## Clinical Study Synopsis

This Clinical Study Synopsis is provided for patients and healthcare professionals to increase the transparency of Bayer's clinical research. This document is not intended to replace the advice of a healthcare professional and should not be considered as a recommendation. Patients should always seek medical advice before making any decisions on their treatment. Healthcare Professionals should always refer to the specific labelling information approved for the patient's country or region. Data in this document or on the related website should not be considered as prescribing advice.
The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

# Clinical Trial Results Synopsis

| Study Design Description | | |
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| Study Sponsor: | Bayer HealthCare AG | |
| Study Number: | 1400418 | NCT00403949<br>EudraCT Number: 2006-002471-40 |
| Study Phase: | II | |
| Official Study Title: | A 6-week vehicle-controlled, randomized, double-blind, parallel-group multicenter pilot study of the efficacy and safety of azelaic acid (AzA) 15% gel in the topical treatment of mild to moderate perioral dermatitis. | |
| Therapeutic Area: | Dermatology | |
| Test Product | | |
| Name of Test Product: | Other<br>Azelaic acid (AzA) 15% gel (SH H 655 BA; gel containing 15% azelaic acid; Skinoren) | |
| Name of Active Ingredient: | Azelaic acid | |
| Dose and Mode of Administration: | Twice daily administration; 0.5 g gel per application, topical application to facial area. | |
| Reference Therapy/Placebo | | |
| Reference Therapy: | Vehicle (VEH) (non-medicated gel base of AzA 15% gel; SH H 655PBA) | |
| Dose and Mode of Administration: | Twice daily administration; 0.5 g gel per application, topical application to facial area. | |
| Duration of Treatment: | 6 weeks | |
| Studied period: | Date of first subjects' first visit: | 23 NOV 2006 |
| | Date of last subjects' last visit: | 22 MAR 2007 |
| Premature Study Suspension / Termination: | No | |
| Substantial Study Protocol Amendments: | None | |
| Study Centre(s): | The study was conducted at 4 centers in Germany. | |
| Methodology: | In this study, subjects were examined by the investigator at bi-weekly intervals, i.e., baseline (screening and baseline visit could be merged to one visit), after week 2 (day 14), after week 4 (day 28), and after week 6 (day 42). At each of these 4 visits, inflammatory lesion count and the severity of single clinical symptoms, the investigator's global assessment (IGA), and adverse events (AEs) were assessed. The assessments were recorded in the case record form (CRF). An investigator's and subject's rating of overall improvement was performed at the end of study treatment. Likewise, the subject's overall assessment of local tolerability was also performed at the end of study treatment. | |
| Indication/ Main Inclusion Criteria: | Indication<br>Mild to moderate perioral dermatitis | |

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| | Main Inclusion criteria<br>• Written informed consent<br>• Male or female subjects with a minimum age of 18 years<br>• Clinical diagnosis of mild to moderate perioral dermatitis, i.e., erythematous papules, papulopustules or papulovesicles, usually not larger than 2 mm in size, frequently surrounded by a diffuse erythema and a scaly background. Predominantly seen periorally but may extend to the paranasal and/or periorbital region. There is a narrow unaffected zone around the vermilion of the lips.<br>• IGA score at baseline of 2 or 3 (on a scale from 0 to 4)<br>• Eight to fifty facial inflammatory lesions (papules, papulopustules, papulovesicles)<br>• Willingness and capability to follow all study procedures |
| Study Objectives: | Overall:<br>The objective of this double-blind, randomized, controlled, multicenter, parallel-group phase II pilot-study was to show a superiority of AzA 15% gel SH H 655BA over its vehicle ("placebo"; SH H 655PBA) in the 6 weeks treatment of subjects with mild to moderate perioral dermatitis. In view of the explorative nature of the study no confirmatory superiority was to be expected.<br><br>Primary:<br>Not applicable<br><br>Secondary:<br>Not applicable |
| Evaluation Criteria: | Efficacy (Primary):<br>a) Perioral dermatitis (POD) sum score (The POD sum score was calculated by summing up the rating scores of burning, tension, erythema, itching and the percent change of total facial count. A range from 0 (all signs and symptoms are “clear” and at least 90% lesion count reduction) to 20 (all signs and symptoms are “severe” and less than 25% lesion count reduction) )<br><br>Efficacy (Secondary):<br>a) Cutaneous POD symptoms: burning, tension, erythema, scaling, dryness, itching were to be assessed on a 5 point score (0 = “none”, 1 = “minimal”, 2 = “mild”, 3 = “moderate”, 4 = “severe”)<br>b) Total facial count (TFC): counting of facial lesions (nflammatory papules, inflammatory papulovesicles, inflammatory pustules/papulopustoles)<br>c) Percentage change of total facial count<br>d) IGA of acute disease status (5 point scale)<br>e) Dichotomized IGA (Success was defined as the scores “clear” or “minimal”; Failure was defined as “mild”, “moderate” or “severe” )<br>f) Investigator’s and patient’s global assessment on overall improvement<br><br>Safety:<br>a) AEs<br>b) Patient’s global assessment on local tolerability |

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| | Pharmacokinetics:<br>Not applicable<br><br>Other:<br>Not applicable |
| Statistical Methods: | Efficacy (Primary):<br>a) Calculation of descriptive statistics, exploratory Wilcoxon rank-sum test<br><br>Efficacy (Secondary):<br>a) Calculation of frequencies and descriptive statistics<br>b) Calculation of descriptive statistics<br>c) Calculation of frequencies, exploratory Wilcoxon rank-sum test<br>d) Calculation of frequencies and statistics, exploratory Wilcoxon rank-sum test<br>e) Calculation of frequencies, exploratory exact Fisher test<br>f) Calculation of frequencies, exploratory Wilcoxon rank-sum test<br><br>Safety:<br>a) Calculation of incidences (all AEs and related AEs)<br>b) Calculation of frequencies |
| | Pharmacokinetics:<br>Not applicable<br><br>Other:<br>Not applicable |
| Number of Subjects: | Planned:<br>AzA: 32 subjects, VEH: 16 subjects<br><br>Analyzed:<br>Safety population (SAF) (safety): AzA: 30 subjects, VEH: 16 subjects<br>Full analysis set (FAS): AzA: 30 subjects, VEH: 16 subjects<br>Per-protocol set (PPS): AzA: 24 subjects, VEH: 12 subjects |

Study Results

Results Summary — Subject Disposition and Baseline

A total of 46 subjects (all Caucasians) were randomized and 30 and 16 subjects were exposed to AzA and VEH, respectively. These subjects comprised the safety set and the FAS set as well. Twenty-four subjects from the AzA and 12 from the VEH group were considered as per protocol evaluable.

Nine subjects (5 AzA, 4 VEH) discontinued study treatment prematurely.

Most subjects were female (93% AzA, 88% VEH). The mean age was 38 and 40 years in the AzA and VEH group, respectively; the overall age range was 18 to 72 years. There was no inhomogeneity between the groups, neither in the demographics, nor in the main baseline variables.

The compliance with study treatment was at least 90% in the vast majority (>90%) of the

subjects of both groups.

Results Summary — Efficacy

At baseline the mean POD sum score in the AzA group was slightly (though not significantly) worse than in the VEH group. During the course of the study there was a decrease of the POD sum score in both groups, particularly until Week 4.

At the end of study the mean of the POD sum score was 5.0 in the AzA group and 4.6 in the VEH group (Table 1).

**Table 1: POD sum score – Results (FAS, after binning and LOCF [last observation carried forward])**

| POD sum score | | AzA N = 30 | VEH N = 16 |
|---|---|---|---|
| | **At Baseline** | | |
| | mean | 11.2 | 10.0 |
| | SD | 3.0 | 2.8 |
| | median | 11.0 | 10.5 |
| | range | 6.0 – 19.0 | 6.0 – 15.0 |
| | **Differences from Baseline to Week 6** | | |
| | mean | -6.2 | -5.4 |
| | SD | 4.8 | 6.4 |
| | median | -7.0 | -8.0 |
| | range | -17.0 – 3.0 | -15.0 – 9.0 |

Neither for the FAS nor for the PPS population significant differences between the two groups were observed at endpoint or at any other visit, with the exception of the POD sum score at Week 2 (favoring VEH, p=0.0491). Considering the number of statistical tests (multiplicity), the likelihood of a chance finding was substantial.

The 6 cutaneous symptoms were burning, tension, erythema, itching, scaling, and dryness whereas the first 4 symptoms were part of the POD sum score. No superiority of AzA over vehicle was indicated. For both groups there was a decrease of the median total facial count - decrease in the median result was greater then 85% in both treatment groups. Another secondary efficacy variable was the percentage change of total facial count. None of those efficacy variables indicated a superiority of AzA over vehicle. The Investigator's Global Assessment (IGA) of disease status resulted in very similar means for the AzA and the vehicle group at beaseline and over time, indicating no significant results for all time points. In the AzA group, 22 out of 30 patients (73.3%) and in the VEH group, 11 out of 16 patients (68.8%) have been rated as successful at the last visit. The investigator's rating was assessed as excellent or marked improvement for 18 out of 29 patients (62.1%) of the AzA group and for 10 out of 16 patients (62.5%) of the VEH group. The opinion of the patients was assessed by 15 out of 29 (51.7%) of the AzA group and by 8 out of 16 (50.0%) of the VEH group as excellent or marked improvement.

Results Summary — Safety

One subject from the AzA group was withdrawn due to adverse events. Five subjects from the AzA group experienced application site irritations, but none from the vehicle group. All these AEs were considered as "related" to study treatment, in these cases to AzA.

There was no serious AE, or any other notable finding or evidence for adverse reactions not yet listed in the current SPC (summary of product characteristics).

The assessment of local tolerability on a 6-point scale was missing for patient 4/38 of the AzA group. The tolerability of the study medication was rated as excellent or good by 15 out of 29 patients (51.7%) in the AzA group and by 11 out of 16 patients (68.8%) in the VEH group and as “acceptable” by 8 patients (27.6%) in the AzA group and by 3 patients (18.8%) in the VEH group.

Results Summary — Pharmacokinetics

Not applicable

Results Summary — Other

Not applicable

Conclusion(s)

This study is not able to support a therapeutic value of AzA in the treatment of mild to moderate POD. This is due to a lack of beneficial effects compared to vehicle and the causing of some local irritation.

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| Publication(s): | None | | |
| Date Created or Date Last Updated: | 04 APR 2012 | Date of Clinical Study Report: | 23 APR 2008 |

Bayer HealthCare

Appendix to Clinical Study Synopsis for study 1400418

# Investigational Site List

| **Marketing Authorization Holder in Germany** | |
|---|---|
| **Name** | Bayer HealthCare AG |
| **Postal Address** | D-51368,<br>Leverkusen,<br>Germany |
| **Sponsor in Germany** | |
| **Legal Entity Name** | Intendis GmbH |
| **Postal Address** | Max-Dohrn-Strasse 10,<br>D-10589,<br>Berlin,<br>Germany |

**List of Investigational Sites**

| No | Facility Name | Street | ZIP Code | City | Country |
|---|---|---|---|---|---|
| 1 | Universitätsklinikum Essen | Hufelandstrabe 55 | 45122 | Essen | Germany |
| 2 | Praxisklinik and Gemeinschaftspraxis | Vollenstrabe 8 | 48249 | Dülmen | Germany |
| 3 | Haut- and Geschlechtskrankheiten, Phlebologie- Berufsdermatologie | Bochumer Strabe 106 | 45661 | Recklinghausen | Germany |
| 4 | Hautarztpraxis | Hauptstrabe 131 | 10827 | Berlin | Germany |

# Product Identification Information

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| **Product Type** | Drug |
| **US Brand/Trade Name(s)** | Finacea |
| **Brand/Trade Name(s) ex-US** | Azelan, Finacea 15% gel, Skinoren, Skinoren gel, Zelaika, |
| **Generic Name** | Azelaic Acid |
| **Main Product Company Code** | BAY39-6251 |
| **Other Company Code(s)** | n. a. |
| **Chemical Description** | Nonanedioic acid |
| **Other Product Aliases** | SH H 655 BA |

Date of last Update/Change: 30 May 2012