2 Synopsis

Sponsor:	Dermapharm AG, Grünwald	
Study title:	Double-blind, randomised clinical study comparing efficacy and safety of Gentamicin 0.1%_Betamethasone 0.05% Ointment (Test) vs. Diprogenta® Ointment (Reference) vs. Vehicle in patients with bacterial infected eczema	
Study phase:	Phase III	
Investigators / study centres:	15 investigators in 15 study centres; a list of investigators and study centres is attached in appendix 16.1.4	
Publication:	No	
Study period:	First patient first visit 29 January 2016	Last patient last visit 09 June 2017
Number of patients:	Planned: 400 (randomised)	Analysed: 405 (safety data set)
Objectives:	Assessment of efficacy and safety of a new ointment with gentamicin 0.1% and betamethasone dipropionate 0.05% in comparison with the approved preparation Diprogenta® Ointment and the underlying vehicle in patients with bacterial infected eczema. The study aims to show non-inferiority of the test preparation as compared to Diprogenta®, and superiority of both active medications over the vehicle.	
Study indication:	Bacterial infected eczema	
Test drug:	Gentamicin 0.1%_Betamethasone 0.05% Ointment: “GentaBet-S”	
Active ingredients:	Gentamicin sulfate (1.67 mg/g), Betamethasone dipropionate (0.64 mg/g)	
Comparators:	Diprogenta® Ointment (gentamicin sulfate (1.67 mg/g), betamethasone dipropionate (0.64 mg/g)): "Diprogenta" Vehicle (to test drug)	
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:	151101 for patients 001 to 560, 170101.2 for patients 561 to 708	
Duration of treatment:	2 weeks (14 days); could be reduced to 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 cm^2
- 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 oedema, itching and pain (each symptom assessed on a scale ranging from 0 (= absent) 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 oedema, 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 examination visit (end of treatment, EOT).

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

Safety

- Number and classification of adverse events
- Evaluation of tolerability by the investigator at all visits during treatment
- Evaluation of tolerability by the patient at all visits during treatment

Statistical methods:

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

Test 1: GentaBet-S vs. Diprogenta (testing for non-inferiority, one-sided with $\alpha = 2.5\%$)

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

Test 3: Diprogenta 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:

With respect to the intention-to-treat (ITT) data set (N = 405), the proportion of patients with clinical treatment success (primary efficacy variable) was 83.9% for the test preparation (GentaBet-S), 81.0% for the active reference preparation (Diprogenta) and 59.3% for the underlying vehicle. The corresponding results for the per-protocol (PP) data set (N = 357) were 85.4%, 80.4% and 65.7%, respectively.

Non-inferiority of GentaBet-S compared to Diprogenta 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 statistically significant differences between the two active treatment groups for all secondary efficacy variables except for the change of the SIRS score between baseline and Visit 1 and the activity parameters *crusting* (at Visit 4) and *tissue oedema* (at Visit 2 and Visit 3). The results for these parameters were all in favour of GentaBet-S (with $p < 0.05$).

Both active treatments proved to be statistically superior in comparison to the underlying vehicle except for a few individual activity parameters. The difference between GentaBet-S and Vehicle was not statistically significant (i.e. $p > 0.05$) for *tissue warmth* (at Visit 4). The difference between Diprogenta and Vehicle was not statistically significant for *tissue warmth* (all visits) and *tissue oedema* (at Visit 4). With respect to *pain*, all comparisons between the active treatments and the vehicle were leading to a p-value > 0.05.

Safety results:

Adverse events (AEs) were reported for 13 patients (8.1%) in the GentaBet-S group, 11 patients (6.7%) in the Diprogenta group and 10 Patients (12.3%) under the vehicle. There were only 2 serious adverse events (SAEs), occurring in the GentaBet-S and the Vehicle group, respectively. The outcomes of both SAEs were reported as *recovered*.

One patient in the GentaBet-S group (0.6%), 2 patients in the Diprogenta group (1.2%) and 2 patients in the Vehicle group (2.5%) had adverse drug reactions (ADRs), i.e. AEs with *possible* or *not assessable* causal relationship with the study medication

Conclusion:

Efficacy conclusions:

- Non-inferiority of GentaBet-S vs. Diprogenta was shown for the primary variable both in the ITT and the PP data set. Both active treatments were superior to the vehicle. The primary objective of the study was therefore met.
- Most secondary efficacy variables showed stronger effects for the active treatment arms than for the vehicle.
- Bacteriological eradication rates and investigator-based assessment of treatment success were markedly higher in the active treatment arms.

Safety conclusions:

- 37 adverse events occurred in 34 patients (8.4%).
- 2 serious adverse events occurred in the study, none of which was assessed as related to the study medication.
- All three study drugs were tolerated well.
- There was no indication of a new safety signal.

Overall conclusions:

- Non-inferiority of GentaBet-S vs. Diprogenta was shown for the primary variable both in the ITT and the PP data set. Both active treatments were superior to the vehicle. The primary objective of the study was therefore met.
- Most secondary efficacy variables showed stronger effects for active treatment arms as compared to vehicle.
- Bacteriological eradication rates and investigator-based assessment of treatment success were markedly higher in the active treatment arms.
- 37 adverse events occurred in 34 patients (8.4%).
- 2 serious adverse events occurred in the study, none of which was assessed as related to the study medication.
- All three study drugs were tolerated well.
- There was no indication of a new safety signal.

Date of report:	02 January 2018 (version 1.0)
Earlier reports:	20 December 2017 (version 0.1)

1. List of investigators

Investigators:	**Study Site:**	
	Adress:	**No.:**
Dr. med. Udo Amann 'Leiter der Klinischen Studie' Coordinating Investigator Deputy Investigator: Dr. med. Karl-Heinz Vehring	Hautarzt- und Allergiezentrum Lingen Georgstraße 51 49809 Lingen	01
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Dr. med. Beatrice Gerlach Deputy Investigator: Dr. med. Katrin Oppers	Praxis für Dermatologie und Venerologie Hauptstr. 36 01097 Dresden	05
Dr. med. Martin Miehe Deputy Investigator: Dr. Ulrike Serfling	Hautarztzentrum Tegel Gorkistr. 3 13507 Berlin	06
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Prof. Dr. med. Uwe Reinhold Deputy Investigator: Dr. med. Anette Ko	Dermatologisches Zentrum Bonn Friedensplatz 16 53111 Bonn	08
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Trial protocol: Double-blind, randomised clinical study comparing efficacy and safety of Gentamicin 0.1%_Betamethasone 0.05% Ointment (Test) vs. Diprogenta® Ointment (Reference) vs. Vehicle in patients with bacterial infected eczema

Report ID: 15-02/GentaBet-S

Study Code: 15-02/GentaBet-S

EudraCT: 2014-005519-18

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