Clinical Study Synopsis

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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		
Study Sponsor:	Bayer HealthCare AG, Consumer Care	
Study Number:	91424 (309189)	NCT00185510 EudraCT Number: 2004-002673-22
Study Phase:	IV Interventional	
Official Study Title:	Double-blind, placebo-controlled, randomized, multicenter, parallel-group study to compare the efficacy and safety of Advantan cream twice weekly with Advabase cream during a maintenance phase of 16 weeks after successful treatment of atopic dermatitis with Advantan cream	
Therapeutic Area:	Dermatology	
Test Product		
Name of Test Product:	Methylprednisolone aceponate (Advantan, BAY 86-4862)	
Name of Active Ingredient:	Methylprednisolone aceponate (ZK 91588)	
Dose and Mode of Administration:	Acute Phase (AP): Advantan cream (1 mg (0.1%) of methylprednisolone aceponate in 1 g of cream) was applied topically once daily and Advabase cream (emollient) was applied topically once daily (both open labelled). Maintenance Phase (MP): Advabase cream (emollient) was applied twice daily seven days a week except on those 2 days a week when Advantan cream (0.1% cream) was applied topically once daily two days in a week. On these 2 days a week the active treatment group received Advantan cream and Vehicle cream. The cream was applied as a thin layer to the affected skin or the predilection sites in a non-occlusive manner.	
Reference Therapy/Placebo		
Placebo Therapy:	Advabase cream (contains no active ingredient - vehicle / matching placebo)	
Dose and Mode of Administration:	Acute Phase (AP): Advantan cream (1 mg (0.1%) of methylprednisolone aceponate in 1 g of cream) was applied topically once daily and Advabase cream (emollient) was applied topically once daily (both open labelled). Maintenance Phase (MP): Advabase cream (emollient) was applied twice daily seven days a week. The cream was applied as a thin layer to the affected skin or the predilection sites in a non-occlusive manner.	
Duration of Treatment:	The subjects were treated for maximum of 4 weeks in AP followed by an MP of 16 weeks.	
Studied period:	Date of first subject's first visit:	25 JUL 2005
	Date of last subject's last visit:	13 JUN 2006
Premature Study	No	

Suspension / Termination:	
Substantial Study Protocol Amendments:	Amendment No. 1, dated 17 DEC 2004, suggested the following change: • A preliminary estimate of the expected results for the safety variable "skin thicknesses" suggested that the data of selected centers only would not be sufficient to show any interpretable result in the statistical analyses. Therefore, skin ultrasound examinations were not to be performed in this study. Amendment No. 2, dated 04 MAY 2005, suggested the following change: • Due to logistic problems, start of the study recruitment was postponed from APR 2005 to 01 AUG 2005. Amendment No. 3, dated 16 NOV 2005, suggested the following change: • The subject recruitment period was prolonged from NOV 2005 to JAN 2006 to meet the target of 250 subjects.
Study Center(s):	This study was conducted in 3 countries with 20 centers: 12 in Germany, 4 in Italy, and 4 in Spain.
Methodology:	This was a multicenter, double blind, placebo controlled, randomized, parallel group maintenance study conducted in two phases (the AP and the MP) in subjects who were initially successfully treated for moderate to severe atopic dermatitis (AD), i.e., an acute flare of the disease. The assessments in AP were done on three visits (visits at baseline/start of treatment/ Day 1 AP, Week 2, and Week 4/end of AP). The assessments in MP were done on four visits (visits at Week 2, Week 6, Week 10, and Week 16 or relapse or end of study). The primary efficacy variable "time to relapse" was assessed at the end of MP. The subject's statement on relapse was also noted on this visit. The number of relapses was assessed as secondary efficacy variable. Other secondary efficacy variables including Investigator's Global Assessment (IGA) score, modified Eczema Area and Severity Index (mEASI), affected body surface area (BSA), target lesions, were assessed on all visits of AP and MP. At baseline, end of AP, and end of MP a questionnaire, the Dermatology Life Quality Index (DLQI), was filled in by the subjects. Subjects of 12 to 16 years of age used a specifically designed questionnaire, the Children's Dermatology Life Quality Index (CDLQI). Subject's and investigator's global assessment of response were assessed at end of AP, and end of MP visits. At baseline, end of AP, and end of MP, subject's assessment of quality of sleep was also noted. Safety variables included assessments of visual assessment of atrophy, adverse events (AEs) and serious AEs (SAEs), throughout the study. Further safety assessments included physical examinations, record of concomitant medications, pregnancy tests, and baseline findings.

Indication/Main Inclusion Criteria:	Indication Atopic dermatitis (AD) Main inclusion criteria: • Acute flare of AD according to the Investigator's Global Assessment (IGA ≥ 4) "severe" or "very severe" at baseline; no minimum affected body surface required • History of moderate to severe form of AD for at least 2 years • Age of at least 12 years at screening
Study Objectives:	• To study long-term management of AD, describing the efficacy and safety of Advantan cream twice weekly in addition to an emollient (Advabase), during a maintenance period of 16 weeks in patients aged 12 years or older with AD.
Evaluation Criteria:	Efficacy (Primary): **Time to relapse**: The time to relapse was defined as the number of days from end of the AP (last continuous Advantan dose) until the disease relapsed and the patient requested more intense treatment than maintenance therapy. The relevant date to calculate the time to relapse was the date of onset of relapse as documented in the "subject's statement of relapse". If this date was missing, the date of the end of study visit was used, i.e., the date the subject returned to a visit to the investigator and requested more intense treatment than the maintenance therapy. Efficacy (Secondary): • **Relapse rate**: A relapse was defined as the need for more intense treatment exceeding the maintenance regimen from the subject's perspective. The evaluation is based on crude number of relapses in MP. • **Investigator's Global Assessment**: It was a static evaluation of the treatment efficacy during the AP and MP. It consists of point scoring system ranging from clear (0) to very severe (5). It was calculated as the difference between baseline and treatment visits (baseline − treatment visit) on the scored point scales for IGA (0 to 5). • **Eczema area and severity index**: The EASI is a composite index, including an assessment of disease extent and the percentage of BSA involved, in four body regions (head and neck, lower limbs, upper limbs, and trunk). The sum of the clinical sign scores (E [Erythema] + I [Induration/Papulation/Edema] + Ex [Excoriations] + L [Lichenification]) multiplied by the proportional area score, multiplied by the proportional body region factor. The EASI is evaluated as the percentage change during the AP and MP in EASI score. The EASI is evaluated as the percentage change from the baseline to end of study medication (EOSM) in EASI score. The severity of AD or clinical sign score was assessed by the investigator on a severity scale of 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe, half steps allowed). Proportional area score for analysis ranges from 0 (being no

	eruption) to 6 (90-100% eruptions). The total EASI score is the sum of the four body region scores with a minimum score of 0 and a maximum score of 72. • **Modified eczema area and severity index**: The mEASI is EASI but includes an additional assessment of itch. Itch was assessed by the intensity of his/her itching during the previous 24 h by using a 10-cm visual analog scale (VAS), indicating "no itch" at one end of the scale (0 cm) and "worst itch imaginable" at the other end of the scale (10 cm), and converted from the VAS to an ordinal scale of 0-3, which will then be multiplied by the investigator's total affected area scale (0-6) to give a maximum score of 18. • **Itch**: This parameter was calculated as a part of the mEASI. • **Affected BSA**: This parameter was calculated as a part of the mEASI. • **Target lesion**: The target area was defined at baseline and followed through the whole study including the AP and MP. Signs like erythema, induration/papulation/edema, excoriation, and lichenification were assessed, and the change during AP and MP was evaluated. • **Subject's and investigator's global assessment of response**: This was evaluated in terms of how the disease had changed during the AP and MP recorded on a categorical scale (much better, better, slight better, same, slightly worse, worse, and much worse). • **Dermatology Life Quality Index**: The DLQI is a simple 10-question validated questionnaire given to the subjects, aged 17 years or older to assess their quality of life. • **Children Dermatology Life Quality Index**: The CDLQI is a simple 10-question validated questionnaire given to the subjects aged 12 to 16 years or older to assess their quality of life. • **Subject's assessment of quality of sleep:** The quality of sleep was assessed at the baseline, Visit 4, and Visit 8 by using a 10-cm VAS, indicating "slept well" at one end of the scale (0 cm) and "slept badly" at the other end of the scale (10 cm). • **Cost-effectiveness:** This parameter was assessed by assessing the needed amount of study treatment. <u>Safety:</u> **Adverse events**: All AEs were assessed and documented by the investigator according to their seriousness, intensity (mild, moderate, or severe), causal relationship to study drug and study conduct, and main pattern (occurring after every drug administration, occurring intermittently or continuously, and any other pattern). The AEs were encoded using the Medical Dictionary for Regulatory Activities (MedDRA), version 8.0. **Skin atrophy**: Signs of skin atrophy, stria formation, and telangiectasia were monitored carefully.
Statistical Methods:	Efficacy and safety were evaluated using the following analysis sets: • Full analysis set (FAS): The FAS included all subjects who were

	dispensed study drugs. • Modified full analysis set (mFAS): Maintanance full analysis set (mFAS). The mFAS is a subset of the FAS. The mFAS included all randomized patients who had drug dispensed for MP. • Per protocol set (PPS): The PPS is a subset of the mFAS. The subjects with major protocol deviations were excluded from the analysis. • The primary analysis set for analysis of the efficacy variables was the mFAS. Additionally, however, efficacy variables were analyzed for the FAS and the PPS. The safety analysis was performed using the FAS (analysis of AP and MP combined) and mFAS (analysis of MP alone). <u>Efficacy (primary):</u> For the primary parameter 'time to relapse', Kaplan-Meier estimates were calculated and presented for 14-day intervals. The time to relapse was compared between the treatment groups using the hazard ratio from a Cox proportional hazards model with center included as a covariate in the model. <u>Efficacy (secondary):</u> The relapse rate, IGA, itch, BSA, and global assessment of response (by subjects and investigators) were analyzed using the Mantel-Haenszel test. The variables mEASI, EASI, CDLQI, DLQI, and quality of sleep were analyzed using the analysis of variance (ANOVA) and the analysis of covariance (ANCOVA) techniques; the medication costs per treatment were analyzed descriptively. Summary tables (descriptive statistics and/or frequency tables) were provided for all original and derived efficacy variables for each visit and for the change from baseline to end of AP and MP and from end of AP to end of MP. The needed amount of study medication and medication costs per treatment were analyzed descriptively. <u>Safety:</u> Descriptive statistics were presented for all safety evaluations of the AEs.
Number of Subjects:	Planned: 250 subjects (125 in each treatment arm) Screened: 252 subjects Analyzed: 249 subjects (112 randomized to Advantan, 109 randomized to Advabase, and 28 not randomized to MP). Randomized: 221 subjects (112 subjects in the Advantan group and 109 subjects in the Advabase group).

Study Results

Results Summary — Subject Disposition and Baseline

Of the 252 subjects who were screened for the study, 249 subjects were dispensed with the study drug for the AP and included in the FAS. The reason for screening failure was failure to meet the study entry criteria (3 subjects). A total of 221 (88.8%) subjects were randomized to the study treatment Advantan (112 subjects) and Advabase

(109 subjects) during the MP and included in the mFAS. Of the 221 randomized subjects included in the mFAS, 35 subjects had at least one major protocol deviation (15 [42.9% of 35] in the Advantan group and 20 [57.1% of 35] subjects in the Advabase group) resulting in exclusion from the PPS giving a total of 186 subjects (97 in the Advantan group and 89 in the Advabase group). Of the 221randomized subjects, 52 (23.5%) subjects prematurely discontinued the study medication [16 (14.3%) in the Advantan group and 36 (33.0%) in the Advabase group]. The primary reason for premature discontinuation was lack of efficacy of the study drug in 9.8% and 30.3% of the subjects in the Advantan and Advabase groups, respectively.

The treatment groups were well balanced with regard to demographic and other baseline characteristics. The study population of FAS and PPS both were similar. In FAS, the subjects in the Advabase group had a median age of 25 years (range: 13-70), median weight of 64 kg (range: 40-118), and median height of 168 cm (range: 140-195). The subjects in the Advantan group had a median age of 27 years (range: 12-70), median weight of 65 kg (range: 35-108), and median height of 170 cm (range: 148-190).

Results Summary — Efficacy

Primary efficacy variable:

Time to relapse: At the end of AP, the vast majority (90.0%) of all subjects in the FAS had reached a sufficient control of the disease, i.e., a score of “clear’ or ‘almost clear’ in the IGA, and were admitted to MP.

Better results were observed for the time to relapse in the Advantan group compared to the Advabase group (primary efficacy variable). The Kaplan-Meier estimates for the proportion of subjects not having experienced a relapse after 2 weeks were 83.5% in the Advabase group compared to 96.4% in the Advantan group. In the Advabase group the proportion decreased to 65.8% at 16 weeks. The Kaplan-Meier estimate after 16 weeks of treatment in the Advantan group was 87.1% and therefore better than the 2 weeks result for subjects treated with Advabase. Due to the low number of events the median time to event cannot be calculated in either group. The hazard ratio for the difference between the two treatments was 0.288 with a 95% confidence interval ranging from 0.155 to 0.535. This means that the risk to get a relapse after previous successful treatment of AD was about 3.5-fold higher under Advabase as compared to Advantan. This difference was statistically significant (p value <0.0001, Cox proportional hazards model controlled for center).

Secondary efficacy variables:

- **Relapse rate:** At end of the study, a statistically significant difference (20.6%, p = 0.0003, extended Mantel-Haenszel test controlled for center) was observed between the treatment groups with smaller relapse rate under the Advantan group (16.1%) compared to the Advabase group (36.7%).

The analysis of the further secondary efficacy variables at the end of MP revealed statistically significantly better results (exploratory p values < 0.05) for Advantan compared to Advabase for all evaluated parameters (except for the CDLQI, analyzed only for the small number of patients aged 12 to 16 years). This applied to the mFAS as well as to the PPS.

- **Investigator’s Global Assessment**: At end of the AP, 90% of all subjects in the FAS showed an improvement of their IGA score to Grade 0 or Grade 1 and were admitted to the MP treatment. At the end of study, 72.3% subjects (81/112 subjects) in the Advantan group and 45.0% subjects (49/109 subjects) in the Advabase group had an IGA score of Grade 0 or Grade 1. This difference between the treatment groups was statistically significant in favor of the Advantan group (p = 0.0001 exploratory, extended Mantel-Haenszel test controlled for center). Results for the PPS were very similar with an exploratory p value of 0.0012 for the difference between

the treatment groups at study end.

- **Eczema area and severity index**: A statistically significant result was seen in favor of Advantan compared to Advabase.
- **Modified eczema area and severity index**: A statistically significant result was seen in favor of Advantan compared to Advabase.
- **Itch**: At end of the AP, the intensity of itching was decreased from the baseline, but the intensity was increased remarkably in the Advabase group compared to slight increase in the Advantan group at end of the study.
- **Affected BSA**: A statistically significant difference between the groups was observed in terms of change in affected BSA in favor of Advantan compared to Advabase at the end of study in the mFAS.
- **Target lesion**: Overall, a slightly more pronounced increase in the mean sum of target lesion score was observed during MP in the Advabase group as compared to the Advantan group was caused by all four single items, with the symptom 'lichenification' giving the smallest contribution (-0.2 points in the Advabase group vs. 0.0 points in the Advantan group)
- **Investigator's Global Assessment of response**: The investigator assessed the status of the disease as "much better" or "better" response to treatment by end of the AP, but the status of the disease was changed to "slightly worse," "worse," or "much worse" response in the Advabase group [59/107 subjects (55.1 %)] compared to the Advantan group [27/109 subjects (24.8%)] by end of the study. These changes were statistically significant in favor of the Advantan group.
- **Subject's global assessment of response**: The majority of the subjects had "much better" or "better" response to treatment by end of the AP, but the assessment of response was changed to "slightly worse," "worse," or "much worse" in the Advabase group [36/96 subjects (37.5%)] compared to the Advantan group [17/104 subjects (16.3%)] by end of the study. These changes were statistically significant in favor of the Advantan group.
- **Dermatology Life Quality Index**: A statistically significant result was seen in favor of the Advantan group compared to the Advabase group. Comparison of the treatment groups concerning the DLQI at end of the MP using an ANOVA showed a statistically significant difference in favor of Advantan in the mFAS ($p = 0.0216$) but not in the PPS ($p = 0.0510$). An additional analysis with DLQI at end of the AP as covariate (ANCOVA) resulted in p-values, which were in favor of Advantan in the mFAS ($p = 0.0037$) as well as in the PPS ($p = 0.0271$).
- **Children Dermatology Life Quality Index**: No statistically significant difference was observed between the two treatment groups at end of the study probably due to the small number of patients aged 12 to 16 years.
- **Subject's assessment of quality of sleep**: The quality of sleep (mean values) was remarkably improved from baseline (50.8 mm to 12.3 mm) by end of the AP (Visit 4), but slight worsening of sleep was observed in the Advantan group (from 8.3 mm at Visit 4 to 11.8 mm at Visit 8) compared to stronger deterioration of sleep in the Advabase group (from 9.8 mm at Visit 4 to 20.1 mm at Visit 8) by end of the study. The results of the ANOVA indicated a statistically significant difference in favor of Advantan concerning the quality of sleep at end of the MP in the mFAS ($p = 0.0217$) and in the PPS ($p = 0.0455$). For the mFAS, this result was confirmed by an ANCOVA with quality of sleep at end of the AP as covariate ($p = 0.0345$). For the PPS, this was not the case ($p = 0.0738$).
- **Cost-effectiveness**: The cost of active treatment during the MP was 0.37 EUR per day. The total costs for MP treatment per day were slightly lower in the Advantan group (1.09 EUR per patient) than in the Advabase group (1.19 EUR per patient).

Results Summary — Safety

Adverse events: During the entire study, a total of 61/249 subjects (24.5%) in the FAS reported at least 1 AE, 24/112 (21.4%) of the subjects in the Advantan group, 29/109 (26.6%) of the subjects in the Advabase group and 8/28 (28.6%) of the not randomized subjects. A total of 43/221 subjects (19.5%) in the mFAS reported at least 1 AE starting during MP, 17/112 (15.2%) in the Advantan group and 26/109 (23.9%) in the Advabase group.

Comparison of the two treatment groups during MP regarding the frequency of distinct MedDRA system organ classes (SOCs) revealed no relevant differences. The most frequently reported AEs in both treatment groups were skin and subcutaneous tissue disorders as well as infections and infestations. In the category “skin and subcutaneous tissue disorders” the most frequently reported preferred term (PT) was neurodermatitis (5.4% of subjects in the Advantan group vs. 13.8% of subjects in the Advabase group). As all AEs of this type were assessed as related to the underlying study disease, the higher frequency in the Advabase group could be expected.

During the entire study there was only one drug-related AE (PT: skin burning sensation) in the group of not randomized subjects. Events of this type are known side effects of therapies with Advantan. In the Advantan and Advabase groups no drug-related AEs were reported.

The intensity of the AEs starting during MP was mostly assessed by the investigators as mild or moderate. Only 2 subjects, both in the Advabase group, reported AEs whose intensity was rated by the investigator as severe. These AEs concerned the PTs neurodermatitis and pruritus (1 subject each). In the Advantan group no severe AEs were reported.

No deaths or nonfatal serious AEs were reported during this study. During the entire study, a total of 14 subjects prematurely discontinued the study medication due to AEs. This applied to 3 subjects during AP (all in the group of not randomized subjects) and to 11 subjects during MP (2 in the Advantan group and 9 in the Advabase group). On a PT basis, the respective AEs during AP were skin burning sensation, impetigo and herpes zoster. The AEs starting during MP were neurodermatitis and dermatitis atopic in the Advantan group, and neurodermatitis (7 subjects), pruritus and dermatitis atopic in the Advabase group. With the exception of skin burning sensation all AEs causing premature discontinuation were not drug-related.

Skin atrophy: Signs of atrophy (skin atrophy, stria formation, and telangiectasia) were recorded as baseline findings before treatment and as AEs after the start of treatment. Overall, only one subject in the Advabase group suffered from signs of atrophy. As this had been the case already before the start of treatment it was documented as baseline finding.

Conclusion(s)

In this study, during AP, the vast majority of subjects achieved a sufficient control over their disease by IGA clear or almost clear by a standard treatment regimen using Advantan cream once daily (and Advabase as an emollient). The twice weekly application of Advantan cream in addition to an emollient (Advabase) during the MP represented an effective treatment regimen for long-term management and control of AD. The Advantan treatment demonstrated significant improvement with regard to all evaluated parameters, particularly in symptoms of AD like itching or quality of sleep as compared to Advabase alone. Both the treatments were well tolerated by the subjects, with a slightly lower incidence of AEs in the Advantan group.

Publication(s):	The results of this study were published in the British Journal of Dermatology 2008 158, pp801–807; DOI 10.1111/j.1365-

	2133.2008.08436.x: Reduction of relapses of atopic dermatitis with methylprednisolone aceponate cream twice weekly in addition to maintenance treatment with emollient: a multicentre, randomized, double-blind, controlled study		
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