2. Synopsis

Name of Sponsor/Company: Maruho Co, Ltd. **Name of Finished Product:** To be assigned **Name of Active Ingredient:** M5161 [redacted]	**Individual Study Table Referring to Part of the Dossier** Volume: Page:	**(For National Authority Use Only)**
Title of study: A Randomized, Placebo-controlled, Double-blind, Parallel Group, Multi-centre Phase IIb Dose-finding Study of M516102 in the Treatment of Pruritus Associated With Atopic Dermatitis		
Investigators [redacted]		
Study sites: [redacted]		
Publication (reference): None		
Studied period (years): [redacted]		**Phase of development**: IIb

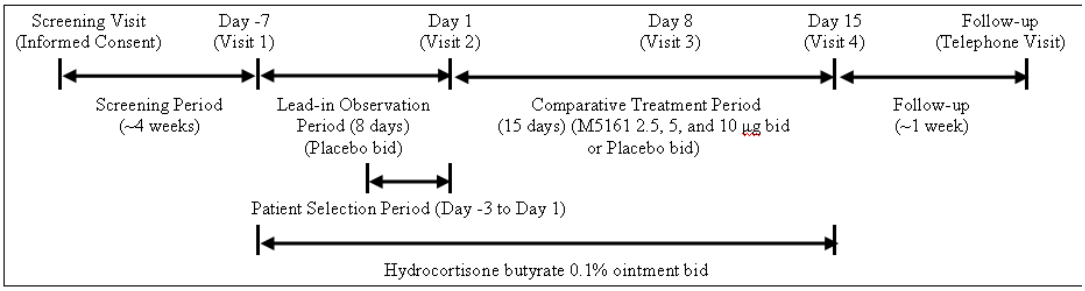
Objectives: The primary objectives of the study were:

- To investigate the efficacy of M516102 in the treatment of pruritus associated with atopic dermatitis (AD) using oral dose regimens of 2.5, 5, and 10 µg twice-daily (bid) for 15 days (once in the evening of Day 1 and in the morning of Day 15, twice daily from Day 2 to Day 14)
- To evaluate the dose-response relationship among 3 doses of M516102 (2.5, 5, and 10 µg) and placebo, in the treatment of pruritus associated with AD.

The secondary objective of the study was to determine the safety of M516102 in patients with AD using oral dose regimens of 2.5, 5, and 10 µg bid for 15 days (once in the evening of Day 1 and in the morning of Day 15, twice daily from Day 2 to Day 14).

Methodology: This study was a randomized, placebo-controlled, double-blind, parallel-group, multi-centre Phase IIb dose-finding study to investigate the efficacy and safety of M516102 and the dose-response relationship among 3 doses of M516102 (2.5, 5, and 10 µg bid) and placebo bid over a 15 day treatment period in patients with pruritus-associated AD.

Study Schematic



The study consisted of a Screening Period (~4 weeks), a Lead-in Observation Period (8 days) and a Comparative Treatment Period (15 days). During the study, 4 visits to the clinic were scheduled after Screening: Visit 1 (Day −7) at the start of the Lead-in Observation Period, Visit 2 (Day 1) at the start of the Comparative Treatment Period, Visit 3 (Day 8) in the middle of the Comparative Treatment Period, and Visit 4 (Day 15) at the end of the Comparative Treatment Period. A Safety Follow-up Visit was conducted by telephone 1 week

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after Visit 4 or 1 week after the final visit attended if the patient did not complete the study.

At the Screening Visit, after giving informed consent to participate, patients were assessed using the screening examinations. Eligible patients with confirmed AD using the Hanifin and Rajka diagnostic criteria (Hanifin and Rajka 1980), and who met all the inclusion criteria and none of the exclusion criteria were enrolled.

Throughout the study, protocol excluded medications were prohibited, but in addition to the study treatments, the use of the patient's current emollient was permitted, as directed by the prescribing physician, or according to the product label. Patients were also supplied with hydrocortisone butyrate 0.1% ointment to be applied topically to affected areas twice daily throughout the Lead-in Observation Period and until completion of the Comparative Treatment Period (from the evening of Day –7 until the morning of Day 15).

Following the Screening Period, eligible patients entered the Lead-in Observation Period. During the single-blind Lead-in Observation Period, all patients received placebo tablets bid (in the morning and in the evening) for 8 days. Before entering the double-blind Comparative Treatment Period, patient selection was confirmed according to the inclusion criteria and eligible patients were randomly assigned to 1 of the 4 parallel treatment regimens by interactive voice response system (IVRS) in a 1:1:1:1 ratio. The treatment regimens were: M516102 (2.5, 5, or 10 µg bid) or placebo bid.

Following completion of the Comparative Treatment Period, there were no restrictions on the treatment for AD.

Patients who were discontinued from study treatment early were asked to return to the investigative site as soon as possible to conduct the assessments scheduled for Visit 4 and a Safety Follow-up Visit was conducted by telephone 1 week later.

Number of patients (planned and analysed): It was planned to enrol approximately 240 evaluable patients, 60 patients per treatment group. In total, 246 patients were enrolled. Before entering the Comparative Treatment Period, patient selection was confirmed according to the inclusion criteria and eligible patients were randomly assigned to 1 of the 4 parallel treatment regimens by IVRS in a 1:1:1:1 ratio.

Diagnosis and main criteria for inclusion: All patients were required to meet the following criteria for inclusion in the study:

At Screening: Male or female patients (aged 18 to 65 years, inclusive) with a diagnosis of AD confirmed at Screening using the Hanifin and Rajka diagnostic criteria (Hanifin and Rajka 1980).

Female patients of childbearing potential were to use a medically acceptable form of contraception throughout the study and for at least 30 days after the last dose of investigational medicinal product (IMP).

Patients who were able and willing to give signed informed consent.

At Visit 1 (start of single-blind Lead-in Observational Period): Patients who had a self-assessed pruritus score (a total of the diurnal and the nocturnal score on the day before Visit 1) greater than or equal to 4 points at Visit 1 (Day –7)

At Visit 2 (start of double-blind Comparative Treatment Period): Patients who had a self-assessed mean pruritus score (a total of diurnal and nocturnal scores) greater than or equal to 4 points for the patient-selection period (ie from the evening of Day 3 to the morning of Day 1).

Test product, dose and mode of administration, batch number:

Test Product	Dose and Mode of Administration	[redacted]
M516102	2.5 µg oral tablets	[redacted]
M516102	5.0 µg oral tablets	[redacted]
Hydrocortisone butyrate	0.1%, ointment for topical application.	[redacted]

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Duration of treatment: The Lead-in Observation Treatment Period was 8 days and the Comparative Treatment Period was 15 days.

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

Test Product	Dose and Mode of Administration	[redacted]
Placebo	Matched Oral tablets	[redacted]

Criteria for evaluation:

Efficacy: Analysis was performed on the Full-Analysis and Per-Protocol Sets.

The primary efficacy variable was the mean change in Visual Analogue Scale (VAS) score during the double-blind Comparative Treatment Period compared with Baseline (the mean score in the patient selection period).

The secondary efficacy variables were:

- Mean change in pruritus score during the double blind Comparative Treatment Period compared with Baseline
- Mean change in VAS score and pruritus score for the first 7 days of the double-blind Comparative Treatment Period compared with Baseline
- Time course changes in VAS score, pruritus score and severity score for AD (SCORAD) index

Safety: Analysis of safety was conducted for either the Lead-in Observation Period Safety Set or the Safety Set.

The safety endpoints were physical examination, vital sign measurements and adverse event (AE) review. Laboratory tests: haematology, serum biochemistry, urinalysis, and hormones were also performed during the study.

Statistical methods: The data from this study were summarised using descriptive statistics, frequency tables, graphs, and data listings.

Continuous data were summarised using descriptive statistics: mean, SD, median, minimum, maximum, and number of valid cases. For the efficacy variables, the lower and upper quartiles were also presented. A row denoted 'Missing' was included in count tabulations where necessary to account for missing values.

All statistical analyses were performed using a 2-sided hypothesis test at the overall 5% level of significance, unless otherwise stated. p values were rounded to 3 decimal places. If a p value was less than 0.001, it was reported as '<0.001'. All SAS software Version 9.1.3 (SAS Institute, Cary, North Carolina) statistical outputs for all analyses performed were included in addition to the main outputs.

Details of the statistical analyses to be performed were specified in the Statistical Analysis Plan before unblinding the study.

In addition, additional exploratory and ad hoc analyses for the M516102-EU03 study were performed after database lock and the unblinding of the study. These were documented in the statistical analysis plan for additional analyses performed post-database lock.

Summary and Conclusions:

Efficacy results: Overall, an improvement in the mean VAS score and pruritus score was seen over time for all treatment groups. The improvement was similar for the M516102 groups and for the placebo group. There were no statistically significant dose-response or treatment effects observed. The ANCOVA showed no significant treatment differences for the mean change in VAS score during the Comparative Treatment Period compared with Baseline.

Analyses were based on the Full-Analysis Set and were repeated for the Per-Protocol Set. The Per-Protocol Set analysis was considered exploratory in nature and therefore no formal inference was made. The overall

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conclusions from both populations were similar.

Overall, there was a slight improvement in the SCORAD index over time. The improvement was similar for the M516102 groups and for the placebo group.

The mean changes in self-assessed itch (VAS score) during the Comparative Treatment Period were summarised by subsets of gender, age categories, race, country, body mass index categories, Baseline VAS score, Baseline pruritus score, and Baseline SCORAD index. Overall the improvement seen in the Full-Analysis Set was also seen in each subset for all treatment groups. The improvement was similar for the M516102 groups and for the placebo group. The lowest pruritus score on the day before Visit 1 (pruritus score - 4) appeared to yield the greatest improvement in the M516102 groups and also seems to show the least improvement for the placebo group. In addition, a higher pruritus score at Baseline seems to show a greater improvement in the M516102 groups when compared with the placebo group.

Additional exploratory and ad hoc analyses for the M516102-EU03 study were performed after database lock and the unblinding of the study. Overall in these analyses, an improvement in the mean VAS score for the last 7 days of the Comparative Treatment Period was seen for all treatment groups and in all subgroups. However, there was a greater difference in the improvement in the treatment effect of M516102 for patients who took pre-treatment AD medications compared with placebo patients who took pre-treatment AD medications. An improvement in the individual SCORAD components was seen for all treatment groups and in all subgroups. The mean change from Baseline of the individual SCORAD components was similar for the M516102 groups and for the placebo group for all subgroups. However, for patients who took pre-treatment AD medications, there was a greater difference in the improvement in the extent of treatment effect of M516102 compared with the placebo group.

Safety results: Overall, M516102 was well tolerated in patients with AD using oral dose regimens of 2.5, 5, and 10 μg bid for 15 days. The majority of TEAEs reported were commonly observed in the previous studies and the TEAEs reported in this study are not considered to add any new clinically significant concerns to the safety profile.

There were no deaths reported, 3 treatment-emergent SAEs (in 3 patients) were reported and none was considered related to study treatment by the investigator. There were 12 patients (4.8%) discontinued from study treatment due to TEAEs. Of these, 9 patients (3.7%) discontinued from study treatment due to related TEAEs: 2 patients (3.3%) in the M516102 2.5 μg group; 6 patients (9.6%) in the M516102 10 μg group; and 1 patient (1.6%) in the placebo group.

There were 254 TEAEs reported in 131 patients (53.5%): 35 TEAEs in 24 patients (39.3%) in the M516102 2.5 μg group; 77 TEAEs in 37 patients (59.7%) in the M516102 5 μg group; 102 TEAEs in 41 patients (66.1%) in the M516102 10 μg group; and 40 TEAEs in 29 patients (48.3%) in the placebo group. The most frequently reported TEAEs occurring in more than 3 patients in any treatment group were eosinophilia, lymphadenopathy, nasopharyngitis, insomnia, sleep disorder, and headache. None of the other TEAEs were reported in more than 3 patients.

The majority of TEAEs reported were considered by the investigator to be mild in intensity. Moderate TEAEs were more frequently reported in the M516102 10 μg group and the reported number of patients who discontinued IMP because of TEAEs was highest in this group. The TEAEs considered by the investigator to be severe in intensity included keratitis, photopsia, nausea, chest pain, chills, thirst, muscle twitching, headache, somnolence, insomnia, dermatitis atopic, and pruritus generalised.

More than half of the TEAEs reported were considered by the investigator to be unrelated to IMP. There was a trend for more related TEAEs with increased M516102 dose. The most frequently reported related TEAEs occurring in more than 3 patients in any treatment group were insomnia, sleep disorder, and headache. None of the other related TEAEs were reported in more than 3 patients in any treatment group.

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Conclusions: The efficacy results showed an overall improvement in the mean VAS score and pruritus score over time for all treatment groups. The improvement was similar for the M516102 groups and for the placebo group. There were no statistically significant dose-response or treatment effects observed. The overall conclusions from both the Full-Analysis Set and the Per-Protocol Set were similar.

From the results of ad hoc exploratory analyses, there was a greater difference in the improvement in the treatment effect of M516102 for patients who took pre-treatment AD medications (an oral anti-histamine or anti-allergic drug and a topical steroid [excluding for use on face] prior to Visit 1) compared with placebo patients who took pre-treatment AD medications. It is therefore suggested that M516102 is efficacious for patients who take an oral anti-histamine or anti-allergic drug and a topical steroid for AD before treatment with M516102.

Overall, M516102 was well tolerated in patients with AD using oral dose regimens of 2.5, 5, and 10 μg bid for 15 days. The majority of TEAEs reported were commonly observed in the previous studies and the TEAEs reported in this study are not considered to add any new clinically significant concerns to the safety profile. The incidence of related TEAEs was similar for the M516102 2.5 μg group and the placebo group. It is therefore suggested by the sponsor that M516102 2.5 μg group has no significant safety concerns.

In this study, there was no statistically significant improvement in patients in M516102 groups in comparison with patients in placebo group: however, there was a greater difference in the improvement in the treatment effect of M516102 for patients who took pre-treatment AD medications compared to placebo patients who took pre-treatment AD medications.

Date of report: [redacted]