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.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer HealthCare, AG Consumer Care	
Study Number:	15616	NCT01359787 EudraCT number: 2010-024279-14
Study Phase:	II	
Official Study Title:	Double-blind, randomized, vehicle-controlled, multicenter, multinational, parallel-group study of the efficacy and safety of mapracorat ointment in three concentrations over max. 4 weeks in subjects with Atopic Dermatitis (AD)	
Therapeutic Area:	Dermatology	
Test Product		
Name of Test Product:	Mapracorat (ZK 245186, BAY 86-5319)	
Name of Active Ingredient:	Mapracorat (ZK 245186)	
Dose and Mode of Administration:	Individual dose of the study drug applied topically as a thin layer in a non-occlusive way in a dose depending on the concentration of ZK 245186 ointment (0.01%, 0.03%, and 0.1%) and the body surface area (BSA) affected by AD, once daily in morning.	
Reference Therapy/Placebo		
Reference Therapy:	Vehicle ointment	
Dose and Mode of Administration:	Individual dose of the vehicle ointment applied topically in a non-occlusive manner, depending on the BSA affected by the disease.	
Duration of Treatment:	Subjects continued treatment for a minimum of 2 weeks and up to a maximum of 4 weeks.	
Studied period:	Date of first subjects' first visit:	09 MAY 2011
	Date of last subjects' last visit:	28 SEP 2011
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	The study was conducted according to the original study protocol version 1.0 from 22 DEC 2010, and included no substantial amendments.	
Study Center(s):	This study was conducted in 5 countries with 35 centers: 4 in Czech Republic, 12 in Germany, 5 in Hungary, 6 in Latvia, and 8 in Poland.	
Methodology:	This was a multicenter, multinational, randomized, double-blind vehicle-controlled study of subjects with ≥5% BSA affected by AD. Each randomized subject received once-daily topical application of one of 0.01%, 0.03%, or 0.1% mapracorat ointment or the vehicle ointment for 4 weeks or until the investigator verified the subject's AD had cleared on all skin areas affected, whichever occurred first. Study duration was approximately of 18 weeks with 7 ambulatory scheduled visits per subject. It included a screening period of up to 12 weeks (Visit 1), a treatment period of up to 4 weeks, and a follow-up period	

	of 2 weeks after application of the last dose of the study medication (End of Study visit/Visit 7). Randomization occurred at the baseline visit (Visit 2) when the subject received their allocated treatment. Four of the ambulatory weekly visits were during the treatment period for assessment of efficacy (Visits 3-6), Vist 6 = end of study medication (EOSM). The primary efficacy parameter, Eczema Area and Severity Index (EASI) was assessed on the basis of change in severity of AD from baseline to 4 weeks. The secondary efficacy parameter included assessment related to EASI called modified EASI (mEASI), and EASI area under curve (EASI AUC) was also assessed at the baseline visit and from Visit 3 to Visit 7. Other secondary parameters included the Static Investigator's Global Assessment (IGA), which was evaluated at all visits, and the affected body surface area (BSA), which was assessed at Visits 1 and 2. Photo-documentation or pictures of the target lesions were taken at Visits 2, 4, 6, and 7. Dermatology Life Quality Index (DLQI) and Euro quality of life 5-domain questionnaire (EQ-5D) were evaluated at Visits 2 and 6 (in countries in which a validated questionnaire in local language was available). The Subject's assessment of pruritus using visual analog scale (VAS) was done from Visit 2 to Visit 7. The subject's daily diary was maintained for recording his/her assessment of treatment response. At Visit 6, the subject's global assessment of treatment response was recorded. Blood samples for population pharmacokinetic (PK) assessment were collected at Visits 2 to 6. Safety variables including adverse events (AEs) were evaluated at Visits 2, 3, 4, 5, 6, and 7. Vitals, electrocardiogram (ECG), and blood chemistry was also recorded. Safety laboratory tests inclusive of biochemistry, hematology, coagulation, and urinalysis were assessed at Visits 1, 2, 4, and 6.
Indication/Main Inclusion Criteria:	Indication:Atopic dermatitis Main inclusion criteria: • Signed written informed consent • Male or female subjects 18 to 65 years of age • Diagnosis of AD according to Hanifin and Rajka Criteria • Body surface area affected by AD lesions ≥5% at screening and start of treatment • Static IGA score ≥3, corresponding to at least moderate AD at screening and start of treatment • Willingness of subject to follow all study procedures • Willingness to avoid excessive exposure of diseased areas to natural or artificial sunlight • Female subjects of non-childbearing age or using an accepted effective method of contraception
Study Objectives:	Primary: • To assess the efficacy of mapracorat ointment in concentrations of 0.01%, 0.03%, and 0.1% in subjects with AD compared to the vehicle.

	Secondary: • To evaluate the safety and tolerability of mapracorat ointment in concentrations of 0.01%, 0.03%, and 0.1%. • To assess the dose-response relationship of mapracorat after topical, non-occlusive application of concentrations of 0.01%, 0.03%, and 0.1%. • To assess the systemic exposure of mapracorat after topical, non-occlusive application of concentrations of 0.01%, 0.03%, and 0.1%.
Evaluation Criteria:	Efficacy (Primary): **Eczema Area and Severity Index**: The EASI is a composite index, including an assessment of disease extent and the percent of BSA involved, in four body regions (head and neck, upper limbs, trunk, and lower limbs). The EASI score for each body region uses the sum of the clinical sign scores (E [erythema] + I [infiltration and/or population] + Ex [excoriation] + L [lichenification]) multiplied by the proportional area score, multiplied by the proportional body region factor. 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 of 72. Efficacy (Secondary): • **IGA**: The IGA is a static evaluation of the overall severity of AD at a given time. It consists of a 6-point scale ranging from totally clear (0) to very severe AD (5). The static IGA score was evaluated as success (combining scores of "clear" and "almost clear") or failure (combining scores of "mild," "moderate," "severe," and "very severe"). • **mEASI**: The mEASI is a modification of the EASI by adding a factor for pruritus. The EASI similar to primary efficacy variable was also evaluated on every visit along with the EASI AUC. • **Affected BSA**: Affected BSA is calculated using the investigator percentage estimates of the extent of BSA involvement of a body region multiplied by the proportions allocated to the body region. The products of the four body regions were summed up to receive the affected BSA, and change from baseline in affected BSA value was evaluated. • **Overall clinical signs of AD**: Overall clinical signs of AD erythema, infiltration/population, excoriation, and lichenification were assessed using the data input from EASI (maximum score of the 4 body regions). The change from baseline at each post-baseline visit was categorized as improved, no change, or worsened. • **DLQI**: The total DLQI score at the EOSM visit was classified as a change from the baseline of <5 and a change from baseline of ≥5. It was also classified on a scale of 0->20 (0: no effect at all on the

	subject's life; >20: extremely large effect on the subject's life). • **EQ-5D**: The EQ-5D is a quality of life index that consists of 5-domain questions about the subject's ability to perform activities and their levels of pain/discomfort and anxiety/depression. Response in each of the 5 domains at the baseline assessment was compared with the EOSM visit. • **Subject's assessment of pruritus using VAS:** This parameter was assessed by the intensity of his/her pruritus during the previous 24 hours by drawing a vertical line through a 100 mm horizontal VAS, indicating no itch at one end of the scale to worst itch imaginable at the other end. • **Subject's global assessment of treatment response**: This was evaluated at the EOSM in terms of how their disease had changed from baseline recorded on a 7-point categorical scale (much better, better, slightly better, same, slightly worse, worse, much worse). • **Subject's itch assessment**: The subject's daily assessments were documented in the diary with the date and time of drug application along with itch assessment (none, mild, moderate, severe). • **Photo-documentation of target lesions**: The photo-documentation was done in selected sites, and the selected lesions were followed till Visit 7. <u>Safety:</u> Safety was assessed by recording of AEs using MedDRA version 14.0, physical examination, ECG, vital signs (including weight), and clinical laboratory evaluations (biochemistry, hematology, coagulation, and urinalysis parameters).
	<u>Pharmacokinetics:</u> Serum concentrations of mapracorat were measured using a validated liquid chromatography tandem mass spectrometry method. Quality control and calibration samples were analyzed concurrently with the study samples.
Statistical Methods:	Efficacy was evaluated using the following analysis sets: • Full analysis set (FAS): All subjects who were randomized and had investigational product dispensed. Randomization was considered completed with the first dispense of study medication to the subject at the baseline (Visit 2). • Per protocol set (PPS): The PPS is a subset of the FAS. The subjects with major protocol deviations and subjects who discontinued from the study prematurely were excluded from the PPS. The primary analysis set for evaluation of the efficacy variables was the FAS using last observation carried forward (LOCF) data. The FAS and PPS using observed data were the secondary analyses for the efficacy variables. The FAS was used for all safety analyses. <u>Efficacy (Primary):</u> The primary analysis of the treatment effect for the percentage change in EASI was investigated by an analysis of covariance (ANCOVA) with treatment and country as the factors, and the baseline

EASI score as the covariate. For subjects with no post-baseline EASI data, the percentage change from baseline was calculated as zero. A point estimate of the mean treatment difference between each dose of mapracorat and the vehicle was presented with associated 95% confidence intervals (CI) and p-values. The treatment-by-country interaction term was investigated in a separate analysis. In addition, subgroup analyses with regard to sex and age (<35 years, ≥35 years) were performed for the primary efficacy variable at the EOSM visit.

All analyses were explorative in nature.

Efficacy (Secondary):

The values of each secondary variable were summarized using descriptive statistics or frequency counts.

- Static Investigator Global Assessment: The proportion of subjects with treatment success was analyzed at each post-baseline visit using the Cochran-Mantel-Haenszel test. The odds ratios for comparing each dose of mapracorat and the vehicle were presented, with associated 95% CIs and p-values. In addition, subgroup analyses with regard to sex and age (<35 years, ≥35 years) were performed for the proportion of subjects with treatment success at the EOSM visit.
- Eczema Area and Severity Index: Nominal values and changes from baseline were summarized for each visit after the baseline visit. ANCOVA was performed on the change from baseline to the Visit 6 (EOSM).
- Modified Eczema Area and Severity Index: The analyses of mEASI were similar to EASI.
- Affected body surface area: The change from baseline in affected BSA value was analyzed at each post-baseline visit using an ANCOVA as described for the primary efficacy variable.
- Overall clinical signs of atopic dermatitis: The categorized change from baseline was analyzed using the Pearson chi-square test.
- Only the number and percentage of subjects in each category were presented for DLQI.
- EuroQol EQ-5D: Summary statistics for the response values in each of the five domains at the baseline and the EOSM visit were presented along with shift tables. The change from baseline to the EOSM visit in EQ-5D VAS score was analyzed using ANCOVA.
- Subject's assessment of pruritus using a VAS: Nominal values and changes from baseline to the EOSM visit were summarized for each visit after baseline, and ANCOVA was performed on change from baseline to EOSM.
- Subject's diary: Only the summary statistics for the number and percentage of subjects with daily itch assessments were presented.
- Subject's global assessment of treatment response: The number and percentage of subjects in each category at the EOSM visit were analyzed using the Pearson chi-square test.

Safety:

Descriptive statistics (n, mean, SD, median, quartiles [where

	appropriate], minimum and maximum) were presented for all safety evaluations of AEs, laboratory, urinalysis, and vital signs data. No imputation was made for missing values. Further details on handling of missing dates for AEs, prior and concomitant medications, and unplanned repeat safety evaluations were described in the SAP.
	Pharmacokinetics: Serum concentrations were listed and described using the summary statistics. Measured serum concentrations below the lower limit of quantification (LLQ) were assumed to be zero for these descriptive statistics. Additionally to the PK data included in this clinical study report, a separate report will be provided.
Number of Subjects:	Planned: 200 subjects Screened: 214 subjects Randomized: 197 subjects (48 subjects, 50 subjects, and 52 subjects in the 0.01%, 0.03%, and 0.1% mapracorat treatment arms, respectively, and 47 subjects in the vehicle treatment arm) Analyzed: 197 subjects

Study Results

Results Summary — Subject Disposition and Baseline

Of the 214 subjects who were screened for the study, 197 subjects were randomized and included in the FAS. The most frequent reasons for screen failure were failure to meet the entry criteria (7 subjects) and withdrawal of consent (7 subjects). Two subjects lost to follow up, and 1 subject failed screening due to other reasons (strong elevation of hepatic enzymes). Of the 197 subjects included in the FAS, 61 subjects (31%) had major protocol deviations resulting in exclusion from the PPS giving a total of 136 subjects.

Of the 197 randomized subjects, 159 subjects (80.7%) completed the study and 38 subjects (19.3%) were prematurely discontinued. A total of 101 (51.3%) subjects were male and 96 (48.7%) subjects were female. Notably more male subjects (29 [61.7%]) than female subjects (18 [38.3%]) were included in the vehicle group.

For baseline characteristics of AD, a significant difference (p-value 0.005) between treatment groups was observed for duration of AD prior to study entry. Otherwise, no significant or major differences were observed between the treatment groups for the baseline characteristics. For 3 subjects, a deviation from the study entry criteria was observed: for one subject (0.01% mapracorat group), exclusion criterion was not checked; one subject was 69 years old at inclusion; one subject had an IGA < 3 at screening.

In the FAS, majority of subjects (186 [94.4%]) were not Hispanic or Latino. In the FAS, the subjects had a mean age of 33.3 years (range: 18-69). Overall, the demographic characteristics in the FAS showed no significant differences between the treatment groups.

Results Summary — Efficacy

Primary efficacy variable:

EASI: Statistically significant improvement in EASI from baseline to Visit 6 (EOSM) was observed for the 0.1% and 0.03% mapracorat groups compared with the vehicle, with the largest treatment difference in mean percentage change observed in the mapracorat 0.1% treatment group.

A statistically significant improvement in change from baseline in EASI, compared with vehicle, was observed for the mapracorat 0.1% group at all post-baseline Visits and for the mapracorat 0.03% group at Visits 3-6.

Secondary efficacy analysis:

- **IGA**: For the static IGA score, the number of subjects with treatment success (IGA 0 or 1) at Visit 6 (EOSM) was greatest in the mapracorat 0.1% treatment group (11 [21.2%]), increasing from Visits 3 to 6. No subject with treatment success was observed in the vehicle treatment group until Visit 6.
- **mEASI**: The percentage change from baseline in mEASI scores, compared with vehicle, was statistically significant for the mapracorat 0.1% and 0.03% treatment groups at all post-baseline visits, with the largest difference occurring at Visits 6 and 3. Similar to the results obtained for EASI (primary efficacy variable), comparable results were also observed for the EASI AUC at Visit 6 for the mapracorat 0.1% and mapracorat 0.03% treatment groups.
- **Affected BSA**: A statistically significant decrease compared with the vehicle in affected BSA value was observed only for the mapracorat 0.1% group from Visit 5 onward, with the largest change noted at Visit 6.
- **Overall clinical signs of AD**: The majority of subjects in the mapracorat 0.1% treatment group experienced an improvement in all clinical signs of AD from baseline to Visit 6 (EOSM), which was statistically significant for erythema, infiltration/papulation, and excoriation, compared to vehicle.
- **DLQI**: At baseline, the majority of subjects in all treatment groups reported a moderate or very large effect of AD on quality of life. The number of subjects in these categories had decreased slightly by Visit 6 (EOSM), with more subjects reporting a small effect of AD on quality of life; however, these changes were not statistically significant.
- **EQ-5D**: A change from baseline in the EQ-5D VAS score was also observed for all treatment groups at Visit 6 (EOSM). The greatest change from baseline occurred in the mapracorat 0.1% and 0.03% treatment groups, although none of these changes were statistically significant when compared with vehicle.
- **Subject's assessment of pruritus using VAS**: For the subject's VAS assessment of pruritus, the greatest mean change (decrease) was observed in the mapracorat 0.1% treatment group with a statistically significant mean change from baseline at Visit 6.
- **Subject's global assessment of treatment response**: At Visit 6, according to the subject's global assessment of treatment response, there was a greater proportion of subjects reporting a "much better" response to treatment in the mapracorat 0.1% treatment group compared to all other treatment groups.
- **Subject's itch assessment**: Assessment of daily diary itch score responses showed that there were no notable differences compared with baseline in the number of subjects reporting severe intensity of pruritus at any time point and no differences between the treatment groups.
- **Photo documentation of target lesion**: In 16 selected sites (1 site in Latvia, 2 sites each in Czech Republic and Hungary, 8 sites in Germany, and 3 sites in Poland), a representative lesion was chosen at baseline, identified in the body template provided, and clinical photographs taken before study medication started (baseline). Most subjects

were skin phototype II (117 [59.4%]) and skin phototype III (65 [33.0%]); no subjects with skin phototype V and VI were included. The selected lesion was followed through the study at Visits 4, 6 and 7. Data on whether pictures were taken of target lesion was listed.

Results Summary — Safety

Overall, frequencies of treatment-emergent AEs (TEAEs) ranged from 32.7% (mapracorat 0.1%) to 58.3% (mapracorat 0.01%). Most frequent occurrence by System Organ Class (SOC) and preferred term were similar in each treatment group, and no relevant differences between treatment groups were observed. However, the frequencies and numbers of TEAEs generally tended to be lower in the mapracorat 0.1% group compared to the other treatment groups. No deaths were reported. Only one serious adverse event (vehicle group, unrelated) was reported.

Overall TEAEs resulting in discontinuation were similar between treatment groups. The most frequent TEAEs resulting in discontinuation by SOC were skin and subcutaneous tissue disorders. All other TEAEs by SOC resulting in discontinuation were infrequent and occurred in <5% of subjects in any treatment group.

Frequencies for cutaneous TEAEs ranged from 19.2% (mapracorat 0.1%) to 31.9% (vehicle group). The most frequent cutaneous TEAE by preferred term was dermatitis atopic and occurred at a similar frequency in all treatment groups. Individual cutaneous TEAEs by preferred term were infrequent. Overall, most TEAEs were of mild or moderate intensity, and most subjects with TEAEs either recovered or were recovering.

Frequencies for drug-related TEAEs (judged by the investigator) ranged from 13.5% (mapracorat 0.1%) to 27.7% (vehicle group). In all treatment groups, the most frequently recorded drug-related TEAEs by SOC were skin and subcutaneous tissue disorders. Individual related TEAEs by preferred term were infrequent. No major differences between baseline and EOSM visit were observed for any other safety parameters in any treatment group. Parameters were similar between treatment groups throughout the medication period.

In accordance with the underlying disease and the safety information for mapracorat ointment recorded in the Investigator's Brochure, no new safety findings have occurred during this study.

No major differences between baseline and Visit 6 (EOSM) were observed for any biochemistry, hematology, coagulation, urinalysis parameter in any treatment group. All safety laboratory parameters were comparable between treatment groups throughout the medication period.

No major differences between baseline and EOSM Visit 6 were observed for ECG parameters in any treatment group. ECG parameters were comparable between treatment groups throughout the medication period.

Physical examination was performed at Visit 1 (screening), Visit 6 (EOSM) and Visit 7 (EOS). New or worsened findings at Visit 6 and/or Visit 7 were reported as AEs.The total number of recorded subjects with any medical and surgical history was infrequent (39 subjects [19.8%]) and comparable between treatment groups. Most frequently a medical or surgical history was observed in the 0.1% mapracorat group (13 subjects [25.0%]), followed by the 0.01% mapracorat group (10 subjects [20.8%]) and the 0.03% mapracorat group (9 subjects [18.0%]); the least frequent occurrence of medical or surgical history was observed in the vehicle group (7 subjects [14.9%]).

No major differences between baseline and Visit 6 (EOSM) were observed for vital signs and weight in any treatment group. Vital signs and weight were comparable between treatment groups throughout the medication period.

Results Summary — Pharmacokinetics
The highest median concentrations of the study drug at each study visit occurred following treatment with mapracorat 0.1%, followed by mapracorat 0.03% and mapracorat 0.01%. There was considerable variability in serum concentrations of study drug at each visit for each treatment group; the median serum concentration for vehicle remained below the LLQ at all study visits.
Conclusion(s)
In this study, 0.1% and 0.03% doses of mapracorat ointment resulted in increased efficacy compared to 0.01% mapracorat ointment and vehicle. Mapracorat 0.1% was more effective as compared to all other treatment groups. The subjects were compliant with the study medication as indicated by median concentration levels of mapracorat for subjects receiving active doses. No new safety findings have been observed during this study, and an acceptable safety profile for mapracorat ointment (0.01%, 0.03%, and 0.1%) was shown.

Publication(s):	None		
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