic pathways in humans, rats, dogs and monkeys are similar. In contrast to the extensive *in vivo* metabolism of retapamulin in rats and dogs after PO dosing, the parent drug was the major component of retapamulin related radioactivity in human skin samples after dermal application *in vitro*, and only two minor metabolites were measured in human plasma after dermal application to abraded skin *in vivo*. Metabolism after dermal application was not investigated in animal studies.

Pharmacokinetic drug interactions

Retapamulin was shown to be a P-glycoprotein [P-gp; a transporter] substrate and inhibited P-gp mediated digoxin transport with an IC_{50} of 28.2µM (14.6µg/mL). This is not expected to be of clinical relevance since the inhibition occurs at concentrations approximately 660-times the clinically anticipated C_{max}. Retapamulin inhibited CYP3A4 via a competitive mechanism and weakly inhibited CYP2B6 [IC_{50} about 3.5 µM (1.8 6µg/mL) and 99 µM (51.3 µg/mL) respectively). At 82 and 2300-times the clinically anticipated C_{max} this is not expected to have any clinical relevance.

Retapamulin did not show relevant inhibition of any of the other tested CYP isoforms (CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6). Oral retapamulin treatment in rats elevated CYP450 levels and activity of CYP1A, CYP3A, CYP2E and CYP4A from ≥150 mg/kg (about 70-fold the anticipated clinical dermal dose on a mg/m^2 basis). CYP induction is therefore not expected to occur clinically after dermal treatment.

Relative systemic exposures

Relative systemic exposure after dermal administration

Rabbit:human plasma exposure (AUC) ratios were < 1 in all dermal repeat-dose toxicity studies for which toxicokinetic data were available (table below). The retapamulin high-dose (0.5 mL of 2% w/w ointment over 6.25 cm^2, white soft paraffin density of 0.93 g/cm^3 at 20°C) in the pivotal rabbit 13-week toxicity study was calculated to be 9.3 mg. The proposed maximum clinical dose is 10 mg retapamulin on 100cm^2 BD. It is unclear whether species differences in absorption and/or clearance contributed to the low systemic exposure ratios observed in the rabbit dermal toxicity studies. In general rabbit skin has been shown to be more permeable than human skin (Barrett 1969[5], Mortensen 1998[6]).

Table 2. Relative exposure in rabbit repeat-dose dermal toxicity studies

Species	Study/Route	Study duration	% BSA[b] (topical area)	Concentration (%)		AUC_{0-t} (ng·h/mL)	Exposure ratio
Rabbit (NZW)	StudySB-275833/RSD-101VP8/1 **Dermal (intact & abraded)[f]**	2 weeks	1.4% BSA [c] (25 cm^2)	0.5%	*intact*	NC	NC
					abraded	82.7^	0.3
				2%	*intact*	70.3^^	0.3
					abraded	82.7^	0.3
				5%	*intact*	48.2	0.2
					abraded	167.2	0.7
	CD2005/00281/00 **Dermal (intact)[f]**	11-13 weeks	0.3% BSA [cc] (6.25 cm^2)	0.5%		NC	NC
				1%		4.28^	0.02
				2%		14.6	0.06
Human (healthy volunteers)	Clinical study 026 **Dermal (abraded)**	Single dose[a]	1% BSA[e] (200 cm^2)	1%		238.4 [$AUC_{0-24\ h}$]	–

NC: not calculated. [a]Highest concentration observed across clinical studies. [b]Body surface area (BSA) for animal studies was estimated using the equations in (c) and (d), weight in kg represented as average of males and females if both sexes were tested. [c]$BSA_{rabbit} = 10 \times 2376^{2/3} = 1781\ cm^2$ (Derelanko and Hollinger CRC Handbook of Toxicology 1995, p. 647) [cc]$BSA_{rabbit} = 10 \times 2994^{2/3} = 2077\ cm^2$ (Derelanko and Hollinger 1995, p. 647), [d]$BSA_{minipig} = 1210 \times 11.8^{0.575} = 5001\ cm^2$(Swindle M.M. 2011). [e]Estimated human adult BSA, mean of males and females: BSA_{human}=18150 cm^2 (Derelanko and Hollinger 1995, p. 647), [f]males only. ^ n=1, ^^n=2.

Plasma AUCs were not calculated in the 10 day adult mini-pig dermal toxicity study due to scarcity of data. C_{max} was only measured in 50% of animals (1/group), close to the lower limit of qualification (0.5 ng/mL), and was used to calculate animal:human exposure ratios, which were

[5] Barrett C.W. Skin Penetration. *J. Soc. Cosmetic Chemists* 1969; 20:487-499 69
[6] Mortensen J T, Brinck P, Lichtenberg J The minipig in dermal toxicology. A Literature Review. *Scand. J. Lab. Anim. Sci.* Suppl. l. 1998; 25:77-83

also very low (table below). Plasma retapamulin levels were below the limit of detection in the dermal toxicity study in juvenile minipigs.

Table 3. Relative exposure in minipig repeat-dose dermal toxicity study

Species	Study/Route	Study duration	% BSA[b] (topical area)	Concentration (%)	C_{max} (ng/mL)	Exposure ratio
Minipig (Göttingen)	WbD2004/01067/00 **Dermal (intact & abraded)**[d]	10 day	1.4% BSA (70 cm^2)[b]	0 & 2%	0.6	0.03
				1 & 5%	0.7	0.03
Human (healthy volunteers)	Clinical study 026 **Dermal (abraded)**	Single dose[a]	1% BSA[c] (200 cm^2)	1%	22.1	–

AUC could not be calculated in this study due to lack of sufficient data. [a]Highest concentration observed across clinical studies. [b]$BSA_{minipig}$ = $1210 \times 12^{0.575} = 5050$ cm^2 (Swindle M.M. 2011). [c]Estimated human adult BSA, mean of males and females: BSA_{human}=18150 cm^2 (Derelanko and Hollinger 1995, p. 647) [d]males only.

Relative exposure after PO administration

Exposure ratios were calculated using the highest plasma levels measured clinically obtained in healthy volunteers after administration of retapamulin ointment at 2-fold the intended clinical concentration (2%) to skin that had been abraded to simulate non intact skin or wounds (clinical study 026). Systemic exposure ratios were adequate in the oral repeat dose studies, reaching 3 times in monkeys and up to 10 times in rats. In the monkey 2-week PO study the doses of 150 and 450 mg/kg/day were discontinued due to emesis and abnormal stool, therefore no repeat dose toxicokinetic data were therefore available for these doses.

Table 4. Relative exposure in repeat-dose PO toxicity studies

Species	Study/Route	Study duration	Topical Concentration/Dose		$AUC_{0-24\,h}$ (ng·h/mL)	Exposure ratio[#]
			% (topical area)	(mg/kg/day)		
Rat Sprague Dawley	SB-275833/ RSD-10151T/1 **PO**	2 weeks (M + F)	-	50	143	0.6
			-	150	517	2
			-	450	2441	10
Monkey cynomolgus	SB275833/RSD -1013TG/1 **PO**	2 weeks (M + F)	-	50	739	3
Human healthy volunteers	**Dermal (abraded)**	Single dose	1% (20 mg) (200 cm^2)		238.4	–

[#] = animal:human plasma $AUC_{0-24\,h}$ M + F = males + females

The duration of systemic exposure in the repeat dose toxicity studies was highly variable, ranging from 0-24 h. Most animals were not exposed to retapamulin for a significant part of each day (0-16 h, pivotal rabbit dermal repeat dose study, intact skin, 20-24 h mini pig dermal repeat dose study on intact and abraded skin in same animal, 16 h pivotal monkey study and 16 h rat PO repeat dose study; lower limit of quantitation (LLoQ): 10ng/mL, except for the minipig study which had an LLOQ of 0.5ng/mL). In contrast, in a clinical study (026) a single dermal application of retapamulin ointment over an area of 200 cm^2 of abraded skin induced systemic exposure to retapamulin in the low ng/mL range over the entire 24h period (LLOQ 0.5ng/mL).

Toxicology

Primary (single dose) dermal irritancy in rabbits

Three primary dermal irritation studies in rabbits collectively tested retapamulin concentrations of 0.5%, 1%, 2% and 5%, on intact and abraded, semi-occluded skin, with recovery periods of 72 h or 7 days.

The dermal single-dose toxicity of up to 5% retapamulin ointment was studied in rabbits using semi occlusive dressing. The maximum area treated in these experiments was 6-times 6.25cm2 (2% of the average rabbit body surface area[7]). 2% retapamulin ointment did not induce local irritation of intact skin, whereas local irritation occurred when applied to abraded skin [erythema (up to well defined) and very slight oedema, with some desquamation, which resolved spontaneously within 7 days]. Systemic toxicity in response to single dermal application was not assessed.

In summary, retapamulin has a low order of skin irritancy after single dermal application to rabbits at up to 5-times the clinically intended concentration over an area that reached the maximum recommendation for paediatric patients (2%). The local irritation potential of retapamulin was increased when applied to superficially damaged skin (removal of stratum corneum).

Repeat-dose dermal irritancy and toxicity

Repeat-dose dermal toxicity studies of 4-days, 2-, 4- and 13-weeks duration investigated dermal irritancy under semi-occlusive conditions in rabbits. The 2- and 4-week studies in rabbits tested both intact and abraded skin, but the pivotal 13-week toxicity study only tested intact skin. The pivotal 13-week study was of sufficient duration to support 5 days clinical use, and also investigated systemic toxicity. To support paediatric use, dermal studies were conducted in neonatal rats and juvenile minipigs (see *Paediatric use* below). Animals were treated only once daily in all of the dermal toxicity studies, most likely due to practical reasons associated with the daily shaving, replacement of occlusive dressings, and washing of sites. The once daily treatment may have contributed to the low systemic exposure ratios (see *Relative Systemic Exposures* above). Animals were not exposed to measurable plasma levels of retapamulin for large parts of each day, as discussed above in *Relative systemic exposures* above. Species differences in drug absorption through the skin and/or clearance might have contributed to the low exposures, but there were insufficient comparative data for these parameters.

Dermal irritancy

The 2-week dermal study (SB-275833/RSD-101P8/1) in rabbits tested retapamulin 0.5%, 2% and 5% ointment on semi-occluded, intact and abraded skin. The 0.5% ointment produced very slight irritation on intact and abraded skin which resolved in 9 days, the 2% formulation elicited erythema and oedema, with desquamation or blanching on intact skin, which was more severe on abraded skin. The 5% ointment elicited very slight to moderate-severe erythema and very slight to slight oedema with blanching and/or fissuring at intact sites, and very slight to severe erythema and very slight to moderate oedema at abraded sites, with blanching, fissuring, subcutaneous haemorrhage, denudation, exfoliation, and necrotic-appearing areas in addition. Microscopy showed an increased incidence/severity of acanthosis/hyperkeratosis, inflammation, ulceration, or dermal fibrosis with 2% or 5% ointment, which was concentration-related and more severe at abraded sites.

[7] Body surface area (BSA) was estimated using the average body weight of 2.5 kg. A BSA of 1890 cm^2 was calculated using the following equation: $BSA = kW^{2/3}$. K is a constant $K_{rabbit} = 10$. Derived from Derelanko and Hollinger. CRC Handbook of Toxicology, CRC Press; 1995, p647

The 4-week dermal study in rabbits tested retapamulin (succinate salt) 0.5%, 2% and 5% ointment on semi-occluded intact and abraded skin. Concentrations of 2% and 5% elicited concentration-dependent irritation associated with skin inflammation and ulceration, which was not tolerated for more than 10-20 days. The 0.5% ointment elicited transient erythema and oedema but no microscopic damage.

The 13-week dermal study in rabbits tested retapamulin 0.5%, 1% or 2% ointment on semi-occluded intact skin. Sites treated with ointment alone showed slight to well-defined erythema from week 2, and none to slight oedema from week 7. Dermal irritation of the 0.5% ointment was similar in incidence and severity to vehicle controls. The 1% ointment elicited very slight to well-defined erythema from week 2, very slight oedema from week 4, and desquamation in 1/6 rabbits. The 2% ointment elicited very slight to moderate/severe erythema and very slight to slight oedema from week 2, with desquamation in 6/6 rabbits in weeks 1-11. The no observed adverse effect level (NOAEL) for local effects was considered to be 1% based on minimal dermal irritation findings in this study.

In humans, it was reported that repeated doses of retapamulin ointment were well tolerated at concentrations up to 1% on intact and abraded skin, but repeated doses of 2% on abraded skin were not tolerated (clinical study SB275833/026).

Systemic toxicity

In rats, the maximum non-lethal dose after IV administration in 0.05M sodium dihydrogen orthophosphate solution was 10 mg/kg. The highest dose tested, 30 mg/kg, induced mortality. Clinical signs prior to death were nonspecific (vocalization during dosing, a single convulsion post-dose, hypoactivity and prostration), necropsy was without findings. Perivascular inflammation was observed in 1/3 males and females each, at 10 mg/kg only. Retapamulin was well tolerated orally in rats and monkeys up to 450 mg/kg/day.

Oral studies of 2-weeks duration were conducted in rats and monkeys. The major systemic toxicities after PO administration were liver induction and associated effects on thyroid function as well as decreases in white blood cells observed in rats, and emesis in monkeys. CYP-enzyme induction was observed in rats from oral doses ≥ 150 mg/kg. In the rat oral 2 week study liver induction manifested in form of increased liver weight (observed at 450 mg/kg, exposure ratio 10) and hepatocellular hypertrophy (males, 450 mg/kg, exposure ratio 10, females, 150 mg/kg, exposure ratio 2). As a consequence of liver induction, increased clearance of thyroid hormones triiodothyronine (T3) (males ≥ 50 mg/kg) and thyroxine (T4) (males and females at 450 mg/kg) was observed. A decrease in serum thyroid hormones has been associated with disinhibition of pituitary synthesis and release of thyroid stimulating hormone (TSH; Barbant 1989[8]). Consequently serum TSH levels were elevated from ≥50 mg/kg (males) and ≥ 150 mg/kg (females) and accompanied by thyroid follicular cell hypertrophy. Species differences between human and rodent thyroid hormone homeostasis have been described previously (Capen, 1997[9]). The percentage of unbound serum T4 is higher in rodents, where binding is limited to albumin and prealbumin, compared to humans in which high affinity binding to thyroxine binding globulins occurs. This results in a decreased circulating T4 half-life in rats due to higher clearance compared to humans. Basal TSH levels are increased in male compared to female rats further exacerbating the effects of TSH elevation in males (Capen, 1997). These effects in thyroid function are expected not to be of clinical relevance in humans due to species differences in thyroid function and greater sensitivity of the rat to disruption of thyroid function. It is noted that in a rat IV distribution study high levels of retapamulin related radioactivity were measured in the pituitary gland and remained measurable for a longer

[8] Brabant G, Ocran K, Ranft U, *et al.* Physiological regulation of thyrotropin. *Biochimie*, 1989;71:293 – 301
[9] Capen CC. Mechanistic data and risk assessment of selected toxic end points of the thyroid gland. *Toxicol Pathol*. 1997;25(1):39-48.

period than observed in most other tissues, for up to 7 days. It is not known if a direct effect of retapamulin on pituitary function also contributed to the disturbance in thyroid hormones.

Retapamulin induced decreases in white blood cells after PO dosing in rats by 16-24% of control from 450 mg/kg/day (exposure ratio 10), mainly due to reduction in lymphocyte counts. In humans, a decrease of 40% in total lymphocytes is known to be clinically relevant (Hannet *et al*., 1992[10]; Luster *et al*., 1993[11]). Retapamulin induced decreases in white blood cell counts were lower and therefore not considered clinically relevant, especially considering the low systemic exposures to retapamulin associated with topical application.

Salivation and hair coat thinning were observed in rat from doses ≥ 150 mg/kg PO. Excessive salivation was also observed in a cardiovascular safety study after IV doses of 30 mg/kg to monkeys. The mechanism of this effect was not investigated. However, salivation is mediated by muscarinic M1 and M3 receptors (Proctor GB, 2007[12]). High levels of retapamulin related radioactivity were measured in the salivary gland in the rat IV distribution study.

The major finding after oral administration in monkeys was emesis which occurred at all doses but increased in incidence and severity from 50 up to 450 mg/kg/day. Emesis restricted the study to the 50 mg/kg dose, the mid and high dose levels were discontinued. Emesis was also seen in a dog safety pharmacology IV study from doses ≥ 10 mg/kg and after a single PO dose in monkeys at 450 mg/kg but was not observed in other species treated orally (rats, rabbits).

Conclusion on systemic toxicity: The lowest observed adverse effect level (LOAEL) was 50 mg/kg in both rats (effects on thyroid hormones) and monkeys (emesis). Effects on the rat thyroid are considered species-specific and are considered to be unlikely to occur in humans. Emesis was inconsistently observed across species, but is considered unlikely in humans given the low systemic exposure after dermal application. Overall, the data suggests that systemic toxicity of retapamulin after dermal application will be unlikely.

Genotoxicity

The potential genotoxicity of retapamulin was investigated in the standard battery of tests. The studies were conducted in accordance with ICH guidelines. A suitable set of *Salmonella typhimurium* and *Escherichia coli* strains was used in the bacterial mutation assay, but the assay was found to be inappropriate due to the antibacterial action of retapamulin. Doses were also limited by cytotoxicity in the other studies. Toxicokinetics were not conducted in this study. In support of a successful systemic exposure, the upper dose level used in the *in vivo* assay for chromosomal aberration produced clinical signs such as convulsions, tremor, irregular breathing, protruding eyes, abnormal gait and lethargy. There was no sign of bone marrow toxicity (decreased %polychromatic erythrocytes) in any of the retapamulin treated groups in the range finding test, whereas the positive control induced bone marrow toxicity. The use of males only was acceptable in the absence of sex related differences in toxicity. All assays were appropriately validated and returned negative results for retapamulin.

Carcinogenicity

No carcinogenicity experiments were submitted. This is considered acceptable due to the negative genotoxicity findings, the low systemic exposure after the clinically proposed dermal route of administration and the short proposed 5 day duration of treatment.

[10] Hannet, I., Erkeller-Yuksel, F., Lydyard, P. *et al.* Developmental and Maturational Changes in Human Blood Lymphocyte Subpopulations. *Immunol. Today,* 1992; 13:215-218.
[11] Luster, M.I., Portier, C., Pait, D.G., *et al*. Risk Assessment in Immunotoxicology I: Sensitivity and Predictability of Immune Tests. *Fundam. Appl. Toxicol*. 1992; 18:200-210.
[12] Proctor GB, Carpenter GH. Auton Neurosci. Regulation of salivary gland function by autonomic nerves. 2007;133(1):3-18.

Reproductive toxicity

The submitted reproductive toxicity studies covered fertility, early embryonic development and embryofetal development. Fertility studies were conducted in rats (PO), embryofetal development studies were conducted in rats (PO) and rabbits (IV) to increase systemic exposure to retapamulin. Numbers of animals and the timing/duration of treatment were appropriate. No studies on pre-postnatal development, placental transfer or excretion into milk were submitted. This is considered acceptable due to the short (5 day) duration of treatment. A study in neonatal rats is discussed under the section repeat dose toxicity above. Exposure comparisons are based on animal:human plasma AUC ratios. In the absence of toxicokinetic data, rough animal:human dose ratio estimates were made by comparing oral to dermal doses.

Table 5. Relative exposure in the reproductive toxicity studies based on AUC

Species	Study	route	Dose (mg/kg/day)	$AUC_{0-24\ h}$ (ng·h/mL)	Exposure ratio#
Rabbit (NZW)	**Embryofetal development**	IV	0.72	NC	-
			2.4	607	2.5
			7.2	1906	8.0
Human (healthy volunteers)	Single dose Clinical study 026	dermal	1% ointment	238.4	–

= animal:human plasma $AUC_{0-24\ h}$

Table 6. Relative exposure in the reproductive toxicity studies based on dose

Species	Study		route	Dose (mg/kg/day)	mg/m^2	Dose ratio (mg/m^2)#
Rat (SD)	**Fertility**	Males treated	PO	50	300	45
				150	900	136
				450	2700	409
		Females treated	PO	50	300	45
				150	900	136
				450	2700	409
	Embryofetal development		PO	50	300	45
				150	900	136
				450	2700	409
Human (healthy volunteers)	Single dose Clinical study 026		dermal	0.2[a]	6.6	–

[a] The maximum amount of retapamulin ointment applied per dose to a subject was estimated to be 200 to 500 mg per 100 cm^2 by the sponsor in the clinical overview document. For BD dosing, the total daily dose applied is estimated to be 0.4 to 1 g of 1% retapamulin ointment per 100 cm^2. This corresponds to 4 to 10 mg of retapamulin. Conversion to mg/kg for a 50kg human gives a daily dose of 0.2 mg/kg. Conversion to mg/m^2 was calculated using a factor of 33 for human and of 6 for rat. # Dose ratios were calculated using human adult body surface areas.

No effects on male or female fertility or early embryonic development were observed in male or female rats treated with doses ≤ 450 mg/kg/day (dose ratio 409), NOAEL 450 mg/kg/day. Embryofetal development studies showed decreased fetal body weight and incomplete

ossification from 150 mg/kg/day PO in rats (dose ratio 136). Maternal body weight gain was decreased only at 450 mg/kg/day in rats (dose ratio 409) and 7.2 mg/kg IV (continuous perfusion) in rabbits (exposure ratio 8). In rabbits massive chronic suppurative phlebitis was observed at the infusion site at 0.72 and 7.2 mg/kg/day. The NOAEL for fetal development in rats was 50 mg/kg/day PO. The dose ratio at NOAEL is 45. The NOAEL for embryofetal development in rabbits was 7.2mg/kg/day IV (relative plasma AUC exposure ratio 8). No evidence of teratogenic effects was observed in rats and rabbits.

Pregnancy classification

The sponsor has proposed Pregnancy Category B3.

The definition of Category B3 is: *"drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed.*

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans."

This is appropriate from a nonclinical perspective due to the findings of decreased fetal growth and incomplete ossification in rats. The appropriateness of this category from a clinical perspective is not evaluated in this nonclinical report and requires clinical comment.

Local tolerance

Retapamulin acts as a dermal irritant in mice, rabbits and guinea-pigs, consistent with rabbit findings in the dermal repeat-dose studies. Retapamulin did not act as a contact sensitiser in mice but showed mild sensitizing potential in guinea-pigs. Reactions upon injection were more severe and included minimal to moderate necrosis of cutaneous muscle (subcutaneous, SC), mild to moderate necrosis of skeletal muscle (intramuscular, IM) in rabbits. In an embryofetal development study in rabbits, IV injection induced massive chronic suppurative phlebitis. There were no studies of eye irritancy. The US product information states that epistaxis has been reported with retapamulin use on nasal mucosa.

The *Precautions* section of the proposed PI states that in the event of sensitisation or severe local irritation, treatment should be discontinued, the ointment wiped off, and alternative therapy instituted. It also states that retapamulin should not be used in the eyes, on or mucous membranes, including the nasal mucosa. These statements are appropriate.

Antigenicity

Skin sensitisation

Retapamulin was shown not to act as a contact sensitizer in mice but showed mild sensitizing potential in guinea pigs. The sponsor's clinical overview reported low potential for contact sensitisation with retapamulin in humans. The finding of sensitisation in guinea pigs is therefore considered not to be clinically relevant.

Photosafety

Photosafety testing is warranted for those chemicals that absorb light in the wavelength of 290-700 nm and are either topically applied, or reach the skin or eyes following systemic exposure (*Note for Guidance on Photosafety Testing*; CPMP/SWP/398/01). Retapamulin did not exhibit absorbance in this range, though the white soft paraffin ointment base exhibited a low level of absorption due to a tail from a peak at approximately 270 nm. Due to the wide spread use of white soft paraffin in dermal prescription and non prescription medicines, and the lack of

absorption exhibited by retapamulin the lack of phototoxicity studies was considered acceptable.

Impurities

Though four of the impurities contained in the retapamulin drug substance exceeded the threshold for qualification, the daily intake of these impurities at the maximum recommended human dose of 10 mg is below the threshold of toxicological concern. None of these impurities requires toxicological qualification.

Paediatric use

Retapamulin is proposed for use in adults, children and infants aged 9 months and over. Dermal toxicity was tested in neonatal and juvenile minpigs. In neonatal rats, 6 weeks of retapamulin 0.5% or 1% treatment commencing on postnatal day (PND) 9 under semi-occlusive conditions induced a concentration dependent increase in incidence of clinical grade 1 erythema flaking and scabbing, without microscopic evidence of skin damage from ≥ 0.5% compared to control. No microscopic signs of skin damage or signs of systemic toxicity were observed up to1% retapamulin ointment. Respective plasma retapamulin exposure multiples at the retapamulin 1% concentration, based on C_{max} values of 1.17 and 2.53 ng/mL on PND 51, were 0.05 and 0.12. There was no dermal study in adult rats for comparison.

Application of retapamulin 0.5%, 1% or 2% ointment daily for 14 days to shaved, semi-occluded intact skin in juvenile minipigs (1/sex/concentration, 11-12 weeks old) elicited no evidence of skin irritancy or systemic toxicity. Toxicokinetics in juvenile minipigs showed all plasma retapamulin levels below the level of detection of 0.5 ng/mL on day 1, measurements were not conducted on day 14 samples. Systemic exposures were also inadequate (<1) in the rabbit dermal studies.

The juvenile minipig (dose range-finding) study was supported by a 10-day study in adult (18-weeks old) minipigs at retapamulin concentrations of 1%, 2% and 5%, which showed no signs of erythema or oedema in intact skin. These results contrast with the severe irritancy of the 2% formulation reported in abraded skin in humans. The structure, permeability and metabolic properties of porcine skin are similar to humans for most compounds (Mortensen 1998[13], Bode 2010[14], van der Laan 2010[15], Swindle 2012[16]).

Nonclinical summary and conclusions

- The sponsor conducted studies on primary, secondary and safety pharmacology, kinetics, dermal irritancy, repeat-dose and reproductive toxicity of retapamulin. Pivotal toxicity studies were GLP-compliant.
- Two species of bacteria, *S. aureus* and *S. pyogenes,* commonly cause impetigo, SITL and SID in both adult and paediatric patients. Retapamulin is bacteriostatic against *S. aureus* and *S. pyogenes*, with only minimal bactericidal activity. Retapamulin was shown to be effective against most single or multi-drug resistant isolates, including those resistant to β-lactams, macrolides, quinolones, fusidic-acid and mupirocin, and MRSA. The mechanism of action is

[13] Mortensen J T, Brinck P, Lichtenberg J. The minipig in dermal toxicology. A literature review. *Scand. J. Lab. Anim. Sci*. Suppl. l. 1998;25:77-83
[14] Bode G, Clausing P, Gervais F, *et al*. The utility of the minipig as an animal model in regulatory toxicology. *J Pharmacol Toxicol Methods*. 2010;62:196–220
[15] van der Laan JW, Brightwell J, McAnulty P. *et al* Regulatory acceptability of the minipig in the development of pharmaceuticals, chemicals and other products. *J Pharmacol Toxicol Methods*. 2010:62:184–195
[16] Swindle MM, Makin A, Herron AJ, *et al*. Swine as models in biomedical research and toxicology testing. *Vet Pathol*. 2012; 49(2):344-56

the inhibition of protein synthesis by interaction with the 50S prokaryotic ribosomal unit. The site of retapamulin action differs from other antibiotic classes.

- Retapamulin 1% ointment applied BD for 4 days was efficacious against *S. aureus* and *S. pyogenes* in a mouse surgical wound infection model. Other animal models of infection were not assessed.
- Secondary pharmacodynamic studies revealed that retapamulin inhibits the muscarinic M1 receptor *in vitro* with an IC_{50} of approximately 3-fold the highest clinically measured concentration. Safety pharmacology studies covered the CNS, respiratory, cardiovascular, renal and gastrointestinal systems. The more severe findings consisted of fatal hypotension, loss of diurnal blood pressure rhythm and heart rate rhythm and seizures in monkeys, as well as a possible centrally mediated increase in expiratory time in rats, after oral or IV dosing. Effects were only observed at concentrations substantially higher than anticipated in patients and were not thought to possess clinical relevance.
- *In vitro* transfer across human intact skin was 0.044% and 0.199% across abraded skin. In line with the low skin flux *in vitro*, the highest plasma C_{max} in human adults after single dermal application of 1% ointment (20 mg retapamulin, 2 times the clinical dose) to 200cm^2 of abraded skin was 22.1 ng/mL (AUC_{0-t} 238.4 ng·h/mL).
- In common with humans, plasma retapamulin levels after once daily dermal application of 2% retapamulin to intact skin were undetectable, and very low (< 0.5-1 ng/mL) after application to abraded skin, in rats, rabbits and minipigs.
- Oral bioavailability in rats was 1-2%. Plasma protein binding *in vitro* was moderate to high (75-94%) in monkeys, rats and humans. In rats, IV application of radiolabelled drug resulted in rapid and wide tissue distribution, CNS penetration was low. Due to very low systemic exposures after dermal application, retapamulin is not expected to induce drug interactions via CYP450 or P-gp. *In vitro* hepatocyte studies showed extensive retapamulin metabolism which was qualitatively similar in toxicity test species and human samples. Metabolism of retapamulin in human skin *in vitro* appeared to be low.
- Retapamulin had a low order of primary irritancy in rabbits after dermal application (semi-occluded) at up to 5-times the clinical concentration over the maximum area recommended for paediatric patients (2% total body surface area). Dermal irritancy of retapamulin was increased (transient erythema up to well defined and very slight oedema) in abraded skin.
- Repeat-dose dermal irritancy studies were conducted on semi-occluded, intact skin in rabbits (13 weeks duration) and minipigs (2 weeks), and intact and abraded skin in rabbits (2 and 4 weeks) and minipigs (10 days), using up to 2 or 5% retapamulin ointment over 0.3 to 1.4% of total body surface area. Animals were treated once daily in all studies. Dermal application of retapamulin to rabbits induced a concentration-dependent minimal to moderate irritation that was similar to vehicle on intact skin (0.5% and 1% concentrations) and more severe on abraded skin. The ointment alone elicited very slight to well defined erythema in intact skin. There was no evidence of systemic toxicity. Plasma retapamulin levels were very low or undetectable, and systemic exposure (AUC) ratios were inadequate (< 1) in all test species.
- Systemic toxicity was consequently investigated in oral studies in rats and monkeys, which attained adequate exposure (AUC) ratios, although the longest treatment duration was only 2 weeks, and dosing was once daily. No clinically relevant systemic toxicity was observed.
- Retapamulin did not act as a contact sensitizer in mice but showed mild sensitizing potential in guinea pigs. There was no study of eye irritancy.
- Paediatric use was supported by studies in neonatal rats and juvenile minipigs. Neonatal rats treated on PND 9-51 with 0.5% or 1% retapamulin on semi-occluded, intact skin

showed grade 1 erythema, without microscopic evidence of skin damage, and no systemic toxicity. Systemic exposure ratios were low (0.05, 0.12). Dermal toxicity was not investigated in adult rats for comparison. Retapamulin up to 5% ointment was also well tolerated in juvenile minipigs, although minipig numbers were low and retapamulin was not quantifiable in plasma.

- Retapamulin was negative in a standard battery of genotoxicity tests. Concentrations and doses were limited by cytotoxicity. Carcinogenicity was not investigated which is acceptable due to the lack of genotoxicity, low systemic exposure and short duration of treatment.
- Fertility was unaffected in male and female rats after oral treatment with retapamulin. Developmental studies showed decreased fetal weight and incomplete ossification in rats after oral treatment. Estimated and measured exposure ratios were adequate in these studies.

Conclusions

- Retapamulin was shown to be active in vitro against Gram-positive bacteria including *S. aureus* and *S. pyogenes*, with respective MIC_{90} values ranging from 0.06-0.5 µg/mL and ≤0.016-0.06 µg/mL. Retapamulin 1% ointment was efficacious against *S. aureus* and *S. pyogenes* in a mouse surgical wound infection model. Other animal models of infection, such as dermatoses, were not tested.
- Secondary pharmacodynamic studies revealed that retapamulin inhibits the muscarinic M1 receptor in vitro with an IC_{50} of approximately 3-fold the maximum plasma retapamulin concentration measured in clinical studies, however safety pharmacology studies at high estimated systemic exposures did not indicate an *in vivo* effect.
- Single and repeat-dose dermal toxicity studies up to 3-months duration in rabbits with retapamulin 0.5%, 1%, 2% and 5% ointment showed a concentration-dependent minimal to moderate irritation that was similar to vehicle on semi-occluded intact skin (0.5% and 1% concentrations) and more severe on abraded skin. The ointment alone elicited very slight to well defined erythema in intact skin. Animals were treated only once daily in all the dermal studies, in contrast to the proposed twice daily clinical regimen. Systemic exposure ratios in dermal studies were inadequate (< 1); hence systemic toxicity was also investigated in oral studies in rats and monkeys. Adequate exposure multiples were attained in these species, although treatment was once daily and for only 2 weeks (4 weeks is recommended to support the 5-day clinical regimen). The studies indicated that systemic toxicity is unlikely at the very low clinical exposure levels.
- Paediatric use was supported by dermal toxicity studies which showed minimal irritancy of intact skin in neonatal rats and no skin irritancy in small numbers of juvenile minipigs. Systemic toxicity was not evident in either species, but systemic exposure ratios were inadequate (< 1). Dermal toxicity was not studied in adult rats for comparison.
- There was no study of eye irritancy.
- Reproductive toxicity studies were conducted by the oral route in rats and IV route in rabbits, systemic exposure ratios were adequate. Decreased fetal growth and incomplete ossification were observed in rats, the proposed Pregnancy Category of B3 is acceptable.

Recommendation

Taking into consideration the above limitations of the nonclinical data, there are no overall objections to registration of retapamulin ointment for the proposed indications.

Recommendations regarding revisions to nonclinical information in the draft PI and the Risk Management Plan (RMP) are beyond the scope of the AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

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 US in April 2007, and was approved in the 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.

Scope of the clinical dossier

The clinical dosser documented a full clinical development program of pharmacology, efficacy and safety studies. The submission included the following clinical information:

· 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 the interaction of retapamulin with ketoconazole, a potent CYP3A4 and P-gp 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, non-comparative 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 4,088 adult and paediatric subjects, of who 2,724 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 the efficacy of retapamulin in subjects with *P. acnes* colonisation of the forehead.

A summary of the clinical studies is shown in Table 7.

The dossier included draft Australian PI and Consumer Medicine Information (CMI) and a *Risk Assessment of Microbial Resistance* [for] *Altargo 1% Ointment.*

Table 7. 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 7 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 7 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 7 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 7 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

Paediatric data

The submission includes paediatric PK, pharmacodynamic, efficacy and safety data.

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.

Pharmacokinetics

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 PK 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 colonised with *S. aureus* (Study ALB110247).

Pharmacokinetic results from Phase II, III, and IV studies are also provided. Phase II Study 029 assessed systemic exposure to retapamulin after topical application of retapamulin ointment, 1%, to the skin of subjects with uncomplicated bacterial skin infections. Phase III Studies 030A and 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 SITL. Phase IV paediatric 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.

Evaluator's overall conclusions on pharmacokinetics

The studies described above, both in healthy and target population studies, provided 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 cm^2 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 (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. 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 $AUC_{(0\text{-}24\ h)}$ and C_{max} by approximately 80% after topical application of retapamulin ointment, 1%, on abraded skin of healthy adult subjects (Study TOC101825). However, due to minimal systemic exposure to retapamulin after topical application of retapamulin ointment, 1%, 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 (AEs) or to require dosage adjustments for retapamulin ointment, 1%, when co-administered with oral CYP3A4 or Pgp inhibitors in patients.

Pharmacodynamics

Studies providing pharmacodynamics data

Table 8. 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

Summary of primary pharmacodynamics (microbiology)

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.[17] 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 no isolates demonstrated a reduction in susceptibility to retapamulin during treatment with retapamulin in the Phase III clinical program, based on outcomes of presumed eradication of pathogens and laboratory investigation of the limited number of subjects with post therapy isolates.

The *in vitro* data characterising the activity of retapamulin and comparator antibacterial agents against various bacterial isolates are summarised above under *Nonclinical data Primary pharmacology* and in the clinical evaluation report (CER, see Attachment 2 of this AusPAR).

The proposed indications for retapamulin are impetigo, SITL and SID. The primary pathogens are usually *S. aureus*, MRSA and *S. pyogenes*. Overall, retapamulin demonstrated good *in vitro* activity against Gram-positive bacteria commonly associated with skin infections and a low propensity for development of resistance *in vitro*.

Antibiotic resistance risk assessment: conclusion

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.

Evaluator's overall conclusions on secondary 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 interval[18] indicated that these were not likely to be issues (even when retapamulin is used 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 h 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 ECGs from healthy adult subjects from Studies 026 and TOC101825 (N=103), no significant effects on QT/QTc interval 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 treated with retapamulin ointment with or without co-administration of CYP3A4 or Pgp inhibitors.

Efficacy

Dosage selection for the pivotal studies

Dosage selection was based on findings from Phase I studies of irritation and tolerance which indicated that the 1% formulation was the maximal tolerated concentration when

[17] 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

[18] QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A lengthened QT interval is a biomarker for ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death. QTc is QT interval corrected for heart rate.

used under proposed therapeutic conditions. Twice-daily (BD) dosing was proposed based on studies done in animal models. The findings of nonclinical studies were further explored in a human Phase I study (029) that evaluated PK and proof-of-concept for administration of retapamulin ointment topically for treatment of uncomplicated skin and skin structure infections (uSSSI).

Studies providing efficacy data

This application contains efficacy data from 7 multi-national Phase III clinical studies (summarised in Table 7 above)

- 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 9.

Table 9. 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 (PPC) for Studies 100224, 030A, 030B, and 032; Intent-to-Treat Clinical (ITTC) for Study 103469, and Intent-to-Treat Clinical Primary Analysis (ITTPA) for Study 977; and Per-Protocol MRSA for Study 978.

Evaluator's overall conclusions on efficacy

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 (EoT) in the ITTC population, retapamulin was superior to placebo, with an 85% versus

52% response rate (statistically significant). Superiority was also achieved in the PPC group (89% versus 53% clinical response).

The other major study assessing this indication was Study TOC100224, in which retapamulin was compared to topical sodium fusidate ointment. Based on the primary efficacy endpoint of clinical response at EoT 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.

Clinical efficacy for SITL

Studies 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 retapamulin and control groups were well balanced overall. Based on the results presented for this study, conservative estimates in the PPC group suggest that retapamulin is, overall, as good as cephalexin for mild SITL (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 [cephalexin] would not be expected to have an 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% confidence interval (CI) of (1.04, 2.87). In the bacteriologically assessable group (ITTB group) outcome of clinical cure was 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 sponsor states that: "Concerns inherent to placebo-controlled studies may have resulted in enrolment of a study population in the mild range of the SITL indication, resulting in a higher than anticipated placebo response rate" and "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 it 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.

In summary, efficacy in SITL was shown for retapamulin ointment (compared to cephalexin) in two pivotal efficacy studies, but not in the placebo controlled study or in the active comparator (linezolid) study specifically examining efficacy in MRSA infected wounds. The evaluator concluded from this that retapamulin probably has some effect for MRSA infected wounds, but linezolid is better. 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.

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.

Safety

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 MRSA, and 1 study (Study 032) for the indication of SID (summarised in Table 7 above). These studies are included in the safety integrated analysis set.

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.

Age ranges of the subjects who participated in the studies are summarised in Table 10. 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 10. 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 11 summarises 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 11. 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 withdrew	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)

Post-marketing experience

Retapamulin has been approved in 60 countries and currently is available in 27 countries. The dosing recommendation is BD application for 5 days in adult and paediatric patients aged 9 months and older. From product launch through to 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 12.

Table 12. 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 13 lists the most frequently reported events from spontaneous case reports from product launch through to 01 December 2011. Local application site reactions are by far the most common.

Table 13. 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

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 serious AEs (SAEs) was low (n/N = 26/4088 subjects): these were reported in approximately 2% of the linezolid group, in <1% of subjects in the retapamulin ointment, cephalexin treatment or placebo ointment groups, and in 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 these 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.

First round benefit-risk assessment

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 is comparable to oral cephalexin and topical sodium fusidate.
- Efficacy for SITL 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 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.

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 (that is progression to abscess/cellulitis).
- Relative poor efficacy for MRSA infections (compared to linezolid).

First round assessment of benefit-risk balance

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

Clinical questions

None

Recommendation regarding authorisation

Pending amendments to the PI, the clinical evaluator recommended approval for the following, amended, Indication (evaluators recommended amendments bolded)

> *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.***

The evaluator also recommended that the *Precautions* section of the PI include the following as the first and second points:

· 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.

Other recommended revisions to the PI are beyond the scope of the AusPAR.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted an EU Risk Management Plan (EU-RMP Version: 03, dated 4 April 2012, with an Australian Specific Annex (ASA) undated) which was reviewed by the TGA's Office of Product Review (OPR). A summary of the RMP is shown in Table 14.

Table 14. Summary of the RMP

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Development of resistance to retapamulin	GSK has completed a European surveillance study in December 2010.GSK will monitor spontaneous reports for evidence of emerging resistance.	No risk minimisation activities are necessary at this time
Off label use and use in very young paediatrics	GSK will monitor prescription data in Europe and US (WWE113149/WEUSKOP3290 and WWE113158/WEUSKOP3084), in order to identify the extent of off-label prescribing and use in the paediatric population and to aid the analysis of spontaneous adverse events. GSK will perform this analysis on an annual basis for the first five years post launch. GSK will monitor spontaneous reports to identify occurrences of off label use in children aged less than 9 months. In addition, IMS health sales data will be broken down by age/country at the time of PSUR. GSK will monitor spontaneous reports and published literature to identify possible off-label use on mucosal surfaces.	No risk minimisation activities are necessary at this time

Safety specification

Subject to the evaluation of the non-clinical aspects of the Safety Specification (SS) by the Toxicology area of the Office of Scientific Evaluation and the clinical aspects of the SS by the Office of Medicines Authorisation, the summary of the ongoing safety concerns as specified by the sponsor is as follows:

- Important identified risks:
  - Hypersensitivity
- Important potential risks:
  - Off-label use – mucosal surfaces
  - Off-label paediatric use
  - Development of resistance
- Important missing information:
  - None

Pharmacovigilance plan

The sponsor states that routine pharmacovigilance activities, consistent with the activities outlined in *3.1.2 Routine pharmacovigilance practices, Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03),* are proposed to monitor all the specified ongoing safety concerns. This includes the use of targeted follow up questionnaires for the important identified risk: 'Hypersensitivity' and the important potential risk: 'Off label Use – Mucosal Surfaces'.

For the important potential risk: 'Off label Use - paediatrics aged less than 9 months', ongoing studies aim to determine the use of retapamulin in children aged less than 9 months by using an administrative medical claims database in the US.

For the important potential risk: 'Development of resistance', the sponsor reports that a prospective surveillance study was conducted in six European countries in order to assess the *in vitro* activity of retapamulin and 14 comparative agents against 1,500 recent clinical isolates of *S. aureus* and *S. pyogenes* from community acquired skin infections. The surveillance study was completed in 2010 and the report was submitted in January 2011 to the European Medicines Agency (EMA).

The sponsor states that retapamulin demonstrated excellent *in vitro* activity against the tested isolates of *S. aureus* and *S. pyogenes*, with MIC_{90} values of 0.12-0.25 and 0.06 g/mL, respectively, regardless of phenotype or country. The sponsor concludes that no further action is required and the ASA states no Australia specific surveillance will be conducted.

Risk minimisation activities

The ASA states: *"As outlined in the EU-RMP, due to the nature of the product, including the predominantly low systemic exposure, rapid clearance and absence of any important safety issues in the targeted population, retapamulin does not require a specific risk minimisation plan."* Therefore the sponsor considers that no additional risk minimisation activities are needed.

Summary of first round evaluation recommendations to the sponsor

The OPR provides these recommendations to the sponsor in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; the submitted EU-RMP is applicable without modification in Australia unless so qualified; and the draft PI and CMI documents are not revised until the Delegates Overview has been received:

1. Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated request for information and/or the Nonclinical and Clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.
2. Notwithstanding the evaluation of the non-clinical and clinical aspects of the SS, it is recommended that for completeness the sponsor include the important missing information: 'Use in pregnant and lactating women' as an ongoing safety concern. Consequently the RMP and/or the ASA will need to be amended accordingly when these documents are next updated.
3. Details of the qualified person responsible for pharmacovigilance within the sponsor company, who has been nominated as the person responsible for the implementation

of the RMP activities within Australia, should be included in the ASA when this document is next updated.

4. The ongoing studies are not considered to be part of the planned clinical studies in the pharmacovigilance plan. Therefore the related study protocols have not been reviewed. Nevertheless an update on the progress/results/analysis of these studies, as outlined in the RMP, will be expected in future periodic safety update reports (PSURs).
5. Notwithstanding the evaluation of the supporting document: *'Risk Assessment of Microbial Resistance [*for] *Altargo (retapamulin)'* by the OMA and the ASA statement that no Australia specific surveillance will be conducted, expert advice as to whether the EU surveillance study is applicable to the Australian context will be sought.
6. The section 'Summary of the EU Risk Management Plan' of the RMP should be amended to include all the specified ongoing safety concerns, including the important missing information: 'Use in pregnant and lactating women' when this document is next updated.
7. The 'Important identified and Potential Risks' of the RMP refers to pharmacovigilance activities rather than risk minimisation activities. Nevertheless the sponsor's conclusion that no additional risk minimisation activities are needed is consistent with the assessments of the US FDA and the Committee for Medicinal Products for Human use (CHMP) and it is agreed the specified ongoing safety concerns would not appear to warrant additional risk minimisation activities.
8. The sponsor should provide at least a short description of information to be included in the EU Summary of Product Characteristics (SmPC) and the Australian PI to minimise risk for all the ongoing safety concerns, including justification for any differences between these two documents. This information should be included in the ASA and no assessment of the proposed routine risk minimisation can be made until such information is provided.

Second round evaluation

Recommendations 1 and 3

Acceptable responses were provided.

Recommendations 2 and 6

The sponsor provided an updated ASA which includes an amended table of ongoing safety concerns with details of the routine pharmacovigilance activities and systems in place relating to the safety concern of use in pregnant and lactating women. The sponsor also provides an assurance that routine pharmacovigilance activities include the collection and follow up of reports in pregnant and lactating women; any SAEs associated with a report in a pregnant or lactating woman would be communicated to the TGA; and such reports are also included in the PSURs. The sponsor does not propose to amend the EU-RMP in this case. This is acceptable.

Recommendation 4

The sponsor has provided an assurance that TGA will be updated on the progress of the ongoing studies in future PSURs. This is acceptable.

Recommendation 5

The discussion concerning the need for ongoing Australian specific surveillance of resistance development is detailed below and remains an outstanding recommendation.

Recommendation 7

The sponsor agrees with the TGA that the specified ongoing safety concerns would not appear to warrant additional risk minimisation activities.

Recommendation 8

The sponsor has provided an updated ASA in which the proposed wording for the Australian PI is compared to the SmPC for ongoing safety concerns. The sponsor claims that although the proposed text is not identical, the meanings are the same in each document. This is acceptable.

Conclusions and recommendation

In summary the sponsor adequately addressed all OPR recommendations, except as follows:

- It was noted that the sponsor had provided the supporting document: *'Risk Assessment of Microbial Resistance* [for] *Altargo (retapamulin)'* in support of this application. In laboratory serial passage and spontaneous rate-of-mutation studies, and in the Phase III clinical studies, the sponsor claims the main skin pathogens *S. aureus* and *S. pyogenes* have demonstrated a low propensity for development of resistance against retapamulin. This suggests that emergence of isolates with reduced susceptibility to retapamulin is likely to be slow in actual clinical use. The sponsor concludes that no further action is required and the ASA states no Australia specific surveillance will be conducted.

  It is recommended to the Delegate that this matter be raised with the ACPM and that their expert opinion be considered as to whether ongoing Australian specific surveillance of resistance development is required if the medicine is approved for registration.

If this application is approved without the need for ongoing Australian specific surveillance of resistance development the following specific conditions of registration should be applied:

- The EU-RMP Version: 03 dated 4 April 2012 with ASA Version: 2.0 dated 18 January 2013, to be revised as specified in the sponsor's correspondence dated 19 February 2013 with an amended nonclinical safety specification as agreed with the TGA, must be implemented.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

In this application, the sponsor seeks the registration of a topical retapamulin ointment, Altargo 1% w/w. The proposed indications are as follows:

> *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*

The in vitro susceptibility to antibiotics varies geographically and with time; the local situation must always be considered when selecting antibiotic therapy.

In the EU, retapamulin (Altargo) was approved in 2007 for the short term treatment of superficial skin infections (including impetigo, infected small lacerations, abrasions, or sutured wounds) in adults, adolescents, infants and children (aged from 9 months), but not for treating abscesses and any infection due to MRSA. The SID indication was not approved.

In Canada, retapamulin (Altargo) was approved by the Health Canada in 2008 for use in adults and paediatric patients 9 months and older for topical treatment of primary impetigo and secondary infected traumatic lesions (small lacerations, abrasions, or sutured wounds) due to *S. aureus* (methicillin-susceptible isolates only) or *S. pyogenes*.

In the US, retapamulin (Altabax) was approved by the FDA in 2007 for topical treatment of impetigo (up to 100 cm^2 in total area in adults or 2% of total body surface area in paediatric patients aged 9 months or older) due to *S. aureus* (methicillin-susceptible isolates only) or *S. pyogenes,* in adults and paediatric patients 9 months and older. Separate applications for SITL and SID indications were submitted to the FDA in 2005. For these two indications, FDA issued "not approvable" letters in 2006 and 2007 respectively. Additional data was requested by FDA to support the SITL indication. For the SID application, the FDA advised that the data did not establish that Altabax was non-inferior to cephalexin.

Quality

The application and the supporting data relating to the composition, development, manufacture, quality control and stability of the product have been assessed and checked for compliance, as applicable, with Australian legislation and requirements for new medicines and in accordance with pharmacopoeial standards and the technical guidelines adopted by the TGA.

The product is non-sterile but is proposed for use on small skin lesions. Limits for four impurities that exceed the relevant ICH qualification threshold have been referred to the Toxicology section for assessment. The sponsor was requested to include tests and limits in the drug substance specification for three potential genotoxic impurities. The finished product specifications include impurity limits within the relevant ICH Q3B thresholds.

The ointment failed specification limits under accelerated conditions (40°C/75% RH) due to the low melting point of the paraffin. However, satisfactory data generated at 30°C/65% RH and 25°C/60 RH support the claimed shelf-life of 24 months below 25°C.

No bioavailability data have been evaluated as the product is a topical ointment. Adequate data was provided to show that the polymorphic form and particle size of the dispersed drug substance in the ointment does not change over 24 months. *In vitro* release rate testing data of stability batches and Phase I and Phase III clinical trial batches support the proposed drug substance particle size limits.

In relation to impurity limits, the toxicology evaluator commented that the daily intake of these impurities at the maximum recommended human dose of 10 mg is at or below the allowable daily intake for genotoxic impurities of 60 µg/day and therefore below the threshold of toxicological concern. None of these impurities requires toxicological qualification.

The submission was considered by the PSC of the ACPM at its 149th meeting on 21 January 2013. The subcommittee endorsed the issues raised by the TGA. All issues have been satisfactorily resolved by the company.

There are no objections to the registration of retapamulin 1% w/w ointment from a pharmaceutical chemistry perspective.

Nonclinical

Retapamulin was shown to be active *in vitro* against Gram-positive bacteria including *S. aureus* and *S. pyogenes*, with respective MIC_{90} values ranging from 0.06-0.5 µg/mL and ≤0.016-0.06 µg/mL. Retapamulin 1% ointment was efficacious against *S. aureus* and *S. pyogenes* in a mouse surgical wound infection model. Other animal models of infection, such as dermatoses, were not tested.

Secondary pharmacodynamic studies revealed that retapamulin inhibits the muscarinic M1 receptor *in vitro* with an IC_{50} of approximately 3-fold the maximum plasma retapamulin concentration measured in clinical studies, however safety pharmacology studies at high estimated systemic exposures did not indicate an *in vivo* effect.

Single and repeat-dose dermal toxicity studies up to 3 months duration in rabbits with retapamulin 0.5%, 1%, 2% and 5% ointment showed a concentration-dependent, minimal to moderate irritation that was similar to vehicle on semi-occluded intact skin (0.5% and 1% concentrations) and more severe on abraded skin. The ointment alone elicited very slight to well defined erythema in intact skin. Animals were treated only once daily in all the dermal studies, in contrast to the proposed twice daily clinical regimen.

Systemic exposure ratios in dermal studies were inadequate (<1), hence systemic toxicity was also investigated in oral studies in rats and monkeys. Adequate exposure multiples were attained in these species, although treatment was once daily and for only 2 weeks (4 weeks is recommended to support the 5 day clinical regimen). The studies indicated that systemic toxicity is unlikely at the very low clinical exposure levels.

Paediatric use was supported by dermal toxicity studies which showed minimal irritancy of intact skin in neonatal rats and no skin irritancy in small numbers of juvenile minipigs. Systemic toxicity was not evident in either species, but systemic exposure ratios were inadequate (<1). Dermal toxicity was not studied in adult rats for comparison.

There was no study of eye irritancy.

Reproductive toxicity studies were conducted by the oral route in rats and the IV route in rabbits; systemic exposure ratios were adequate. Decreased fetal growth and incomplete ossification were observed in rats. The proposed use in pregnancy category of B3 is acceptable.

Taking into consideration the above limitations of the nonclinical data, there are no overall objections to registration of retapamulin for the proposed indications. The evaluator recommends a number of amendments to the draft PI.[19]

Clinical

Pharmacokinetics

Three strengths of retapamulin (0.5%, 1.0%, and 2.0% w/w) were assessed in the Phase I studies. The 1.0% w/w ointment was used in Phase II-IV clinical studies. The commercial formulation is identical to the 1% w/w formulation used in the clinical studies.

The PK of retapamulin ointment was analysed in Phase I Studies 025, 026, and 027, Phase II Study 029, Phase III Studies 030A and 030B, and Phase IV paediatric Study TOC106489.

[19] Details of these are beyond the scope of the AusPAR.

Overall, there were a limited number of measurable concentrations in adult and paediatric subjects. There is either minimal or no systemic exposures following repeat application of 1% retapamulin ointment BD to wound surface areas up to 100 cm^2 in subjects with SITL, SID, impetigo, or other uncomplicated bacterial skin infections (Study 029, Study 030A, Study 030B, and Study TOC106489). The systemic exposure to retapamulin in the majority of subjects with measurable concentrations following repeat applications of 1% retapamulin ointment was ≤2.5 ng/mL.

The PK results from Study 026 suggested that surface area was a more important determinant of systemic retapamulin exposure than the concentration of the ointment. The highest exposures observed with retapamulin 1% applied to abraded skin in Study 026 (highest C_{max} 22.1 ng/mL and $AUC_{(0\text{-}24\ h)}$ 238 ng·h/mL) were still below the steady state C_{max} (124 ng/mL) and AUC(739 ng·h/mL) at the NOAEL for oral administration in monkeys (50 mg/kg/day).

There is limited PK data available in subjects with impetigo or SID. However, the 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.

Study TOC101825 evaluated the PK of 1% retapamulin, applied to abraded skin, with and without oral ketoconazole, a potent inhibitor of CYP3A4 and the P-gp transporter. Ketoconazole increased the retapamulin $AUC_{(0\text{-}24\ h)}$ and C_{max} by about 80%. Due to the minimal systemic exposure, the magnitude of the increase is unlikely to increase the incidence of AEs or to require retapamulin dosage adjustments when it is co-administered with oral CYP3A4/Pgp inhibitors (Study TOC101825, Study 029, Study 030A and Study 030B).

Systemic exposure following 1% retapamulin (200 mg BD) applied to the anterior nares of healthy subjects colonized with *S. aureus* was evaluated in Study ALB110247. The highest $AUC_{(0\text{-}t)}$ and C_{max} in this study was 24.1 ng·h/mL and 2.74 ng/mL, respectively.

Due to the very low systemic exposures, the elimination half-life following retapamulin ointment could not be determined in Study 026 or Study TOC101825. Tissue distribution and elimination of retapamulin has not been investigated in humans. No PK data are available in patients with renal or hepatic impairment.

The Phase IV study (TOC106489) assessed the retapamulin exposure in children ≤2 years of age: 46% of PK samples had measurable retapamulin levels (range 0.52-177.3 ng/ml) and 75% of which were <5.0 ng/mL. Measurable concentrations were more common in younger subjects, with a minority of subjects having retapamulin concentrations above that previously recorded in paediatric subjects (18.5 ng/mL). Relative wound size and subsequent treatment may have affected systemic exposure to retapamulin.

Pharmacodynamics

Retapamulin ointment was shown to be well-tolerated (Study 025, 026, 027, and TOC101825). The studies examining local irritation, sensitisation and effects on QTc interval indicated that these were not likely to be issues, even when retapamulin ointment is used in combination with CYP3A4 inhibitors. On intact and abraded skin, 1% retapamulin ointment was not a primary or cumulative irritant after daily 24 h application for 2 days and 21/14 days (Study 025). Only 1 of 206 subjects in Study 027 demonstrated sensitisation upon challenge and re-challenge to retapamulin ointment, 1% and 2%. In post-hoc analyses of ECGs from healthy adults from studies 026 and TOC101825 (N=103), no significant effects on QT/QTc interval were observed after topical use of retapamulin on intact and abraded skin.

Due to low systemic exposure to retapamulin, it is considered that QTc interval prolongation is unlikely to occur in the patient population treated with retapamulin ointment with or without co-administration of CYP3A4 or Pgp inhibitors.

The global surveillance study assessed the *in vitro* retapamulin MIC_{50} and MIC_{90} against 975 global isolates of coagulase-negative staphylococci (CoNS). Retapamulin demonstrated excellent activity against isolates of CoNS, *S. agalactiae* and viridans streptococci. All isolates of CoNS were inhibited by ≤ 0.5 µg/mL of retapamulin. The MIC_{50} and MIC_{90} for retapamulin were 0.06 and 0.25 µg/mL, respectively, against the 930 isolates 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% internationally. 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 MIC_{50} and MIC_{90} of 0.06 and 0.12 µg/mL, respectively, and was the most active compound tested.

Overall, retapamulin demonstrated good *in vitro* activity against gram-positive bacteria commonly associated with skin infections and a low propensity for development of resistance *in vitro*.

Results from Phase I studies indicated that the 1% formulation was the maximal tolerated concentration when used under proposed conditions. The BD dosing was proposed based on studies conducted in animal models. The 1% formulation BD regimen was selected for use in Phase III studies.

Antibiotics resistance risk assessment

Australian studies of susceptibility assessment

A number of studies were conducted to assess the *in vitro* susceptibility of clinical isolates of staphylococci, *S. pyogenes*, and *P. acnes* from within Australia. The first study assessed current retapamulin *in vitro* activity and spectrum against 1,166 *S.aureus*, 23 CoNS and 111 *S. pyogenes* clinical isolates recovered from hospitalised 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 ($MIC_{50/90}$ = 0.06/0.12 mg/L), regardless of susceptibility to oxacillin or mupirocin, and inhibited all strains at ≤ 0.25 mg/L, except for 2 strains with reproducible MIC values of 2 mg/L.

Minimum inhibitory concentration results against CoNS ($MIC_{50/90}$ =0.06/0.05 mg/L) strains were equivalent to those obtained against *S. aureus* ($MIC_{50/90}$, 0.06/0.12 mg/L). Higher MIC_{90} values were observed against CoNS due to a small sample size (23 isolates) and detection of 3 isolates with non-wild type MIC results (0.5 to 32 mg/L). Retapamulin demonstrated very good $MIC_{50/90}$ (≤ 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 7 comparative agents against 107 *P. 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.

Overall, in studying 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 retapamulin. 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 characterised for 9 isolates.

The development of resistance to retapamulin appears to be low based on the available information.

EAGAR importance rating

Under the definitions described for the Expert Advisory Group on Antimicrobial Resistance (EAGAR) Importance Rating[20], the significance of Altargo, considered by itself, would be categorised as 'Low'. The rationale for this is that currently existing products, including topical Bactroban (mupirocin) and Fucidin (fusidic acid), are available for use in the treatment of uncomplicated skin infections toward which Altargo is targeted. In addition, a number of oral antibiotics retain activity against many of the causative pathogens responsible for impetigo and SITL.

The unmet medical need and the role that Altargo should fulfil are in the treatment of uncomplicated skin infections due to retapamulin-susceptible infections where the physician would prefer to prescribe a potent topical antibiotic when there is an expectation or confirmation that the pathogen is resistant to the other commonly utilised therapeutics. This selection likely would be driven by the physician's experience with local treatment failure rates and epidemiology resistance data, where available. In addition, selection of Altargo would be preferable for therapy in patients with demonstrated allergy/hypersensitivity to other antibiotic classes or in instances where reported AEs for other classes would limit their implementation.

Clinical efficacy

A total of 7 Phase III studies were submitted to support the proposed indications. There were two studies for impetigo (Studies 100224 and 103469), one study for SID (Study 032), and two identically designed studies for SITL (Studies 030A and 030B). In addition, there was one placebo-controlled study (Study TOC110977) for SITL and one active-comparator study (Study TOC110978) for SITL and impetigo due to MRSA. All 7 studies enrolled both adult and paediatric subjects and randomisation was in 2:1 ratio (retapamulin: placebo or active comparator). In each study the primary objective was to compare the efficacy and safety of topical retapamulin with active or placebo treatments (as appropriate) for the indications under study. Four analysis populations were defined as follows:

- Intent to Treat Clinical (ITTC): All randomised and treated (at least one dose).
- Intent to Treat Bacteriology (ITTB): All ITTC patients with a baseline pathogen isolated from the primary lesion and sent to the central laboratory.
- Per Protocol Clinical (PPC): ITTC patients who did not violate the protocol.

[20] According to the sponsor's *Risk Assessment of Microbial Resistance* document, these ratings are defined as:
High: These are essential antibiotics for treatment of human infections where there are few or no alternatives for many infections. Also they have been called "critical", "last resort" or "last line" antibiotics.
Medium: There are other alternatives available but less than for those classified as
Low: There are a reasonable number of alternative agents in different classes available to treat most infections even if antibiotic resistance develops.

· Per Protocol Bacteriology (PPB): ITTB patients who did not violate the protocol.

In all studies the primary efficacy endpoint was the clinical response (success or failure).

The primary efficacy populations were: PPC for Studies 100224, 030A, 030B and 032; ITTC for Study 103469, and ITTC Primary Analysis for Study 110977; and Per-Protocol MRSA (PPMRSA) for Study 110978.

Impetigo

One placebo-controlled study (Study 103469) and one active-comparator study (Study 100224) were submitted to support the impetigo indication. For both studies, the eligible subjects were adults and children (≥ 9 months) with 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 Skin Infection Rating Scale (SIRS) score of at least 8.

Study TOC 103469 was a randomised, double-blind, multicentre, superiority study that compared retapamulin with placebo. A conclusion of superior efficacy for retapamulin was to be drawn if the lower limit of the 95% CI for the treatment difference in the ITTC population was greater than zero.

The primary efficacy endpoint was the clinical response (clinical success) at the End of Therapy (EoT, Day 7) in the ITTC population. The secondary efficacy endpoints included clinical response and microbiological response at EoT and at Follow-Up (FU) visit (Day 14). Overall, 210 subjects enrolled and took at least one dose of study medication. Of these, 139 subjects were in the retapamulin group and 71 were in the placebo group; these formed the ITTC population. A total of 175/210 (83.3%) subjects were paediatric (<18 years). The majority of subjects had the non-bullous form of impetigo.

In the ITTC population, a clinical success was achieved in 85.6% of subjects in the retapamulin group, compared to 52.1% in the placebo group at EoT. The lower limit of the 95% CI for the difference was greater than zero, indicating superiority of retapamulin over placebo. Superiority was also achieved in all the analysis populations.

Table 15. Clinical success at the End of Therapy (Study TOC 103469)

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)

In terms of other efficacy outcomes, the clinical success at FU visit was superior in the retapamulin group compared with the placebo group in all four analysis populations. The microbiological response rate was higher for retapamulin at both the EoT and FU visits in comparison to placebo.

The majority of subjects had one or more pathogens identified at baseline. *S. aureus* was the most frequently isolated pathogen. 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 groups, although slightly more *S. pyogenes* were isolated in the retapamulin 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 was 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 groups.

Study TOC100224 was a randomised, observer-blind, multicentre, non-inferiority study. The study compared retapamulin 1% ointment (BD for 5 days) with topical 2% sodium fusidate ointment three times daily (TID) for 7 days. A conclusion of non-inferior efficacy was to be drawn if the lower limit of the 95% CI for the difference was greater than or equal to –10%. The primary efficacy endpoint was the clinical response at EoT in the PPC population. The study enrolled 519 patients. The ITTC population consisted of 517 subjects (345 in the retapamulin group and 172 in the sodium fusidate group). The PPC population accounted for 87% of the ITTC population.

Nearly 80% of patients had non-bullous impetigo. The two groups were balanced with respect to gender, race and ethnicity. Overall, 69.4% were paediatric subjects (<18 years). The majority of subjects had one or more pathogen identified at baseline.

Retapamulin was shown to be non-inferior to sodium fusidate, based on the clinical response at EoT in the PPC population. The lower limit of the 95% CI for the difference was greater than the non-inferiority margin of -10% (1.1 to 9.0). It is also noted that in the PPC, PPB and ITTB populations, the lower limit of the 95% CI for the difference was greater than zero.

Table 16. Clinical response at EOT (Study TOC 100224)

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)

The results of the secondary efficacy results are discussed in detail in the CER (see Attachment 2 of this AusPAR). *S. aureus* was the most frequently isolated pathogen. 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 was 0.12, 0.12 and 0.03-0.25 µg/mL, respectively, indicating excellent *in vitro* activity against *S. aureus* isolates recovered from subjects at baseline. In general, all of the MIC values were similar between the two treatment groups.

Secondarily infected traumatic lesion (SITL)

Four studies were submitted to support the SITL indication. Studies 030A and 030B were conducted in adults and paediatric subjects older than 9 months, and Studies TOC110977 and TOC110978 were conducted in adults and paediatric subjects older than 2 months of age. For SITL, it is required that the lesions should be a small laceration, sutured wound or abrasion with the infected portion not exceeding 10 cm in length and surrounding erythema not extending more than 2 cm from the edge of the lesion. Abrasions were not to exceed 100 cm^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.

Studies 030A and 030B were two randomised, double-blind, double-dummy, multi-centre, non-inferiority studies. The two studies were identical in design. The non-inferiority margin was pre-defined as 10%. These studies compared the efficacy and safety of topical retapamulin and oral cephalexin. Samples for PK analysis were 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.

Study 030A: a total of 996 patients enrolled, of which 988 made up the ITTC population (662 subjects in retapamulin group and 326 subjects in cephalexin group). The two groups were balanced with respect to age, gender, race and distribution of wound sites. There were 164 paediatric subjects (<18 years old). The PPC population consisted of 83.6% of the ITTC population. Most of the patients had secondarily infected open wounds (SIOW) while the remainder had simple abscesses. The primary efficacy endpoint was clinical

response at FU visit (7-9 days post-therapy) in the PPC population. Clinical success was achieved in 88.7% of the retapamulin group compared to 91.9% of the cephalexin group (see the table below). Non-inferiority of retapamulin versus cephalexin was demonstrated as the lower limit of the 95% CI for the treatment difference was greater than -10%, with the upper limit crossing zero. Success rates were comparable between the two groups for the ITTC and ITTB populations.

Table 17. Clinical Response at Follow-Up visit (Study 030A)

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)

For subjects with any pathogen isolated from a wound sample at baseline, the microbiological success rate at follow-up was similar between the treatment groups for the PPB population. For *S. aureus* and *S. pyogenes* isolated from subjects in the PPB population, the microbiological success rates at follow-up were comparable between groups. For MRSA isolates from these subjects, the microbiological success rates were lower for the retapamulin group (72.0%) compared to cephalexin group (81.8%).

Study 030B: a total of 922 patients enrolled, of which 916 made up of the ITTC population (606 in Retapamulin group and 310 in cephalexin group). The PPC population consisted of 83.6% of the ITTC population. The two groups were balanced with respect to age, gender, race, and ethnicity. There were 77 paediatric subjects (8.4%). Most patients had SIOW rather than simple abscesses. The primary efficacy endpoint was clinical response at FU visit in the PPC population. Clinical success was achieved by 90.4% at for the retapamulin group compared to 92.0% in the cephalexin group in the PPC population. The non-inferiority of retapamulin versus cephalexin was demonstrated, as the lower limit of the CI for the treatment difference was greater than -10%.

Table 18. Clinical response at the Follow-Up visit (Study 030B)

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)

For subjects with *S. aureus* or *S. pyogenes* isolated from a wound sample at baseline, the success rates at follow-up were generally similar between the treatment groups. The efficacy rates against MRSA were lower at follow-up for the retapamulin group (65.4%) compared to the cephalexin group (93.3%).

Study TOC110977 was a randomised, prospective, multicentre, double-blind, placebo-controlled superiority study. The study compared retapamulin ointment with placebo ointment, both applied BD for 5 days. This study was required by the FDA as the primary basis of approval for SITL indication. Studies 030A and 030B were deemed by the FDA to have insufficient evidence for the approval of the SITL indication. Study TOC110977 was also intended to estimate the treatment effect to justify the non-inferiority margins used in Studies 030A and 030B, but changes to the outcome definitions in Amendment No. 1 precluded this. The study protocol was amended twice. 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 electronic case report form (eCRF). Both amendments required

adaptations to the Reporting and Analysis Plan (RAP) which were incorporated and finalised before the final Database Freeze.

Table 19. Analysis population in Study TOC110977

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

The first analysis population (subjects from A+C) using the new definition of clinical response in the protocol amendments was designated as the primary efficacy analysis population. A total of 507 subjects made up of the ITTC population (Groups A+B+C+D) which included 343 subjects in the retapamulin group and 165 subjects in the placebo group. The ITTC Primary Efficacy Population (Groups A+C) consisted of a total of 359 subjects.

The primary efficacy endpoint was the clinical response (success or failure) in the ITTC Primary Efficacy Population (Groups A+C) at the FU visit. A status of 'unable to determine' was assigned due to a subject's failure to attend the FU visit and in such a case, the subject was categorised as a clinical failure.

In the primary efficacy population, the clinical success for retapamulin (74.8%) was higher than for placebo (66.4%), however, the difference (8.4%) was not statistically significant (95% CI included zero). In the ITTB population, the clinical success in the retapamulin group (76.4%) was also higher than for the placebo group (64.3%). The difference (12.1%) and the corresponding 95% CI (0.6, 23.6) suggested that retapamulin has a statistically significant benefit in the treatment of bacteriologically confirmed SITL patients. The treatment difference of 8.1% at FU visit for all subjects enrolled (Groups A+B+C+D) was similar to that seen in the ITTC primary efficacy population (Groups A+C).

Table 20. Clinical response at Follow-up, by Analysis Population

	Retapamulin		Placebo		Diff. in	95% CI [1] (%)
Analysis Population	n / N	Success Rate (%)	n / N	Success Rate (%)	Success Rates (%)	
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, retapamulin treatment was found to be superior to placebo treatment (p = 0.0336), with an odds ratio estimate of 1.73 and 95% CI of (1.04, 2.87).

Study TOC110978 was a randomised, double-blind, double dummy, multicentre, comparative study. The primary objective was to evaluate the clinical and bacteriological efficacy of retapamulin versus oral linezolid in the treatment of SITL or impetigo due to MRSA. Retapamulin was applied BD for 5 days while linezolid was dosed either BD or TID for 10 days depending on subject age. The On-therapy, EoT, and FU visits were therefore staggered due to the difference in duration of the treatment regimens. Subjects could be enrolled as follows: those who had a SITL (excluding abscesses) 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 localised 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.

The primary efficacy endpoint was the clinical response at FU visit in subjects with MRSA as the baseline pathogen (PPMRSA population). There were many secondary endpoints as listed in the CER (see AusPAR Attachment 2). The ITT-MRSA population was the Intent to Treat MRSA population which include all randomised subjects who took at least one dose of study medicine. PPMRSA is the Per Protocol MRSA population which included subjects from the ITTMRSA population who adhered to the protocol (did not violate the protocol).

A total of 410 subjects were enrolled, 267 received at least 1 dose of retapamulin and 137 received at least 1 dose of linezolid. Of these subjects, 234 retapamulin-treated subjects and 122 linezolid-treated subjects completed the study. The primary endpoint is measured for the PPMRSA analysis set, for which an approximately equivalent proportion of subjects in both groups were included at the FU visit. Overall, the demographic characteristics were similar between groups. The majority of isolates were *S. aureus*. In the linezolid group, 40% of isolates were MRSA and 31% were MSSA. In the retapamulin group 36% were MRSA and 38% were MSSA. Approximately 10% of isolates were *S. pyogenes*, approximately 13% of isolates were Gram-negative pathogens. The table below summarises the results for the primary comparison of interest.

Table 21. Clinical success at Follow-up in subjects with baseline MRSA Study TOC110978

	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%)

For subjects in the PPMRSA population, the success rate in the retapamulin group (63.9%) was significantly different from the linezolid group (90.6%). The results suggest that topical retapamulin is an inferior treatment compared to oral linezolid. Clinical success rate at FU by baseline pathogen indicates that the linezolid group had approximately 30% greater success rate than 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-treated subjects.

Secondarily infected dermatoses (SID)

Study 032 was a randomised, double-blind, double-dummy, multicentre, non-inferiority study. The study compared the efficacy and safety of topical retapamulin (BD for 5 days) with oral cephalexin (500 mg in adults or 12.5 mg/kg in children, BD for 10 days) for SID treatment. The claim of non-inferiority was achieved if the lower limit of the 95% CI was greater than -10%. The study subjects were adults and children (≥ 9 months) with a diagnosis of atopic dermatitis, psoriasis or allergic contact dermatitis that had a secondary bacterial infection. A total of 546 subjects were randomised (363 to retapamulin and 183 to cephalexin) and 496 subjects completed the study. There were 124 paediatric subjects. A representative number of subjects were enrolled in each of the 3 paediatric age strata. Most were enrolled in the 9 months to <6 years stratum, as this age group has relatively high rates of atopic dermatitis. The majority of subjects had one or more pathogen at baseline, most had a single pathogen isolated. The primary efficacy endpoint was the clinical response at FU visit in the PPC population. Patients with an outcome of Unable to determine (UTD) at EoT or at FU visit were counted as failures.

The clinical success at FU visit was 85.9% in the retapamulin group and 89.7% in the cephalexin group. The lower CI for the treatment difference was just within -10% and retapamulin was therefore considered to be non-inferior to cephalexin. In other patient populations (Table 22 below), retapamulin gave consistently lower clinical success rates

than cephalexin and the lower 95% CI were between -9.7 and -13.9. The results in the ITTC population were supportive of the results in the PPC population. The magnitude of the differences in clinical success rates was greater for the ITTB and PPB populations. However, this study was not powered to assess non-inferiority in these populations.

Table 22. Clinical response at Follow-Up by analysis population (Study 032)

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)

The clinical success rates at EoT for subjects in retapamulin group were similar to subjects in the cephalexin group. Although the study was not designed to show non-inferiority for secondary endpoints, the efficacy of retapamulin was suggested to be non-inferior to cephalexin (Table 23).

Table 23. Clinical success rate at EOT (Study 032)

Analysis Population	SB-275833		Cephalexin		Difference in Success Rates (%)	95% CI[2] (%)
	n/N[1]	Success Rate (%)	n/N[1]	Success Rate (%)		
PPC	312/339	92.0	152/162	93.8	-1.8	(-6.5, 2.9)
PPB	182/199	91.5	95/101	94.1	-2.6	(-8.6, 3.4)

Of the 27 (8.0%) PPC subjects in the retapamulin group who were assigned a clinical failure at EoT, 15 subjects had an outcome of UTD due to missing the scheduled EoT visit and the remaining 12 subjects had a clinical failure assigned by the investigator. In the cephalexin group, 10 (6.2%) subjects were assigned a clinical failure, of which 2 subjects had an UTD outcome due to missing the scheduled visit. If subjects with UTD outcome (and who did not withdraw) were removed from the PPC population, the success rate for retapamulin at EoT would change from 92.0% (Table 23) to 96.0%, and would remain unchanged for cephalexin (success rate of 93.8%). Hence, a greater percentage of subjects would have been considered as clinical successes for retapamulin at EoT. Similar results were seen at FU, with clinical success of 89.9% for retapamulin and 89.7% for cephalexin. The resulting CI for the difference in clinical success rate at FU would be (-5.7%, 6.0%), compared to (-9.9%, 2.3%) in Table 22.

Clinical Safety

In the integrated safety analysis set, one or more AEs were reported in 20% of subjects in the retapamulin 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 than the retapamulin group experienced the systemic AEs of diarrhoea and nausea considered to be related to study treatment. 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 serious AEs (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 1 subject in the cephalexin group; all other SAEs were each reported in no more than 1 subject. Five deaths occurred in the studies. None of these was 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 interval 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 7-9 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 systemic 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.

Recommendation from the clinical evaluator

The clinical evaluator considers that the benefit-risk balance of topical retapamulin, given the proposed usage, is favourable. The evaluator recommends approval pending amendments to the PI and suggested the indication should be amended to the followings:

> *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.***

The evaluator also recommends that the first and second points in the *Precautions* section of the PI 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.

Risk management plan

The sponsor initially submitted EU-RMP Version 03 (dated 4 April 2012) and then later submitted an updated ASA Version 2.0 (dated 18 January 2013). The evaluator states that

the sponsor has adequately addressed most of the OPR recommendations with only one outstanding issue being: there is no current global susceptibility surveillance for retapamulin and there is no plan to initiate surveillance studies in Australia. The sponsor states that the post-marketing European surveillance study demonstrated excellent *in vitro* activity of retapamulin against the tested isolates of *S. aureus* and *S. pyogenes*, with MIC_{90} values of 0.12-0.25 and 0.06 µg/mL, respectively, regardless of phenotype or country (Study UD2009/00186/00 completed in 2010).

The RMP evaluator recommends that ACPM expert opinion be sought as to whether post-marketing, Australian specific microbiological surveillance is required if Altargo is approved for registration.

Risk-benefit analysis

Delegate's considerations

For the treatment of impetigo, retapamulin was shown to be superior to placebo for the primary endpoint of clinical success rate (85% versus 52%) in StudyTOC103469, and was non-inferior to topical sodium fusidate (94% versus 91%) in Study TOC100224.

For the treatment of SITL, in Studies 30A and 30B, non-inferior efficacy of retapamulin compared to oral cephalexin was shown with the pre-defined 10% margin. The 10% margin was questioned by the FDA. The available information from the European Public Assessment Report (EPAR) for retapamulin indicated that the pooled analysis of Studies 30A and 30B showed that the clinical success rate at FU visit was 89.5% for retapamulin and 91.9% for cephalexin and the 95% CI was -5.4 to 0.5. For SIOW, the 95% CI around the treatment difference (-2.2%) was -5.4% to 1.0%, while for simple abscesses, the 95% CI around the difference (-4.2%) was -12.8% to 4.4%. For the two studies combined, 86% of subjects had SIOW and 14% had abscess. A higher proportion of the abscesses were associated with *S. aureus* and, specifically, with MRSA infections than seen with SIOW. The CHMP is of the view that while these studies were not stratified by diagnosis and were not powered to provide reliable comparisons between treatments within each diagnostic category, there appeared to be some problem for retapamulin in treating abscesses. Based on these analyses, retapamulin has not been approved by EMA for treating abscesses and any infection due to MRSA.

In Study TOC110977, retapamulin was not shown to be superior to placebo in the primary efficacy analysis. Clinical success rates in the retapamulin group were slightly higher (and reached significance) in other analysis (those where clinical improvement was counted as success or bacteriological cure was assessed). When a logistic regression analysis was used to adjust for the differences in baseline wound characteristics for the primary endpoint, retapamulin was found to be superior to placebo (p=0.0336), with an odds ratio estimate of 1.73 (95% CI: 1.04 to 2.87). In the ITTB group, clinical cure was statistically higher in the retapamulin group. It was also higher for retapamulin in the group with MRSA.

In Study TOC110978, topical retapamulin was shown to be an inferior treatment compared to oral linezolid (an antibiotic effective for MRSA) in subjects with SITL or impetigo secondarily infected with MRSA.

For the treatment of SID, Study 032 compared topical retapamulin with oral cephalexin. The study showed that retapamulin was non-inferior to cephalexin in the primary efficacy analysis. The treatment difference was -3.8 (95% CI: -9.9 -2.3). The available information from the EPAR indicated that the overall and sub-group treatment differences were smaller after removal of UTD patients. In other words, if the patients who were UTD at EoT and so declared as failures at FU visit were removed from analysis, the difference in

success rates between the two groups would become smaller. These two types of analyses showed inconsistent results. According to the EPAR, the CHMP is of the opinion that the reason for this inconsistency seemed to be the imbalance between the two groups in numbers and percentages of subjects who had an outcome of UTD at EoT that defaulted to failure at FU visit. In view of the unexplained imbalance and the discrepancy between analyses, the SID indication has not been granted by the EMA.

Proposed action

Pending the advice from the ACPM, the Delegate proposed to approve the registration of Altargo ointment containing 1% retapamulin for:

> *the treatment of superficial skin infections (including impetigo, infected small lacerations, abrasions, or sutured wounds) in adults, adolescents, infants and children aged from 9 months, in the absence of abscesses formation and infection due to MRSA.*
>
> *The in vitro susceptibility to antibiotics varies geographically and with time; the local situation must always be considered when selecting antibiotic therapy.*

The Delegate considered that the Indications should specify patient age groups and refer to the maximum treatment areas. In the *Precautions* section of the PI, the first and second 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.

The decision relating to the SID indication and the requirement for an Australia specific microbiological surveillance program would be made following the advice of the ACPM.

Implementation of the RMP agreed with the TGA and its subsequent updates would be a condition of registration if this product is approved.

Details of the Delegate's proposed revisions to the PI other than those stated above are beyond the scope of the AusPAR.

Request for ACPM advice

The Delegate proposed to seek general advice on this application from the ACPM and to request discussion of the following specific issues:

With regards to the SITL indication:

- Is the ACPM of the view that the submitted 4 studies for SITL indication provided sufficient evidence to support the use of retapamulin 1% ointment for the treatment of SITL?
- Does the ACPM have any concerns about the 10% non-inferiority margin used in Study 030A and 030B in relation to the SITL treatment?
- Does ACPM have any concern about the results of Study TOC110977 in which topical retapamulin was not shown to be superior to placebo in the primary efficacy analysis?
- Does ACPM consider that retapamulin should not be used to treat abscess and SITL infections due to MRSA?

With regards to the SID indication

- Does ACPM consider that the data from Study 032 provide sufficient evidence to support the use of retapamulin ointment for the treatment of SID? Does ACPM have any concerns about the unexplained imbalance and the discrepancy between analyses observed in Study 032?

With regards to the requirement for post-marketing Australia specific microbiological surveillance program

Sponsors of new antibiotics (for PO and IV administration) have been required to conduct post-marketing Australia specific microbiological surveillance to monitor the resistance development to antibiotics. What is the view of the ACPM with regards to the requirement of the Australia specific microbiological surveillance program for topical retapamulin ointment?

Response from sponsor

Executive summary

GlaxoSmithKline Australia Pty Ltd (GSK) submitted an application for Altargo for the indication of *"topical treatment of the following bacterial skin and skin structure infections (SSSI); primary impetigo, secondarily infected traumatic lesions (SITL) (e.g. small lacerations, abrasions, sutured wounds), and secondarily infected dermatoses (SID) including infected psoriasis, infected atopic dermatitis and infected contact dermatitis"*, in adults, children, and infants aged 9 months and older.

However, the Delegate has recommended approval of a restricted indication of *"treatment of superficial infections (including impetigo, infected small lacerations, abrasions, or sutured wounds) in adults, adolescents, infants and children aged from 9 months, in the absence of abscesses formation and infection due to MRSA"*. The Delegate seeks advice from the ACPM in relation to the proposed SITL and SID indications and the need for an Australian microbiological surveillance study. Of note, the Delegate has not raised any safety concerns.

SITL indication: The efficacy of Altargo has been established in three SITL studies and further supported by data from a MRSA study.

SID indication: The data from the single pivotal study fully supports the approval of Altargo for use in the treatment of SID as the study showed that retapamulin was non-inferior to cephalexin in the primary efficacy analysis.

Australian specific microbiological surveillance study: GSK does not believe that an Australian specific microbiological surveillance program is warranted, as *in vitro* susceptibility data in Australian isolates suggest that the likelihood of development of resistance to retapamulin is low.

Response to issues raised by the TGA Delegate for ACPM advice

- **SITL indication**

Delegate comment: Is the ACPM of the view that the submitted 4 studies for SITL indication provided sufficient evidence to support the use of retapamulin 1% ointment for the treatment of SITL?

GSK does not agree with the Delegate's evaluation of the clinical efficacy data relating to a more restricted SITL indication. The Delegate did not raise any concerns in relation to the safety profile of topical retapamulin for use in SITL.

The efficacy of retapamulin for the treatment of SITL was demonstrated across four clinical studies; two identical studies using oral cephalexin as a comparator (Studies 030A

and 030B), a placebo-controlled study (TOC110977), and a study using linezolid as a comparator in subjects with MRSA (TOC110978).

Studies 030A and 030B provide strong evidence that retapamulin is an effective antibacterial product for the treatment of SITL. In both studies, retapamulin treatment and the cephalexin control were similarly efficacious in the primary efficacy analyses (Per Protocol Clinical), with a success rate in Study 030A of 88.7% retapamulin versus 91.9% cephalexin (treatment difference -3.2, 95% CI: -7.4, 0.9), and in Study 030B of 90.4% retapamulin versus 92.0% cephalexin (treatment difference -1.6, 95% CI: -5.8, 2.6). In the intent-to-treat clinical (ITTC) population (all treated patients), which is the population most relevant to the future use of this product in typical practice settings, the success rate in Study 030A was 85.2% retapamulin versus 84.0% cephalexin (treatment difference 1.1, 95% CI: -3.7, 6.0), and was 87.5% retapamulin versus 87.4% cephalexin (treatment difference 0, 95% CI: -4.5, 4.6) in Study 030B. These confidence intervals convincingly include zero.

Additionally, in both Studies 030A and 030B, retapamulin and the cephalexin control were similarly efficacious in the intent-to-treat bacteriological (ITTB) population, which reflects outcomes in all patients with a laboratory-confirmed bacterial infection. The 95% CI for the difference in success rates for retapamulin minus cephalexin were (-6.5, +7.2) for Study 030A and (-3.7, +9.9) for Study 030B. Again, these confidence intervals convincingly include zero.

In Study TOC110977, the primary endpoint of superiority of retapamulin over placebo in the ITTC population was not met (that is, the difference in the clinical success rate [8.4%] at the follow-up visit was not statistically significant). The ITTC population was chosen for the primary analysis as this was a superiority study and the most conservative approach to statistical analysis was to use this 'patient-like' population. Clinical success was defined as resolution of clinically meaningful signs and symptoms of infection recorded at Baseline including a pus/exudate skin infection rating scale score of '0'. This was different from the previous SITL studies (030A and 030B), as 'improvement of signs and symptoms of the infection recorded at Baseline' was not included in the definition of clinical success.

It should be noted that a statistically significant treatment-by-country interaction effect was observed in Study TOC110977 and therefore covariate analysis was undertaken. As a result, both infection and baseline wound areas were significantly associated with the clinical response at follow up. Subsequent logistic regression analysis was undertaken that adjusted for baseline wound characteristics; the results indicate that for the primary endpoint, retapamulin was superior to placebo (p=0.0336) with an odds ratio of 1.73 and a 95% CI of (1.04, 2.87). In the ITTB population, clinical response in the retapamulin group was statistically superior to placebo (p=0.04).

In Study TOC110978, retapamulin had a significantly lower rate of clinical response than linezolid when response is defined as clinical success only (63.9% retapamulin, 90.6% linezolid). Clinical success rate was not significantly different between groups when clinical success was defined as a clinical outcome of success or improvement (91.8% retapamulin, 100% linezolid).

In summary, the totality of the data from the four studies demonstrates that topical retapamulin is an effective treatment alternative to systemic oral agents for patients with SITL.

Delegate Comment: Does the ACPM have any concern about the 10% non-inferiority margin used in Study 030A and 030B in relation to the SITL treatment?

GSK contends that the 10% non-inferiority margin used in the SITL studies is scientifically valid.

Studies 030A and 030B were prospectively designed and powered to evaluate the efficacy of retapamulin in the treatment of SITL and were designed with a 10% non-inferiority test (the claim of non-inferiority was achieved if the lower limit of the 95% CI was greater than -10%). This margin was considered appropriate due to the greater than 20% difference between the assumed efficacy rate for placebo and the active comparators, as well as the assumption that efficacy rates would be approximately 90% or lower.

In fact, the efficacy results for Studies 030A and 030B, in all the evaluated clinical populations, unequivocally show that the lower limit of the CI is greater than -10%, with the upper limit crossing zero, thereby demonstrating non-inferiority (Tables 24 and 25).

Table 24. Efficacy results at Follow-Up for Study 030A by Analysis Population

Analysis Population	Retapamulin		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)

[1] Confidence intervals are not adjusted for multiplicity
ITTB = Intent to Treat Bacteriologically evaluable, ITTC = Intent to Treat Clinical Primary Efficacy Population, PPC = Per Protocol Clinical Primary Efficacy Population, PPB = Per Protocol Bacteriologically evaluable.

Table 25. Efficacy results at Follow-Up for Study 030B by Analysis Population

Analysis Population	Retapamulin		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 are not adjusted for multiplicity

The Delegate has noted that the FDA questioned the 10% margin; however, GSK believes that use of a 10% non-inferiority margin in Studies 030A and 030B is reasonable and appropriate in view of established precedents with other anti-infective drugs that utilised either a 10% or 15% margin. At the time the studies were conducted, the 10% margin was selected based on FDA guidance in effect at the time for skin and soft tissue infections (SSTIs) and also on the EU guidances for studies in skin infection. Additionally, in pre-Phase III discussions with the FDA and special protocol assessments, the 10% non-inferiority margin was agreed to by the FDA. The 10% non-inferiority margin was the most demanding non-inferiority margin that had been applied at the time to studies of treatments for uncomplicated skin and skin structure infections.

Delegate comment: Does ACPM have any concerns about the results of Study TOC110977 in which topical retapamulin was not shown to be superior to placebo in the primary efficacy analysis?

GSK acknowledges that the primary endpoint of superiority of retapamulin over placebo on the clinical response was not met in Study TOC110977 in subjects ≥2 months of age with SITL (clinical success rate of 74.8% retapamulin compared with 66.4% placebo; treatment differences 8.4% (95% CI: -1.6, 18.4)). However, when adjusted for Baseline wound characteristics using logistic regression analysis for the primary endpoint, the retapamulin treatment was found to be superior to placebo. In addition, sensitivity analyses demonstrated that the efficacy rates observed on retapamulin were similar to those seen in previous studies (Study 030A, Study 030B) when the definition of clinical success included clinical improvement as a component of clinical success, as was done for the previous studies.

Significant retapamulin treatment benefit on the secondary efficacy endpoint of bacteriological response was clearly demonstrated. Retapamulin was statistically superior

to placebo in the ITTB population (76.4% versus 64.3%) with a 95% CI: 0.6, 23.6 and p value = 0.04.

Treatment of SITL with retapamulin was beneficial particularly in subjects with *S. aureus* as the baseline pathogen (Table 26).

Table 26. Efficacy results for Study TOC110977 (ITTC, Primary Efficacy Population)

	Retapamulin		Placebo		Difference in Success Rates (%)
Baseline Pathogens[1]	n / N	Success Rate (%)	n / N	Success Rate (%)	
All Pathogens	186/243	76.5	69/110	62.7	13.8
No Pathogens	45/64	70.3	21/29	72.4	- 2.1
S. aureus	117/147	79.6	43/65	66.2	13.4
MRSA[2]	15/24	62.5	2/8	25.0	37.5
MSSA[2]	102/123	82.9	41/57	71.9	11.0
mupRSA[3]	3/4	75.0	0/0		
mupSSA[3]	114/143	79.7	43/65	66.2	13.6
fusSSA[4]	117/147	79.6	43/65	66.2	13.4
S. pyogenes	29/36	80.6	12/15	80.0	0.6
Other Streptococcus species	5/8	62.5	0/1	0	62.5
Other Gram (+) pathogens	3/4	75	5/6	83.3	- 8.3
Gram (-) pathogens	32/48	66.7	9/23	39.1	27.5

1. Subjects may be represented in this table more than once as they may have had more than one pathogen at baseline
2. MRSA/MSSA are methicillin-resistant/susceptible *S. aureus*, as defined by susceptibility to cefoxitin.
3. Mupirocin breakpoints defined as susceptible ≤4 µg/mL, resistant ≥8 µg/mL
4. Fusidic acid breakpoints defined as susceptible ≤1 µg/mL, intermediate 2 µg/mL, resistant ≥4 µg/mL

mupSSA = Mupirocin-susceptible *S. aureus*; mupRSA = mupirocin-resistant *S. aureus*; fusSSA = Fusidic acid-susceptible *S. Aureus*

Furthermore, the decrease in lesion size at end of therapy for retapamulin versus placebo provides evidence that a benefit occurs sooner with treatment intervention, particularly in those patients with the presence of a pathogen at baseline. Variability in the study population enrolled across the participating countries with respect to baseline wound characteristics, evaluation of clinical response by the sites, and study execution issues have possibly contributed to the variability in study results. As discussed above, when baseline covariates are taken into account, the differences in clinical response rates between retapamulin and placebo become statistically significant. Also, higher success rates for retapamulin versus placebo in Study TOC110977 were observed in many subgroups though treatment benefit with respect to the primary endpoint was not of the magnitude anticipated.

In summary, although Study TOC110977 did not meet the primary endpoint the secondary bacteriological response benefits suggest that retapamulin has a statistically significant clinical benefit in the treatment of bacteriologically confirmed SITL subjects, and shows that retapamulin is a viable option for treatment of SITL, particularly in subjects who have a proven bacterial infection of the lesion or who cannot tolerate systemically administered antibacterials.

Delegate comment: Does ACPM consider that retapamulin should not be used to treat abscess and SITL infections due to MRSA?

The Delegate has recommended that retapamulin not be used to treat abscesses or SITL infections due to MRSA. GSK accepts the Delegate's proposal that retapamulin not be used to treat abscesses. Following this, GSK proposes to include the following statement in the Precautions section of the Product Information: *"Retapamulin should not be used to treat abscesses."*

GSK however strongly contend that the body of clinical data submitted support treatment of SITL infections due to MRSA as discussed below. The clinical data demonstrate that retapamulin is efficacious not only in infections involving methicillin-susceptible *S. aureus* (MSSA), but also in infections where the organism is either Panton-Valentine Leukocidin (PVL)-negative MRSA or non-USA300 MRSA clinical isolates.

Retapamulin demonstrated *in vitro* activity against MRSA during preclinical development. As part of a global surveillance study, *in vitro* susceptibility testing found retapamulin to be the most potent of a panel of 15 antibacterials tested against 649 clinical MRSA isolates. The MIC_{90} of retapamulin against MRSA overall was 0.12µg/mL. In an *in vivo* murine model of wound infection, a 1% concentration of retapamulin applied twice daily for four days was efficacious against strains of MRSA, including strains that were also resistant to other antibacterials (for example, mupirocin).

Retapamulin also demonstrated activity against MRSA during the late stage clinical development program. The retapamulin ointment clinical success rate for primary impetigo and SID subjects with MRSA as a Baseline pathogen were high (83.3% to 100%) and comparable to the active comparators tested. The clinical success rate for subjects with MRSA at Baseline in the SITL studies was lower in the retapamulin ointment group (64.9%; 95% CI: 51%, 77%) than in the cephalexin group (81.8%; 95% CI: 65%, 93%). In Europe and International regions, the clinical success rates for retapamulin ointment in subjects with MRSA were high (80% to 92%) as opposed to a lower rate (56.1%) in North America. The clinical efficacy for subjects with PVL-negative MRSA was much higher than for those subjects with PVL-positive MRSA as their Baseline pathogen (84.0% versus 57.5%, respectively). Genetic characterisation of the isolates from the Primary Phase III studies reveals that 56 (51.9%) of the global Baseline MRSA isolates were PVL-positive, and of those 54 (96.4%) were shown by Pulsed-Field Gel Electrophoresis (PFGE) pattern analysis to be the USA300 clone. The overwhelming majority of USA300 MRSA isolates (50 out of 54; 92.6%) were from North America: no USA300 MRSA isolates were recovered from European centers.

GSK conclude that these data support the use of retapamulin for the treatment of SITL due to MRSA, especially MRSA of the PVL negative or non-USA 300 clone types.

- **SID indication**

Delegate comment: Does ACPM consider that the data from Study 032 provide sufficient evidence to support the use of retapamulin ointment for the treatment of SID? Does ACPM have any concerns about the unexplained imbalance and the discrepancy between analyses observed in Study 032?

The clinical evaluator recommended approval of the proposed indication for retapamulin for SID including infected psoriasis, infected atopic dermatitis, and infected contact dermatitis, noting that Study 032 *"does not appear to have any major flaws"*. The Delegate however has deferred their decision on the proposed SID indication following advice from the ACPM. GSK contends that the data from Study 032 provides sufficient evidence to demonstrate the efficacy of retapamulin for the treatment of SID.

Study 032 was a randomised, double-blind, double-dummy, multicentre, non-inferiority Phase III study assessing the safety and efficacy of retapamulin applied twice daily versus oral cephalexin 500 mg in adults, or 12.5 mg/kg (250 mg/5 mL) in children, twice daily, in the treatment of SID.

This study was designed with at least 90% power to detect a treatment difference greater than 10%, with a 2.5% one-sided Type 1 error rate. The final analysis of the primary endpoint was performed using confidence intervals based on the normal approximation, and the claim of non-inferiority was achieved if the lower limit of the 95% confidence interval was greater than -10%.

Study 032 showed that retapamulin was non-inferior to cephalexin in the primary efficacy analysis (PPC population). The clinical success was 85.9% in the retapamulin group and 89.7% in the cephalexin group; treatment difference -3.8 (95% CI: -9.9, 2.3). The efficacy results in the primary clinical population show that the lower limit of the confidence

interval is greater than -10%, with the upper limit crossing zero, thereby demonstrating non-inferiority.

The observed lower limit of the CI for the treatment difference for the SID indication was the result of GSK's deliberately conservative approach regarding the determination success in the Per Protocol population (PPP). All subjects who were assigned a clinical outcome by the investigator as "Unable to Determine" (UTD, that is, either lost to follow-up or withdrew consent) were assigned a clinical response of failure, but were kept in the PPP. The standard approach normally excludes these subjects from the Per Protocol analyses. While it is acknowledged that there was a numerical difference in the number of subjects defined as UTD, this favoured the control arm (cephalexin) in the analysis. Therefore, the analysis of response including UTD as failures may represent a 'worst case' of retapamulin effectiveness versus cephalexin. Under these conditions, the lower limit of the 95% CI for retapamulin was within the prespecified success range.

In conclusion, retapamulin is an effective treatment for SID. Overall, Study 032 is robust and adequately powered to prove efficacy.

- **Requirement for post-marketing Australia specific microbiological surveillance program**

Delegate comment: What is the view of the ACPM with regards to the requirement of the Australia specific microbiological surveillance program for topical retapamulin ointment?

GSK does not believe that an Australia specific microbiological surveillance program is warranted. GSK conducted *in vitro* susceptibility studies in Australian isolates (Studies TOC116556 and TOC1165567) in support of the registration of Altargo (retapamulin), and considers that these are adequate when considered in the context of the European surveillance study (Study UD2009/00186/00 completed in 2010) and results from Phase III studies regarding retapamulin susceptibility and resistance. The results suggest that the likelihood of resistance to retapamulin developing is low in Australia.

Of note, the TGA *Antibiotic Resistance Risk Assessment* also concluded that, *"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"* (see Appendix in Attached CER). Furthermore, the Delegate's Overview stated that an EAGAR Importance Rating of low be assigned to retapamulin on the basis that a reasonable number of alternative agents in different classes are available to treat most infections even if antibiotic resistance were to develop. It would therefore appear that the risk of resistance developing in Australia is not of major concern.

EU Surveillance Study (UD2009/00186/00): This was a prospective surveillance study conducted in six European countries in order to assess the *in vitro* activity of retapamulin and 14 comparative agents against 1500 recent clinical isolates of *S. aureus* and *S. pyogenes* from community acquired skin infections. Retapamulin demonstrated excellent *in vitro* activity against the tested isolates of *S. aureus* and *S. pyogenes*, with MIC_{90} values of 0.12-0.25 and 0.06 µg/mL, respectively, regardless of phenotype or country.

Study TOC1165567: *S. aureus* and *S. pyogenes* are the major pathogenic species for which therapy with retapamulin is appropriate. Australian bacterial isolates demonstrated a MIC distribution nearly identical to previous global and regional studies conducted outside of Australia (*S. aureus* $MIC_{50/90}$ = 0.06/0.12 mg/L and *S. pyogenes* $MIC_{50/90}$ ≤0.015/≤0.015 mg/L). Adequate efficacy has been demonstrated in clinical studies against infections due to bacterial isolates of these species with MICs in this range, and it would be expected that similar clinical responsiveness would be observed for infections in Australia.

Study TOC116556: This study was conducted in Australia for susceptibility of recent *P. acnes*. All *P. acnes* isolates tested were inhibited by retapamulin at concentrations of

≤1 μg/mL. There was no apparent evidence of any pool of retapamulin resistance that might be transferable from this cutaneous bacterial species.

As with the remainder of the World there is no pleuromutilin-class antibacterial approved for oral use in humans, nor is there another topical form of a pleuromutilin such as retapamulin, therefore resistance selection and commensal transfer of resistance among human subjects is highly unlikely. In addition, low-level cross resistance which has been reported to be selected to pleuromutilins through use of streptogramin antibacterials, most commonly mediated through the VgaA protein, is of limited significance. There are no topical streptogramin antibiotics approved, oral use of the streptogramin antibacterial pristinamycine A/B (Pyostacine) is limited to France and some former French colonies, and there is limited use of the parenteral streptogramins such as quinupristin-dalfopristin (Synercid). Finally, Cfr-methylase mediated cross resistance to all large-ribosomal subunit binding antibiotics as selected by linezolid (Zyvox) use has been of such limited occurrence that retapamulin susceptibility should not be impacted.

The *in vitro* susceptibility of recent clinical isolates collected from Australia suggests the likelihood of resistance to retapamulin to be low within Australia. The low potential for development of resistance to retapamulin is also supported by the lack of treatment-associated reduction in susceptibility to retapamulin in the Phase III retapamulin clinical program, based on outcomes of presumed eradication of pathogens and laboratory investigation of the limited number of subjects with post-therapy isolates.

As stated in the RMP, GSK will continue to monitor for the development of resistance to retapamulin through routine proactive pharmacovigilance including regular review of medical literature and incoming case reports.

On the basis of the above data, and having already fulfilled regulatory requirements for surveillance studies in other regions, GSK does not plan on conducting generalised global susceptibility surveillance for retapamulin. Furthermore, GSK does not expect an Australian-specific surveillance study for retapamulin would provide any additional clinical benefit.

Advisory committee considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered this product to have an overall positive benefit–risk profile for the amended indication;

> *Altargo is indicated for the treatment of superficial skin infections (including impetigo and secondarily infected dermatoses) in adults, adolescents, infants and children aged from 9 months, in the absence of abscesses formation and infection due to MRSA.*
>
> *The in vitro susceptibility to antibiotics varies geographically and with time; the local situation must always be considered when selecting antibiotic therapy.*

The ACPM advised that the evidence relating to the SID indication was not robust but did meet non-inferiority criteria.

Proposed conditions of registration:

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed PI/CMI amendments:

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Altargo ointment containing retapamulin 1% w/w. The approved indications for this therapeutic good are:

> *Altargo is indicated for the short term treatment of superficial skin infections (including impetigo, infected small lacerations, abrasions, sutured wounds, and secondarily infected dermatoses) in adults, adolescents, children and infants aged from 9 months, in the absence of abscess formation and infections due to MRSA.*
>
> *The in vitro susceptibility to antibiotics varies geographically and with time; the local situation must always be considered when selecting antibiotic therapy.*

Specific conditions applying to the registration of these therapeutic goods

- The Altargo retapamulin 1% w/w ointment Risk Management Plan (RMP), version 03, dated 04 April 2012 with updated ASA Version 2.0 dated 18 January 2013, included with submission PM-2012-01489-3-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

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