

2 Synopsis

Sponsor:	Dermapharm AG, Grünwald	
Study title:	Double-blind, randomised clinical study comparing efficacy and safety of fusidic acid 2%_betamethasone 0.1% cream vs. Fucicort [®] cream vs. vehicle in patients with bacterial infected eczema	
Study phase:	Phase III	
Investigators / study centres:	14 investigators in 14 study centres; a list of investigators and study centres is attached in appendix 16.1.4	
Publication:	No	
Study period:	First patient first visit 07 September 2012	Last patient last visit 26 June 2014
Number of patients:	Planned: 400 (randomised)	Analysed: 394 (safety data set)
Objectives:	Assessment of efficacy and safety of a new cream with fusidic acid 2% and betamethasone valerate 0.1% in comparison with the approved preparation Fucicort [®] cream and the underlying vehicle in patients with bacterial infected eczema. The study aims to show non-inferiority of the test preparation as compared to Fucicort [®] , and superiority of both active medications over the vehicle.	
Study indication:	Bacterial infected eczema	
Test drug:	Fusidic acid 2%_betamethasone 0.1% cream: "FusBet-C"	
Active ingredients:	Fusidic acid 0.5 H ₂ O 20.4 mg/g, betamethasone valerate 1.214 mg/g	
Comparators:	Fucicort [®] cream (fusidic acid 0.5 H ₂ O 20.4 mg/g, betamethasone valerate 1.214 mg/g): "Fucicort" Vehicle	
Daily dose:	According to size of affected area	
Mode of administration:	To be rubbed in slightly on the affected skin area twice daily (in the morning, in the evening)	
Batch no:	120401 for patients 001 to 270, 130901 for patients 351 to 670	
Duration of treatment:	2 weeks (14 days); 1 week (7 days) in case of complete healing at Visit 2 (Day 7)	

Main criteria for inclusion:

- Women and men ≥ 18 years of age
- Diagnosis of “bacterial super-infected eczema” based on clinical symptoms in a treatment area between 5 and 25 cm²
- At least moderately severe clinical picture, i.e. patients must have a SIRS score ≥ 8 . The SIRS (*Skin Infection Rating Scale*) score is defined as the sum score of the 7 clinical parameters exudate/pus, crusting, erythema, tissue warmth, tissue edema, itching and pain (each symptom assessed on a scale ranging from 0 to 6)
- Presence of the clinical parameter “exudate/pus” (i.e. score ≥ 1)

Methodology:

- Randomised, double-blind, multi-centre study with three parallel treatment groups
- 2 weeks study treatment and 1 week follow-up
- Evaluation of the clinical activity parameters exudate/pus, crusting, erythema, tissue warmth, tissue edema, itching and pain in the test area at each study visit by means of a 7-point rating scale. The SIRS score is defined as the sum of the individual score values.
- Evaluation of therapeutic success by the investigator and the patient by means of a 5-point rating scale
- Evaluation of overall therapeutic success by the investigator by means of a 4-point rating scale
- Bacteriological investigation for identification of pathogens
- Documentation of adverse events
- Evaluation of tolerability by the investigator and by the patient by means of a 4-point rating scale

Criteria for evaluation:

Efficacy

Primary efficacy variable:

Number (percentage) of patients with *clinical treatment success* at the main visit (Visit 3).

Clinical treatment success is defined as follows:

- SIRS score < 8
- Score value for activity parameters exudate/pus = 0
- No need for further treatment of study diagnosis

Secondary efficacy variables:

- Change of the SIRS score between Visit 1 and Visit 2, Visit 3 and Visit 4, respectively
- Course of the individual activity parameters exudate/pus, crusting, erythema, tissue warmth, tissue edema, itching and pain at Visit 2, Visit 3 and Visit 4
- Value of the SIRS score at Visit 2, Visit 3 and Visit 4
- Number (percentage) of patients with bacteriological success at Visit 3
- Evaluation of therapeutic success at Visit 2 and Visit 3 by the investigator
- Evaluation of therapeutic success at Visit 2 and Visit 3 by the patient
- Evaluation of overall therapeutic success at Visit 4 by the investigator
- Number (percentage) of patients with clinical relapse / re-infection at Visit 4

Safety

- Number and classification of adverse events
- Evaluation of tolerability by the investigator at Visit 2 and Visit 3
- Evaluation of tolerability by the patient at Visit 2 and Visit 3

Statistical methods:

Three simultaneous statistical tests based on pairwise comparison of the primary efficacy variable between treatments:

Test 1: FusBet-C vs. Fucicort (testing for non-inferiority, one-sided with $\alpha = 2.5\%$)

Test 2: FusBet-C vs. Vehicle (testing for superiority, two-sided with $\alpha = 5\%$)

Test 3: Fucicort vs. Vehicle (testing for superiority, two-sided with $\alpha = 5\%$)

For confirmatory analysis the non-inferiority test is carried out for the per protocol data set, whereas the two tests for superiority are based on the intention-to-treat data set.

All other statistical tests are exploratory.

Summary of results:

Efficacy results:

Regarding the intention-to-treat (ITT) data set, the proportion of patients with clinical treatment success (primary efficacy variable) was 84.7% for the test preparation (FusBet-C), 75.3% for the active reference preparation (Fucicort) and 56.8% for the underlying vehicle. For the per-protocol (PP) data set the percentages were slightly higher in each group.

Non-inferiority of FusBet-C compared to Fucicort with respect to the primary efficacy variable and superiority of both active treatments over the vehicle could be statistically proven for both efficacy data sets (ITT and PP). Accordingly, the primary objective of the study was achieved.

There were no significant differences between FusBet-C and Fucicort for almost all secondary efficacy variables. The only exceptions were the outcomes of the clinical activity parameters exudate/pus and crusting at the end of the follow-up period, where the results were statistically superior ($p < 0.05$) for FusBet-C.

The improvements as measured by the SIRS score were more pronounced for the two active treatments than for the vehicle at all visits after baseline. The pairwise differences were statistically significant ($p < 0.05$) except for the comparison between Fucicort and the vehicle at the end of the follow-up period.

Statistically significant superiority of the two active preparations over the vehicle were also observed for the bacteriological success rates (FusBet-C: 77.5%, Fucicort: 69.0%, Vehicle: 22.0%), the evaluation of therapeutic success by both the investigator and the patient, and the majority of the individual activity parameters.

Safety results:

Adverse events (AEs) were reported for 21 patients (FusBet-C: 10, Fucicort: 7, Vehicle: 4). There were no serious adverse events (SAEs), and no AE was suspected to have a possible or not assessable causal relationship with the study medication, i.e. there were no adverse drug reactions (ADRs).

Tolerability of the study medication was assessed as either *very good* or *good* for more than 90% of all patients, irrespective of the treatment group. This applies for both the ratings by the investigators and the evaluations by the patients themselves.

Conclusion:

Efficacy conclusions:

- Non-inferiority of FusBet-C in comparison with Fucicort was shown for the primary efficacy variable. Both active treatments were superior over the vehicle. The primary objective of the study was therefore met.
- FusBet-C and Fucicort led to a more pronounced reduction of SIRS score at all visits after baseline compared to the vehicle.
- Bacteriological success rates of FusBet-C and Fucicort were statistically superior to the vehicle.
- Investigator/Patient-based assessments of treatment success rated FusBet-C and Fucicort as more successful than the vehicle.

Safety conclusions:

- There were no serious adverse events or adverse drug reactions (ADRs) in any treatment group.
- There was no sign of a new safety signal.
- Tolerability of all treatments were assessed favourably both by the physicians and the patients.

Overall conclusions:

- The primary objective of this study of showing non-inferiority of FusBet-C versus Fucicort and superiority over the vehicle was met.
- There were no serious adverse events or ADRs in any treatment group.
- There was no sign of a new safety signal.
- Tolerability of all treatments were assessed favourably both by the physicians and the patients.

Date of report:	13 November 2014 (version 1.0)
Earlier reports:	None

1. List of Investigators:

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Trial protocol: Double-blind, randomised clinical study comparing efficacy and safety of fusidic acid 2%_betamethasone 0.1% cream vs. Fucicort® cream vs. vehicle in patients with bacterial infected eczema

Report ID: 11-03/FusBet-C

Study Code: 2011-004370-28

EudraCT: 2011-004370-28

There were no changes or amendments to the trial protocol in the course of the study. The clinical trial was not ended prematurely.