Result Synopsis

Name of Company: Biofrontera Bioscience GmbH	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product:	Volume: Page:	
Name of Active Ingredient: Riluzole		

Title of Study:

Phase IIa, multi-center, randomized, double-blind, vehicle-controlled study to determine the efficacy and safety/tolerability of a topical Riluzole formulation in patients with atopic eczema

Study No. BF-37-CT001; EudraCT-no: 2006-006653-27

Investigator(s):

Principal Investigator J. Gassmueller

Study center(s):

2 centers, Germany

Publication (reference):

Not applicable to this study

Studied period (years):	Phase of development:
2007	IIa

Objectives:

The aim of this study was to assess the clinical skin condition after treatment with a topical Riluzole formulation in patients with atopic eczema.

Methodology:

Topical treatment of two comparable lesional areas (20 - 50 cm^2) twice daily for four weeks by the patients at home, one area was treated with Riluzole Cream (4 %), the other with vehicle.

Once a week, on study days 1, 8, 15, 22 and 29, the patients were seen at the centers for the clinical and other assessments. Clinical assessments of erythema, edema/infiltrate, excoriations and papules were conducted using a 4-point score. Epidermal barrier impairment was evaluated by measurement of transepidermal water loss (TEWL) and skin redness by chromametry. Blood chemistry, hematology, and urinalysis were evaluated at screening, on study days 8, 15 (clinical chemistry only) and 29. Riluzole plasma levels were evaluated in ten patients on study days 1 and 29 before application, and 0.5, 1, 2, 4 and 6 hours after application.

Number of patients (planned and analyzed):

30 male or female patients were included in the study. Two patients discontinued the study prematurely. Thirty evaluable patients were included in the safety analysis and the Intent-to-Treat (ITT) analysis. Twenty-eight patients were included in the Per-Protocol analysis.

Diagnosis and main criteria for inclusion:

Patients with manifest mild to moderate atopic dermatitis aged 18 to 64 years

Test product(s), dose and mode of administration, batch number:

Riluzole Cream (4 %), batch nos. 702083-1 and 705105
Topical application twice daily of approx. 2 - 5 mg/cm^2 on a treatment area of 20 - 50 cm^2

Duration of treatment:

Four weeks

Reference therapy or controls, dose and mode of administration, batch number:

Active ingredient-free vehicle to Riluzole Cream (4 %), batch nos. 702081-1 and 705103
Topical application twice daily of approx. 2 - 5 mg/cm^2 on a treatment area of 20 - 50 cm^2

Duration of treatment:

Four weeks

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Criteria for evaluation:

Efficacy: Clinical assessment of erythema, edema/infiltrate, excoriations and papules, measurement of epidermal barrier impairment by TEWL and skin redness by chromametry.

Safety/tolerability: Screening and final clinical examinations, blood chemistry, hematology, and urinalysis, blood levels of Riluzole, subjective assessment of itching and burning using a 4-point score, recording of adverse events.

Statistical Methods:

Efficacy populations

Intent-to-Treat (ITT) Set: The Intent-to-Treat Population (ITT) comprised all randomized patients who had their baseline assessments, received at least one dose of the investigational products and had at least one corresponding on-therapy efficacy assessment.

Per-Protocol (PP) Set: The Per-Protocol (PP) Set consisted of all patients who completed the 28-day treatment period without relevant study protocol violations.

The PP Population included all patients from the ITT Population who did not meet any of the following criteria:

- Violation of the inclusion and exclusion criteria.
- intake of concomitant medication interfering with the study objectives
- premature termination of the treatment (not applicable, if the discontinuation was due to a treatment-related adverse event or documented inefficacy of treatment).
- use of less than 1 mg/cm² or more than 10 mg/cm² of the stipulated amount of investigational products in at least one test field for two consecutive weeks.

The Last Observation Carried Forward (LOCF) method was applied to missing efficacy assessments for both analysis sets.

Safety population

The safety population comprised all randomized patients who received at least one dose of the investigational products. All safety and tolerability analyses were based on this population.

Primary efficacy variables

- clinical assessment of erythema, edema/infiltrate, excoriations and papules by the investigators on study days 1, 8, 15, 22, and 29

  The intensity of each symptom was graded by the investigator according to the following 4-point scale:

  0 = absent, 1 = mild, 2 = moderate, 3 = severe.
- TEWL-values as measured with an evaporimeter (EP 1, Servomed AB, Stockholm/Sweden) on study days 1, 8, 15, 22, and 29

  TEWL-measurements were conducted in a controlled air-conditioned environment. The final read-out was taken only after a stable value had been reached.
- skin redness as measured with a chromameter (Chroma-Meter CR 300, Minolta) on study days 1, 8, 15, 22, and 29
- Assessments were performed using the L*a*b system, with the a* values being a correlate for erythema.

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Statistical Methods (continued):

Three measurements were taken from each test area. Their arithmetical mean was the final read-out of the assay.

Primary safety variables

- safety laboratory at screening and on study days 8, 15 and 29 (on study days 8 and 15 clinical chemistry only)
- plasma levels of the active ingredient Riluzole were measured in ten patients on study days 1 and 29 at pre-dose and 0.5, 1, 2, 4 and 6 hours post-dose.

Other safety or tolerability variables

- subjective assessment regarding itching and burning on study days 1, 8, 15, 22 and 29 (on study day 1 only itching before treatment).

  The severity of itching during the previous week was assessed in each test area by the patients using the following 4-point scale: 0 = no itching, 1 = mild itching, 2 = moderate itching, 3 = severe itching.

  The severity of burning directly after the treatment was assessed in each test area by the patients using the following 4-point scale: 0 = no burning, 1 = mild burning, 2 = moderate burning, 3 = severe burning.

Statistical Methods

Data from both centers were pooled for the efficacy, safety and tolerability analyses.

Demographics and baseline characteristics

Demographic and background data were summarized using descriptive statistical methods. Continuous data were summarized by sample size (n), mean, median, standard deviation, minimum, maximum. Categorical demographic data were summarized by frequency tables.

Physical examination outcomes and previous and concomitant medications were listed.

Vital signs were discussed with respect to the defined normal ranges.

Values outside these normal ranges required an explanation regarding their clinical relevance by the investigator.

Compliance

The actual use of the investigational products was controlled by weighing the dispensed and returned tubes.

Total amount of used investigational product was determined in relation to the size of the treated area (mg/cm^2) and was described by sample size (n), mean, median, standard deviation, minimum, maximum.

Discontinuations and drop-outs

In case a patient dropped out, i.e. terminated the study prematurely, all assessments of the final visit were to be performed, if possible. All drop-outs were listed in tabular form sorted by reason for discontinuation including the last study visit and the last dose of investigational product given. They were not replaced.

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Statistical Methods (continued):

Efficacy analyses

Calculation of derived variables

For the assessment of skin redness (a*-value), the mean of the three individual chromameter measurements was calculated and was used for further analyses.

Changes from baseline were calculated for the clinical scores, TEWL and chromameter data (a*-value) by subtracting the baseline value from the value at the actual study day for each patient and test field.

Clinical assessments of erythema, edema/infiltrate, excoriations and papules as well as their change from baseline were summarized by listing the sample size (n), mean, median, standard deviation, minimum, maximum and score frequencies by treatment and study day. Statistical comparisons between Riluzole Cream (4 %) and the vehicle were performed using changes from baseline for each clinical score. Depending on the distribution of the data the parametric paired t-test or the nonparametric Wilcoxon matched pairs test were used for the comparison (two-sided, alpha = 5 %).

TEWL and chromameter measurements and their changes from baseline were evaluated descriptively by treatment and study day by listing sample size (n), mean, median, standard deviation, minimum and maximum. Statistical comparisons between Riluzole Cream (4 %) and the vehicle were performed using changes from baseline for TEWL and chromameter data. Depending on the distribution of the data the parametric paired t-test or the nonparametric Wilcoxon matched pairs test were used for the comparison (two-sided, alpha = 5 %).

Since this was a proof-of-concept study, no type I error correction was performed. All obtained p-values were interpreted descriptively.

Safety analyses

Laboratory safety analyses

Laboratory parameters were summarized by visit with the descriptive statistics of sample size (n), mean, standard deviation, median, minimum and maximum or frequencies and percentages, as appropriate. For liver values and neutrophils the change to baseline was determined and summarized accordingly.

Plasma levels of the active ingredient

Plasma levels of the active ingredient Riluzole were measured in blood samples taken at predefined time points in ten patients. The measurements were performed by a German bioanalytical laboratory. A preliminary PK-analysis was performed on the basis of the individual values. Individual and PK-data along with a safety assessment are reported in separate documents.

Adverse events

The number and percentage of patients experiencing adverse events (AE) were presented. The number and percentage of AEs by seriousness, maximum severity and relation to study medication were shown. A listing of all AEs was provided, including the description of the event, its maximum severity, onset and stop date, relation to study medication as judged by the investigator, actions taken (if applicable) and outcome.

Serious adverse events (SAE) were to be documented throughout the whole study period and were to be described individually using all available data.

Safety evaluation was based on the incidence and type of AEs.

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Statistical Methods (continued):

Tolerability analyses

The subjective assessment of itching and burning by the patient was summarized by score frequencies and by descriptive statistics as sample size (n), mean, median, standard deviation, minimum and maximum for each treatment and study day. Change from baseline was derived for the subjective assessment of itching and was summarized by descriptive statistics.

No formal testing of any statistical hypotheses was performed.

Summary, conclusions:

Efficacy results:

Under the given conditions in this study each of the evaluated clinical symptoms erythema, edema/infiltrate, excoriations and papules showed a slight improvement but no clinically relevant effect on atopic dermatitis when treated with Riluzole Cream (4 %) and the corresponding vehicle. However, for none of the evaluated clinical symptoms and time points, the change to baseline value was statistically significant between Riluzole Cream (4 %) and vehicle. The same was true for the TEWL measurements, which showed a slight improvement during the study period, but no significant difference between Riluzole Cream (4 %) and the vehicle. The chromametric assessments of the skin redness revealed practically no effect, with the values on Day 29 being nearly identical to those on Day 1. With the exception of Day 22 (value for Riluzole Cream (4 %) significantly lower than for vehicle, p=0.0174), there was no statistically significant difference between the two formulations tested.

	Clinical assessment (Mean ± SD), ITT				Measurements (Mean ± SD), ITT	
	Erythema	Edema/Infiltrate	Excoriations	Papules	TEWL (g/m²/h)	Chromametry (a*-value)
Riluzole Cream 4%						
Day 1	1.90 ± 0.607	1.50 ± 0.731	1.13 ± 0.730	1.10 ± 0.548	27.11 ± 9.458	12.99 ± 3.268
Day 8	1.63 ± 0.556	1.50 ± 0.630	0.70 ± 0.535	0.87 ± 0.507	20.55 ± 10.533	12.44 ± 3.755
Day 15	1.57 ± 0.626	1.47 ± 0.730	0.70 ± 0.596	0.90 ± 0.548	22.71 ± 11.659	12.19 ± 4.120
Day 22	1.47 ± 0.681	1.27 ± 0.828	0.93 ± 0.828	0.77 ± 0.626	19.75 ± 10.337	11.12 ± 3.999
Day 29	1.57 ± 0.728	1.37 ± 0.718	0.90 ± 0.759	0.83 ± 0.648	22.99 ± 10.880	12.43 ± 3.646
Vehicle to Riluzole						
Day 1	1.90 ± 0.548	1.57 ± 0.728	1.00 ± 0.695	1.07 ± 0.583	27.07 ± 10.060	12.78 ± 3.207
Day 8	1.70 ± 0.651	1.47 ± 0.776	0.70 ± 0.651	0.83 ± 0.648	21.60 ± 12.172	12.65 ± 3.528
Day 15	1.53 ± 0.776	1.57 ± 0.626	0.67 ± 0.711	0.77 ± 0.679	20.45 ± 10.733	12.31 ± 3.406
Day 22	1.53 ± 0.730	1.37 ± 0.809	1.00 ± 0.910	0.73 ± 0.583	20.78 ± 11.867	12.24 ± 4.093
Day 29	1.53 ± 0.730	1.40 ± 0.894	0.87 ± 0.900	0.87 ± 0.730	23.15 ± 11.777	12.77 ± 4.009

In summary, under the particular conditions of this study, there was a slight improvement in most of the tested efficacy parameters, which, however, was not significantly different between Riluzole 4% Ceam and vehicle.

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Summary, conclusions (continued):

Safety/tolerability results

There was no SAE during the study. Only 12 out of 30 patients reported AEs at all, in total 15 AEs were documented. The only AE of severe intensity (worsening of atopic dermatitis) was considered to be unlikely related to the study medication, but led to the discontinuation of the study for this patient. All other 14 AEs were of mild or moderate severity. All were considered to be unlikely or not related to the study medication. One AE was based on an out-of-range laboratory value which was considered to be clinically relevant. At the follow-up visit this value had returned to normal without any intervention.

Within the 6 hour sampling period, plasma levels rose to maximum and returned nearly to baseline. The maximum values were reached within approx. 1 hour post-dose, the mean maximum was approx. 6 ng/ml on Day 1 and approx. 17 ng/ml on Day 29. The "steady-state" levels (Day 29 pre-dose) were approx. 5 ng/ml. The plasma levels (C_{max}) of the active ingredient Riluzole were more than 10-fold lower after topical administration than values reported after single administration of 50 mg p.o., the therapeutic standard dose for treatment of amyotrophic lateral sclerosis (ALS).

The subjective assessments of itching by the patient showed an improvement during the study with both formulations, but the difference between Riluzole Cream (4 %) and vehicle was not statistically significant at any time point tested.

The vast majority of patients did not report burning in their subjective assessments and the proportion who did continued to decrease over the course of the study.

With the one exception mentioned above, no clinically significant laboratory values were noted throughout the study.

The final physical examination did not reveal relevant findings in any of the patients.

There were no AEs reported in this study that are frequently observed after oral treatment of ALS with Riluzole.

The plasma exposure to Riluzole resulting from topical treatment under the conditions of this study, does not seem to induce a significant safety issue.

In summary, the safety and tolerability of the tested formulations were excellent.

Conclusion:

In the present study the efficacy and safety/tolerability of a topical Riluzole formulation was examined in patients with atopic eczema.

Overall, there was a slight improvement in most of the tested efficacy parameters, which, however, was not significantly different between Riluzole Cream (4 %) and vehicle. The safety of the tested formulations was excellent.

Date of the report: August 05, 2009