Sponsor:	InfectoPharm Arzneimittel und Consilium GmbH	
Study title:	Multicentre, prospective, double-blind, two-armed phase III study on the efficacy and safety of topical impetigo therapy with two 2% mupirocin ointments	
EudraCT-No.	2011-002001-30	
Protocol number / Study code:	IMUP	
Study phase:	Phase III	
Investigators / study centres:	14 paediatric study centres in Germany	
Study period:	First patient first visit November 04, 2011	Last patient last visit June 07, 2012
Number of patients:	Planned: 120 (with a positive initial bacteriological finding)	Analysed: 150 (120 with a positive initial bacteriological finding as inclusion criterion + 30 without) (average age 5.4 years; range 1 month to 15.1 years).
Objectives:	The primary objective of the study is to prove that the generic test preparation InfectoMupi ointment 2% is statistically equivalent to the original preparation Bactroban® ointment 2% with respect to the proportion of patients who are clinically cured at the final visit (Day 14, 7 days after the end of a 7-day treatment). Secondary objectives include the investigation of further aspects of efficacy (e.g. microbiological cure) and safety (e.g. adverse drug reactions).	
Study indication:	Impetigo	
Test drug:	InfectoMupi ointment 2% (Infectopharm)	
Active ingredients:	Mupirocin 2%	
Comparator:	Bactroban® ointment 2%	
Dose:	Three times per day	
Mode of administration:	Both ointments are to be applied topically in thin layers on the affected parts of the skin	
Duration of treatment:	7 consecutive days	

Main criteria for inclusion:

- Age between 28 days and 15 years
- Clinically diagnosed impetigo
- Skin Infection Rating Scale (SIRS) ≥ 4
- Presence of ≥ 3 SIRS signs/symptoms (individual score values ≥ 1)
- Detection of staphylococcus aureus and/or streptococcus pyogenes in the initial swab from the affected region of the skin

Main criteria for exclusion:

- Necessity of systemic therapy with antibiotics due to the severity and/or expansion of the impetigo or of a concomitant infection
- Extensively infected skin areas
- Affection of critical body regions as the auditory canal and the corner of the eye
- Impetigo as a secondary infection of a bite injury
- Impetigo in the area of central venous catheters
- Impetigo with intranasal affection
- Dermatological diseases that could impair the assessment of the impetigo (e.g. ecthyma, furunculosis, abscess, contact dermatitis, bite injuries)
- Clinically relevant primary or secondary immunodeficiency
- Current or less than 6 months dating back malign tumour diseases, chemotherapy or radiotherapy
- Inadequately adjusted clinically relevant diabetes
- Known moderate or severe renal insufficiency
- Other severe diseases that the investigator assesses as conflicting with participation in this study
- Systemic or dermal therapy with antibiotics, antimycotics or corticoids during the past 7 days
- Dermal application of antiseptics during the past 7 days
- Girls of child-bearing potential
- Known intolerance to macrogol or mupirocin
- Inability of the parents to understand the instructions of the study
- Obvious unreliability of the parents or missing willingness to cooperate

Methodology:

- Randomised, double-blind, multicentre, parallel group study with active comparator
- Study duration for each patient: 14 days (7 days treatment, 7 days follow-up)
- Evaluation of the clinical signs/symptoms blistering, exudate/pus, crusting, erythema/inflammation and itching/pain by means of the Skin Infection Rating Scale (SIRS)
- Investigation of bacteriological swab for presence or absence of staphylococcus aureus and streptococcus pyogenes
- Assessment of further need of antibiotic therapy for treatment of impetigo

Criteria for evaluation:

Efficacy

Primary efficacy variable:

Clinical cure rate at Day 14, defined as the percentage of patients who fulfil all of the following properties:

- No need for further antibiotic therapy of impetigo
- SIRS score = 0 (absent) for signs/symptoms blistering and exudate/pus
- SIRS score ≤ 1 (absent or mild) for signs/symptoms crusting, erythema/inflammation and itching/pain

Secondary efficacy variables:

- Microbiological cure rate at Day 14, defined as the percentage of patients with negative result regarding both staphylococcus aureus and streptococcus pyogenes in the bacteriological swab
- Clinical cure rate at Day 7 (defined analogous to the primary efficacy variable)
- Microbiological cure rate at Day 7
- Percentage of patients with premature discontinuation at Day 3 due to lack of efficacy
- SIRS total score values at Day 7 and Day 14
- Changes in SIRS total score between Day 0 and Day 7, Day 0 and Day 14, and between Day 7 and Day 14

Safety

- Number and classification of adverse events and adverse drug reactions (ADRs).
- Premature discontinuations

Statistical methods:

Testing for equivalence of the two treatment groups with respect to the primary efficacy variable in accordance with the FDA Draft Guidance on Mupirocin. Confirmatory analysis is based on the per-protocol data set.

The test of equivalence was based on the following (two-sided) hypotheses:

H_0: $p_{InfectoMupi} - p_{Bactroban} < -0.20$ or $p_{InfectoMupi} - p_{Bactroban} > 0.20$ versus

H_1: $-0.20 \leq p_{InfectoMupi} - p_{Bactroban} \leq 0.20$

where

$p_{InfectoMupi}$ = clinical cure rate at Day 14 after start of treatment with InfectoMupi and

$p_{Bactroban}$ = clinical cure rate at Day 14 after start of treatment with Bactroban

According to the method of Westlake a two-sided 90% confidence interval was calculated for the difference in observed cure rates. Statistical equivalence is proven, if the confidence interval lies entirely inside the recommended equivalence interval [-0.20 ; 0,20].

All other statistical tests are exploratory.

Summary of results:

Efficacy results:

Primary efficacy variable:

The clinical cure rate at Day 14 for the PP data set was 1.0 (100.0%) for InfectoMupi and 0.95 (95.0%) for Bactroban according to the predefined criteria. As the 90% confidence interval [-0.01 ; 0.11] for the difference in cure rates was entirely inside the interval [-0.20 ; 0.20], recommended by the FDA Draft Guidance on Mupirocin, statistical equivalence of both medications was proven. This result was confirmed by the corresponding analysis for the mITT data set.

With the exception of 3 patients in the Bactroban group, all patients were clinically cured. Two of these 3 patients terminated the study at Day 3 resp. Day 7 because of treatment failure and one patient had a SIRS score value 1 (=mild) for the symptom exudate/pus.

Secondary efficacy variables:

Secondary efficacy variables were analysed based on the modified ITT data set and confirmed by PP analysis.

The microbiological cure at Day 14 (negative result for both staphylococcus aureus and streptococcus pyogenes in the bacteriological swab) is demonstrated for 100% (56 patients) under InfectoMupi and 98.4% (61 patients) under Bactroban.

At Day 7, 73.2% (41 patients) under InfectoMupi and 69.8% (44 patients) under Bactroban fulfilled the criterion for clinical cure.

At Day 7, 85.7% (48 patients) in the InfectoMupi group and 91.9% (57 patients) in the Bactroban group fulfilled the criterion for microbiological cure.

Only 1.6% (1 patient) in the Bactroban group discontinued the study at Day 3 due to lack of efficacy.

The mean baseline values of the SIRS total score were 8.7 in both treatment groups. At Day 7, the mean was 1.5 in the InfectoMupi group and 1.7 in the Bactroban group. Until Day 14, the values further decreased to 0.3 in the InfectoMupi group and to 0.7 in the Bactroban group. The group differences were not statistically significant.

The mean total score in the SIRS at Day 7 compared to baseline decreased by 7.2 for InfectoMupi and 7.0 for Bactroban. In the 7 days after the end of the treatment phase further reduction of the average scores was observed by 1.2 for InfectoMupi and 1.0 for Bactroban. There were no statistically significant differences between the two treatment groups.

Safety results:

Overall, AEs were reported for 17 patients (InfectoMupi: 5, Bactroban: 12). The total number of events was 28 (InfectoMupi: 11, Bactroban: 17).

All AEs were mild to moderate and there were no serious adverse events (SAEs) and no dropouts due to AEs.

Adverse drug reactions (ADR), i.e. AEs with suspected causal relationship with the study medication were reported for one patient in the InfectoMupi group. An erythema with mild intensity occurred after application, but was resolved two days later without any remedial measure. According to the SmPC of Bactroban® Ointment 2 %, erythema is an expected adverse drug reaction occuring with a frequency of 0.1 % to 1 % during the application of Bactroban® Ointment 2 %.

Conclusion:

Statistical equivalence between InfectoMupi and Bactroban with respect to the primary efficacy variable could be proven in accordance with the methods recommended in the FDA Draft Guidance on Mupirocin, based on the fact that the 90 % confidence interval of the difference of both cure rates [-0.01 ; +0.11] is contained within [-0.20 ; +0.20], which is required to show therapeutic equivalence of both treatments, and was confirmed by the analysis in the mITT population. Thus, InfectoMupi and Bactroban proved to be therapeutically equivalent.

The high efficacy demonstrated by the analysis of the primary efficacy variable was further supported by the corresponding microbiological cure rates at Day 14 with only one patient in the Bactroban group not being microbiologically cured. All assessed secondary efficacy variables regarding microbiological cure, clinical cure, or the SIRS score did not indicate any relevant treatment differences and none were statistically significant after 7 or 14 days of observation.

There were no differences in the safety profile of InfectoMupi and Bactroban. No serious adverse events (SAEs) and no dropouts due to AEs occurred.

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