SCIENTIFIC DISCUSSION

1. Introduction

For those SSTIs that are sufficiently superficial to be amenable to topical therapy the most commonly used antibacterial agents are fusidic acid (fucidin) and mupirocin. However, there are problems with increasing resistance to both these agents. Retapamulin has been developed for cutaneous use only in the management of superficial SSTIs.

The claimed indication for retapamulin 1% ointment was the short term treatment of the following uncomplicated skin and skin structure infections:

- Impetigo
- Secondary skin infections: infected dermatoses (e.g. atopic dermatitis, atopic contact dermatitis, psoriasis), infected traumatic lesions (e.g. small lacerations, sutured wounds, cuts, abrasions, superficial cutaneous abscesses not requiring drainage)

The approved indication is short term treatment of the following superficial skin infections:

- Impetigo
- Infected small lacerations, abrasions or sutured wounds

2. Quality aspects

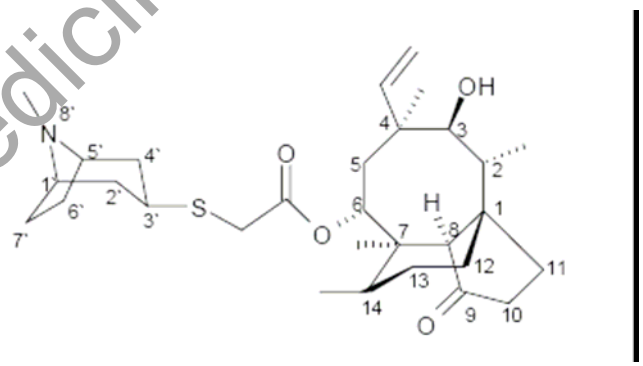
Introduction

Altargo is presented as a smooth off-white ointment containing 1% w/w retapamulin (free base) as active substance. The only excipient used in the formulation of Altargo is white soft paraffin containing a trace of antioxidant (BHT), as allowed in the PhEur monograph.

Altargo is for topical administration and is packed into either 500 mg aluminium foil sachets or aluminium tubes (5, 10 and 15 grams) with polyethylene or polypropylene cap.

Drug Substance

Retapamulin is chemically designated as (1*S*,2*R*,3*S*,4*S*,6*R*,7*R*,8*R*,14*R*)-4-ethenyl-3-hydroxy-2,4,7,14-tetramethyl-9-oxotricyclo[5.4.3.$0^{1,8}$]tetradec-6-yl{[(3-*exo*)-8-methyl-8 azabicyclo[3.2.1]oct-3-yl]thio}acetate, and its structure is as follows:.



Retapamulin is a white to pale yellow crystalline solid with a melting point range of 125-127°C. Two solid state forms exist, Form 1 and Form 2. These are distinguishable by their melting points, such that

Form 1 has a melting point at 126°C whereas Form 2 has a melting point of 143°C. Form 1 is used commercially.

The solubility of retapamulin in water is 0.07mg/mL at 25°C. Its aqueous solubility is pH dependant and it decreases with increased pH. Retapamulin is also soluble in non-aqueous solvents, showing a greater than 10mg/mL solubility in both propylene glycol and ethanol at 25°C.

Retapamulin is milled to produce a range of particle sizes which are measured by laser diffraction analysis.

Manufacture

Retapamulin is manufactured by a semi-synthetic process, starting with a fermentation step from *Clitopilus passeckerianus* CP2 to yield the key intermediate pleuromutilin and then progressing via a 5-step synthetic process to give retapamulin.

Details and spectra were provided for elemental analysis, ^{1}H-NMR, ^{13}C-NMR, MS, IR and X-ray crystallography for the primary reference standard of retapamulin. The data confirmed the proposed structure.

Specification

The active substance specification includes tests for appearance (visual), identity (IR spectroscopy), assay (HPLC), solid state form (X-ray powder diffraction), impurities (HPLC), residual solvents (GC), water content, residue on ignition, optical rotation, microbial purity and particle size distribution (laser diffraction).

The analytical methods used were sufficiently described and validated according to the ICH guideline on "Validation of Analytical Methods". The methods were suitable to control the active substance on a routine basis. The IR spectroscopy method was validated for specificity, the XRPD method was suitably validated with respect to accuracy, precision (repeatability and intermediate precision), reproducibility, specificity, limit of detection and robustness. The HPLC method for retapamulin content and impurity content was validated with respect to specificity, linearity, precision, quantitation limit and stability of solutions. The GC method was validated respect to specificity, linearity, range, accuracy, precision, quantitation limit and robustness. The water content method was validated for specificity, linearity, range and precision. The laser diffraction method was validated for range, accuracy, precision and robustness.

Data were provided for four production scale batches manufactured at the proposed commercial site. Data were also provided for three additional pilot scale batches. All batches complied with the requirements in the active substance specification.

Stability

Stability studies were performed on three pilot scale batches of retapamulin. Batches were tested under ICH conditions of real time (25°C/60%RH) up to 36 months, intermediate (30°C/65%RH) up to 24 months and accelerated (40°C/75%RH) for 6 months. Additionally, photostability studies (ICH conditions: xenon source, 1.2 million lux hrs, UV 200 watts hours/m^2) were performed on all batches and forced degradation / stress testing was performed on one batch (2 months storage at -20°C, 40°C/75% RH/exposed, 50°C and 50°C/exposed). Stress study batches were examined for appearance, retapamulin content (HPLC), drug-related impurities (HPLC) and water content. These parameters as well as x-ray powder diffraction were examined for all other stability studies. Full analytical and validation details were provided for all tests. Up to 24 months data were provided.

Long term, intermediate and accelerated studies showed that all batches meet proposed specification limits. No significant changes or trends were observed in any parameters demonstrating chemical and

physical stability of the active substance. No significant changes were observed for samples stored for two months at -20°C, 40°C/75% RH/exposed, 50°C and 50°C/exposed.

Photostability studies were carried out on three pilot scale batches of retapamulin. The results showed that the active substance is not affected by exposure to light.

Four batches manufactured at the proposed manufacturing site have been placed on stability.

The data provided is sufficient to confirm the proposed re-test period for the active substance.

Drug Product

Pharmaceutical Development

The aim of the pharmaceutical development was to produce a topical formulation containing retapamulin that was of minimum complexity and displayed good product quality. Retapamulin was chosen for development as a topical antibacterial agent because it showed *in-vitro* antibacterial activity against susceptible and multi-drug-resistant organisms commonly associated with bacterial skin infections. It was found that there was minimal systemic exposure and rapid metabolism following topical administration.

The formulation development for Altargo was based on an already approved ointment formulation marketed by the Applicant. It consists of the milling of the active substance followed by suspension in white soft paraffin. Three strengths of ointment were prepared, 0.5%, 1.0% and 2.0%. The final proposed commercial formulation chosen was1.0% w/w ointment.

The product is not sterilised but it is manufactured under clean conditions. The low water activity of the matrix is unlikely to support adventitious microbial growth. The product is also tested for microbial purity before release.

Adventitious Agents

The only excipient used in the formulation of retapamulin ointment is white soft paraffin which is not of animal origin.

Manufacture of the Product

The manufacturing process for Altargo uses standard pharmaceutical techniques for topical ointments, i.e., heating and homogenisation of the white soft paraffin followed by blending of the active substance.

The manufacture of the finished product comprises (1) heating and homogenisation of the white soft paraffin (2) blending of the active substance in the white soft paraffin while stirring (3) cooling of the product while stirring (4) filling process.

The ointment is filled into aluminium tubes, tested and released. For sachet filling, pre-shipping analytical testing is performed (description, identification, retapamulin content, drug related impurities, microbial limit test) before shipping to the filling site in Canada. On receipt at the filling site, ID testing is performed, the ointment sachets filled, tested and released.

There were no in-process controls during the manufacture of the ointment since process development studies showed the manufacturing method to be robust and capable of producing high quality product even with some process variation. In-process controls applied for filling of aluminium tubes and sachets include weight, seal quality, product and package appearance. Prior to shipping for sachet fill, the bulk ointment is tested to the full release specification except for weight check.

Three primary stability batches were prepared using three different batches of active substances. Samples taken from various positions in the mixing vessel (top, middle, bottom, centre of vessel) showed acceptable results for retapamulin content, confirming a homogenous product. Further process scale up and optimisation were performed on eight commercial scale batches to determine the effect of operating parameters and drug particle size. Results confirmed that a reliable product was obtained.

Product Specification

The product specifications include methods for appearance, identification and assay (HPLC), drug related impurities (HPLC) and microbial purity.

The drug product specifications have been justified and all methods of analysis have been described and adequately validated.

Stability of the Product

Data was provided for three primary manufactured at the proposed site and packed into either aluminium tubes (2.5, 5, 10 and 15g) or the sachet (500mg). All three batches were tested under ICH conditions of real time (25°C/60%RH, up to 36 months), accelerated (30°C/65%RH, up to 24 months) and stressed (40°C/75%RH, 6 months). The following parameters were tested for: description, active substance content and drug-related impurities by HPLC at one month and then three month intervals. Microbial limit tests were performed initially and at 12, 24 and 36 months. All aluminium pack sizes were placed on stability testing but only 2.5g and 15g tubes were tested. The intermediate presentation sizes (5g and 10g) would only be tested if significant change had been seen in 2.5g and 15g tubes stored at 25°C/60%RH.

Several additional tests were performed including photostability (four batches of ointment in aluminium tubes and exposed in a transparent glass Petri dish and a batch of bulk ointment in a transparent glass Petri dish were tested (ambient laboratory light, 2 weeks)), stress conditions (four batches of ointment in aluminium tubes tested at 50°C for 2 weeks), low temperature storage (one batch of ointment in an aluminium tube was tested at 5°C at 0, 1, 3 and 6 months). Temperature cycling (freeze thaw) and forced degradation studies were also performed. Temperature cycling showed no effects on the physical properties of the product.

Based on the available stability data, the proposed shelf life and storage conditions, as stated in the SPC, are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and drug product has been presented in a satisfactory way. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

3. Non-clinical aspects

Introduction

The majority of non-clinical studies were conducted with the free base of retapamulin (known as SB275833), the form proposed for clinical use.

All definitive safety pharmacology and toxicology studies, as well as analyses in support of the studies were performed in compliance with GLP regulations.

Pharmacology

Primary pharmacodynamics

Retapamulin is a novel antimicrobial agent that inhibits bacterial protein synthesis. The antimicrobial spectrum of activity was studied *in vitro* against a broad range of organisms including Gram-positive and Gram-negative aerobes, anaerobes as well as biothreat organisms. In addition, *in vivo* efficacy of retapulmin has been evaluated in animals using the mouse experimental surgical wound infection model.

Further details of the microbiological properties of retapamulin are provided with the description of the clinical data (Pharmacodynamics).

Secondary pharmacodynamics

There were few findings in the secondary pharmacodynamic studies and none of clinical relevance in view of the very low systemic exposure in patients.

Safety pharmacology programme

Retapulmin was evaluated for potential adverse effects in a full series of safety pharmacology studies including cardiovascular, respiratory and central nervous system. Additionally, supplemental studies were performed to examine effects on renal and gastrointestinal systems.

Retapulmin was found to exhibit some binding to muscarinic M1 receptor in vitro and diminished contractile response to acetylcholine in isolated guinea pig ileum segments. In mice, a decrease in intestinal motility was seen following high oral dose, as well as analgesia and a decrease in motor activity. Additional binding studies on muscarinic receptors were reassuring.

In mice and rats small decrease in body temperature was noted, and transient and mild effects on blood pressure and heart rate occurred following high oral dose. Intravenous doses were associated with vomiting, trembling, increased heart rate in the dog, and decreased blood pressure and body temperature, seizures and deaths in the monkey.

However, none of the adverse findings in safety pharmacology studies is of clinical relevance since the doses administered to various animal species would have resulted in most instances in plasma concentrations several orders of magnitude greater than those achieved clinically.

The same applies to the *in vitro* investigation of potential effects on QTc interval. In this instance, the inhibition of hERG channels (IC50=3.3µg/ml) occurred at concentrations of at least 150x the highest human plasma concentration.

Pharmacokinetics

In vivo studies were conducted in the species used in the toxicity programme including rat (adult and neonatal), cynomolgus monkey, rabbit and minipig. In addition to dermal application, toxicokinetic studies using the oral and intravenous routes were conducted in support of the repeated-dose toxicity studies.

In vitro studies included those on metabolism as well as drug-drug interactions.

Absorption and distribution have been well characterised and metabolic studies indicate the existence of more than 100 metabolites. Information concerning potential inhibitory activity of the mono-oxygenated metabolites could not be provided because of their large number and low concentrations.

Exposure following oral administration to rats and monkeys established suitable safety margins for most of the few adverse findings in toxicity studies. Accumulation of drug-related material in some melanin-containing tissues – in particular the uveal tract – should not be of clinical concern.

Interaction with the cytochrome P450 system has been fully investigated. Again, there were no findings of clinical concern even though in a clinical study in which an inhibitor of CYP3A4 (ketoconazole) was co-administered there was an increase in systemic exposure by 81%.

Toxicology

Single dose toxicity

In rats, oral doses of 450mg/kg and IV doses of 10mg/kg were well tolerated. In contrast, oral doses of 50mg/kg or greater administered to monkeys resulted in emesis.

Repeat dose toxicity (with toxicokinetics)

High oral (450mg/kg) and iv (10mg/kg) doses were administered for 14 days to rats. The main finding was hepatic enzyme induction with secondary effects on the thyroid. These findings are commonly seen in rats and should be considered a species-specific adaptive response.

The main finding in monkeys was emesis at oral doses ≥50mg/kg administered for 14 days.

Neither of these findings is considered to be of clinical concern

Toxicokinetics has been well quantified and the data provide reassurance for the topical use of retapamulin.
Genotoxicity

There was no evidence of genotoxicity when evaluated in vitro for gene mutation and/or chromosomal effects in the mouse lymphoma cell assay, in cultured human peripheral blood lymphocytes, or when evaluated in vivo for chromosomal effects in a rat micronucleus test

Carcinogenicity

No carcinogenicity studies have been submitted

Reproduction Toxicity

The applicant conducted standard ICH3 fertility and teratogenicity studies but did not include a pre- and post-natal study. However, juvenile toxicity studies were conducted.

In an embryotoxicity study in rats, developmental toxicity (decreased *fetal* body weight and delayed skeletal ossification) and maternal toxicity were observed at oral doses of ≥ 150 mg/kg/day (corresponding to ≥ 3 times the human estimated exposure. There were no treatment-related malformations in rats

Local tolerance

Dermal irritancy (and toxicity) studies on intact and abraded skin of rabbits using concentrations up to 5% revealed evidence of irritancy even at concentrations lower than that proposed for clinical use (1%). In contrast, there were no signs of erythema or oedema in minipigs when 5% retapamulin was applied to abraded skin for 10 days.

Other toxicity studies

Data from sensitization studies in guinea pig and mouse have been superseded by findings in clinical use which indicate that 1% retapamulin is not a sensitizer in humans.

Ecotoxicity/environmental risk assessment

The environmental risk assessment of retapamulin followed primarily the draft of guidelines related to this issue. From the results obtained, it is concluded that retapamulin for topical use is of no immediate risk to the environment and no proposals for labelling provisions are necessary to reduce any potential environmental risks.

Discussion on the non-clinical aspects

With the exception of oncogenicity studies and a pre- and post-natal study, the applicant has submitted an otherwise complete and appropriate programme of toxicity studies. Compared with many other xenobiotics there were relatively few indications of toxicity. The most significant findings were hepatotoxicity with subsequent thyroid toxicity in the rat and emesis in monkeys. These are given suitable consideration and it is convincingly argued that they are not of clinical concern. Retapamulin was not genotoxic. Reproduction toxicity was only observed in an embryotoxicity study in the rat, in which reduced fetal weights and a delay in ossification of the skull occurred concurrently with maternal toxicity. Juvenile toxicity studies via the dermal route in neonatal rats and the juvenile minipig did not reveal systemic toxicity. The only adverse finding was minimal erythema.

Contrary to CHMP advice provided during drug development, the applicant did not conduct further repeated-dose toxicity studies. The maximum duration of dosing therefore remains 14 days at the time of submission of the dossier. However, this issue is considered to be largely superseded by the existing clinical data.

4. Clinical aspects

Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

Data were obtained from healthy subjects and from patients to establish the extent of systemic exposure to retapamulin after topical applications of various strengths of ointment to intact and abraded skin or superficial infected lesions.

An overview of the studies is provided hereafter:

Healthy subjects

- Study 026 in which daily applications of 0.5%, 1% and 2% ointment were made for up to 7 days to large surface areas of intact skin (400 – 1600cm^2) and abraded skin (200cm^2). The study included an assessment of retapamulin metabolites in plasma and urine. Ointment application was made by study personnel and spread evenly in four demarcated areas on the leg using a metal spatula. The application sites were then occluded with plastic film secured in place using an overlay of transparent dressing. Each dose was applied for 22.5 hours.
- Study TOC101825 in which a single application of 1% ointment to 50 cm^2 abraded skin was made with and without oral ketoconazole (200 mg twice daily for 4 days).

Patients

- Study 029 (Phase II efficacy) during twice daily applications of 1% ointment for 5 days to secondarily-infected open lesions or other uncomplicated bacterial skin infections.
- Studies 030A and 030B (Phase III efficacy) during twice daily applications of 1% ointment for 5 days to secondarily infected traumatic lesions (SITL).

Human plasma samples were analysed for retapamulin using a validated analytical method.

Absorption

In **study 026** applications of retapamulin to healthy volunteers were as follows:

	Intact			Abraded		
Cohorts	1 and 4	2 and 5	3 and 6	7 and 10	8 and 11	9 and 12
Formulation (or Placebo1)	0.5%	1%	2%	0.5%	1%	2%
Total Area to cover (cm2)	400	800	1600	100	200	100
Sub-sites to cover (# sites x cm2)	4 x 100	4 x 200	4 x 400	4 x 25	4 x 50	4 x 25
Total Ointment to cover area (g)	4	8	16	1	2	1
Sub-site Ointment to cover area (# sites x g)	4 x 1	4 x 2	4 x 4	4 x 0.25	4 x 0.5	4 x 0.25
Total retapamulin (mg)	20	80	320	5	20	20

After single applications to intact skin (i.e. Cohorts 1-3 and Day 1 of Cohorts 4-6) plasma concentrations were generally non-quantifiable so that no PK analysis was performed. The data for the other cohorts on days 1 and 7 were as follows:

Summary of measurable retapamulin plasma concentrations

Day 1						
	Cohort	Regimen	Dose (mg)	AUC(0-24) (ng.h/mL) (GM)	Cmax (ng/mL) (GM)	tmax (h) Median (range)
Single Abraded	7	0.5% 100 cm_2	5	22.3[1] (14.0-35.4)	1.45[1] (0.89-2.39)	12.0[1] (4.0-22.5)
Single Abraded	8	1% 200 cm_2	20	152.6[3] (97.4-238.4)	10.65[3] (5.62-22.12)	6.0[3] (4.0-16.0)
Single Abraded	9	2% 100 cm_2	20	72.0[1] (46.1-90.4)	5.51[1] (3.19-8.90)	12.0[1] (8.1-24.0)
Repeat Abraded	10	0.5% 100 cm_2	5	44.1[3] (39.2-49.0)	2.99[3] (2.54-3.82)	8.0[3] (4.0-12.0)
Repeat Abraded	11	1% 200 cm_2	20	142.0[3] (79.2-195.4)	9.75[3] (5.84-14.55)	6.0[3] (4.0-16.0)
Repeat Abraded	12	2% 100 cm_2	20	77.8[3] (47.5-96.1)	4.83[3] (2.76-7.17)	6.0[3] (4.0-22.5)

Day 7						
	Cohort	Regimen	Dose (mg)	AUC(0-24) (ng.h/mL) (GM)	Cmax (ng/mL) (GM)	tmax (h) Median (range)
Repeat Intact	4	0.5% 400 cm_2	20	22.3[1] (15.5-38.8)	1.68[1] (0.87-6.30)	19.3[1] (16.0-24.0)
Repeat Intact	5	1% 800 cm_2	80	49.6[2] (19.8-146)	2.86[2] (1.20-7.84)	22.4[2] (16.0-24.0)
Repeat Intact	6	2% 1600 cm_2	320	121.2[2] (49.5-358)	7.10[2] (3.32-20.1)	22.5[2] (0.0-23.9)
Repeat Abraded	10	0.5% 100 cm_2	5	15.3[1] (14.1-17.5)	0.98[1] (0.81-1.15)	0.0[1] (0.0-16.0)
Repeat Abraded	11	1% 200 cm_2	20	134.9[3] (115.6-157)	8.79[3] (6.68-12.8)	22.5[3] (0.0-22.6)
Repeat Abraded	12	2% 100 cm_2	20	126.7[4]	7.22[4]	0.00[4]

1. n=4, 2. n=5, 3. n=6, 4. n=1 (subject 107), as others in this cohort withdrew before Day 7

Clearly there was higher systemic absorption in abraded *vs* intact skin with measurable exposures in Cohorts 7-12 on Day 1 but unquantifiable exposures in Cohorts 1-6 on Day 1. Also, after multiple applications to 1-200 cm2 of abraded skin the plasma concentrations were similar to those seen after multiple applications to 4-1600 cm2 of intact skin.

With a 4-fold difference in ointment strength between Cohorts 7 and 9 but with the same application area, the AUC(0-24) and Cmax increased by less than 4-fold. For Cohort 8, with twice the application area and twice the strength compared to Cohort 7, the increase in exposure was considerably more than 4-fold. These findings suggested that surface area is more important in determining systemic exposure than strength of the ointment formulation.

In **study 029** the range of wound sizes was 0.04~100 cm^2, with a median value of 1.40 cm^2. Blood samples were collected over 12 hours on Day 1 and Day 5 after the first daily dose and single samples were collected on Days 3, 4 and 7 to determine plasma levels. Only nine out of 355 samples (from seven out of 35 subjects) had measurable retapamulin concentrations, ranging from 0.5~4.3 ng/ml. All other samples were < LOQ (0.5 ng/ml). There was no trend for increasing retapamulin plasma concentrations with increasing wound size. The subject with the highest observed plasma concentration (4.3 ng/ml) had a wound size of 2.5 cm^2 while the subject with the maximum wound size (100 cm^2) had non-measurable concentrations.

During **studies 30A and 30B**, single plasma samples were to be obtained before the first daily treatment at the on-therapy visit (Day 3 or 4 of treatment) for the first 500 patients ≥18 years of age across both studies. Single samples were also to be collected from all paediatric patients (≥ 9 months and < 18 years old) that were to be randomly spread in one of three windows (0-4 h, 4-8h or 8-12h) following the first dose on Day 3 or Day 4.

Samples from 516 patients treated with retapamulin were analysed across both studies. These samples were apparently obtained at variable time points across the dosing interval even in adults although the exact spread of timings is not analysed. Nevertheless, the results indicated low systemic absorption following repeat administration of retapamulin 1% ointment twice daily on wounds with a mean area of about 8 cm2 (max up to 112 cm2).

	Adult and Paediatric	**Adult**	**Paediatric**
Samples	516	380	136
Measurable Samples n (%) (Range, ng/mL)	56 (11%) (0.52-18.47)	47 (12%) (0.52-10.72)	9 (7%) (0.54-18.47)
Non-measurable Samples	460	333	127
Wound Size, Mean (Range, cm2)	6.82 (0.03-112)	7.58 (0.04-112)	4.69 (0.03-85)

Thus there was no discernible relationship between plasma concentrations and age.

The percentage of patients with measurable concentrations appeared to increase with increasing wound size presumably due to the larger total dose administered. However, there was no apparent relationship between wound size and the magnitude of the observed concentration. The percentage of measurable samples was also influenced by the type of dressing, with lowest proportions for non-occlusive, increasing to semi-occlusive and again when an occlusive dressing was applied. Semi-occlusive and occlusive dressing groups were associated with higher plasma concentrations than the no dressing group.

Distribution

No data are available regarding distribution in man

Elimination

In Study 026, $t_{1/2}$ could not be estimated due to the variability as well as the relatively flat PK profiles even on sampling for up to 36 h post-dose in Cohorts 6 and 12.

Dose proportionality and time dependencies

Absorption through skin is not dose-proportional or likely to be time dependent.

Special populations

Due to the low systemic exposures observed, no specific studies have been performed in special populations.

The available date indicated that renal and hepatic impairment and/or increasing age would not result in significantly higher systemic retapamulin exposure after topical application.

With respect to use in infants and children aged from 9 months to 2 years, and in the absence of specific PK data from this age group, a review of relevant issues (such as changes in skin structure and

function with age, CYP3A4 activity and renal function) supported a conclusion that the systemic retapamulin exposures that would occur in patients aged 9 months to 2 years were unlikely to differ significantly from those that were observed in children aged 2-5 years.

Pharmacokinetic interaction studies

In-vitro studies

- Retapamulin was shown to be a P-gp substrate and inhibited P-gp transport of digoxin with an IC50 of 28.2 µM or 14601.3 ng/mL. However, the maximum individual systemic exposure in humans following topical application of 1% ointment on 200 cm^2 of abraded skin (C_{max}= 22 ng/mL; $AUC_{(0-24)}$ = 238 ng.h/mL) was 660-fold lower than the retapamulin IC_{50} for P-gp inhibition.

- The in-vitro oxidative metabolism of [^{14}C] retapamulin in human liver microsomes was primarily mediated by CYP3A4 with minor contributions from CYP2C8 and CYP2D6. Co-incubation with the CYP3A4 inhibitors ketoconazole or troleandomycin resulted in complete or partial inhibition of the formation of retapamulin metabolites. In-vitro metabolism of [^{14}C] retapamulin by human skin occurred to a very limited extent. Parent compound was the predominant radio-component with very low amounts of three mono-oxygenated metabolites.

- In human liver microsomes, retapamulin was a strong inhibitor of CYP3A4 when midazolam (Ki 0.42 µM or 217.5 ng/mL), nifedipine (Ki 7.3 µM or 3779.8 ng/mL) and atorvastatin (Ki 0.75 µM or 388.3 ng/mL) were used as substrates. Inhibition did not appear to be metabolism-dependent. However, since systemic exposures to retapamulin in most patients with secondary infected traumatic leasions were < 0.5 ng/mL the applicant considered that application of the 1% ointment was unlikely to cause clinically relevant CYP 3A4 inhibition in patients.

- The highest systemic exposure to retapamulin with topical application of 1% ointment (C_{max}= 22 ng/mL; $AUC_{(0-24)}$ = 238 ng.h/mL) was 3.5-fold lower with respect to Cmax and similar with respect to AUC compared to the lowest exposure (C_{max} 77 ng/ml, AUC 319 ng.h/mL) that caused a slight induction of CYP enzymes in rats.

In-vivo studies

In study TOC101825, healthy subjects applied retapamulin 1% ointment over 50 cm2 abraded skin alone and on the 4th day of dosing with ketoconazole 200 mg twice daily. Each application site was occluded for approximately 24 hours. There were statistically significant 1.8-fold increases in AUC(0-24) and Cmax when retapamulin ointment was administered with ketoconazole. However, none of the individual Cmax or AUC(0-24) values exceeded the highest values observed in study 026 (i.e. Cmax 22.12 ng/mL and AUC(0-24) 358 ng.h/mL) or the NOAEL for oral administration in monkeys.

Despite the effect of ketoconazole on plasma levels this is unlikely to increase the incidence of adverse events so that no dose adjustment for retapamulin is recommended when it is co-administered with CYP-3A4 inhibitors.

Pharmacodynamics

Mechanism of action

Pleuromutilins inhibit the elongation phase of bacterial protein synthesis by interacting at a specific site on the 50S subunit of the prokaryotic ribosome that is distinct from binding sites of other antibacterial agents with a ribosome-directed mechanism of action. This binding site involves ribosomal protein L3 and is in the region of the ribosomal P site and peptidyl transferase centre. As a result the pleuromutilins block P-site interactions as well as inhibiting peptidyl transfer.
Inhibition of fmet-tRNA binding to the P-site *in vitro* suggests that pleuromutilins also have an effect on translation initiation and they have been shown to prevent the normal formation of active 50S

ribosomal subunits. Therefore inhibition of bacterial protein synthesis possibly occurs *via* multiple mechanisms.

Primary pharmacology

Most of the in-vitro data on the antibacterial activity of retapamulin are derived from a large, global surveillance study of 6747 isolates collected from community- and hospital-associated skin and soft tissue infections (SSTIs) in 2004 to 2005. Testing was by broth microdilution according to CLSI standard methodology.

- For *S. aureus* retapamulin MIC_{50} and MIC_{90} values were 0.06 and 0.12 µg/ml, respectively, irrespective of the geographic region and all isolates were inhibited by 0.5 µg/ml. Activity was unaffected by presence of the *lukS* and *lukF* genes that encode for the Panton-Valentine Leucocidin (PVL) toxin or by resistance to methicillin, macrolides, fusidic acid or mupirocin.

- Against 1,918 isolates of *S. pyogenes* the MIC_{50}/MIC_{90} values for retapamulin were 0.03/0.03 µg/ml. The highest MIC recorded was 0.25 µg/ml.

- The MIC_{50} and MIC_{90} values for retapamulin against the 975 global isolates of coagulase-negative staphylococci were both 0.06 µg/ml and all were inhibited by 0.5 µg/ml.

- Against 941 isolates of *S. agalactiae,* the MIC_{50} and MIC_{90} values were 0.03 µg/ml and 0.06 µg/ml and all were inhibited by 0.25 µg/ml.

- Against 226 isolates of various anaerobic bacteria the overall MIC_{90} for retapamulin was 2 µg/ml. least susceptible were *Bacteroides* and *Clostridium* species.

- With the exception of *Haemophilus influenzae* and *Moraxella catarrhalis*, retapamulin showed poor activity against Gram-negative organisms.

Resistance to pleuromutilins appears to be possible through point mutations in ribosomal protein L3 (encoded by the *rplC* gene), which reduce binding at the peptidyl transferase centre.

In laboratory studies two *S. aureus* isolates were consistently less susceptible to pleuromutilins relative to others in the species (MICs of 1 and 2 µg/ml compared to ≤0.016-0.06 µg/ml). Decreased activity seemed to be due to the presence of a transposon-borne gene (previously named *vgaAv*) encoding a putative ABC transporter. Of 36 *S. aureus* confirmed to be quinupristin/dalfopristin-resistant amongst a specific collection of resistant strains from the SENTRY programme, 30 possessed the *vgaAv* gene and these, but not the other 6, had elevated pleuromutilin MICs including retapamulin MICs from 2-32 µg/ml. The reduced susceptibility (retapamulin MIC of 64 µg/ml) exhibited by a single *S. aureus* isolate from global surveillance studies was due to the presence of a 5,782 base pair plasmid containing the *vgaA* efflux pump.

Secondary pharmacology

Irritation and sensitisation

Study 025 compared the primary and cumulative irritation scores of the regimens described in the table below. The same treatment was reapplied to the same location on subsequent days.

There were four cohorts in this study, each of which received 2, 14, or 21 days repeat dosing under an occlusive patch on either intact or abraded skin as follows:

- Cohort 1 received **two** 24-h topical applications of retapamulin and controls on **intact** skin.
- Cohort 2 as in 1 but on tape-stripped (**abraded**) skin
- Cohort 3 received **twenty-one** 24-h topical applications on **intact** skin
- Cohort 4 received **fourteen** 24-hour topical applications on tape-stripped (**abraded**) skin

Regimen Code	Cohorts	Study Medication	Method and Quantity of Application to Patch
A	All	0.5 % retapamulin	0.2 ml by pipette or syringe
B	All	1 % retapamulin	0.2 ml by pipette or syringe
C	All	2 % retapamulin	0.2 ml by pipette or syringe
D	All	Vehicle Control (petrolatum)	0.2 ml by pipette or syringe
E	All	Patch Control	-
F	1 and 2 Only	Primary Positive Irritant Control (0.5% SLS in sterile distilled water for injection [USP])	0.2 ml by pipette or syringe
G	3 and 4 Only	Cumulative Positive Irritant Control (0.1% SLS in sterile distilled water for injection [USP])	0.2 ml by pipette or syringe
H	All	Negative Irritant Control (sterile distilled water for injection [USP])	0.2 ml by pipette or syringe

- On intact skin (Cohort 1), each of the tested concentrations of retapamulin and the negative controls had a similar level of irritation after 2 days of dosing and 2 days of follow-up.

- On abraded skin (Cohort 2), irritation levels were higher than for intact skin. The 2% formulation and the positive control (0.5% SLS) were associated with a higher level of irritation relative to the patch control for both the average and maximum irritation scores.

- The degree of cumulative irritation of induced by retapamulin (0.5%, 1% or 2%) on intact skin (Cohort 3) was less than that with the positive control (0.1% SLS).

- For the abraded skin (Cohort 4) the score for the 2% retapamulin ointment was similar to that for the 0.1% SLS positive control the scores for 0.5% and 1% ointments were similar to the vehicle and sterile water controls.

Study 027 assessed the potential for sensitisation of three strengths of retapamulin ointment (0.5%, 1% and 2%) and a vehicle placebo when applied under occlusion to a single cohort of subjects. There was a three-week induction period during which time there were nine repeated occluded patch applications, each application representing approximately 48 or 72 h skin contact time. This was followed by a 14-17 day rest phase and then a challenge phase that consisted of a parallel application of each study medication to naïve skin sites for approximately 48 hours. The challenge phase could be repeated once (with a second rest period of at least 4 weeks and one re-challenge using naïve test sites) for subjects with an intermediate, equivocal skin response to the first challenge. Each subject (N=232) received all four treatments in parallel during the induction, challenge and re-challenge (if applicable) phases.

Only one subject demonstrated sensitisation to retapamulin at concentrations of 1% and 2%. No reaction was observed against placebo. This subject had challenge scores at 1 h and 48 h of 0.5 and 1 for 0.5% retapamulin, 2 and 2 for 1% and 1 and 2 for 2% ointment compared to 0.5 and 0 for placebo. After re-challenge the readings at the two time points were 0 and 0.5 for 0.5% ointment, 0 and 1 for 1%, 0.5 and 1 for 2% and 0 and 0.5 for placebo.

Since it appeared that retapamulin has a low propensity to cause sensitisation and irritation and since study 027 included a challenge phase it seemed unlikely that there would be a marked increment in sensitisation of irritation with repeated treatment courses. However, this cannot be ruled out before

licensure. The risk management plan (RMP) requires that special attention should be paid to possible hypersensitivity reactions.

Clinical efficacy

Dose response studies

The choice of 1% ointment has been based on achieving a balance between efficacy as demonstrated with various strengths in animal models of infection and the local irritation potential as demonstrated in healthy subjects. The choice of twice daily applications was based on animal studies in which administration of ointment twice daily was as good as three times daily.

The restriction on the maximum area to be treated in all the studies and SPC (100 cm2 and/or 2% BSA in persons aged < 18 years) was chosen based on considerations of systemic exposures and use across all age groups from 9 months upwards.

Main studies

The Phase III clinical development programme consisted of five double blind (placebo controlled or double dummy) studies in which retapamulin 1% ointment was applied twice daily for 5 days.

	Retapamulin N[1]	**Comparator N**[1]
Impetigo (103469) vs placebo	139	71
Impetigo (100224) vs fusidic acid	317	150
Secondarily infected traumatic lesions		
SITL (030A) vs cephalexin	592	260
SITL (030B) vs cephalexin	540	249
Secondarily infected dermatoses	320	156
SID (032) vs cephalexin		
TOTAL	**1908**	**886**

[1] The primary population is Per Protocol Clinical (PPC) for all studies, except for 103469, for which it is Intent-To-Treat Clinical (ITTC).
Numbers shown are those included in the primary analysis (i.e. primary population at the chosen primary endpoint)

METHODS

Study Participants

Studies enrolled adults, adolescents, children and infants from the age of 9 months. An Independent Data Monitoring Committee (IDMC) reviewed unblinded safety data from the initial 600 patients enrolled into the two SITL studies (030A and 030B), which were initially limited to patients aged ≥ 13 years. Following the data review, the IDMC recommended that it was safe to reduce the minimum age to 9 months. In studies 030A, 030B and the SIDs study 032, enrolment was then extended to include patients from 9 months up to 13 years. The two studies in impetigo (TOC103649 and TOC 100244) were initiated later and so enrolled patients from 9 months of age from the outset.

- In each indication a Skin Infection Rating Scale (SIRS) score ≥ 8 was required for study entry.
- *In the Impetigo studies (TOC103469 and TOC100224)* patients had a clinical diagnosis of primary impetigo (bullous or non-bullous), defined as a lesion or group of ≤10 lesions characterised by red spots or blisters without crusts that later progressed to lesions which oozed and formed yellow or honey-coloured crusts surrounded by an erythematous margin.
- *In the SITL studies (030A and 030B)* lesions were to include surgical wounds, burns, minor cuts and abrasions, lacerations and crush injuries, with local abscess formation subsequently possible.

- *In the SID study (032)* patients were to have secondarily-infected atopic dermatitis [AD], psoriasis or allergic contact dermatitis [ACD]).

Treatments

Retapamulin 1% ointment was applied twice daily for 5 days. Sodium fusidate ointment was applied three times daily for 7 days and cephalexin was given for 10 days at 500 mg twice daily (or 12.5 mg/kg twice daily in children aged < 13 years).

Use of gauze, bandage or similar to cover the lesions was permitted. Treatment was to continue for the full duration even if the lesion(s) had fully healed but could be terminated at any time if the investigator decided that the infected lesion(s) had failed to respond.

Systemic antibacterial agents (other than the assigned comparator in SITL and SID studies) and steroids (other than up to 10 mg daily prednisolone or equivalent in the SIDs study) were prohibited during therapy and for 7 days after the end of therapy. Other systemic medications were allowed as usual.
The use of topical therapeutic agents (including glucocorticoids, antibacterials and antifungals) was prohibited from 24 h (72 hours for the SID study)prior to study entry until the end of the study except that non-infected lesions in the SIDs study could be treated as deemed appropriate by the investigator. Antibacterial/antiseptic soaps, lotions or wipes were prohibited for use on the infected lesion(s) during the course of the study. In the SIDs study bleach baths were banned.

Randomisation

Randomisation was in a 2:1 ratio (retapamulin: placebo or active comparator).

Objectives

In each study the primary objective was to compare the efficacy and safety of retapamulin with active or placebo treatments (as appropriate) for the treatment of the indications under study.

TOC103469 was a 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% confidence interval (CI) for the treatment difference in the ITTC population was greater than zero.

TOC100224 was a non-inferiority study that compared retapamulin with sodium fusidate 2% ointment. A conclusion of non-inferior efficacy was to be drawn if the lower limit of the 95% CI for the treatment difference in the PPC population was ≥ –10%.

030A, 030B and 032
These were non-inferiority studies that compared retapamulin with cephalexin. A conclusion of non-inferiority was to be drawn if the lower limit of the 95% CI for the treatment difference in the PPC population was ≥ -10%.

Outcomes/endpoints

Four patient 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.
- *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).

- In the impetigo studies the primary endpoint was to be determined at the end of treatment (EOT) Visit in the ITTC (TOC103649) or PPC (TOC100224) population.
- In the SITL (030A and 030B) and SIDs (032) studies the primary endpoint was to be determined at the follow-up visit in the PPC population.

In impetigo studies and SIDs studies, failures could be associated with either the principal lesion or other lesions and this was denoted in the classification of failures.

Statistical methods

The normal approximation, without continuity correction, was to be used to construct all confidence intervals.

In addition to the comparisons made between treatments as described above each study included an evaluation of the effect of age, compliance, centre, baseline SIRS score and wound/lesion size at baseline.

All of these covariates except for centre were included in logistic regression models.

RESULTS

Impetigo

TOC103469 enrolled 213 patients of which 210 were treated, 84% were included in the PPC, 81% in the ITTB and 71% in the PPB populations. Most patients (81.2% retapamulin and 84.5% placebo) had non-bullous impetigo.

The results at EOT were similar in the defined populations and in all cases the difference *vs* placebo exceeded 33% with lower 95% CI that exceeded 20%.

Clinical Response at End of Therapy by Analysis Population

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

No statistically significant association was detected between any of age, gender, bullous or non-bullous impetigo, number of lesions, racial and ethnic groups and clinical response in the ITTC or PPC populations.

At the follow-up visit, success rates with retapamulin were again superior to those in the placebo group in all four analysis populations. Failures at EOT were carried forward such that overall failure rates were 24.5% [34/139] for retapamulin and 60.6% [43/71] for placebo. Twelve retapamulin and 6 placebo group ITTC patients were deemed failures due to clinical recurrences.

Clinical response at follow-up (Day 14)

Analysis Population	Retapamulin		Placebo		Difference	95% CI (%)
	N	(%)	N	%	%	
ITTC	105/139	75.5	28/71	39.4	36.1	(22.7, 49.5)
PPC	98/119	82.4	25/58	43.1	39.2	(24.8, 53.7)
ITTB	91/114	79.8	19/57	33.3	46.5	(32.2, 60.8)
PPB	86/102	84.3	18/48	37.5	46.8	(31.4, 62.2)

Clinical response by pathogen (next table) reflected the overall differences seen between active and placebo groups except for Gram-negative pathogens, which were not likely to have been true causative pathogens in this and other studies. Microbiological responses by patient and by pathogen were similar to those for clinical success rates since eradication was almost always presumed due to lack of material for culture.

Clinical response at EOT by pathogen (ITTC)

Baseline Pathogen	Retapamulin		Placebo		Difference (%)
	N	%	N	%	
S. aureus (all)	84/95	88.4	27/51	52.9	35.5
MSSA	84/95	88.4	27/51	52.9	35.5
mupSSA	84/95	88.4	27/51	52.9	35.5
fusRSA	9/10	90.0	2/6	33.3	56.7
fusSSA	74/83	89.2	24/44	54.5	34.6
S. pyogenes	30/34	88.2	3/8	37.5	50.7
Other *Streptococci*	2/2	100.0	0	0	NA
Other Gram (+) pathogens	2/2	100.0	0	0	NA
Gram (-) pathogens	9/14	64.3	2/7	28.6	35.7
All Pathogens	127/147	86.4	32/66 9/14	48.5 64.3	37.9
No Pathogens	18/25	72.0			7.7

Study TOC100224 enrolled 519 patients of which 517 were treated. The PP population accounted for 87% of the total treated, the ITTB population consisted of 394/517 (76%) and the PPB population contained 66% of the total treated. Nearly 80% of patients had non-bullous impetigo.

Clinical success rates at EOT were numerically higher for retapamulin. In each comparison the lower limit of the 95% CI for the treatment difference was greater than -1%. In the PPC, PPB and ITTB populations the lower limit of the confidence interval was greater than zero.

Clinical response at EOT by analysis population

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

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

Baseline SIRS scores were shown to be a significant predictor of clinical and microbiological response with higher scores resulting in lower probabilities of success. The observed data indicated no difference in retapamulin success rates at EOT between bullous (69/70; 98.6%) and non-bullous (245/247; 99.2%) impetigo or between age strata (all 98-100%).

Clinical response at follow-up resulted in smaller differences between groups than seen at EOT. The lower 95% CIs were within -4% for all populations described but did not exceed zero. Of the 35 retapamulin and 22 sodium fusidate patients in the ITTC population who had failed by the time of the follow-up visit 11 and 8 in respective groups had failed due clinical recurrence.

Clinical response at follow-up (Day 14)

Analysis Population	Retapamulin		Sodium fusidate		Difference	95% CI (%)
	N	%	N	%	%	
PPC	297/308	96.4	134/143	93.7	2.7	(-1.8, 7.2)
ITTC	310/345	89.9	150/172	87.2	2.6	(-3.3, 8.6)
PPB	227/235	96.6	99/107	92.5	4.1	(-1.4, 9.6)
ITTB	237/263	90.1	111/131	84.7	5.4	(-1.8, 12.5)

Clinical responses by pathogen showed numerical advantages for retapamulin against the two major species.

Clinical success rate at EOT by pathogen (PPC)

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

Microbiological success rates by patient and pathogen were very similar to clinical success rates.

The fact that the applicant conducted one placebo-controlled and one active controlled study in this indication was considered to be highly appropriate. The placebo-controlled study established the advantage of applying retapamulin in this condition. In the active-controlled study non-inferiority with respect to sodium fusidate was established satisfactorily.

Secondarily infected dermatoses (SID)

Study 032 enrolled 545 ITTC patients of which 85% were included in the PPC population. There was no baseline pathogen isolated from 41.3% retapamulin and 36.6% cephalexin patients and 10% of the ITTB population was excluded from the PPB population.

In the primary efficacy analysis (PPC population) patients with an outcome of Unable to determine (UTD) at EOT or at follow-up (FU) were counted as failures. Based on this analysis the lower CI for the treatment difference was just within -10%. In other pre-defined patient populations retapamulin gave consistently lower clinical success rates than cephalexin and the lower 95% CI were between -9.7 and -13.9.

Clinical response rates at follow-up by population

	Retapamulin	%	Cephalexin	%	Diff	95% CI
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)

Using the primary analysis approach the clinical success rates by underlying disease group at follow-up suggested that there might be a particular problem in atopic dermatitis as shown below.

Clinical success at follow-up by underlying skin disease (PPC)

	Retapamulin	%	Cephalexin	%	Difference (95% CI)
Atopic Dermatitis (AD)	128/148	86.5	67/73	91.8	-5.3 (-13.7, 3.1)
Psoriasis	55/63	87.3	34/39	87.2	0.1 (-13.2, 13.5)
Allergic Contact Derm (ACD)	91/108	84.3	39/44	88.6	-4.4 (-16.0, 7.2)

The overall and sub-group treatment differences after removal of UTD patients were smaller and the 95% CI for the overall analysis were -6.4, 4.9. Thus, removing the patients who were UTD at EOT and so declared failures at FU reduced the difference in success rates between treatments. However, both types of analyses would be expected and would be compared for consistency. Thus, there remained the problem that the findings were inconsistent. The reason for this inconsistency seemed to be the imbalance between groups in numbers and percentages that actually had an outcome of UTD at EOT that defaulted to failure at FU. However, this imbalance could not be explained, the discrepancy between analyses could not be dismissed and so the indication has not been granted.

Secondarily infected traumatic lesions (SITL)

Study 030A enrolled 996 patients of which 988 were treated. The PPC population consisted of 83.6% (826/988) of the ITTC population. Most of the patients (87% retapamulin and 86% cephalexin ITTC patients) had secondarily infected open wounds while the remainder had simple abscesses.

At follow-up in the PPC population clinical success was achieved in 88.7% (525/592) treated with retapamulin compared to 91.9% (239/260) treated with cephalexin.

Clinical success rates at follow-up by population

	Retapamulin		Cephalexin		Difference	95% CI (%)
	N	%	N	%	%	
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)

At the EOT visit, the clinical success rates in the PPC population were 90.6% for retapamulin and 93.0% for cephalexin. Similar findings applied to the ITTC, ITTB and PPB populations.

The logistic regression analysis found that clinical success was more likely when baseline SIRS scores were low. There was also a statistically significant association (Fisher's exact test) between clinical response and exudate/pus SIRS scores at follow-up ($p<0.001$ for the retapamulin group and $p=0.001$ for the cephalexin group). The response rates in the PPC/PPB population suggested that retapamulin was particularly less efficacious than cephalexin in abscesses as shown in the table below.

	Retapamulin			Cephalexin				
Clinical Success	N	Success	Rate	N	Success	Rate	Diff	95% CI (%)
Secondarily infected open wounds	521	463	88.9%	223	205	91.9%	-3.1%	(-7.5,1.4)
Simple abscess	71	62	87.3%	37	34	91.9%	-4.6%	(-16.3,7.1)
Micro Success								
Secondarily infected open wounds	264	231	87.5%	113	101	89.4%	-1.9%	(-8.8,5.1)
Simple abscess	38	32	84.2%	19	17	89.5%	-5.3%	(-23.3,12.8)

For those with methicillin-susceptible *S. aureus* or *S. pyogenes* at baseline the success rates at follow-up were similar between the treatment groups. However against MRSA clinical success rates were 72.0% (18/25) for retapamulin and 81.8% (9/11) for cephalexin.

Study **030B** enrolled 922 patients of which 916 were treated and the PPC population consisted of 83.6% [766/916] of the ITTC population. Most patients (around 85%) had secondarily infected open wounds rather than simple abscesses.

At follow-up, clinical success was achieved in 90.4% retapamulin and 92.0% cephalexin patients in the PPC population.

Clinical Response Rate at Follow-Up by Analysis Population

	Retapamulin		Cephalexin			95% CI
	N	%	N	%	Diff	
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)

At the EOT visit the clinical success rates in the PPC population were 92.7% for retapamulin and 91.5% for cephalexin with 95% CI of -2.8%, 5.2%. Similar results were observed for the ITTC, ITTB, and PPB populations.

The tests for association between diagnosis and clinical or microbiological outcomes were not significant but the response rates in the PPC/PPB population suggested that retapamulin was less efficacious than cephalexin in abscesses as shown in the assessors' table below.

	Retapamulin			Cephalexin				
Clinical Success	N	Success	Rate	N	Success	Rate	Diff	95% CI (%)*
Secondarily infected open wounds	464	422	90.9%	217	200	92.2%	-1.2%	(-5.6,3.2)
Simple abscess	76	66	86.8%	32	29	90.6%	-3.8%	(-16.4,8.6)
Micro Success								
Secondarily infected open wounds	221	205	92.8%	109	98	89.9%	2.9%	(-3.8,9.5)
Simple abscess	43	37	86.0%	14	14	100.0%	-14%	(-24.3,-3.7)

* Assessor's calculation derived using the normal approximation to the binomial distribution.

For *S. aureus* or *S. pyogenes* isolated at baseline the success rates at follow-up were generally similar between the treatment groups although rates for those with MRSA were lower (65.4%, 17/26) for retapamulin compared to cephalexin (93.3%, 14/15), despite the fact that all laboratories would report all MRSA as resistant to cephalexin.

Microbiological success rates by patient and by pathogen at follow-up in the CPB population were very similar to clinical success rates.

Pooled data from studies 030A and 030B showed that the clinical success rates at follow-up were 89.5% for retapamulin and 91.9% for cephalexin, with 95% CI of -5.4, 0.5. However:

- For secondarily-infected open wounds 95% CI around the observed treatment difference of -2.2% were -5.4%, 1.0%.
- For the -4.2% treatment difference for simple abscesses the 95% CI were -12.8%, 4.4%.

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. .

Pooled data reflected the individual studies in showing that the success rates for retapamulin were lower among patients enrolled in N. America and against MRSA compared to cephalexin despite the fact that all MRSA are deemed to be resistant to currently available cephalosporins. Tying up these observations, the applicant noted that the success rate for retapamulin against MRSA was considerably lower in North America (50%) than elsewhere (80% to 92%).

In the SITL studies combined 86% had a secondarily infected open wound (SIOW) and 14% had a diagnosis of abscess. Overall a higher proportion of abscesses were associated with *S. aureus* and, specifically, with MRSA infections than seen with SIOW and this finding applied in both treatment groups.

Therefore, there was an association between a clinical presentation of abscess and infection with MRSA and, particularly, with Panton Valentine Leucocidin (PVL)-positive USA300 Community Acquired -MRSA.

Based on the findings retapamulin has not been approved for treating abscesses and has not been approved for treating any infection when due to MRSA (regardless of PVL status and clone).

Clinical safety

Patient exposure

In the studies in healthy subjects the maximum exposure was to 2% ointment applied to 1600 cm2 intact skin or to 100 cm2 abraded skin once daily for 7 days.

In the Phase III studies there were 2115 patients treated with retapamulin 1% ointment. In studies 030A, 030B and 032 the double blind design meant that these patients were also exposed to matching placebo to cephalexin (suspension or tablet). Another 35 patients were exposed to retapamulin 1% ointment in the Phase II study 029.

Adverse events

Healthy subjects

Multiple applications to intact skin and single and multiple applications to abraded skin were occasionally accompanied by folliculitis, vesicles, burning or warmth, pruritus, oedema or erythema at the application site. Contact dermatitis was reported in one subject. In the three studies that examined local irritation and sensitisation potential the only AEs of note that were recorded as related to retapamulin were TSH increase, LFT increase, myalgia, pruritus and maculopapular rash.

Continuous Lead-II cardiac monitoring and multiple scheduled 12-Lead ECGs were analysed automatically and after manual readings by a cardiologist. No clinically significant association was found between retapamulin applications and ECG changes.

Patients

The overall incidence of AEs among retapamulin-treated patients was similar to total AE rates in other treatment groups.

Incidences of individual AEs were low for all treatment groups, with the majority occurring in <1% of patients. The majority of AEs were mild to moderate in intensity and only 1-2% in total per treatment group had an AE that was rated as severe.

Most Common AEs (≥ 1%) in Any Treatment Group (ITTC Phase III Combined)

	Number (%)			
Preferred Term	**Retapamulin N = 2115**	**Cephalexin N = 819**	**Sodium Fusidate N = 172**	**Placebo N = 71**
Any Adverse Event	458 (22)	205 (25)	25 (15)	18 (25)
Headache	38 (2)	16 (2)	0	0
Diarrhoea	31 (1)	22 (3)	2 (1)	0
Application site irritation	30 (1)	4 (<1)	0	1 (1)
Nasopharyngitis	27 (1)	7 (<1)	0	0
Application site pruritus	21 (<1)	3 (<1)	0	1 (1)
Nausea	19 (<1)	15 (2)	0	0
Pruritus	13 (<1)	3 (<1)	1 (<1)	1 (1)
Pyrexia	11 (<1)	3 (<1)	0	1 (1)
Abdominal pain	9 (<1)	5 (<1)	0	1 (1)

Rhinitis	6 (<1)	0	0	1 (1)
Hyperglycaemia	5 (<1)	5 (<1)	0	1 (1)
Urinary tract infection	5 (<1)	2 (<1)	4 (2)	0
Urine analysis abnormal	5 (<1)	0	0	1 (1)
Pain in extremity	4 (<1)	3 (<1)	0	1 (1)
Application site paraesthesiae	4 (<1)	0	0	1 (1)
Excoriation	3 (<1)	1 (<1)	4 (2)	0
Impetigo	3 (<1)	0	0	2 (3)
Otitis externa	1 (<1)	0	0	1 (1)
Toothache	1 (<1)	0	0	1 (1)
Urticaria	1 (<1)	0	0	1 (1)
Arthropod bite	0	1 (<1)	2 (1)	0
Xerosis	0	0	0	2 (3)
Neurodermatitis	0	0	0	1 (1)
Pharyngitis bacterial	0	0	0	1 (1)
Sciatica	0	0	0	1 (1)

AEs coded to the general disorders and administration site conditions were reported by 3% of pooled retapamulin patients [95% CI: 2.0%, 3.4%] and 4% in the placebo group [0.88%, 11.86%] of study TOC103649. However, AEs in this SOC were reported by <1% in the pooled cephalexin group [0.34%, 1.75%] even though the dummy ointment applied was the same as the placebo ointment in TOC103649. Application site AEs were not reported by any patient who applied sodium fusidate ointment.

AEs related to application and instillation site (ITTC: Phase III Combined)

	Number (%) of Subjects			
	Retapamulin N =2115	**Cephalexin N = 819**	**Sodium Fusidate N = 172**	**Placebo N = 71**
Any AE n (%)	56 (3)	7 (<1)	0	3 (4)
App site irritation	30 (1)	4 (<1)	0	1 (1)
App site pruritus	21 (<1)	3 (<1)	0	1 (1)
App site pain	7 (<1)	0	0	0
App site paraesthesiae	4 (<1)	0	0	1 (1)
App site erythema	2 (<1)	0	0	0
App site hypersensitivity	0	1 (<1)	0	0

Logistic regression analyses performed on patients treated with retapamulin did not show any correlation between AEs (and in particular AEs related to application site reactions) and the total wound size at baseline. There did not appear to be a relationship between dressing type and application site irritation but due to the small numbers no definitive conclusion can be drawn. For retapamulin there were generally similar AE reporting rates across the different age categories and between genders. Logistic regression analyses performed for the retapamulin group did not demonstrate any relationship between age and AEs. There were differences between racial groups and regions but these followed a similar pattern as for the other treatment groups and so more likely reflect different patient/investigator attitudes to reporting.

The overall frequency of drug-related AEs was low, with the highest rate of 7% reported in the cephalexin group. The only individual drug-related AEs that were reported in at least 1% were application site irritation (1%) in the retapamulin group and diarrhoea (2%) in the cephalexin group. The drug-related AEs in the placebo group included application site pruritus (1%) and application site paraesthesiae (1%).

Serious adverse event/deaths/other significant events

There were two deaths reported in Phase II/III studies, both of which occurred in study 030A and in the retapamulin group. However, these were considered to be unrelated to retapamulin.

There were no SAEs in study 029 or in the sodium fusidate ointment or placebo groups in Phase III studies while < 1% of patients had SAEs in the retapamulin and cephalexin groups. The only SAE reported in > 1 patient was cellulitis, which occurred in two patients treated with retapamulin and one treated with cephalexin. However, in each case the cellulitis was not related to the wound that was being treated in the study.

Laboratory findings

Healthy subjects

In study 026, thyroid function (TFT) was monitored (free T3 and T4 and TSH). Overall 8 retapamulin patients had any treatment emergent elevation in LFTs and four had any abnormal TFT. However, there was no relationship between exposure to retapamulin and abnormalities in these or any other laboratory test. Four retapamulin subjects had elevations in liver function tests of potential clinical concern that were treatment emergent. One of these had the elevation noted as an AE although the most marked abnormality was an ALT of 141 IU/L. However, he was in the group allocated to 2% ointment to 1600 cm2 of intact skin and he did have the highest plasma exposure in the study (day 7 AUC 358 ng.h/ml) with the second highest Cmax (20 ng/ml). Two others had abnormal glucose values and two had raised potassium levels on a single day.

In study 025 abnormalities of potential clinical concern included two with elevated LFTs but the highest values were < 200 IU/L. TSH, free T3 and free T4 were obtained at screening and at 24 h after the last patch application for all subjects. Levels were also measured on Day 8 of dosing for subjects that received 14 or 21 days of repeat dosing. No significant changes were noted in the median values of free T3, free T4 or TSH. Two subjects had slightly elevated TSH at FU but normal free T3 and T4.

In the ketoconazole interaction study (**TSC101825**) TSH was measured at screening and FU (7-14 days after dosing ended) and at pre-specified times during each regimen. Free T4 values were obtained for subjects with abnormal TSH values. No trends in median TSH were noted but two subjects at one time-point each had TSH abnormalities during ketoconazole dosing alone.

In study 034 there were several subjects with raised blood glucose at follow-up but none was considered to be clinically significant.

Patients

For all the clinical laboratory values, there were no large mean changes from baseline for the total population or for the individual age strata. Also, numbers of patients with values outside the normal reference range was low throughout the study for all treatment and age groups.

The incidence of shifts from normal to high or low blood glucose values was similar across the treatment groups in each age category.

Discontinuation due to adverse events

Healthy subjects

In 026 there were 5 subjects discontinued retapamulin due to AEs and all were in the maximum exposure group (2% ointment once daily for 7 days to 100 cm2 abraded skin) of which four subjects had papules and vesicles and one had erythema at the application site.

Patients

In Phase III studies, AEs leading to withdrawal were reported with a similar and low incidence (≤ 2% in any group) with each treatment. The most commonly-reported AEs leading to withdrawal were cellulitis and diarrhoea, each occurring in two patients in the retapamulin and cephalexin groups, while vomiting led to withdrawal in four patients in the cephalexin group only.

Discussion on clinical safety

There were no major concerns raised by the data.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan.

The applicant proposed that the low systemic exposure and rapid clearance of retapamulin means that the potential for adverse reactions is small. It is acknowledged that hypersensitivity reactions resulting in systemic effects such as angioedema, urticaria and anaphylaxis could occur. Contact dermatitis was encountered in clinical studies. There will be monitoring of literature and spontaneous reports to investigate any possible association between retapamulin use and hypersensitivity reactions. It is considered that there is no need for a specific risk minimisation plan.

Table Summary of the risk management plan

Safety issue	**Proposed pharmacovigilance activities**	**Proposed risk minimisation activities**
Development of resistance to retapamulin	GSK will conduct a European surveillance study. The objective of this surveillance study will be to monitor for changes in the *in vitro* activity of retapamulin against pathogens relevant to the approved indications (i.e. *S. aureus* and beta-haemolytic streptococci). The study will begin two years after the approval of Altargo, and will be conducted in compliance with CHMP guidelines. Isolates studied will be confined to those very recently recovered from patients. If possible, the data will predominantly reflect community-acquired infections. These investigations will be supplemented by provision of publicly available data on susceptibility derived from reliable sources (e.g. reference public health laboratories) in EU Member States. Regarding the CHMP's requests to seek patients who have failed to respond to retapamulin for testing and to include genetic characterisation of *S. aureus*, GSK agree to discuss these formally with the Rapporteur, Co-Rapporteur and CHMP	No risk minimisation strategies are necessary at this time

	by 4Q2007.	
Off-label use in very young paediatrics	GSK will conduct a PK study in paediatric subjects aged 2 months and older to determine whether there is an increase in systemic exposure in these subjects. GSK will monitor prescription data in Europe and USA, in order to identify the extent of off-label prescribing and use in the paediatric population, and to aid the analysis of adverse events. GSK will perform this analysis on an annual basis for the first five years post-launch.	No risk minimisation strategies are necessary at this time

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

6. Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the clinical performance of the product have been investigated and are controlled in a satisfactory way.

Non-clinical pharmacology and toxicology

Long-term studies in animals to evaluate carcinogenic potential have not been conducted. However, retapamulin is not shown to be genotoxic.

In an embryotoxicity study in rats, developmental toxicity and maternal toxicity were observed at oral doses of ≥ 150 mg/kg/day. No studies to evaluate effects of retapamulin on pre-/postnatal development were performed. Appropriate warnings have been incorporated in sections 4.6 and 5.3 of the Summary of Product Characteristics.

Efficacy

The efficacy of Altargo has been shown in randomised, controlled studies in which retapamulin achieved similar clinical and microbiological success rate to comparative therapies for the treatment of impetigo and infected small lacerations, abrasions or sutured wounds. However, the efficacy of retapamulin in abscesses and in infections due to MRSA was inadequate. Hence, retapamulin has not been approved for the treatment of abscesses or for the treatment of any infections known or thought likely to be due to MRSA. In addition, retapamulin was not approved for the treatment of secondary infected dermatoses.

Safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

User consultation

User testing has been performed on the Patient Information Leaflet and from the results it can be concluded that the relevant information is accessible and understandable for the patients.

Risk-benefit assessment

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Altargo in the short term treatment of the following superficial skin infections: *Impetigo; Infected small lacerations, abrasions or sutured wounds* was favourable and therefore recommended the granting of the marketing authorisation.