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.: TOC103469

Title: A Randomised, Double-blind, Multicentre, Superiority Placebo-controlled, Phase III Study to Assess the Efficacy and Safety of Topical 1% SB-275833 Ointment versus Placebo Ointment Applied Twice Daily for 5 days in the Treatment of Adults and Paediatric Subjects with Impetigo

Rationale: Impetigo is a highly contagious common bacterial skin infection that is commonly treated with antibacterial agents. However, the emergence and spread of antibiotic resistance in hospital and community pathogens has significantly eroded the utility of established antibacterial agents, creating a need for new antibiotics with modes of action distinct from those of established agents. SB-275833 Ointment, 1%, is currently being developed as a topical antibiotic for bacterial skin infections including impetigo, secondarily-infected traumatic lesions (SITL) and secondary infected dermatoses (SID). This study supports the use of SB-275833 Ointment, 1%, in adults and children for the treatment of impetigo.

Phase: III

Study Period: 27 April 2005 - 02 January 2006

Study Design: Randomised, double-blind, multi-centre, superiority, placebo-controlled study

Centres: This study was conducted in 17 centres in four countries (Netherlands, India, Peru and Mexico).

Indication: Impetigo

Treatment: Subjects received one of two treatments: topical SB-275833 Ointment, 1%, twice daily for 5 days or placebo ointment twice daily for 5 days. Subjects were randomised to treatment in a ratio of 2:1 (active:placebo).

Objectives: To compare the efficacy and safety of topical application of SB-275833 Ointment, 1%, with topical placebo ointment given twice daily for 5 days, in the treatment of adult and paediatric subjects with impetigo.

Primary Outcome/Efficacy Variable: The primary efficacy endpoint was the clinical response (clinical success or clinical failure) to study medication at End of Therapy, 2 days after treatment (Day 7; Visit 2) in the Intent to Treat Clinical (ITTC) population. The hypothesis to be tested by the primary endpoint was that the clinical efficacy of SB-275833 Ointment, 1%, at End of Therapy was superior to that of placebo in the treatment of adult and paediatric subjects with impetigo.

Secondary Outcome/Efficacy Variables: The secondary efficacy endpoints were as follows:

- Clinical response at End of Therapy - Day 7; Visit 2 (2 days after study treatment)
- Clinical response at Follow-Up - Day 14; Visit 3 (9 days after study treatment)
- Assessment of lesion(s) area at each visit
- Microbiological response at End of Therapy - Day 7; Visit 2 (2 days after study treatment)
- Microbiological response at Follow-Up - Day 14; Visit 3 (9 days after study treatment)
- Number and percent of subjects who had methicillin-resistant *Staphylococcus aureus* (MRSA), mupirocin-resistant *S. aureus* (mupRSA) or fusidic acid-resistant *S. aureus* (fusRSA) isolated at screening (Day 1) and by clinical response at End of Therapy Day 7; Visit 2 (2 days after treatment)
- Number and percent of subjects who had various pathogens including MRSA, mupRSA and fusRSA isolated at baseline by clinical response at Follow-Up Day 14; Visit 3 (9 days after treatment)

Statistical Methods: This was a superiority study, with 90% power and a one-sided alpha of 2.5%. A 2:1 randomisation scheme of SB-275833 Ointment, 1%: placebo ointment was employed. A conclusion of superior efficacy of SB-275833 Ointment, 1%, was to be drawn if the lower limit of the 95% confidence interval for the treatment difference was greater than zero. Conclusions of superiority were also confirmed with Fisher's Exact Tests.
Four subject populations were defined for the analysis of clinical efficacy and bacteriology data, and one population was defined for the safety analyses, as follows:

- Intent to Treat Clinical (ITTC): All randomised subjects who took at least one dose of study medication.
- Intent to Treat Bacteriology (ITTB): All ITTC subjects who had evidence of a bacterial infection at baseline.
- Per Protocol Clinical (PPC): Subjects from the ITTC population who adhered to the protocol (did not violate the protocol).
- Per Protocol Bacteriology (PPB): Subjects from the ITTB population who adhered to the protocol (did not violate the protocol).
- Safety Population: All subjects who took at least one dose of study medication, (i.e., the ITTC population).

Study Population: Subjects aged ≥9 months (or ≥18 months in The Netherlands) with a clinical diagnosis of primary impetigo (bullous or non-bullous), defined as a lesion or a group of lesions characterised by red spots or blisters without

crusts, which later progress to lesions that ooze and form yellow or honey-coloured crusts surrounded by an erythematous margin; no more than 10 discrete localised impetigo lesions (lesion(s) not exceeding 100 cm^2 in total area) suitable for topical treatment; with a minimum of a Skin Infection Rating Scale Score (SIRS) of at least 8. Subjects were excluded from the study if they had a previous hypersensitivity to the SB-275833 ointment any component of the ointment, they had an underlying skin disease or skin trauma with clinical evidence of secondary infection, they had signs and symptoms of systemic infection, they had a bacterial skin infection which in the opinion of the investigator could not be appropriately treated by a topical antibiotic or they had received a systemic antibacterial, steroid, or applied any topical therapeutic agent directly to the impetigo lesion(s), less than 24 hours prior to study entry.		
Number of Subjects	SB-275833	Placebo
Planned, N	140	70
Randomised, N	140	73
Randomised and Treated, N	139	71
Completed, n (%)	122 (88%)	40 (56%)
Total Number Subjects Withdrawn, N (%)	17 (12%)	31 (44%)
Withdrawn due to Adverse Events n (%)	1 (<1%)	1 (1%)
Withdrawn due to Lack of Efficacy or Disease Progression n (%)	8 (6%)	27 (38%)
Withdrawn for other reasons n (%)	8 (6%)	3 (4%)
Demographics	SB-275833	Placebo
N (ITTC Population)	139	71
Females: Males	73:66	34:37
Mean Age, years (SD)	12.3 (14.02)	8.9 (8.95)
Paediatric (<18 years), n (%)	111 (80%)	64 (90%)
Adult, n (%)	28 (20%)	7 (10%)
Race, n (%)		
Asian – Central/South Asian heritage, n (%)	59 (42%)	30 (42%)
White – Caucasian/European Heritage, n (%)	52 (37%)	23 (32%)
American Indian or Alaskan native, n (%)	23 (17%)	13 (18%)
Other, n(%)	5 (3.6%)	5 (7.0%)
Primary Efficacy Results:	SB-275833	Placebo
Clinical Response at End of Therapy (ITTC population)	N=139	N=71
Success rate, %	85.6	52.1
Difference in success rate	33.5	
95% confidence intervals	20.5, 46.5	
Secondary Efficacy Results:		
Clinical Response at Follow up (ITTC population)	N=139	N=71
Success rate, %	75.5	39.4
Difference in success rate	36.1	
95% confidence intervals	22.7, 49.5	
Assessment of Lesion Area (ITTC population)		
End of therapy, mean % change from baseline	69.8	-43.3
Follow up, mean % change from baseline	75.1	-20.8
Microbiological Response at End of Therapy (ITTB population)	N=114	N=57
Success rate, %	91.2	50.9
Difference in success rate	40.4	
Microbiological Response at Follow up (ITTB population)	N=114	N=57
Success rate, %	80.7	36.8
Difference in success rate	43.9	
Clinical Response at End of Therapy by Baseline Pathogen (ITTC population)		
All pathogens	N=147	N=66
Success rate, %	86.4	48.5
Difference in success rate	37.9	
FusRSA*	N=10	N=6
Success rate, %	90.0	33.3
Difference in success rate	56.7	

Clinical Response at Follow up by Baseline Pathogen (ITTC population)		
All pathogens	N=147	N=66
Success rate, %	78.9	30.3
Difference in success rate	48.6	
FusRSA*	N=10	N=6
Success rate, %	70.0	33.3
Difference in success rate	36.7	

* no MRSA or mupRSA were isolated in this study

Safety Results: Adverse events (AEs) were collected during the treatment and follow-up period (serious adverse events [SAEs] were recorded from consent to fulfil international regulatory reporting requirements). All AEs and SAEs occurring during this period were followed until resolution, until the condition stabilised, until the event was otherwise explained, or until the subject was lost to Follow-Up.

Most Common AEs (Greater than or Equal to 2 Subjects - 1% for SB-275833 and 3% for Placebo) in Either Treatment Group

Adverse Event (Preferred Term)	Number (%) of Subjects SB-275833 N=139	 Placebo N=71
Any Event	34 (24.5)	18 (25.4)
Application site pruritus	11 (7.9)	1 (1.4)
Application site paraesthesia	3 (2.2)	1 (1.4)
Headache	4 (2.9)	0
Impetigo	2 (1.4)	2 (2.8)
Pyrexia	3 (2.2)	1 (1.4)
Application site irritation	2 (1.4)	1 (1.4)
Puritus	2 (1.4)	1 (1.4)
Application site pain	2 (1.4)	0
Diarrhoea	2 (1.4)	0
Xerosis	0	2 (2.8)

Serious Adverse Events (SAEs) – On- therapy n(%)[considered by the investigator to be related]	SB-275833 N=139	Placebo N=71
Eczema herpeticum	1 (0.7%) [0]	0
Impetigo	1 (0.7%) [0]	0

Note: both events experienced by the same subject

Conclusion:

- SB-275833 Ointment, 1%, applied twice daily for 5 days, was demonstrated to be superior to placebo, applied twice daily for 5 days, in the treatment of subjects with impetigo.
- SB-275833 Ointment, 1%, was effective at eradicating the key pathogens associated with impetigo: *S. aureus*, including fusidic acid-resistant isolates, and *S. pyogenes*.
- The overall rate of AEs was low in this study and was comparable between the treatment groups. Most of the AEs were mild or moderate in intensity and the number of subjects withdrawn due to an AE was very small. Drug-related AEs (mostly application site reactions) were more frequently reported in the SB-275833 Ointment, 1%, group.

Publications: No Publications

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