The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: SB-275833/032
Title: A Randomized, Double-blind, Double-Dummy, Multicenter, Non-inferiority Phase III Study to Assess the Safety and Efficacy of Topical SB-275833 Ointment, 1%, Applied Twice Daily, versus Oral Cephalexin, 500mg in Adults, or 12.5mg/kg (250mg/5mL) in Children, Twice Daily, in the Treatment of Secondarily-Infected Dermatoses
Rationale: Chronic inflammatory skin diseases (i.e., dermatoses), such as atopic dermatitis, psoriasis, and allergic contact dermatitis are common. One consequence of these dermatoses is that the integrity of the skin barrier is compromised, making the skin of patients more susceptible to colonization and infection with pathogens such as *Staphylococcus aureus* and *Streptococcus pyogenes*. Overt, secondary bacterial infection is a common problem in patients with inflammatory skin disease. At the time of this study, retapamulin (SB-275833) is being developed as a topical antibiotic for the treatment of patients with uncomplicated bacterial skin infections. Study 275833/032 evaluated the use of retapamulin ointment, 1%, versus oral cephalexin, in adults and children for the indication of secondarily-infected dermatoses (SID) due to confirmed or suspected *S. aureus* and/or *S. pyogenes*.
Phase: III
Study Period: 24 September to 12 April 2005
Study design: Randomized, double-blind, double-dummy, multi-center, non-inferiority study.
Centers: A total of 105 centres in 11 countries participated in the study. The countries (number of centers) participating were Austria (3), Canada (6), Germany (14), India (3), Italy (3), Peru (2), Poland (4), Russian Federation (3), South Africa (7), United Kingdom-CMD (9), and United States (51).
Indication: Secondarily-Infected Dermatoses (SID; including atopic dermatitis, psoriasis and allergic contact dermatitis) due to confirmed or suspected *S. aureus* and/or *S. pyogenes.*
Treatment: All subjects were randomized in a 2:1 (retapamulin:cephalexin) ratio to treatment with either topical retapamulin Ointment, 1%, twice daily (b.i.d.) for 5 days, and oral cephalexin placebo b.i.d. for 10 days, or placebo ointment, b.i.d. for 5 days and oral cephalexin b.i.d. for 10 days.
Objectives: To evaluate whether topical retapamulin ointment, 1%, was at least as effective clinically as oral cephalexin in the treatment of secondarily-infected dermatoses.
Primary Outcome/Efficacy Variable: • clinical response at end of therapy (2-4 days post-therapy; Day 7-9 [retapamulin] and Day 12-14 [cephalexin]) in the per protocol clinical (PPC) population.
Secondary Outcome/Efficacy Variables: • clinical response at end of therapy (2-4 days post-therapy; Day 7-9 [retapamulin] and Day 12-14 [cephalexin]) in the PPC population; • clinical response on Day 7-9; • clinical response on Day 12-14; • clinical response on Day 17-19; • microbiological response at follow-up (7-9 days post-therapy; Day 12-14 [retapamulin] and Day 17-19 [cephalexin]) in the per protocol bacteriological (PPB) population; • microbiological response at end of therapy (2-4 days post-therapy; Day 7-9 [retapamulin] and Day 12-14 [cephalexin]) in the PPB population; • microbiological response on Day 7-9; • microbiological response on Day 12-14; • microbiological response on Day 17-19; • clinical response at end of therapy for subjects who had methicillin-resistant *S. aureus* (MRSA) isolated at baseline • clinical response at follow-up for subject who had MRSA isolated at baseline • therapeutic response (combined clinical and microbiological response) at follow-up (7-9 days post-therapy; Day 12-14 [retapamulin] and Day 17-19 [cephalexin]) in the PPB population; • therapeutic response at end of therapy (2-4 days post-therapy; Day 7-9 [retapamulin] and Day 12-14 [cephalexin]) in the PPB population.
Statistical Methods: Four populations were defined for efficacy analyses: intent-to-treat clinical (ITTC) included all randomized subjects who took at least one dose of active study medication (also used for the safety analyses), intent-to-treat bacteriological (ITTB) included all randomized subjects who took at least one dose of active study medication

and who had evidence of a bacterial infection at baseline, PPC included the subject of the ITTC population who subsequently adhered to the protocol and PPB included the subset of the ITTB population who adhered to the protocol. This study was a non-inferiority trial, with at least 90% power to detect a treatment difference greater than 10% (delta=10%), with 2.5% one-sided alpha. A 95% two-sided normal approximation confidence interval for the difference in treatment efficacy rates was used to test for non-inferiority. Non-inferiority was declared if the lower limit of this confidence interval was greater than -10%. Assuming the clinical success rates for retapamulin ointment, 1% and cephalexin groups were approximately 90%, it was estimated that, using a 2:1 randomization scheme, a sample size of 284 evaluable subjects in the retapamulin ointment, 1%, group, and 142 in the cephalexin group, were required. It was anticipated that approximately 532 subjects were to be enrolled into the study in order to provide 426 evaluable subjects at follow-up (i.e., assume 20% subject non-evaluability).

Study Population: To be enrolled, subjects with SID had to have atopic dermatitis, psoriasis, or allergic contact dermatitis, along with one or more clinical signs and symptoms of infection, including a sudden exacerbation of the skin disease, weeping, crusting, or the appearance of superficial pustules or purulent discharge. The area of the infected lesion receiving topical treatment was to be no larger than 100cm^2 in area, or up to a maximum of 2% body surface area for subjects <18 years of age. A subject could be enrolled with multiple-infected lesions, provided the total area for all infected lesions combined did not exceed 100cm^2 (or 2% body surface area for subjects <18 years of age). In addition, the infections were to be those which had a high likelihood of having *S. aureus* and/or *S. pyogenes* as the causative infectious agent. Initially, subjects ≥13 years of age were enrolled, regardless of race or gender. Once the safety review of an Independent Data Monitoring Committee for retapamulin studies 275833/030A and 275833/030B was completed and approved, the age range was extended to include infants and children ≥9 months of age.

Number of Subjects:	Retapamulin	Cephalexin
Planned N	355	177
Randomised N	363	183
Completed n (%)	320 (88)	176 (96)
Total Number Subjects Withdrawn n (%)	43 (12)	7 (4)
Withdrawn due to Adverse Events n (%)	5 (1)	0
Withdrawn due to Lack of Efficacy n (%)	14 (4)	4 (2)
Withdrawn for Other Reasons n (%)	24 (7)	3 (2)
Demographics	Retapamulin	Cephalexin
N (ITT)	363	183
Females: Males	131:232	78:105
Mean Age in Years (SD)	33.7 (20.2)	34.8 (22.1)
Children (<13 years):Adolescents (≥13 to <18 years)	70:11	37:6
White n (%)	213 (59)	106 (58)
Asian – Central/South Asian heritage n (%)	72 (20)	31 (17)
Primary Efficacy Results:		
	Retapamulin	Cephalexin
Clinical Response at Follow-Up (7-9 days post-therapy; Day 12-14 [retapamulin] and Day 17-19 [cephalexin]) in the PPC Population		
Success rate, n/N (%)	275/320 (85.9)	140/156 (89.7)
Difference in Success Rates, % (95% CI)	-3.8 (-9.9, 2.3)	
Secondary Efficacy Results:		
	Retapamulin	Cephalexin
Clinical Response at End of Therapy (2-4 days post-therapy; Day 7-9 [retapamulin] and Day 12-14 [cephalexin]) in the PPC Population		
Success rate, n/N (%)	312/339 (92.0)	152/162 (93.8)
Difference in Success Rates, % (95% CI)	-1.8 (-6.5, 2.9)	
Clinical Response on Day 7-9 in the PPC Population		
Success rate, n/N (%)	311/338 (92.0)	162/166 (97.6)
Difference in Success Rates, % (95% CI)	-5.6 (-9.3, 1.9)	
Clinical Response on Day 12-14 in the PPC Population		
Success rate, n/N (%)	275/320 (85.9)	149/159 (93.7)
Difference in Success Rates, % (95% CI)	-7.8 (-13.0, -2.4)	
Clinical Response on Day 17-19 in the PPC Population		
Success rate, n/N (%)	255/307 (83.1)	140/156 (89.7)

Difference in Success Rates, % (95% CI)	-6.7 (-13.0, -0.3)	
Per-Subject Microbiological Response at Follow-Up (7-9 days post-therapy; Day 12-14 [retapamulin] and Day 17-19 [cephalexin]) in the PPB Population		
Success rate, n/N (%)	163/187 (87.2)	90/98 (91.8)
Difference in Success Rates, %	-4.7	
Per-Subject Microbiological Response at End of Therapy (2-4 days post-therapy; Day 7-9 [retapamulin] and Day 12-14 [cephalexin]) in the PPB Population		
Success rate, n/N (%)	185/199 (93.0)	95/101 (94.1)
Difference in Success Rates, %	-1.1	
Microbiological Response on Day 7-9 in the PPB Population		
Success rate, n/N (%)	184/198 (92.9)	102/105 (97.1)
Difference in Success Rates, %	-4.2	
Microbiological Response on Day 12-14 in the PPB Population		
Success rate, n/N (%)	163/187 (87.2)	93/99 (93.9)
Difference in Success Rates, %	-6.8	
Microbiological Response on Day 17-19 in the PPB Population		
Success rate, n/N (%)	151/181 (83.4)	90/98 (91.8)
Difference in Success Rates, %	-8.4	
Clinical Response at End of Therapy for Subjects who had MRSA Isolated at Baseline in the PPC Population		
Success rate, n/N (%)	5/5 (100)	2/2 (100)
Clinical Response at Follow-Up for Subjects who had MRSA Isolated at Baseline in the PPC Population		
Success rate, n/N (%)	5/5 (100)	2/2 (100)
Therapeutic Response at Follow-Up (7-9 days post-therapy; Day 12-14 [retapamulin] and Day 17-19 [cephalexin]) in the PPB Population		
Success rate, n/N (%)	158/187 (84.5)	89/98 (90.8)
Difference in Success Rates, %	-6.3	
Therapeutic Response at End of Therapy (2-4 days post-therapy; Day 7-9 [retapamulin] and Day 12-14 [cephalexin]) in the PPB Population		
Success rate, n/N (%)	180/199 (90.5)	95/101 (94.1)
Difference in Success Rates, %	-3.6	
Safety results: For this study, the safety population was defined as all subjects who took at least one dose of coded study medication. The safety population was therefore identical to the ITT Clinical population.		
	Retapamulin (N = 363)	Cephalexin (N = 183)
Most Frequently Reported Adverse Events	n (%)	n (%)
Any Event	79 (22)	40 (22)
Nasopharyngitis	10 (3)	5 (3)
Headache	6 (2)	3 (2)
Diarrhea	4 (1)	5 (3)
Upper Respiratory Tract Infection	4 (1)	3 (2)
Application site irritation	4 (1)	0
Application site pruritis	4 (1)	0
Eczema	4 (1)	0
Rhinitis	4 (1)	0
Abdominal pain	3 (<1)	3 (2)
Dermatitis atopic	2 (<1)	2 (1)
Folliculitis	0	2 (1)
Rhinitis allergic	0	2 (1)
NOTE: all other adverse events occurred in <1% of subjects.		
Serious Adverse Events, n (%) [n considered by the investigator to be related to study medication]		
Subjects with non-fatal SAEs		
Status asthmaticus	1 (<1) [0]	0
Syncope	0	1 (<1) [0]
Subjects with fatal SAEs	0	0

Conclusions:
The condition of non-inferiority for the primary endpoint of the study was met. Retapamulin Ointment, 1%, b.i.d. for 5 days, was demonstrated to be non-inferior to cephalexin, b.i.d. for 10 days, in the treatment of subjects with SID, based on the clinical response at follow-up.
Adverse events were reported in 79 (22%) subjects in the retapamulin group and 40 (22%) subjects in the cephalexin group. Nasopharyngitis and headache were the most frequently reported AEs in the retapamulin group, and nasopharyngitis and diarrhea were the most frequently reported AEs in the cephalexin group. A serious adverse event was reported in one subject in each treatment group. No fatal serious adverse events were reported.

Publications: No Publications

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