CLINICAL STUDY SYNOPSIS

Name of Company: Maruho Co.,Ltd..
Volume: (For national authority use only)
Name of Finished Product: M518101
Page:
Name of Active Ingredient: M5181

Title of Study: A randomised, placebo-controlled, double-blind, left-right comparison, multi-centre phase IIa study to investigate the efficacy and safety of M518101 in plaque psoriasis patients

Protocol Number: M518101-EU03

Study Period: **Phase of Development:** IIa
Date of first enrolment: [redacted]
Date of last completed: [redacted]

Study Centres: [redacted]

Publication(s): Not applicable.

Objectives: The primary objective of the study was to evaluate the efficacy of M518101 in plaque psoriasis patients. The secondary objective was to investigate the safety and tolerability of M518101 in plaque psoriasis patients.

Study Design: This was a randomised, placebo-controlled, double-blind, multi-centre, left-right comparison, phase IIa study to investigate the efficacy and safety of M518101 in male and female patients, aged between 18 and 65 years, with mild to moderate plaque psoriasis with refractory plaques.

Study duration was a maximum of 12 weeks, i.e., 2 weeks of wash-out period, 2 weeks of lead-in period, and 8 weeks of comparative treatment period. There were a total of 8 visits.

For left-right comparison, two symmetrical **target plaques** (minimum size: 10 cm^2) were selected on the left and right side of the trunk (either chest, abdomen, or upper/lower back), or on the left and right upper or lower extremities. The target plaques were selected on the same body part, i.e., front side of trunk, back side of trunk, or upper or lower extremities. Around each target plaque, an area of 70 to 150 cm^2 (including a target plaque and other plaques) was selected as the **target area**. The bilateral target areas were to be similar with regard to number and condition of plaques. The left and right target areas on the trunk (either chest, abdomen, or upper/lower back) had to be separated by healthy skin.

At Visit 2, up to three "target plaque candidates" were selected from each side. At Visit 3, the target plaque candidate which was the most appropriate (i.e., most similar in size, PSI sore, and condition) was determined as the "target plaque". The psoriasis severity index (PSI) score of each target plaque candidate at Visit 2, and of each target plaque at Visit 3 had to be ≥12. A difference between the left and right target plaque in the total PSI score of up to ±4, and in each element of the PSI score of up to ±2, was allowed.

Number of Patients (planned and analysed):
It was planned to randomise 144 patients for this study. The patients were randomised to 4 treatment pairs (36 patients per treatment pair), with each treatment pair further divided into two groups (of 18 patients each) depending on the allocation of the treatments to the left and right side:

- Placebo (left side) vs 25 µg/g M518101 (right side) N=18
- Placebo (right side) vs 25 µg/g M518101 (left side) N=18
- 25 µg/g M518101 (left side) vs 50 µg/g M518101 (right side) N=18
- 25 µg/g M518101 (right side) vs 50 µg/g M518101 (left side) N=18
- 50 µg/g M518101 (left side) vs 100 µg/g M518101 (right side) N=18
- 50 µg/g M518101 (right side) vs 100 µg/g M518101 (left side) N=18
- 50 µg/g M518101 (left side) vs calcipotriol (right side) N=18
- 50 µg/g M518101 (right side) vs calcipotriol (left side) N=18

Name of Company: Maruho Co.,Ltd..
Volume:
(For national authority use only)
Name of Finished Product: M518101
Page:
Name of Active Ingredient: M5181

Number of patients analysed:

	Placebo vs M 25 µg/g	M 25 µg/g vs M 50 µg/g	M 50 µg/g vs M 100 µg/g	M 50 µg/g vs calcipotriol	Overall
Safety set	34	37	38	39	148
Full analysis set	35	36	38	39	148
Per protocol set	29	31	34	33	127

Abbreviations: M=M518101; vs=versus

Diagnosis and Main Criteria for Inclusion: The study population consisted of patients with mild to moderate plaque psoriasis with refractory plaques. Mild to moderate plaque psoriasis patients were defined as patients who had less than 20% of body surface area (BSA) of psoriatic plaques. A refractory plaque was defined as a psoriatic plaque with a PSI score ≥ 12. Patients were randomised into this study only if they met all of the following criteria:

1. Who were able and willing to give signed informed consent at Visit 1.
2. Who were male or females aged between 18 and 65 years, inclusive, on the day of signing the ICF with plaque psoriasis confirmed by the Investigator at Visit 1.
3. Who had less than 20% of BSA afflicted with plaques at Visits 1, 2, and 3.
4. Who had symmetrical (i.e., similar on the left and right side) psoriatic plaques (minimum size of each plaque: 10 cm^2), each of which had a PSI score ≥ 12 (at trunk [either chest, abdomen, or upper/lower back], upper or lower extremities) at Visit 3. A difference between the left and right target plaque in the total PSI score of up to ±4, and in each element of the PSI score of up to ±2, was allowed.
5. Whose PSI score did not decrease by more than 6 on any of the symmetrical psoriatic plaques (target plaques) during the lead-in period (between Visits 2 and 3).
6. Who were neither pregnant nor breast-feeding, nor planned to become pregnant during the study. Females with childbearing potential had to have a negative serum pregnancy test on the day of signing the ICF (Visit 1), and had to use a highly effective method of oral or injectable contraception during the study and for 90 days following completion of the last dose of study drug (non-childbearing potential was defined as post-menopausal for at least two years, or surgical sterilisation or hysterectomy at least 12 weeks before Visit 1). If male, he had to be willing to use contraception to avoid contributing to pregnancies during the study and for 90 days following completion of the last dose of study drug.
7. Who were willing and able to comply with the trial procedures and to communicate clearly with the Investigator.

Test Product, Dose and Mode of Administration, and Lot Numbers: Three different strengths of M518101 (25, 50, and 100 µg/g), Placebo, and calcipotriol were used as study drug.
Labelled lot no.: 09PCT01, expiry date: April 2010.

The Investigator instructed the patients how to administer the study drug for the right side (right from patient's side) on the plaques within the right target area, and the study drug for the left side (left from patient's side) on the plaques within the left target area. The study drug was applied by the patient as instructed by the Investigator in a thin layer on all psoriatic plaques within each target area twice a day (maximum of 4 g/day of each study drug in each target area; 5 cm of ointment was about 1 g). At Visit 3 after randomisation, the patients administered their first dose of study drug under the supervision of the Investigator to ensure that they administered the correct amount of study drug. Patients were instructed to keep the same treatment on the same side of the body as per the tube labelling throughout the study, and never to use an apparently more effective treatment on both sides.

Duration of Treatment: 8 weeks.

Name of Company: Maruho Co.,Ltd..
Volume:
(For national authority use only)
Name of Finished Product: M518101
Page:
Name of Active Ingredient: M5181

Criteria for Evaluation:

Primary endpoint was:

- Change of PSI total score at Visit 8 (i.e., after 8 weeks of double-blind treatment) from Visit 3 (baseline).

Secondary endpoints were:

- Change of PSI total score at Visits 4, 5, 6, and 7 (Weeks 1, 2, 4, and 6) from Visit 3 (baseline).
- Change of each component of PSI score (erythema, induration, scaling) at Visit 8 (Week 8) from Visit 3 (baseline).
- Investigator overall assessment (IOA) at Visit 8 (Week 8).
- Patient overall assessment (POA) at Visit 8 (Week 8).
- Left-right side comparison at Visit 8 (Week 8).

Safety variables were:

- Adverse events (AEs).
- Physical examination findings.
- Safety laboratory parameters.

Statistical Methods:

General considerations: All statistical tests were two-sided and performed at the 5% level of significance, unless otherwise stated. Confidence intervals (CIs) were two-sided at the 95% confidence level. Continuous data were summarised using descriptive statistics. Categorical data were summarised using frequency tables (frequencies and percents).

Primary efficacy endpoint: Descriptive statistics for the PSI total score at Visit 3 (baseline) and Visit 8 and for the change in PSI total score from baseline to Visit 8 were presented by treatment within each treatment pair. The descriptive statistics were repeated, first stratified by side (left, right), and then stratified by country. For the within-patient treatment comparisons of mean changes from baseline in the 4 treatment pairs, intra-individual treatment differences were calculated and summarised by means of descriptive statistics for Visit 3 and Visit 8, and for the changes from Visit 3 to Visit 8. This analysis was done overall, and stratified by country, age, gender, target area, and baseline PSI. Paired t-tests were applied to the changes to compare treatments within the treatment pairs (only overall, not within strata).

Determination of sample size: No formal sample size calculation was conducted. The study of Barker et al. with a similar design, using left-right comparisons in 150 patients (5 treatment pairs with 30 patients each), showed statistically significant treatment differences between Placebo and active study drugs. Based on the above study, and taking into consideration patients' withdrawal, it was possible to evaluate M518101's effect on plaque psoriasis with 144 patients (4 treatment pairs with 36 patients each) in this study. Dose-response relationship was not considered in the sample size determination as this was evaluated mainly by descriptive statistics.

Efficacy Results:

Primary endpoint

In all treatment pairs, there was a decrease in the PSI total score between baseline and Week 8 for each treatment.

In the FA set, the mean (SD) change of the PSI total score from baseline to Week 8 in the M518101 25 µg/g treatment group with –10.8 (3.4) points was larger than the one in the Placebo group with –6.5 (3.9) points in the Placebo vs. M518101 25 µg/g treatment pair. No relevant differences in mean changes were observed in the other treatment pairs.

The difference of mean change of the PSI total score from baseline to Week 8 in the Placebo vs. M518101 25 µg/g treatment pair was statistically significant (t-test $p<0.001$; positive difference), meaning that M518101 25 µg/g was superior to Placebo in reducing the PSI total score after 8 weeks of treatment.

Name of Company:	**Volume:**	(For national authority use only)
Maruho Co.,Ltd..		
Name of Finished Product:	**Page:**	
M518101		
Name of Active Ingredient:		
M5181		

The differences of mean changes within the other treatment pairs were not statistically significant.

The mean (SD) change of the PSI total score from baseline to Week 8 stratified by baseline PSI results (less than or equal to 16 vs. greater than or equal to 18) were analysed as ad-hoc analysis.

In the FA set, the differences of mean (SD) changes within the treatment pairs of the PSI total score stratified by baseline PSI (both sides were greater than or equal to 18) from baseline to Week 8 were 5.3 (3.9) points for Placebo minus M518101 25 µg/g, and -1.5 (1.8) points for M518101 50 µg/g minus calcipotriol.

The differences of mean change in the Placebo vs. M518101 25 µg/g treatment pair and in the M518101 50 µg/g vs. calcipotriol treatment pair were statistically significant (t-test p=0.003, positive difference, and p=0.024, negative difference, respectively), meaning that M518101 25 µg/g was superior to Placebo and M518101 50 µg/g was superior to calcipotriol in reducing the PSI total score stratified by baseline PSI (both sides were greater than or equal to 18) after 8 weeks of treatment. The differences of mean changes within the other treatment pairs were not statistically significant.

From these results, M518101 25 µg/g is superior to Placebo in the mean change of the PSI total score from baseline to Week 8 in the Placebo vs. M518101 25 µg/g treatment pair. Relevant differences were not observed in other treatment pairs.

Secondary endpoints

In the FA set, differences of mean (SD) changes within the treatment pairs in the PSI total score from baseline to Weeks, 1, 2, 4, and 6 were statistically significant in the Placebo vs. M518101 25 µg/g treatment pair in all weeks (p=0.006 in Week 1, p<0.001 in other weeks), also indicating superiority of M518101 25 µg/g over Placebo, starting at one week of treatment. The differences of mean changes within the other treatment pairs were not statistically significant.

In the FA set, the differences of mean (SD) changes within the treatment pairs in the PSI subscores (erythema, induration, and scaling) from baseline to Week 8 were statistically significant (p<0.001) in the Placebo vs. M518101 25 µg/g treatment pair, indicating superiority of M518101 25 µg/g over Placebo in reducing the PSI subscores. The differences of mean changes within the other treatment pairs were not statistically significant.

In the FA set, analyses of differences within the treatment pairs in the IOA, POA and of left-right comparison by the Investigator at Week 8 showed that M518101 25 µg/g was statistically superior to Placebo. The differences within the other treatment pairs were not statistically significant.

Overall, there were no relevant differences in the evaluation of the primary endpoint and secondary endpoints regarding analyses with restricted last observation carried forward (LOCF) or in the PP set.

Safety Results:

The median duration of treatment was 57 days in all treatment pairs. The mean (SD) amount of study drug administered during the study ranged from 80.5 (60.1) grams (calcipotriol treatment group) to 91.3 (55.0) grams (M518101 50 µg/g treatment group).

Overall, 53 (35.8%) patients experienced 105 treatment-emergent adverse events (TEAEs) during the study. Overall 3 (2.0%) patients had severe TEAEs, and 16 (10.8%) patients had study drug-related TEAEs. Overall 2 (1.4%) patients had serious adverse events (SAEs), one (0.7%) patient had a TEAE of serum calcium increased, and 6 (4.1%) patients had TEAEs leading to discontinuation of the study drug. No patients died during the study. There were no statistically significant differences between the treatment pairs with regard to the incidence of AEs.

Most frequently, TEAEs were reported in the system organ classes (SOCs) infections and infestations (in

Name of Company:	**Volume:**	(For national authority use only)
Maruho Co.,Ltd..		
Name of Finished Product:	**Page:**	
M518101		
Name of Active Ingredient:		
M5181		

25 [16.9%] patients overall) and general disorders and administration site conditions (12 [8.1%] patients). The most frequently reported TEAEs (by preferred term) were nasopharyngitis (11 [7.4%] patients), application site pruritus (6 [4.1%] patients), and upper respiratory tract infection (5 [3.4%] patients).

The majority of TEAEs were of mild or moderate intensity. Dermatitis contact (2 patients), urinary tract infection, application site pruritus, arthralgia, and colitis ulcerative (1 patient for each event) were of severe intensity.

Most frequently, drug-related TEAEs were reported in the SOCs general disorders and administration site conditions (10 [6.8%] patients overall) and skin and subcutaneous tissue disorders (5 [3.4%] patients). The most frequently reported drug-related TEAEs (by preferred term) were application site pruritus (6 [4.1%] patients) and application site irritation and dermatitis contact (both 4 [2.7%] patients).

Analyses of TEAEs attributable to an application side showed that application site pruritus and dermatitis contact occurred more frequently with M518101 50 µg/g and M518101 100 µg/g, compared to the M518101 25 µg/g dose or Placebo. However, due to the small number of events, the comparison has to be interpreted with caution.

There were 2 patients with SAEs (hospitalisation) during the study. One patient who received left M518101 50 µg/g, right M518101 100 µg/g experienced dermatitis contact, application site pruritus and arthralgia, and one patient who received left M518101 50 µg/g, right calcipotriol experienced colitis ulcerative. Dermatitis contact, application site pruritus, and arthralgia were considered as related, and colitis ulcerative as unrelated to the study drug. The events led to the discontinuation of study drug. All events resolved.

There was one patient with mild serum calcium increased. The event led to the discontinuation of study drug. The event resolved.

There were 6 patients who discontinued the study drug due to TEAEs. The 2 patients with SAEs (dermatitis contact and colitis ulcerative), the patient with serum calcium increased, 2 other patients with dermatitis contact, and one patient with dermatitis allergic. All events resolved except one event of dermatitis contact which was reported as ongoing at the last evaluation.

There were no clinically relevant mean changes observed during the course of the study for any laboratory parameter (including calcium tests), overall and in the treatment pairs, and there were few abnormal findings outside the normal ranges. Abnormal clinically significant findings were observed in no more than two patients for any parameter in any treatment pair.

The percentage of patients with abnormal physical examination findings remained fairly constant during the study in all body systems. There were no relevant differences between the treatment pairs. There was no case of a positive pregnancy test during the study.

Conclusions:

- The 25 µg/g dose of M518101 was significantly more effective than Placebo in the treatment of mild to moderate plaque psoriasis.
- Tests on differences between the 25 µg/g, 50 µg/g, and 100 µg/g dose of M518101 and calcipotriol in the efficacy of treatment of mild to moderate plaque psoriasis were not significant.
- All doses of M518101 were safe and well tolerated.

Date of Report: [redacted]