SYNOPSIS

Name of Sponsor/Manufacturer: LEO Pharma A/S	Location of study report in Regulatory Dossier for authorities	(For National Authority Use only)
Name of Investigational Product/ Finished Product, if available: Fucidin® cream	Volume:	
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Title of study/Protocol Code Number:

Fucidin® cream in the treatment of impetigo/FUC 0301 INT.

Centre details:

A total of 18 centres: 15 in Sweden and 3 in Norway.

Publication references:

To be decided.

Study period details:	Phase of development:
First patient was enrolled on 12-May-2004 Last patient completed the study on 11-Mar-2005	IV

Objectives/hypothesis, if applicable:

- To investigate the clinical and bacteriological efficacy of Fucidin® cream in the treatment of impetigo.
- To assess the validity of *in vitro* susceptibility-testing of *S. aureus* to fusidic acid as a prediction of clinical and bacteriological outcome in impetigo patients treated with Fucidin® cream.
- To investigate the genetic relationship between *S. aureus* strains isolated from impetigo patients.

Study methodology:

An international, multicentre, prospective, randomised, double-blind, 2 arm, parallel group, vehicle-controlled, phase IV study.

Number of patients enrolled:

It was planned to include 360 patients in the study in the proportion of 3:1 with 270 patients in the Fucidin® cream treated group and 90 patients in the Fucidin® cream vehicle treated group, but due to a very low recruitment rate in Sweden and Norway and inability to include UK (rejection from IEC) in the study, only 59 patients were enrolled during 10 months. 58 were randomised in the proportion of 3:1 to treatment groups as follows:

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– 42 to Fucidin® cream

– 16 to Fucidin® cream vehicle

Diagnosis and main criteria for patient selection:

Diagnosis: Impetigo

Main criteria for inclusion:

1) Clinical diagnosis of impetigo, with a severity score of minimum 1 for at least one of the following signs: pustules/infected bullae, erythema and infiltration/induration.
2) Patients aged 2-11 years.
3) Patients who had a definable target lesion of at least 1×1 cm.
4) Patients of either sex.
5) Following receipt of verbal and written information about the trial, the parent(s) or legal guardian had to provide signed and informed consent before any trial related activity was carried out.

Main criteria for exclusion:

6) Patients with duration of impetigo for more than 5 days.
7) Patients with other active inflammatory dermatitis (e.g. atopic dermatitis) at the site of impetigo.
8) Patients with temperature above 38.5°C rectally (or equivalent).
9) Patients with impetigo lesions too extensive to be amenable to topical therapy.
10) Patients who had been administered topical or systemic antibacterial agents, including topical or systemic Fucidin®, within the previous 4 weeks (or use during the study, except for the investigational product).
11) Patients who had been administered antiseptic treatment (e.g. Microcid® or Hibiscrub®) on the impetigo lesions within the previous 7 days (or use during the study).
12) Patients with other primary or secondary skin and soft tissue infections (e.g. ecthyma, carbuncle, furuncle, erysipelas, cellulites).
13) Patients with another bacterial disease or viral skin infection.
14) Patient known to be HIV positive and/or had known diminished immune response.
15) Known or suspected hypersensitivity to component(s) of Investigational Products.

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16) Current participation in any other interventional clinical trial.
17) Patients who had received treatment with any non-marketed drug substance (i.e. an agent which had not yet been made available for clinical use following registration) within the last 4 weeks.
18) Previously enrolled/randomised in this trial.
19) Patient known or suspected of not being able to comply with a trial protocol (e.g. alcoholism, drug dependency or psychotic state).
20) Female patients between menarche and age 11 (excluded due to contraception requirements).

Investigational product, dose, method of administration, lot numbers:

Fucidin® cream (fusidic acid 20 mg/g), applied three times daily for 10 days on all impetigo lesions, lot number 03 214 61 01.

Reference product, dose, method of administration, lot numbers:

Fucidin® cream vehicle, applied three times daily for 10 days on all impetigo lesions, lot number 03 244 61 01.

Duration of treatment:

The study was divided into two phases: A 10 days' treatment phase followed by a 14 days' follow-up phase. Hence, the total duration of the study was 24 days. Visits were scheduled at days 1, 4 and 11 (treatment phase) and 25 (follow-up phase for clinical effect and for adverse events, if applicable).

Criteria for evaluation

Efficacy :

Primary Response Criterion

The proportion of patients with 'Clinical and bacteriological success' at end of treatment.

Secondary Response Criteria

1) The proportion of patients with 'Clinical success' at visit 2, 3 and at end of treatment.
2) The proportion of patients with 'Bacteriological success' at visit 2, 3 and at end of treatment.
3) The actual change in Total Severity Score from baseline to end of treatment.
4) The distribution of individual sign scores at end of treatment.

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Safety:

Evaluation of (Serious) Adverse Events

1) The proportion of patients with adverse events.
2) The proportion of patients with lesional/perilesional adverse events.

Statistical methodology:

The proportion of patients with 'Clinical and bacteriological success' at end of treatment was compared between the two treatment groups using the Cochran-Mantel-Haenszel test. The proportion of patients with 'Clinical success' and with 'Bacteriological success' at visit 2, 3 and at end of treatment were analysed in the same way as the primary response criterion. The actual change in Total Severity Score from baseline to end of treatment was compared between treatment groups using analysis of covariance. Log-linear analysis was used to compare the two treatment groups regarding the distribution of individual signs scores at end of treatment. The proportion of patients who experienced adverse events and lesional/perilesional adverse events were compared between treatment groups using Fisher's exact test.

Summary – Conclusions

Efficacy results:

Primary response criterion:

From the analysis of the primary response criterion involving the proportion of patients with 'Clinical and bacteriological success' at the end of treatment (LOCF), Fucidin® cream was statistically significantly more effective than Fucidin® cream vehicle. Robustness analysis supported this result.

Clinical and bacteriological success	Fucidin® cream 20 mg/g (n=33)	Fucidin® cream vehicle (n=13)	Treatment difference Odds ratio (95% CI)	P-value
Success	16 (48.5%)	1 (7.7%)	13.2 (1.4 to 120.4)	P=0.009[1]
Failure	17 (51.5%)	12 (92.3%)		P=0.81[2]
Total	33 (100.0%)	13 (100.0%)		P=0.016[3]

1) Cochran-Mantel-Haenszel test for the hypothesis of odds ratio equal to 1.
2) Breslow-Day test for homogeneity of odds ratio across countries.
3) Fisher's exact test.

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Secondary response criteria:

The results for the secondary response criteria involving the proportion of patients with 'Clinical success' at visit 2, 3 and at end of treatment (EOT) were as follows:

Clinical success	Fucidin® cream 20 mg/g (n=40)	Fucidin® cream vehicle (n=16)	Treatment difference Odds ratio (95% CI)	P-value[1]
Visit 2	18 (45.0%)	2 (12.5%)	5.7 (1.1 to 28.6)	P=0.023
Visit 3[2]	27 (79.4%)	7 (70.0%)	1.7 (0.3 to 8.1)	P=0.54
EOT (LOCF)	27 (67.5%)	7 (43.8%)	2.7 (0.8 to 8.8)	P=0.10

1) Cochran-Mantel-Haenszel test for the hypothesis of odds ratio equal to 1.
2) n=34 for Fucidin® cream 20 mg/g group, n=10 for Fucidin® cream vehicle group.

The results for the secondary response criteria involving the proportion of patients with 'Bacteriological success' at visit 2, 3 and at end of treatment (EOT) were as follows:

Bacteriological success	Fucidin® cream 20 mg/g (n=33)	Fucidin® cream vehicle (n=13)	Treatment difference Odds ratio (95% CI)	P-value[1]
Visit 2	6 (18.2%)	0 (0.0%)		P=0.10
Visit 3[2]	17 (63.0%)	1 (16.7%)	8.5 (0.9 to 83.5)	P=0.043
EOT (LOCF)	17 (51.5%)	1 (7.7%)	12.8 (1.5 to 109.6)	P=0.007

1) Cochran-Mantel-Haenszel test for the hypothesis of odds ratio equal to 1.
2) n=27 for Fucidin® cream 20 mg/g group, n=6 for Fucidin® cream vehicle group.

From the analysis of the secondary response criteria involving the actual change in Total Severity Score from visit 1 to end of treatment for patients in the full analysis set there was a statistically significant difference in response in favour of the Fucidin® cream group (mean change -3.9) compared to the Fucidin® cream vehicle group (mean change -1.3) (P=0.008).

From the analysis of the secondary response criteria involving individual sign scores (pustules/infected bullae, erythema, infiltration/induration, erosion and crusting), there was a statistically significant difference in response at end of treatment in favour of the Fucidin® cream group compared to the Fucidin® cream vehicle group for erythema, infiltration/induration, erosion and crusting (P=0.024, P=0.014, P=0.007 and P=0.005, respectively) but not for pustules/infected bullae (P=0.074).

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In vitro susceptibility testing to fusidic acid in the Fucidin® cream group was able to predict a higher 'Clinical and bacteriological success' at end of treatment in patients infected with susceptible *S. aureus* compared with patients infected with resistant *S. aureus*.
Fucidin® cream was statistically significantly more effective than Fucidin® cream vehicle for patients infected with *S. aureus* susceptible to fusidic acid (P=0.008). The difference between the treatment groups was not statistically significant for patients infected with *S. aureus* resistant to fusidic acid (P=0.28).

PFGE analysis indicated that most of the *S. aureus* isolates were representant of a single clone similar to the clone already reported in Sweden and Norway (2, 36, 37).
PFGE analysis showed the high degree of homology of the strains isolated during the study confirming the presence of a clonal outbreak in the recruiting centres.

Safety results:

The analysis of the proportion of patients with at least one adverse event showed no statistically significant difference when comparing Fucidin® cream treatment with Fucidin® cream vehicle treatment; 12.5% versus 25.0%, respectively (P=0.26). The proportion of patients with at least one lesional/perilesional adverse event was lower in the Fucidin® cream group than in the Fucidin® cream vehicle group; 5.0% versus 18.8%, respectively, although the difference was not statistically significant (P=0.13). One withdrawal due to adverse event, which was considered not related to the study medication by the investigator, was reported in the Fucidin® cream group. There were no deaths or serious adverse events reported in the study.

Conclusion:

The present study confirmed that Fucidin® cream was statistically significantly more effective than Fucidin® cream vehicle for the topical treatment of impetigo patients.

In vitro susceptibility testing of fusidic acid resistance was able to predict a better clinical and bacteriological outcome after treatment with Fucidin® cream for patients infected with susceptible *S. aureus* than for those infected with resistant *S. aureus*. The majority of the resistant strains (almost 85%) isolated during this study were belonging to the previously

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reported clone (2, 36, 37).

Furthermore patients treated with Fucidin® cream 20 mg/g reported relatively fewer adverse events than those treated with the vehicle although the difference was not statistically significant.

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13-Jul-2009