2. CLINICAL STUDY SYNOPSIS

Name of Company: MetrioPharm AG	**Volume:** (For national authority use only)
Name of Finished Product: MP1032 hard gelatin capsules 50 mg	**Page:**
Name of Active Ingredient(s): 5-Amino-1,4-dioxo-1,2,3,4-tetrahydrophthalazine-3-id, sodium salt	
Title of Study: A Randomized (1:1), Double-Blind, Parallel, Placebo-Controlled Exploratory Pilot Study to Evaluate the Safety, Pharmacokinetics and Efficacy of Systemic (po) Application of MP1032 in Patients with Moderate to Severe Chronic Plaque Psoriasis	
Protocol Number: MP1032-CT02	
Study Period: **Date of first enrollment:** 17 May 2016 **Date of last completed:** 29 Dec 2016	**Phase of Development:** 2a
Investigator(s): Four (4) Investigators in one country (Germany) participated. Namely, Anke Gauliard, Wolfgang Vanscheidt, Peter Heymer and Rami Hamscho.	
Study Center(s): Four (4) study centers in one country (Germany) were involved. The study centers were: Early Phase Clinical Unit (Berlin PAREXEL International GmbH), Dermatologische Gemeinschaftspraxis (Freiburg), Klinische Forschung Dresden GmbH (Dresden) and Rothaar GmbH (Berlin).	
Publication(s): Not applicable	
Objectives: The primary objective of this study was to evaluate the safety and pharmacokinetics (PK) of orally administered 100 mg MP1032 twice a day (bid) when taken for 42 days by patients with moderate to severe chronic plaque psoriasis. The secondary objectives of this study were to evaluate the efficacy of orally administered 100 mg MP1032 bid when taken for 42 days by patients with moderate to severe chronic plaque psoriasis as assessed by: • Psoriasis Area Severity Index (PASI) • Physician's Global Assessment (PGA) • Dermatology Life Quality Index (DLQI) • EQ-5D 5L visual analogue scale (VAS) • Modified Nail Psoriasis Severity Index (mNAPSI)	
Study Design: This was a randomized, double-blind, parallel, placebo-controlled exploratory pilot study to evaluate the safety, PK and efficacy of systemic oral administration of 100 mg MP1032 bid in adult patients with moderate to severe chronic plaque psoriasis. The study design consisted of a 28 day screening/run-in period, a 42 day treatment period, and a 28 day follow-up period. Forty-four (44) patients who met the entry criteria were to be randomized on Day 1 in a 1:1 ratio to receive either 100 mg MP1032 or placebo orally twice daily for 42 days. The goal was to have 40 patients (20 in each treatment group) complete the study. Pharmacokinetic sampling was to occur on Day 1, Day 15, Day 29 and Day 43: • Day 1: at 15 minutes, 30 minutes, 1 hour, and 2 hours post-dose • Day 15: any time post-dose (time of the last dose was to be recorded) • Day 29: any time post-dose (time of the last dose was to be recorded) • Day 43: post-dose (time of the last dose was to be recorded) Safety was to be monitored from the signing of the informed consent form until the last follow-up visit on Day 71. Efficacy was to be assessed at screening and Days 1, 15, 29, 43, 57, and 71 using the following assessments: PASI, PGA, DLQI, mNAPSI, and EQ-5D 5L (VAS).	

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Number of Patients (planned and analyzed): Approximately, 44 patients were planned to be enrolled and randomized on Day 1 in a 1:1 ratio to receive either 100 mg MP1032 or placebo orally twice daily for 42 days (22 in each treatment group). In total, 46 patients were enrolled after screening, and randomized to receive study treatment (MP1032 or placebo; 23 patients per treatment group). All patients were dosed and 44 patients (95.65%) patients completed the study. One patient from the MP1032 group was withdrawn from the study as the patient was lost to follow-up after Study Day 15 visit, and 1 patient from the placebo group discontinued treatment due to an adverse event (AE) of psoriatic arthropathy.

Analysis populations included the following:

- Full Analysis Set (FAS) consisted of all 46 randomized patients who received either MP1032 or placebo.
- Per Protocol Set (PPS) consisted of all 44 patients who completed the study.
- Pharmacokinetic Analysis Set (PKAS) consisted of the 22 patients who received treatment with MP1032 and completed the study.

Diagnosis and Main Criteria for Inclusion: The target population for this study was patients with moderate to severe chronic plaque psoriasis.

Main Inclusion Criteria:

1. Participants legally competent to sign and give informed consent.
2. Adult male and female patients aged 18 to 65 years with chronic plaque psoriasis:
   a) PASI score > 10 at screening and
   b) Disease duration of ≥ 6 months at the initiation of study medication.
3. Body Mass Index (BMI) between 18.5 and 34.9 kg/m^2.
4. Diagnosis of chronic plaque psoriasis confirmed by a dermatologist/physician.
5. Women of childbearing potential (WCBP) must have had a negative urine pregnancy test at screening (Visit 1). In addition, sexually active WCBP must have agreed to use two forms of adequate contraception throughout the trial.
6. Post-menopausal women must have had spontaneous amenorrhea for at least 12 months and serum follicle stimulating hormone (FSH) levels indicating post-menopausal state as per local laboratory reference ranges. Females on hormone replacement therapy (HRT) and whose menopausal status was in doubt must have discontinued HRT to allow confirmation of post-menopausal status prior to study enrollment. For most forms of HRT, at least 2 to 4 weeks must have elapsed between the cessation of therapy and the blood draw; this interval depended on the type and dosage of HRT. Following confirmation of their post-menopausal status, they could resume use of HRT during the study. Sterilized women might have been included.
7. Patients must have met the following clinical laboratory criteria:
   a) White blood cell count ≥ 3.5 x 10^9/L
   b) Platelet count ≥ 100 x 10^9/L
   c) Serum creatinine ≤ 1.5 x upper limit of normal (ULN); estimated glomerular filtration rate > 60 mL/min
   d) Total bilirubin ≤ 1.5 x ULN
   e) Aspartate aminotransferase (AST), alanine aminotransferase (ALT) ≤ 1.5 x ULN
   f) Hemoglobin ≥ lower limit of normal as per local laboratory reference ranges for women and men accordingly.
   g) No coagulopathy (International Normalized Ratio [INR] < 1.5).
8. Patients must have agreed not to increase normal sun exposure during the course of the study.

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9. Patients must have been able to swallow 2 small capsules during each administration.
10. Patients must have been considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, or medication intake according to the judgment of the Investigator.

Test Product, Dose and Mode of Administration, and Lot Number(s):
Test Product: MP1032 hard gelatin capsules 50 mg
Dose: 2 x 50 mg (100 mg) MP1032 hard gelatin capsules twice daily for 42 days
Mode of Administration: Oral
Lot numbers: 20160118, 20160202

Reference Therapy, Dose and Mode of Administration, and Lot Number(s):
Reference Therapy: Placebo product in the form of hard gelatin capsules comprising of the following excipients (995 parts mannitol and 5 parts colloidal anhydrous silica)
Dose: 2 x hard gelatin capsules twice daily for 42 days
Mode of Administration: Oral
Lot numbers: 20151116-2

Duration of Treatment: Treatment period was 42 days (6 weeks).

Criteria for Evaluation:

Safety:

- Comparison of AEs experienced by patients treated with MP1032 and those who received placebo.
- Comparison of the changes in clinical laboratory test results, changes in vital signs, changes in physical examination parameters for patients treated with MP1032 and those who received placebo.

Pharmacokinetics:

- Determination of MP1032 concentration levels in plasma on Day 1, at 4 time points (15 minutes, 30 minutes, 1 hour, and 2 hours post-dose).
- Determination of MP1032 concentration levels in plasma on Day 15, Day 29, and Day 43, at 1 time point post-dose to determine exposure.

Efficacy:

- PASI:
  - Mean score and change of score from Baseline to Day 43.
  - Comparison of mean PASI reduction between MP1032 and placebo from Baseline at Day 43.
  - Percentage of patients who achieved a 30% or more reduction in their PASI score from Baseline (PASI 30) and PASI 50 in comparison to placebo from Baseline at Day 29 and at Day 43.
  - Percentage change in PASI score from Day 1 to Day 29 and Day 1 to Day 43.
- PGA: Mean score and change from Baseline at Day 43.
- DLQI: Score and change from Baseline and estimation of the relevant improvement ($\geq$ 4 units) at Day 29 and Day 43.
- EQ-5D 5L (VAS): Mean score and change from Baseline at Day 43.
- mNAPSI: Mean score and change from Baseline at Day 43.

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Statistical Methods:

Efficacy:

All quantitative efficacy variables (PASI, DLQI, EQ-5D 5L [VAS], PGA and mNAPSI) were listed by patient and visit for the FAS, and summarized by descriptive statistics for absolute values and changes from Baseline. Individual values were presented graphically for these variables and summary plots were also produced.

Psoriasis parameters (PASI, DLQI) at Day 29 and End of Treatment (Day 43) were analyzed using an analysis of covariance (ANCOVA) with Baseline data as a covariate and treatment as factor. Estimated means and differences from placebo, and 95% confidence intervals (CIs) were presented by treatment groups. The difference between placebo and active treatment was assessed formally using a 2-sided test at the 5% significance level for the PASI parameter. For PASI, the percentage change from Day 1 to Day 29 and Day 1 to Day 43 was additionally calculated and listed by area under the concentration-time curve (AUC) subgroups, overall (MP1032) and placebo for the PPS. The percentage change from Day 1 was also summarized by descriptive statistics (n, mean, standard deviation, median, minimum and maximum) by AUC subgroups, overall (MP1032) and placebo for the PPS.

Response parameters like PASI50 and PASI30 were displayed in frequency tables and analyzed using chi square and Fisher's exact test at Day 29 and End of Treatment (Day 43).

Safety:

Adverse events were coded according to a coding dictionary (Medical Dictionary for Regulatory Activities [MedDRA], version 18.1). Treatment emergent adverse events (TEAEs) were summarized by system organ class (SOC) and preferred term (PT) as well as by severity/causality to investigational medicinal product (IMP).

Vital signs, electrocardiograms (ECGs), and laboratory data were listed by patient and treatment group including changes from Baseline. Descriptive statistics for absolute values and changes from Baseline were presented by treatment group and time point. Results of the physical examination data were listed by patient and time point.

Pharmacokinetics:

The analysis and summary of the PK data was based on the PKAS. Individual concentrations were listed and displayed graphically on a linear and semi-logarithmic scale. They were summarized using the number of available observations, mean, median, standard deviation, minimum, maximum, geometric mean, and geometric coefficient of variation (assuming log-normally distributed data). Mean MP1032 plasma concentration-time profiles were displayed graphically on a linear and semi-logarithmic scale.

Individual PK parameters were listed and summarized. T_{max} (time of occurrence of maximum plasma concentration) was summarized using the number of available observations, median, minimum and maximum only. C_{max} (observed maximum plasma concentration) and AUCs were summarized using the number of available observations, mean, median, standard deviation, minimum, maximum, geometric mean, and geometric coefficient of variation (assuming log-normally distributed data). Patients were grouped into the following AUC subgroups according to AUC_t and AUC_{2h} values estimated using the linear-logarithmic trapezoidal method on Day 1:

- Group 1: 6 patients with lowest AUCs;
- Group 2: 5 patients with the next highest AUCs;
- Group 3: 6 patients with the next highest AUCs;
- Group 4: 5 patients with the highest AUCs.

The $AUC_{t(lin\text{-}log)}$ and $AUC_{2h(lin\text{-}log)}$ per each AUC subgroup and overall were summarized using the number of available observations, mean, median, SD, coefficient of variation, minimum, maximum and geometric mean, based on the PPS.

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Efficacy Results:

- There was no statistically significant difference from placebo for the MP1032 group in the change in PASI scores from Baseline at Day 43. However, subgroup analysis of patients according to their AUC values on Day 1 showed that at Day 43, the median reduction from Baseline in PASI score was notably greater (approximately 3-fold) in patients with the 2nd highest AUC_{2h} values (Group 3) and 3rd highest AUC_t values (Group 2), compared to placebo treated patients. Upon treatment cessation, mean PASI scores in the MP1032 treatment group trended back upwards.
- There was no statistically significant difference in the response rates for PASI30 and PASI50 between MP1032 and placebo treated patients.
- There was no notable effect of MP1032 on PGA, DLQI and EQ-5D 5L (VAS) scores compared to placebo.
- In patients with psoriatic nail disease, mean and median mNAPSI scores trended downwards during the treatment period while the placebo group remained relatively unchanged.

Pharmacokinetic Results:

- MP1032 mean plasma concentration reached maximum level within 15 minutes after administration on Day 1 and then rapidly declined over approximately 2 hours.
- Upon treatment cessation, MP1032 was rapidly eliminated as on Day 43, plasma concentration levels for majority of patients were below the limit of quantification.
- The median reduction from Baseline in PASI score at Day 43 was notably greater in patients with median AUC_{2h} of 137.246 h*ng/mL and median AUC_t of 114.100 h*ng/mL.

Safety Results:

- In total, 59 TEAEs were reported by 29 patients (63.04%) during the study. The number of patients who experienced at least one TEAE was comparable between both treatment groups with 14 patients (60.87%) in the MP1032 group and 15 patients (65.22%) in the placebo group.
- No serious adverse events or deaths occurred during the study.
- One patient in the placebo group discontinued from the study due to a TEAE of psoriatic arthropathy.
- The majority of TEAEs reported across both treatment groups were mild or moderate in nature; 1 severe TEAE of psoriatic arthropathy was reported in 1 patient in the placebo group.
- The number of patients who experienced at least one related TEAE was similar across both treatment groups with 5 patients each in the MP1032 and placebo groups. No notable differences were seen between the two treatment groups with regard to the overall pattern of patients experiencing related TEAEs.
- Clinical laboratory evaluations did not reveal any significant findings. A small number of clinically significant abnormalities were observed. However, these appeared to be sporadic with no notable pattern observed.
- Analysis of vital signs, ECG assessments and physical findings did not reveal any significant findings. No treatment-related trends or clinically meaningful differences were observed between both treatment groups.
- Overall, no new safety signal was identified in this study. MP1032 was well tolerated.

Conclusions:

The findings of this study show that after only six weeks of treatment, there is a clinically meaningful response in patients who achieve the appropriate drug exposure levels. As MP1032 is well tolerated, further studies using higher doses of MP1032 and longer treatment durations need to be conducted to fully evaluate the efficacy of MP1032 for the treatment of moderate to severe psoriasis.

Date of Report: 30 Jun 2017