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.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer Healthcare AG	
Study Number:	308962	NCT00000000
Study Phase:	IV Interventional	
Official Study Title:	Double-blind, randomized, reference-controlled, multicenter, parallel-group study to compare the efficacy and safety of Advantan ointment once daily with Protopic 0.03% ointment twice daily over maximum 3 weeks in 250 children and adolescents with atopic dermatitis	
Therapeutic Area:	Dermatology	
Test Product		
Name of Test Product:	Advantan 0.1% ointment (Methylprednisolone Aceponate, BAY86-4862)	
Name of Active Ingredient:	Methylprednisolone aceponate	
Dose and Mode of Administration:	Once a day over maximum 3 weeks, topical non-occlusive application. Vehicle control provided as the second daily application.	
Reference Therapy/Placebo		
Reference Therapy:	0.03% tacrolimus (Protopic ointment)	
Dose and Mode of Administration:	Twice a day, topical, non-occlusive application.	
Duration of Treatment:	Minimum of 2 weeks, maximum of 3 weeks.	
Studied period:	Date of first subjects' first visit:	01 Mar 2005
	Date of last subjects' last visit:	23 Aug 2005
Study Center(s):	25 active centers treated 265 patients in 3 countries:Germany,Italy and Spain.	
Methodology:	This was a multicenter, randomized, double-blind, reference-controlled, parallel-group study of Advantan 0.1% ointment in children and adolescents aged 2-15 years with moderate to severe atopic dermatitis experiencing an acute severe or very severe flare of the disease. For blinding reasons: Neribas ointment, once a day (at second timepoint) was given as vehicle control.	
Indication/ Main Inclusion Criteria:	Age 2-15 years at baseline Acute flare of atopic dermatitis according to the Investigator's Global Assessment (IGA >= 4) 'Severe' or 'Very severe' History of moderate to severe form of atopic dermatitis for at least one year Affected body surface area at least 5 %	
Study Objectives:	<u>Overall:</u> The objective of this study was to compare the efficacy and safety of	

	Advantan 0.1% ointment applied once daily (plus application of Neribas for blinding reasons at second timepoint) for at least 2 weeks and not more than 3 weeks with the twice daily application of Protopic 0.03% ointment in children and adolescents with moderate to severe atopic dermatitis. Primary: Not applicable Secondary: Not applicable
Evaluation Criteria:	Efficacy (Primary): Static investigators global assessment score (IGA) Efficacy (Secondary): -Eczema area and severity index (EASI) -Modified eczema area and severity index (mEASI) -Children's dermatology life quality index (CDLQI) -Patient's assessment of global response -Patient's assessment of itch and quality of sleep -Total affected body surface area (BSA) -Medication costs Safety: Incidence of adverse events (AEs) and cutaneous AEs.
Statistical Methods:	Efficacy (Primary) - if applicable: The primary study efficacy parameter IGA was dichotomized into treatment success (IGA score clear or almost clear at the end of treatment) and no success (IGA score worse than almost clear or missing) and analyzed using the extended Mantel-Haenszel test, controlled for centre. A one-sided 2.5% significance level was used. Results from centres which recruited less than 10 patients were pooled for analysis. Change from baseline for secondary efficacy parameters was compared using the Student's t-test. The last-observation-carried-forward principle was applied to impute missing values in secondary analyses. Explorative tests were two-tailed and a 5% significance level was applied. Efficacy was assessed for both the Full Analysis Set (FAS) patients and for the Per Protocol (PP) patients. Safety was assessed for the FAS patients, including all randomized patients to whom medication was dispensed. The results from the FAS and PP groups were comparable. Efficacy (Secondary) - if applicable: An ANCOVA model was used for the analysis of the main treatment effect for the percentage change in mEASI, EASI, intensity of itching, CDLQI, patients assessment of quality of sleep from baseline to end of

	study medication Mantel-Haenszel test was used for the analysis of patient's assessment of global response and affected Body surface area by visit and the mean change from baseline. Safety: The safety variables were analyzed using descriptive statistics.
Number of Subjects:	It was planned to randomize 250 patients and 265 patients were actually randomized to treatment with either Advantan (129) or Protopic (136).

Study Results

Results Summary — Subject Disposition and Baseline

A total of 266 patients were screened and only one failed to meet the inclusion criteria giving a total FAS population comprising 265 patients. Of these, 129 were randomized to Advantan ointment and 136 to tacrolimus ointment. A total of 257/265 patients (96.9%) completed the study. All but 2 patients (1.6%) in the MPA group completed the study as planned (one patient was lost to follow-up and one had a major protocol deviation). In the tacrolimus group, six patients (4.4%) failed to complete the study (4 withdrew because of adverse events, 1 withdrew consent and 1 was lost to follow-up). The PP population consisted of 101 patients.

Demographic features were comparable for the two treatment groups (Table 2). Analysis did not reveal effects that could be attributed to variation between centres or seasonal factors

Results Summary — Efficacy

Primary end point

The assessment of the primary efficacy parameter IGA at the end of treatment is shown in Table 1. In both groups, the therapy was evaluated as being successful in the majority of patients (IGA score 'Clear' or 'Almost Clear') by the end of treatment: Advantan 86/129 (66.6%) and tacrolimus 91/136 (66.9%). The difference between treatment groups was 0.3 % (95% confidence limits: 11.6% – 11.1%) and was not statistically significant (p=0.9314). At day 14 the success rate was 50.3% (65/129) for MPA compared to 41.1% (56/136) for tacrolimus. The number of patients cleared at the end of treatment were 48/129 (37.2%) for MPA and 40/136 (29.4%) for tacrolimus. All patients in the Advantan group and 132/136 (97.1%) in the tacrolimus group reported an improved IGA score at the end of treatment.

Secondary endpoints

Eczema Area and Severity Index

Substantial improvement in EASI was noted at days 4 and 7 for both treatment groups. However, there was a greater mean percentage change from baseline for EASI with MPA compared to tacrolimus during the study. At the end of treatment the mean percentage change from baseline for EASI was 89.7% in the MPA group compared to 85.3% in the tacrolimus group. The difference between the two groups was significant after 7 days of treatment (p=0.0352) and after 14 days of treatment (p=0.0214) but not at day 21 (p=0.0667).

Body Surface Area affected

The percentage of affected BSA decreased from approximately 29% at baseline for both treatment groups to 6.8% in the MPA group compared to 7.7% in the tacrolimus group at the end of the study.

Patients' Assessment of Itch

The mean intensity of itching declined substantially from baseline to end of treatment and was particularly pronounced in the Advantan group. The mean VAS decreased from 68.0 mm at baseline to 6.3 mm at the end of treatment with MPA compared to 63.6 mm at baseline and 13.8 mm at end of treatment with tacrolimus. The change in assessment of itch was already statistically significant in favour of MPA by day 4 (day 4: p=0.026; day 7: p=0.0006; day 14: p=0.0007; day 21: p=0.0004).

Effect on Quality of Sleep

Starting from mean values of 54.6 mm (MPA) and 51.5 mm (tacrolimus) at baseline, the quality of sleep improved in both groups to 5.3 mm (MPA) and 11.0 mm (tacrolimus) at the end of treatment. The improvement in quality of sleep with MPA was significantly better than tacrolimus at day 14 (p=0.0409), and at the end of treatment (p=0.0094).

Medication costs

The mean amount of study medication needed for treatment in the MPA group was 53.7 g of MPA ointment compared with 89.3 g of tacrolimus ointment in the tacrolimus group. The mean cost of treatment in the MPA-treated group was 14.59 euros, compared to 100.99 euros in the tacrolimus group. Both findings were significantly in favour of MPA (p=0.0001).

Additional Analyses

mEASI scales revealed similar results to EASI. Results for CDLQI in the categories 'Symptoms and Feelings' and 'Sleep' reflected the more pronounced effect of MPA compared to tacrolimus on itch and quality of sleep detailed in the previous sections (data not shown). No patients in the MPA group but two patients in the tacrolimus group reported a worsening of the disease compared to baseline.

Table 1: Success Rate at the End of Therapy

	Number of patients	Success (success rate)	Difference*	95% CI of difference	p value
Advantan (FAS)	129	86 (66.6%)	-0.25%	(-11.59% – 11.10%)	0.9314
Protopic (FAS)	136	91 (66.9%)			
Advantan (PPS)	101	69 (68.3%)	-0.65%	(-13.03% – 11.73%)	0.7941
Protopic (PPS)	116	80 (68.9%)			

Difference* = (Advantan- Protopic)

Results Summary — Safety

No patients in the MPA treatment group experienced adverse events attributed to treatment, while 6 patients (4.4%) in the tacrolimus treatment group did. These patients reported pruritus, erythema, skin burning and hot flushes.

A total of four patients (all in the tacrolimus group) discontinued the study due to adverse events (1 pruritus, 1 pruritus and skin burning, 1 pruritus and hot flushes, 1 scarlet fever). With the exception of the patient with scarlet fever, these were assessed by the investigator as being drug-related. The dose of study medication was reduced for one patient in the MPA group, who had varicella. This adverse event was not assessed as drug-related

Conclusion(s)

While both treatment groups showed similar efficacy results regarding treatment success (IGA), significant advantages were observed for EASI, itch and sleep with MPA 0.1 %. These advantages and the significantly lower treatment costs highlight the benefits of MPA treatment, underlining its first line role in treatment of children and adolescents with severe AD.

In conclusion, once daily application of Advantan ointment provided a relevant clinical benefit

for children and adolescents with moderate to severe atopic dermatitis in this trial. While both treatment groups showed similar efficacy results regarding treatment success (IGA), significant advantages were observed for EASI, itch and sleep with MPA 0.1 %. With respect to safety, the therapy with both treatments was well tolerated by the patients with a lower incidence of AEs in the Advantan group.

Date Created or Date Last Updated:	17 Aug 2011