RESULT SYNOPSIS

Name of Sponsor/Company: Biofrontera Bioscience GmbH	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: BF-37 cream 4%	Volume:	
Name of Active Ingredient: Riluzole (BF-37)	Page:	

Title of Study: A Phase II Proof-of-Concept, Randomized, Double-blind, Vehicle-controlled Study, Including an Open-label Comparison to an Active Control, To Assess the Efficacy and Safety/Tolerability of Topical Riluzole in Patients with Stable Plaque-type Psoriasis

Study No. BF-37-CT002; EudraCT-no: 2007-007037-39

Investigator(s): Prof. Dr. Ulrich Mrowietz (coordinating investigator)

Study centers: 2 sites, Germany

Publication (reference): None

Studied period (years): Date of first patient enrolled: 02 APR 2008 Date of last patient completed: 23 JAN 2009	**Phase of development:** Phase II (Proof-of-concept)

Objectives: The primary objective of the study was to assess the antipsoriatic efficacy of a topical riluzole formulation (BF-37 cream 4%) in patients with stable psoriatic plaques in an intraindividual comparison vs. vehicle and an active control. The secondary objectives of the study were the measurement of the skin redness at the treatment areas as well as the evaluation of the safety/tolerability of the topical riluzole formulation.

Methodology: This study was designed as a randomized, double-blind, vehicle-controlled, phase II proof-of-concept study. In addition, it comprised an open-label comparison to an active control (Betnesol®-V cream 0.1% with the active ingredient betamethasone valerate).

Number of patients (planned, randomized and analyzed): A total of 11 patients were randomized as planned. Analysis of safety was performed for the safety data set (SS), comprising all 11 patients randomized and treated. Analysis of efficacy was performed for the full analysis set (FAS) and per protocol set (PPS), both also comprising all 11 patients.

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Diagnosis and main criteria for inclusion: Male or female patients aged at least 18 years with stable plaque-type psoriasis with plaques of at least 2 cm in diameter at five comparable treatment areas, which are separated from each other by at least 2 cm for occluded and by at least 5 cm for non-occluded treatment areas. The local Psoriasis Area and Severity Index (PASI) had to be at least 6 for each treatment area, i.e. a minimum score of 2 (on the 5-point scoring system) for each of the three clinical symptoms erythema, induration, and scaling. In order to avoid potential interactions with other topical or systemic medication for psoriasis, a 2-week washout period (topical pre-treatment) or a 4-week washout period (systemic pre-treatment) was to be applied before treatment with the study medication.

Test product, dose, batch number, mode of administration: BF-37 cream 4%, batch numbers C0801001 and C0704005, daily topical application of approximately 1 mg (200 µL per treatment area).

Reference therapy, dose, batch number, mode of administration: Vehicle (BF-37 cream without active ingredient), batch number C0801001 and C0704005, daily topical application of approximately 1 mg (200 µL per treatment area); active control (Betnesol®-V cream 0.1%), batch number C304591, daily topical application of approximately 1 mg (200 µL per treatment area).

Duration of treatment: BF-37 cream 4% and vehicle were applied daily under occlusive or non-occlusive conditions for 14 consecutive days. The active control was also applied daily for 14 consecutive days but only non-occlusively tested.

Criteria for evaluation:

Efficacy:

The primary efficacy endpoint was the change in psoriasis severity measured by the local PASI (i.e. the sum of the three single items erythema, induration and scaling) between predose (day 1) and the end of the study (day 15).

Secondary variables for the efficacy assessment were the change between predose (day 1) and the end of the study (day 15) in the single items of the local PASI (i.e. erythema, induration and scaling) and in skin redness of the psoriatic lesions (colorimetric measurements).

Safety:

The assessment of safety was based on the occurrence and duration of local skin reactions and other adverse events (AEs), the assessment of vital signs and physical examinations and on safety laboratory assessments.

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Statistical methods:

All analysis sets in this study (SS, FAS, PP) were identical. Demographics and baseline characteristics as well as the efficacy endpoints were analyzed for patients in the FAS only.

The primary efficacy endpoint, i.e. the change in local PASI between predose (day 1) and the end of the study (day 15), was analyzed descriptively for each treatment resp. treatment condition and timepoint. The analysis comprised the following comparisons:

- BF-37 cream 4% occluded vs. vehicle occluded
- BF-37 cream 4% non-occluded vs. vehicle non-occluded
- BF-37 cream 4% occluded vs. BF-37 cream 4% non-occluded
- Vehicle occluded vs. vehicle non-occluded
- BF-37 cream 4% occluded vs. Betnesol®-V cream 0.1% (active control)
- BF-37 cream 4% non-occluded vs. Betnesol®-V cream 0.1% (active control)
- Betnesol®-V cream 0.1% (active control) vs. vehicle occluded
- Betnesol®-V cream 0.1% (active control) vs. vehicle non-occluded

An analysis of variance model (ANOVA) was used. The treatment pairs were tested using two-sided paired t-tests at a significance level of $\alpha=0.05$. As a sensitivity analysis, data were also analysed using the non-parametric paired Wilcoxon rank test. To check for comparability of the different treatment areas before treatment, a paired t-test and paired Wilcoxon rank test were conducted for the absolute values at day 1 (predose). The secondary efficacy endpoints were analyzed using descriptive statistics. The same statistical comparisons using two-sided paired t-test and paired Wilcoxon rank test were performed as for the primary parameter. In addition, the Bowker test was performed for the single items of the local PASI at the end of study (day 15).

The safety endpoints were analyzed for patients in the SS. AEs were coded and summarized by MedDRA system organ class (SOC) and preferred term (PT). They were displayed in summary tables using descriptive statistics. They were grouped by SOC and PT and analyzed with regard to their severity and relationship to study treatment. Local AEs, i.e. local skin reactions, were displayed in summary tables broken down by treatment area. Further safety endpoints were summarized by descriptive statistics.

Descriptive statistics for all recorded and derived variables used appropriate descriptive summary tables (continuous data: sample size, mean, standard deviation (SD), minimum, median, maximum; categorical data: sample size, absolute and relative frequency).

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SUMMARY / CONCLUSIONS

EFFICACY RESULTS:

Compared to predose values (ranging from 7.5 to 8.0) a reduction in local PASI throughout the study could be observed for all treatments. Reduction was strongest for the two occluded treatments BF-37 cream 4% and vehicle which showed very similar results (-4.3 and -4.2, respectively). Treatment with the non-occluded BF-37 cream 4% resulted in a distinctly lower reduction in local PASI (-2.8) which was comparable to the effect observed for the non-occluded vehicle (-3.0).

Treatment with the comparator drug Betnesol-V® cream 0.1% resulted in a slightly lower reduction at day 15 (-4.0 points) compared to the occluded treatments. This reduction is not as effective as expected. However, the negative slope in the progression of local PASI within the second week of treatment may indicate a further improvement of the score after the 14-day treatment which cannot be stated for the other treatments.

The descriptive results were underlined by the statistical comparison of the treatments. A significantly larger reduction in local PASI from predose to end of study was only observed for the BF-37 cream 4% occluded compared to the BF-37 cream 4% non-occluded (p=0.0074 and p=0.0156 in the paired t-test and Wilcoxon rank test, respectively).

Most of the decrease in mean local PASI occurred already in the first 7 days of treatment. This applied to all study medications. Until this time point the occluded treatments were not only superior to the corresponding non-occluded treatments but also to the comparator drug Betnesol-V® cream 0.1%. However, it is a well-known phenomenon that occlusion of topically administered drugs has a distinctive effect within a short treatment period.

The results were not influenced by differences in the treatment areas before treatment, as the test of comparability of the absolute values at day 1 (predose) revealed no significant result for any of the comparisons.

Regarding the secondary efficacy endpoints, the three single local PASI items erythema, induration and scaling, a reduction throughout the study was observed for all of these parameters. Whereas in erythema only a slight reduction occurred which was similar for all treatments, a more distinct change to study end was observed for induration and, even stronger, for scaling. Concerning these two parameters, the mean reduction to study end was higher for the two occluded treatments BF-37 cream 4% and vehicle as compared to the corresponding non-occluded treatments and similar to the comparator drug Betnesol-V® cream 0.1%. Again, this result may be mainly influenced by the occlusion itself.

Accordingly, the statistical comparison of the different treatments concerning the change in the three single local PASI items from predose to study end revealed a statistically significant difference only for two comparisons, i.e. for the BF-37 cream 4% occluded compared to the BF-37 cream 4% non-occluded (p=0.0011 and p=0.0078) and for the vehicle occluded compared to the vehicle non-occluded (p=0.0047 and p=0.0195) concerning the item scaling.

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EFFICACY RESULTS (continued):

For the items erythema and induration no significant difference between any of the treatments could be detected For all secondary parameters the test of comparability of the different treatment areas before treatment revealed no statistically significant result for any of the comparisons

SAFETY RESULTS:

After the start of study treatment a total of 10 AEs in 5/11 patients (45.5%) were reported. Nine of these events were local reactions from the MedDRA PT ‘application site pruritus’ (MedDRA LLT ‘application site itching’) which were all assessed by the investigators as related to study medication. This kind of AE was already known from former psoriasis studies with topical riluzole.

The local reactions occurred under all treatments with a similar frequency for the occluded and non-occluded treatments (5 and 4 events, respectively).

All AEs (including the event ‘bruising of foot’, MedDRA LLT ‘contusion’) were of mild intensity and did not require treatment. At study end all patients had recovered from their AE(s) without residual effects.

No deaths, serious adverse events or AEs leading to withdrawal of a patient occurred in the study.

For all clinical laboratory variables mean changes from screening to the last value were small with no clinically relevant differences found. Individual laboratory values which changed from normal at screening to out of normal range during the course of the study were assessed by the investigators as clinically not relevant.

CONCLUSION:

In conclusion, application of the BF-37 cream 4% in an occluded manner is distinctly more effective than the corresponding non-occluded treatment. Based on the data from the present trial the active ingredient riluzole did not lead to a higher antipsoriatic effect, as shown by the similar results using BF-37 cream 4% or vehicle alone. The mean reduction in local PASI at study end was higher for the two occluded treatments BF-37 cream 4% and vehicle as compared to the corresponding non-occluded treatments and similar to the comparator drug Betnesol-V® cream 0.1%. The present study also shows that the use of topical riluzole in the treatment of psoriasis is a safe and well-tolerated approach. No previously unknown AE was observed in this study. Local reactions occurred under all treatments with a similar frequency.

Date of the report: 09 NOVEMBER 2009