2. Synopsis

Name of Sponsor/company: MetrioPharm AG	Individual study table referring to part V of the dossier Volume: Page:	*(For national authority use only)*
Name of finished product: Not applicable (n.a.)		
Name of active ingredient: MP1032		
Title of trial: A Phase II, Multicenter, Double-blind, Placebo-controlled, Efficacy and Safety Study of Two Oral Doses (150 mg bid/ 300 mg bid) of MP1032 in Male and Female Patients with Moderate-to-Severe Chronic Plaque Psoriasis		
International Coordinating Investigator (CI) name, number of trial centers and countries: International CI: Prof. Dr. Petra Staubach-Renz A total of 17 trial centers recruited patients: 8 trial centers in Germany and 9 trial centers in Poland		
Publication (reference): Not applicable (n.a.) to this trial		
Studied period (years): Date trial initiated (first patient first screening): 27FEB2018 Date trial completed (last patient last visit): 12JUN2019	Phase of development: II (Proof of concept [POC])	
Objectives: *Primary objective* To evaluate the clinical efficacy and safety of two oral doses of MP1032 (150 mg twice daily [bis in die, bid, twice daily] and 300 mg bid) when taken for 12 weeks by patients with moderate-to-severe chronic plaque psoriasis *Secondary objectives* To evaluate the effect of each oral doses of MP1032 (150 mg bid and 300 mg bid) compared to placebo (bid) on the psoriasis area severity index (PASI) score, physician's global assessment (PGA) score, and body surface area (BSA) score as well as to evaluate the systemic exposure of both oral doses when taken for 12 weeks by patients with moderate-to-severe chronic plaque psoriasis		
Methodology: This trial was a randomized, double-blind, parallel, placebo-controlled trial to evaluate the efficacy and safety of two oral doses of MP1032 (150 mg bid and 300 mg bid) in adult patients with moderate-to-severe chronic plaque psoriasis. The trial design consisted of a 28-day screening period, a 12-week treatment period, and subsequently a 28-day follow-up (FU) period. Each patient had 6 visits (Visit 1 [Screening Visit], Visit 2 [Day 1, baseline], Visit 3 [Day 28], Visit 4 [Day 56], Visit 5 [Day 84] and Visit 6 [FU Visit, Day 112]) and unscheduled visits as needed.		

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2. Synopsis (continued)

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Methodology (continued):

Approximately 150 patients who met the entry criteria were planned to be randomized on Day 1 to receive either 150 mg MP1032, 300 mg MP1032 or placebo orally twice daily for 12 weeks.

The treatment allocation was on a 1:1:1 ratio (50:50:50 patients) in a blinded manner. Patients were randomized by using an Interactive Web Response System (IWRS) to one of the following three treatment arms:

- MP1032 300 mg bid
- MP1032 150 mg bid
- Placebo bid

The administration of IMP stopped after end of trial (in maximal 13 weeks). Recruitment was competitive between the sites, but enrollment was limited to 12 patients per site. A recruitment of more than 12 patients was allowed after Sponsor approval.

Safety parameters were monitored from the signing of the ICF until the last FU Visit.

Efficacy was evaluated through PASI, PGA and the determination of BSA at Screening Visit, Day 1, Day 28, Day 56, Day 84 and at FU Visit on Day 112.

Photographic documentation was only performed in a subgroup at three sites (15 patients) on Day 1, Day 28, Day 56, and at FU Visit on Day 112.

PK samples were collected in a subgroup at five selected trial sites (two sites in Germany and three sites in Poland) in 26 patients who had accepted to have blood drawn for PK analysis on Day 1 and Day 84.

Safety was assessed through physical examination at Screening Visit, Day 1 (baseline), Day 84 and at FU Visit on Day 112, vital signs and safety laboratory at Screening Visit, Day 1, Day 28, Day 56, Day 84 and Day 112 (serology only at Screening Visit), and at each visit through AE monitoring (including serious AEs [SAEs] and treatment-emergent AEs [TEAEs]). A serum pregnancy test was done for all women at Screening Visit followed by urine pregnancy tests for at Visits 2 and 5.

Number of patients (planned and analyzed):

Planned: approximately 150 patients were to be randomized into three treatment arms in a 1:1:1 ratio (MP1032 300 mg, MP1032 150 mg, and placebo bid arm, approximately 50 patients each) in order to have 120 evaluable patients

Analyzed: a total of 204 patients was screened and 155 patients were randomized.

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2. Synopsis (continued)

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Number of patients (planned and analyzed) (continued):

	MP1032 300 mg bid	**MP1032 150 mg bid**	**Placebo bid**	**Total**
Number of patients randomized	48	52	55	155
Patients included in SES[1]	48 (100%)	51 (98%)	55 (100%)	154 (99%)
Patients included in FAS[1]	47 (98%)	50 (96%)	54 (98%)	151 (97%)
Patients included in VCS[1]	36 (75%)	32 (62%)	34 (62%)	102 (66%)
Patients included in PKS[1]	8 (17%)	6 (12%)	9 (16%)	23 (15%)

bid: bis in die (twice daily); FAS: full analysis set; PKS: pharmacokinetic evaluation set; SES: safety evaluation set; VCS: valid cases set

[1]Percentages calculated on number of patients randomized

One patient of the MP1032 150 mg bid arm was excluded from the SES, FAS and VCS because of withdrawal of patient before first IMP administration. Other three patients (one patient in each treatment arm) were excluded from the FAS and VCS as the patients had no post-baseline assessments. Further 49 were excluded from the VCS for various reasons, mostly because of withdrawal of patient reported in a similar share across treatment arms (28 patients in total), followed by non-completion of Week 12 Visit (end of treatment [EoT]) (12 patients in total).

Diagnosis and main criteria for inclusion:

Male and female, between 18 years and 70 years with moderate-to-severe chronic plaque psoriasis, PASI score ≥10 to ≤20 at baseline, BSA score >10%

Trial products

Test product(s), dose and mode of administration, batch number:

IMP: MP1032 50 mg hard gelatin capsules, batch nos. MP4176, MP4186 and MP4187

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

IMP placebo: Placebo hard gelatin capsules (identical appearance as MP1032 50 mg capsules), batch nos. MP4176, MP4186 and MP4187

MP1032 50 mg capsules and/or placebo were administered orally as follows in a blinded version twice daily (bis in die, bid):

- *Treatment A:* 3 × 50 mg (150 mg) MP1032 plus 3 × placebo hard gelatin capsules (per dosage)
- *Treatment B:* 6 × 50 mg (300 mg) MP1032 hard gelatin capsules (per dosage)
- *Treatment C:* 6 × placebo hard gelatin capsules (per dosage)

Oral treatment (6 capsules), twice daily administered by the patient at home (last day at site), patients of the pharmacokinetic (PK) subgroup administrated the first and last treatment at the site (Day 1 and 84, respectively).

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2. Synopsis (continued)

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Duration of treatment:
12 weeks (84 days)

Criteria for evaluation:

Efficacy variables:

- Psoriasis Area Severity Index (PASI)
- Physician's global assessment (PGA)
- Assessment of body surface area (BSA)

The primary efficacy variables were:

1. 75% improvement (response) in their PASI score (PASI 75) and
2. Improvement (1 or more points on a 7-point scale) in their PGA score.

The secondary efficacy variables were:

3. 50% improvement (response) in their PASI score (PASI 50).
4. Mean PASI score and change to baseline.
5. Time to achieve PASI 50 and PASI 75.
6. Mean score and change from baseline in the PGA.
7. Mean score and change from baseline in the BSA.
8. PK data.

Safety variables:

- Adverse events (AEs)
- Laboratory variables: Laboratory parameters
- PK variables: PK data (results of blood MP1032 concentration)
- Other safety variables:
  - Physical examination
  - Vital signs (blood pressure and heart rate)

Statistical methods:

Efficacy populations

Intent-to-treat (ITT)

The full-analysis-set (FAS) included all randomized patients who received at least one dose of IMP and had at least one post-baseline assessment. The ITT analysis was based on the FAS. The FAS was considered primary analysis set for the efficacy analysis.

Per-protocol (PP)

The valid-cases-set (VCS) included all patients from the FAS, who completed the assessments of the co-primary endpoints without any protocol violation interfering with the precise evaluation of treatment efficacy and with sufficient exposure to IMP, i.e.,

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Statistical methods (continued):

- who completed the Visit 5 (Day 84) assessments of PASI and PGA
- who did not take any prohibited concomitant medications up to the Visit 5 (Day 84)
  During the blind data review meeting (BDRM) concomitant medications were reviewed considering timing, duration of concomitant treatment, and influence on the efficacy assessments to determine prohibited medication usage that warranted exclusion from the VCS.
- who were compliant with the dosing regimen. A patient was considered compliant, if the patient had taken ≥80% of the planned capsules.

Patients who prematurely discontinued the treatment due to an AE at least possibly related to IMP were not to be excluded from the VCS as long as the criteria above were met.

The per-protocol (PP) analysis was based on the VCS. Primary efficacy endpoints were evaluated on VCS to assess the sensitivity.

Safety populations

Safety-evaluation-set (SES)

The SES included all patients who received any trial medication at least once; all safety analyses were based on the SES.

Pharmacokinetic-evaluation-set (PKS)

All patients without any protocol deviations that could have interfered with the administration of the treatment or the evaluation of systemic concentrations of MP1032, who received at least one dose of IMP and who had any completed determination of MP1032 levels were included in the PKS.

Efficacy analyses

Hypotheses

Since this was an exploratory trial no formal hypotheses were postulated. The data were evaluated descriptively.

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Statistical methods (continued):

Statistical analyses

Primary efficacy endpoints

The co-primary endpoint response in PASI 75 at Week 12 (Day 84) was defined as rate of patients reaching 75% improvement in PASI score compared to baseline (i.e., percent of change from baseline ≤-75%). The co-primary endpoint improvement in PGA at Week 12 (Day 84) was defined as rate of patients reaching a reduction of 1 or more points on the PGA scale in comparison to baseline.

The comparisons of the treatment arms MP1032 300 mg bid and MP1032 150 mg bid, each vs. the placebo bid treatment, with respect to each, the PASI 75 rate and PGA improvement rate, at Week 12 (Day 84) were evaluated by the CMH test stratified by (pooled) analysis center (i.e., small centers were pooled). The common odds-ratio with 95% confidence interval was provided. The homogeneity of the individual odds-ratios was assessed by the Breslow-Day test.

Secondary efficacy endpoints

Secondary efficacy endpoints were evaluated descriptively. The methodology outlined above was applied for pairwise treatment comparisons vs. placebo:

The PASI 50 responder rate at Week 12 (Day 84) was evaluated according to the primary efficacy endpoints, as well as the PASI 75, PASI 50 and PGA improvement rate at Week 4 (Day 28) and Week 8 (Day 56) of the treatment phase as well as at FU, 4 weeks after EoT.

The change in the PASI score from baseline to each post baseline visit, respectively, was evaluated using an analysis of covariance (ANCOVA) model, with treatment arm and (pooled) analysis center as factors and baseline outcome as covariate, in both analysis sets, FAS and VCS.

The time to achievement of PASI 50 and PASI 75, respectively, was evaluated using the Kaplan-Meier method. The trial day of first achievement of PASI 50 and PASI 75, respectively, was the considered event, with trial day of last assessment as the time point of censoring, in case of no occurrences of PASI 50 or PASI 75. Pairwise treatment arm differences were tested by the log-rank test.

Location shift in change from baseline in PGA was assessed using Hodges-Lehmann Estimation with comparison by the Wilcoxon rank sum test, in both analysis sets, FAS and VCS.

Descriptive summaries are provided for each parameter by treatment arm and by visit, if applicable. Percentages are provided based on the number of non-missing cases, if not otherwise stated. For PASI and PGA the descriptive summaries were performed in both analysis sets, FAS and VCS.

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2. Synopsis (continued)

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Statistical methods (continued):

Subgroup analyses

The following subgroups, based on baseline parameter, were evaluated with respect to the primary efficacy variables PASI and PGA for each post-baseline visit within the FAS

Subgroups:

Center:	• Analysis (pooled) centers		
Age:	• 18–40 years	• >40 years	
Sex:	• Male	• Female	
BMI:	• ≤24.9 (normal)	• 25.0–29.9 (pre-obesity)	• ≥30.0 (obesity)
Years of psoriasis:	• 1–10	• >10	
Smoking:	• Current	• Never or former	
Cigarette smoking:	• <1–10	• >10	
PGA:	• 3–4	• 5–6	
PASI:	• ≤15	• >15	
CRP:	• <10 mg/dL	• ≥10 mg/dL	

BMI: body mass index; CRP: c-reactive protein; PASI: psoriasis area severity index; PGA: physician's global assessment; PK: pharmacokinetic

The change in PASI and PGA was evaluated utilizing following analyses:

- Mean change from baseline in PASI by ANCOVA model.
- Location shift in change from baseline in PGA by Wilcoxon rank sum test and Hodges-Lehmann Estimation.

If applicable, the analyses were stratified by country.

Safety analyses

Adverse events

All AEs reported during the trial were listed, documenting course, severity, Investigator assessment of the relationship to the IMPs, and outcome. AEs were coded using the MedDRA mapping system for PTs and SOC.

TEAEs, i.e., AEs with an onset (or worsening) on or after the time of the first IMP application were summarized by the number of TEAEs and number (percent) of patients reporting TEAEs by primary SOC, PT, severity, and relationship to IMP (i.e., causality assessment). When summarizing TEAEs by severity or relationship to IMP, each patient was counted once within a SOC or a PT by using the event with the greatest severity or with the strongest relationship to IMP, respectively, within each category. Listings of SAEs occurred and of patients who prematurely discontinued treatment due to AEs are given.

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Statistical methods (continued):

Laboratory analyses

All safety laboratory parameters of hematology and clinical chemistry were summarized descriptively, including their changes from baseline. Shift tables of low, normal and high outcomes, determined with respect to the normal ranges, are presented for each post-baseline visit, in comparison to the baseline outcome. Incidence of any clinically significant outcome, i.e., number of patients having any clinically significant outcome during the trial is presented for each laboratory parameter.

Urinalysis outcomes were summarized by frequency counts and by shift tables of normal and abnormal outcomes. Incidence of clinically significant urinalysis parameters is presented.

Individual patient's listings of all assessed safety laboratory parameters, scheduled or unscheduled, are provided.

Pharmacokinetic analyses

Blood MP1032 concentration-time data for both MP1032 treatment arms in the PKS were listed, summarized and displayed graphically, including the nominal and actual blood sampling time relative to the corresponding IMP administration time.

Summary statistics of MP1032 levels by nominal sampling time are provided with following summary statistics for each nominal sampling time: geometric mean, geometric standard deviation (re-transformed standard deviation of the logarithms) and geometric coefficient of variation (CV), arithmetic mean, standard deviation, CV, minimum, median, maximum, and the number of measurements.

Generally, summary statistics are only presented if at least six quantifiable outcomes were available, i.e., if at least six concentrations were above the lower limit of quantification (LLQ). For the calculation of the summary statistics, pre dose/trough levels below LLQ were substituted by zero and post dose levels were substituted by LLQ/2.

Individual and mean concentration vs. time curves of M1032 concentration (using the actual sampling times for individual plots and the planned sampling times for mean plots) was plotted by treatment. Plots of geometric means on linear concentration scale and of geometric means on semilogarithmic scale are presented.

Based on the concentration time data the following non-compartmental analysis (NCA) parameter was derived for both visits separately:

- C_{max}: Maximum MP1032 concentration observed
- t_{max}: Time point (effective) at which the C_{max} was observed
- $AUC_{(0,t)}$: Area under the concentration-time curve (AUC) up to the last quantifiable sample drawn.

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Statistical methods (continued):

The AUC was approximated using the trapezoid formula and calculated with the effective time points 0, … t. The pre dose value was defined as 0 for calculation of $AUC_{(0,t)}$ and missing intermediate concentrations were excluded from the calculations.

Pharmacokinetic characteristics were listed and summarized by the statistics mentioned above in the PKS for each treatment and visit. The parameter t_{max} was described utilizing minimum, maximum and median.

Other safety analyses

Vital signs were summarized descriptively, including changes from baseline. Shift tables of normal and abnormal outcomes and incidence of clinically significant vital sign parameter are presented.

Findings in the physical examination were listed.

Extent of exposure to study drug

The overall extent of exposure to study drug was summarized by

- total number of applications =
  # planned applications – # missed applications + # overdose applications
- total number of dosed capsules =
  6 * # planned applications – # missed capsules + # overdose capsules
- average number of capsules per application =
  total number of dosed capsules / total number of applications
- duration of the treatment (days of treatment) =
  duration from first dose to last dose in days, start and end day included.
- average number of capsules per day =
  total number of dosed capsules / days of treatment
- % exposure =
  100 * total number of dosed capsules / (84 * 2 * 6)

For each treatment descriptive statistics are given. Duration of treatment is additionally presented by a frequency table for categorized numbers of days (less than 26 days, 26 – 53 days, 54 – 83 days, 84 days and more) and % exposure is presented by exposure of less than 80% and 80% and more.

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2. Synopsis (continued)

Name of Sponsor/company: MetrioPharm AG	Individual study table referring to part V of the dossier Volume: Page:	*(For national authority use only)*
Name of finished product: n.a.		
Name of active ingredient: MP1032		

Summary, conclusions:

Efficacy results

This phase II, POC, multi-centric, 3-arm randomized parallel group double-blind trial in patients with plaque psoriasis demonstrated a slight dose-dependent anti-inflammatory effect with two doses of MP1032 (150 mg bid and 300 mg bid) when administered orally bid. This could be seen in the PASI 50 responder rate at Week 12 and in the PGA at both earlier assessment points (Weeks 4 and 8). However, in the primary analyses, the responder rates were low regarding PASI 75 and PGA for both oral doses of MP1032 at Week 12 and no statistically significant treatment effect for MP1032 over the placebo could be detected in this exploratory trial.

Primary analyses

The co-primary efficacy analyses showed the same outcome in both active treatment arms (MP1032 300 mg bid and MP1032 150 mg bid): four patients (8.5%, and 8.0%) with 75% improvement in PASI score and 14 patients (29.8% and 28.0%) with a 1- or more point reduction on the 7-point PGA scale compared to baseline at Week 12 (EoT). In the placebo bid arm less responders were reported: 1 PASI 75 responder (1.9%) and 10 PGA responders (18.5%) were identified at EoT. Because of the low number of responders the CMH tests showed no statistically significant differences regarding both primary endpoints neither for *MP1032 300 mg bid vs. placebo bid* nor for *MP1032 150 mg bid vs. placebo bid* at Week 12. This primary efficacy outcome of the ITT analyses based on the FAS was supported by the PP sensitivity analysis based on the VCS showing similar results.

Secondary analyses

PASI

At both earlier assessment points (Weeks 4 and 8), less PASI 75 responders were reported in both active treatment arms, and at the FU (Week 16) only one patient more was identified in the MP1032 300 mg bid arm (in total 5 PASI 75 responders, 12.5%) when compared to Week 12. PASI 50 responders were reported in a greater share of patients in the MP1032 300 mg bid arm than in the MP1032 150 mg bid or the placebo bid arms at Week 12 (EoT) (21.3% vs. 16.0% and 11.1%, respectively). Although this trend of a greater share of responders in the MP1032 300 mg bid arm was reported, no statistically significant differences were found between the active and the placebo treatment arms neither in PASI 75 nor in PASI 50 using the CMH test at any assessment point.

Over the trial period, only slight mean changes in PASI scores were seen. The greatest mean change with -1.9 was reported for the MP1032 300 mg bid arm at Week 8. No statistically significant differences regarding changes from baseline in PASI were found with ANCOVA model using LS mean estimates neither for the treatment comparison *MP1032 300 mg bid vs. placebo bid* nor for *MP1032 150 mg bid vs. placebo* bid at any assessment point.

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2. Synopsis (continued)

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Summary, conclusions (continued):

PGA

Again, a slightly greater share of responders showing 1- or more point reduction on the 7-point PGA scale was reported in the MP1032 300 mg bid arm when compared to the placebo bid arm at both earlier assessment points Weeks 4 and 8 as well as at the FU at Week 16 (27.7% vs. 16.7%, 34.0% vs. 25.9%, and 32.5% vs. 27.3%, respectively). For the MP1032 150 mg, the responder rate was slightly greater compared to the placebo bid at Week 4 (22.0% vs.16.7%) and Week 16 (36.8% vs. 27.3%), vice versa at Week 8 (24.0% vs. 25.9%).

However, the CMH test showed no statistically significant differences neither for *MP1032 300 mg bid vs. placebo bid* nor for *MP1032 150 mg bid vs. placebo bid* at any assessment point.

Despite the above-mentioned dose dependent trend seen at Weeks 4 and 8, no clinically relevant reductions in disease severity were seen in the PGA in any treatment arm over the trial period; the average disease severity remained 'moderate' as for baseline. The greatest mean change in PGA with -0.4 was reported for the MP1032 300 mg bid arm at Weeks 8, 12 and 16.

The Wilcoxon rank sum test showed no statistically significant differences regarding change from baseline neither for the treatment comparison *MP1032 300 mg bid vs. placebo bid* nor for *MP1032 150 mg bid vs. placebo bid* at any assessment point.

BSA

Over the trial period, only minor mean changes were seen in % BSA affected in each treatment arm.

Subgroup analyses

The results of the subgroup analyses by analysis center, age, sex, BMI, years of psoriasis, smoking, cigarette smoking, PGA, PASI and CRP underline the 'overall' outcome of the secondary efficacy analyses showing no statistically significant differences regarding changes from baseline in PASI or PGA neither for the treatment comparison *MP1032 300 mg bid vs. placebo bid* nor for *MP1032 150 mg bid vs. placebo bid* at any assessment point.

The only treatment comparisons showing a p-value <0.05 were:

- *MP1032 300 mg bid vs. placebo bid* for the subgroup 'PASI ≤15' regarding change from baseline in PASI at Week 12/EoT (p=0.048).
- *MP1032 300 mg bid vs. placebo bid* for the subgroup 'age >40 years' at Week 4 and Week 12/EoT (p=0.049 and 0.046, respectively) in favor of the active treatment, and *MP1032 150 mg bid vs. placebo bid* for the subgroup 'BMI ≥30.0 (obesity)' in favor of the placebo (p=0.028) regarding change from baseline in PGA.

Overall, although not very pronounced and not statistically significant, there was a trend to see in the 300 mg bid treatment arm showing slightly better ratings in the secondary analyses when compared to the placebo bid treatment arm, this difference was not apparent in this way in the MP1032 150 mg bid arm.

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Summary, conclusions (continued):

Pharmacokinetic results

The PK analysis showed that the mean (geometric and arithmetic) and median C_{max} and $AUC_{(0,t)}$ values were 1.2 to 1.8 times higher/larger and the median t_{max} somewhat (7.5 minutes) later in the treatment arm with the higher concentration MP1032 300 mg bid than in the MP1032 150 mg bid arm on Day 1. The geometric mean and the mean $AUC_{(0,t)}$ were 437.6 ng/mL and 21818.2 ng/mL * min in the MP1032 300 mg bid arm and 366.9 ng/mL and 14882.2 ng/mL * min in the in the MP1032 150 mg bid arm; median t_{max} times were 22.5 and 15 min, respectively. For Week 12 (EoT), no NCA parameters were calculated as less than 6 quantifiable values were available.

Safety results

Treatment with orally administered MP1032 hard gelatin capsules at both dosages tested (300 mg bid and 150 mg bid) was safe and generally well tolerated. This was confirmed by evaluation of AEs, laboratory results, vital signs, and physical findings. Safety results of MP1032 300 mg bid and 150 mg bid vs. placebo bid can be summarized as follows:

AEs

- 3 SAEs were reported in three patients, all belonging to the placebo bid arm; all 3 SAEs were considered to be 'not related' to IMP treatment and 'not related' to study procedure. No SAE occurred in the MP1032 300 mg bid or 150 mg bid arm.
- 130 non-serious TEAEs were reported in 69 patients (45%) over the trial. The incidence of patients with TEAEs (including SAEs) was lowest in the MP1032 300 mg bid arm, followed by the MP1032 150 mg bid arm and highest in the placebo bid arm (31.3%, 43.1%, and 60.0%, respectively).
- Most of the 133 TEAEs were of 'mild' intensity, less TEAEs were assessed with 'moderate' intensity. 'Severe' TEAEs were reported in none of the patients in the MP1032 300 mg bid arm, but in two patients of the MP1032 150 mg bid arm (2 events) and in four patients of the placebo bid arm (5 events).
- Most of the TEAEs in all three treatment arms were 'unlikely' or 'not related' to IMP and had 'recovered/resolved' (including the 3 SAEs) or were 'recovering/resolving' at the end of the trial. 15 TEAEs in nine patients had 'not recovered/not resolved', with the highest incidence in the placebo bid arm (12 TEAEs in six patients).
- 2 TEAEs with a 'probable' relationship to IMP were reported in two patients: one patient, each of the MP1032 150 mg bid (exacerbation of psoriasis) and the placebo bid arm (diarrhea).
- 24 TEAEs with a 'possible' relationship to IMP were reported in 15 patients. The incidence was lowest in the MP1032 300 mg bid arm, followed by the MP1032 150 mg bid arm and highest in the placebo bid arm:

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Summary, conclusions (continued):

- *MP1032 300 mg bid:* 2 'possibly' related TEAEs in two patients (worsening of pruritus and itching of psoriatic plaques)
- *MP1032 150 mg bid:* 5 'possibly' related TEAEs in four patients and 1 'probably' related TEAE in one patient (fatigue, cystitis, palpitations, stomach pain, neutropenia, and exacerbation of psoriasis)
- *Placebo bid:* 17 'possibly' related TEAEs in nine patients and 1 'probably' related TEAE in one patient (soft fecal, softer fecal increased stool frequency, headache, vomiting, gastrointestinal discomfort, glycosuria, atrial hypertension, ketonuria, increase of pruritus, psoriasis plaques cracked, folliculitis of periumbilical area, bone aches, watery stool, upper respiratory tract infection, pain in the right hypochondrium, sore throat and diarrhea).

- 2 TEAEs, 1 'certainly' and 1 'possibly' related to study procedure, were reported in one patient of the MP1032 150 mg (subcutaneous hematoma) and in one patient of the placebo bid arm (neutropenia), respectively.

→The incidence, intensity, relationship to IMP, and causality to IMP for AEs seen in this trial were lower for both MP1032 dosages compared to placebo; statistically significant lower only for *MP1032 300 mg bid vs. placebo bid arms* in all four aspects, but not *for MP1032 150 mg bid vs. placebo bid arms.*

- In total, three patients discontinued the trial due to TEAEs: two patients prematurely during the treatment period (MP1032 150 mg bid arm: exacerbation of psoriasis; placebo bid arm: pain in the right hypochondrium) and one patient prematurely during the FU period (placebo bid arm: diarrhea). None of the TEAEs in the MP1032 300 mg bid arm had led to discontinuation from trial.
- Less TEAEs were treated with a concomitant medication in the MP1032 300 mg bid and 150 mg bid arm compared to placebo bid arm (14 and 19 TEAEs vs. 33 TEAEs).

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Summary, conclusions(continued):

Laboratory examinations

- In total, 15 clinically significant laboratory findings in seven patients were considered as non-serious TEAEs:
  - 3 clinically significant hematology findings in one patient of the MP1032 150 mg bid arm were considered as one non-serious, moderate TEAE (neutropenia), possibly to be related to IMP.
  - 3 clinically significant clinical chemistry findings reported in two patients were considered as non-serious, mild TEAEs, not to be related to IMP (placebo bid arm: 'alanine aminotransferase increased' and 'aspartate aminotransferase increased'; MP1032 150 mg bid arm: 'aspartate aminotransferase increased').
  - 9 clinically significant urinalysis findings reported in four patients of the placebo bid arm were rated as 5 non-serious TEAEs of mild or moderate intensity: The 2 AEs 'glycosuria' and 'ketonuria' reported in one patient were considered to be possibly related to IMP, the 3 other AEs (urinary tract infection, hematuria, and nephrolithiasis) to be not or unlikely related to IMP.
- None of these clinically significant laboratory findings had led to premature trial discontinuation.

Vital signs

- A clinically relevant abnormal vital sign parameter was reported in one of the randomized patients of the placebo bid arm, first time post-dose: An elevated diastolic blood pressure measured at Week 12 was rated as non-serious, moderate TEAE (hypertension). This AE was considered to be possibly related to IMP but had not led to withdrawal from trial.

Physical examination

- In the physical examination, 8 clinically significant findings were noted in 5 of the randomized patients across treatment arms (N=1, 2 and 2 for MP1032 300 mg bid, MP1032 150 mg bid, and placebo bid arm, respectively) at Week 12 (EoT), Week 16 (FU) or at Unscheduled Visits. All findings were reported first time post-dose and were recorded as 6 non-serious TEAEs, most of these AEs concerned the skin (3 events of pyoderma, 1 event each of pustular psoriasis and herpes zoster as well as 1 event of influenza). All AEs were considered to be not or unlikely related to IMP.

There were no other clinically relevant observations related to safety in this trial.

(continued)

2. Synopsis (continued)

Name of Sponsor/company: MetrioPharm AG	Individual study table referring to part V of the dossier Volume: Page:	*(For national authority use only)*
Name of finished product: n.a.		
Name of active ingredient: MP1032		

Summary, conclusions (continued):

Conclusion

The purpose of this Phase II, multicenter, double-blind, placebo-controlled trial was to evaluate the efficacy and safety of two oral doses (150 mg bid/ 300 mg bid) of MP1032 in male and female patients with moderate to severe chronic plaque psoriasis.

In this exploratory trial, a non-significant dose dependent anti-inflammatory effect with two oral doses of MP1032 could be demonstrated. This could be seen in the PASI 50 responder rate at Week 12 and in the PGA at both earlier assessment points (Weeks 4 and 8). However, no clear benefit of MP1032 could be shown in the overall population with regard to both co-primary variables, clinical assessment using PASI and PGA, as both active treatment arms (MP1032 300 mg bid and 150 mg bid) showed rather low responder rates at Week 12 (EoT):

- 75% improvement in PASI score: four patients (8.5% and 8.0).
- 1- or more point reduction on the 7-point PGA scale: 14 patients (29.8% and 28.0%).
- No statistically significant differences were seen for both doses when compared to placebo: 1 PASI 75 responder (1.9%) and 10 PGA responders (18.5%) at EoT.

The methods for evaluation in this trial were a combination of different investigator assessments (PASI, PGA, and assessment of affected % BSA) which overall correlated showing similar efficacy outcomes.

A limitation of this trial was that only patients with 'moderate-to-severe' chronic plaque psoriasis (PASI score ≥10–≤20, BSA score: >10% at baseline) were included; 'mild', 'mild-to-moderate', 'moderate' or 'severe' forms of psoriasis were not included. These populations may have shown different efficacy results. Indeed, in the pre-specified subgroup 'PASI ≤15', a statistically significant greater PASI reduction from baseline was observed for MP1032 300 mg bid vs. placebo bid after 12 weeks.

The PK analysis showed that the mean (geometric and arithmetic) and median C_{max} and $AUC_{(0,t)}$ values were 1.2 to 1.8 times higher/larger and the median t_{max} somewhat (7.5 minutes) later in the treatment arm with the higher concentration MP1032 300 mg bid than in the MP1032 150 mg bid arm on Day 1. The geometric mean and the mean $AUC_{(0,t)}$ were 437.6 ng/mL and 21818.2 ng/mL * min in the MP1032 300 mg bid arm and 366.9 ng/mL and 14882.2 ng/mL * min in the in the MP1032 150 mg bid arm; median t_{max} times were 22.5 and 15 min, respectively.

Overall, the safety evaluation revealed that MP1032 at both dosages was safe and generally well tolerated. Most of the TEAEs in all three treatment arms were 'unlikely' or 'not related' to IMP.

(continued)

2. Synopsis (continued)

Name of Sponsor/company: MetrioPharm AG	Individual study table referring to part V of the dossier	*(For national authority use only)*
Name of finished product: n.a.	Volume: Page:	
Name of active ingredient: MP1032		

Summary, conclusions (continued):

The incidence of TEAEs with a relationship/causality to IMP was significantly lower in the MP1032 300 mg bid arm and lower in the MP1032 150 mg bid arm when compared to placebo bid arm:

- *MP1032 300 mg bid:* 2 'possibly' related TEAEs in two patients (worsening of pruritus and itching of psoriatic plaques)
- *MP1032 150 mg bid:* 5 'possibly' related TEAEs in four patients and 1 'probably' related TEAE in one patient (fatigue, cystitis, palpitations, stomach pain, neutropenia, and exacerbation of psoriasis)
- *Placebo bid:* 17 'possibly' related TEAEs in nine patients and 1 'probably' related TEAE in one patient (soft fecal, softer fecal, increased stool frequency, headache, vomiting, gastrointestinal discomfort, glycosuria, atrial hypertension, ketonuria, increase of pruritus, psoriasis plaques cracked, folliculitis of periumbilical area, bone aches, watery stool, upper respiratory tract infection, pain in the right hypochondrium, sore throat and diarrhea).

In general, no systemic side effects were observed. All these 'possibly/probably drug-related' TEAEs were evaluated as non-serious and were mainly of mild to moderate intensity, except for one case of severe exacerbation of psoriasis in the MP1032 150 mg bid arm. 3 of the 'possibly/probably drug-related' TEAEs led to withdrawal in three patients (2%) (*MP1032 150 mg bid arm:* exacerbation of psoriasis, *placebo bid arm*: diarrhea and pain in the right hypochondrium). Most of the 'possibly/probably drug-related' were recovered or recovering at the end of the trial with the exception of glycosuria and arterial hypertension reported in one patient of the placebo bid arm which had 'not recovered/not resolved'.

These overall results indicate a very positive safety profile. There were no trends detected indicating any specific treatment-related reactions and furthermore, the frequency of AEs detected in both treatment arms was comparable or even lower than in the placebo bid arm. Compared to presently marketed systemic treatments for psoriasis which all have significant safety and tolerability related side effects, this is a beneficial advantage.

Furthermore, 2 TEAEs, 1 'certainly' and 1 'possibly' related to study procedure were reported in one patient of the MP1032 150 mg bid and in one patient of the placebo bid arm (subcutaneous hematoma and neutropenia, respectively).

The evaluation of physical findings, vital signs and ECG raised no concerns about safety.

In conclusion, MP1032 did not achieve the primary endpoints, 75% improvement in PASI score and 1- or more point reduction in PGA, in a considerable number of patients, but was well tolerated and showed a beneficial safety profile and a trend to a statistically significant efficacy in patients with moderate PASI scores (10-15) after 12 weeks of treatment (EoT).

Date of the report: 24APR2020