Appendix 16.1.1

Protocol and protocol amendments

CCI [redacted]

Contents

Clinical Trial Protocol

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.

Confidential

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Synopsis

Sponsor	MetrioPharm AG Bleicherweg 45 8002 Zurich Switzerland
Sponsor's EU Representative	MetrioPharm Deutschland GmbH Am Borsigturm 100 13507 Berlin Germany
Trial no.	**MP1032-CT04 / 370205BS**
EudraCT-no.	2017-003484-36
Title	A Phase II, Multicenter, Double-blind, Placebo-controlled, Efficacy and Safety Trial of Two Oral Doses (150 mg bid / 300 mg bid) of MP1032 in Male and Female Patients with Moderate-to-Severe Chronic Plaque Psoriasis.
Title lay people	Study to evaluate efficacy and safety of MP1032 after oral administration in patients with moderate-to-severe chronic plaque psoriasis
Phase	II (POC)
Coordinating/ Investigator	PPD [redacted]
Trial center(s)	Multicenter Europe, approximately 14 centers Germany (7) and Poland (7). Site numbers may be revised to accommodate recruitment.
Trial period (planned)	January 2018 to September 2018 The duration of patient participation is approximately 16 weeks (12 weeks treatment phase and 4 weeks follow-up) and will require up to 6 visits with unscheduled visits, as needed
Objective(s)	The primary objective of this trial is to evaluate the clinical efficacy and safety of two oral doses of MP1032 (150 mg bid and 300 mg bid) when taken for 12 weeks by patients with moderate-to-severe chronic plaque psoriasis
Trial design	Three-arm randomized, double-blind, placebo-controlled, parallel group phase II multi-center trial
Number of patients (planned)	Planned number of patients: approx. 150 (120 + 30), ratio 1:1:1 • 150 mg bid arm: approx. 50 patients • 300 mg bid arm: approx. 50 patients • Placebo bid arm: approx. 50 patients

(continued…)

Synopsis (continued)

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 - ≤20 at baseline, BSA score > 10%
Investigational medicinal product (IMP)	MP1032 will be supplied as 50 mg capsules. Identical appearing placebo capsules will be provided.
Dose	MP1032 50 mg capsules or placebo will be administered orally as follows in a blinded version bid for 84 days: • 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)
Duration of treatment	12 weeks (84 days)
Mode of administration	Oral treatment (6 capsules), twice daily administered by the patient at home (last day at site), patients of the PK subgroup will administrate the first and last treatment at the site.
Efficacy assessments	Psoriasis Area Severity Index (PASI) The PASI is the most commonly used and validated assessment for grading the severity of psoriasis in clinical studies. The PASI is a physician's assessment of psoriasis that is a therapeutic standard in clinical studies for this disease. The PASI quantifies the severity and extent of the disease and weighs these with the body surface area involvement. It involves the assessment of erythema, infiltration, desquamation, and body surface area involvement over 4 body regions: head, trunk, upper and lower extremities. The Investigator assesses the redness, thickness, and scaliness of lesions on a 5-point scale (from 0 = none, through 4 = severe). The PASI score ranges from 0 to 72, with a higher score indicating increased disease severity. The PASI will be completed by the Investigator or designee at the time points prior to and following IMP administration as defined in the trial schedule. Physician`s Global Assessment (PGA) The PGA provides an overall evaluation of the severity of the disease. The PGA is a 7-point physician's assessment of psoriasis that is a therapeutic standard in clinical studies for this disease. The Investigator or designee will complete a PGA form to evaluate the disease severity at a single time point. Scoring is on a 7-point scale: 0 = clear; 1 = almost clear; 2 = mild; 3 = mild to moderate; 4 = moderate; 5 = moderate to severe, and 6 = severe.

(continued…)

Synopsis (continued)

Efficacy assessments	Assessment of body surface area (BSA) The total surface area of the body affected with psoriasis plaques will be determined by the Investigator. Calculation should include psoriasis on the palms of the hands and soles of the feet as well as on the face and scalp. The investigator will calculate the approximate BSA by assuming that 1% BSA is approximately equal to the surface area of one outstretched hand (with fingers) of the patient.
Baseline and safety parameters	Medical history including psoriasis history, physical examination focusing on the skin, demographic data, previous and concomitant medication, vital signs, recording of adverse events, serum pregnancy test at screening, safety laboratory scheduled at all visits (except serology), extent of exposure.
Rationale for sample size	It is planned to recruit approximately 150 patients for this clinical trial in Germany and Poland (each country approximately 75 patients) to achieve 120 evaluable patients. No formal sample size calculations were performed for this explorative trial. A sample size of 40 in each group is adequate to detect a difference in rates of at least 0,274, with 80% power, using a two group χ^2 test with a 0,100 two-sided significance level.
Statistical methods	Hypotheses: Since this is an exploratory trial no formal hypotheses are postulated. The data will be evaluated descriptively. Primary efficacy endpoints Two primary co-parameters will be analyzed as described in the EMA Guideline. The comparisons of the treatment groups MP1032 300 mg bid and MP1032 150 mg bid, each vs. the placebo treatment, with respect to each, the PASI 75 rate and PGA improvement rate, at Week 12 (Day 84) will be evaluated by the CMH test stratified by (pooled) analysis center. The common odds-ratio with 95% confidence interval will be provided. The homogeneity of the individual odds-ratios will be assessed by the Breslow-Day test. Secondary efficacy endpoints Secondary efficacy endpoints will be evaluated descriptively. The change in the PASI score from baseline to each post baseline visit, respectively, will be evaluated using an analysis of covariance (ANCOVA) model, with treatment group and (pooled) analysis center as factors and baseline outcome as covariate.

(continued…)

Synopsis (continued)

Statistical methods	The time to achievement of PASI 50 and PASI 75, respectively, will be evaluated using the Kaplan-Meier method. Pairwise treatment group differences will be tested by the log-rank test. Descriptive summaries will be provided for each parameter by treatment group and by visit, if applicable. Percentages will be provided based on the number of non-missing cases, if not otherwise stated. **Other endpoints:** Blood MP1032 concentration-time data will be listed 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 will be provided. Statistical analyses will be performed using non-compartmental analysis (NCA) methods, as appropriate, providing Cmax, tmax and AUC(0,t). Listings and summary statistics of NCA parameters will be provided. **Safety analysis:** All AEs reported during the trial will be listed, documenting course, severity, investigator assessment of the relationship to the IMPs, and outcome. AEs will be coded using the MedDRA mapping system for preferred terms (PTs) and system organ class (SOC). Treatment-emergent adverse events (TEAEs), i.e. AEs with an onset or worsening on or after the time of the first IMP application, will be summarized by the number of patients reporting TEAEs, primary system organ class (SOC), preferred term (PT), severity, and relationship to IMP. Listings of serious adverse events (SAE) and patients who prematurely discontinued treatment due to AEs will be given. Safety laboratory parameter (hematology, clinical chemistry) and vital signs will be summarized descriptively, including changes from baseline. Urinalysis outcomes will be summarized by frequency counts.
Date of issue	September 22, 2017

Signatures of sponsor

This clinical trial protocol was subject to critical review and has been approved by the sponsor. The information it contains is consistent with:

- the current risk-benefit evaluation of the investigational product
- the moral, ethical, and scientific principles governing clinical research as set out in the currently valid revision of the Declaration of Helsinki and the principles of GCP as described in ICH GCP.

The investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

PPD

Signatures of bioskin

The undersigned hereby declare their consent to performance of the clinical trial in compliance with regulations as laid down in this clinical trial protocol, in the currently valid revision of the Declaration of Helsinki and in the ICH-GCP guideline and applicable national laws and regulations. Changes to this protocol require written agreement of both investigator and sponsor.

The investigator has acquainted himself with the results of the pharmacological and toxicological trials of the investigational product and the results of other trials as described in the investigator's brochure or other appropriate information.

PPD

Signature of International Coordinating Investigator

The undersigned hereby declare their consent to performance of the clinical trial in compliance with regulations as laid down in this clinical trial protocol, in the currently valid revision of the Declaration of Helsinki and in the ICH-GCP guideline and applicable national laws and regulations. Changes to this protocol require written agreement of both investigator and sponsor.

The investigator has acquainted himself with the results of the pharmacological and toxicological trials of the investigational product and the results of other trials as described in the investigator's brochure or other appropriate information.

PPD

Responsible person for SAE notifications:

PPD, CCI

SAE reporting to:

CCI

Table of Content

Tables

1. Abbreviations

ADP	Adenosine diphosphate ribose
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AMG	German drug law (Arzneimittelgesetz)
AST	aspartate aminotransferase
AUC	area under the curve
BfArM	Federal institute for drugs and medical devices (Bundesinstitut fuer Arzneimittel und Medizinprodukte)
BMI	body mass index
CA	competent authority
CMH	Cochran-Mantel-Haenszel
CRF	case report form
EC	ethics committee
ENT	Ear nose throat
EoS	End of study
EoT	end of treatment
FAS	full analysis set
(c)-fms	colony-stimulating factor-1 receptor
GCP	good clinical practice
GMP	good manufacturing practice
GOT	glutamic oxaloacetic transaminase
GPT	glutamic pyruvic transaminase
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	investigator's brochure
ICH	international conference on harmonisation
IL-6	interleukin-6
IMP	investigational medicinal product
IMPD	investigational medicinal product dossier
ITT	intent-to-treat
IWRS	Interactive Web Response Systems
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	medical dictionary for regulatory activities
PARP-1	poly(adenosine diphosphate [ADP]-ribose) polymerase 1
PP	per-protocol
PT	preferred term
PV	Pharmacovigilance
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis system
SES	safety evaluation set
SGK-2	serine / threonine-protein kinase
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction

TACE	metalloprotease TNF-α converting enzyme
TEAE	treatment emergent adverse event
TMF	trial master file
TNF-α	Tumor Necrosis Factor α
VCS	valid cases set
WBC	white blood cell
WCBP	women of childbearing potential
WHO	world health organization

2. Introduction

MP1032 is a small-molecule macrophage modulator currently not available as a registered or approved medicinal product within the borders of the European economic area, the United States, or Japan. Experimental data have shown that MP1032 can inhibit inflammation by reducing Tumor Necrosis Factor α (TNF-α) and Interleukin-6 (IL-6) [1]. MetrioPharm AG is developing MP1032 as an anti-inflammatory compound. The first target indication is psoriasis.

Psoriasis is a relatively common skin condition, affecting 1.5 to 3% of the general population in Europe [2]. Psoriasis can have a particularly negative effect on quality of life, affecting a sufferer's physical, social, and psychological functioning so the need for effective therapies is high. Psoriasis is characterized by outbreaks of skin inflammation interspersed by varying periods of remission. The underlying mechanisms of the inflammatory flares in psoriasis are poorly understood, but the therapeutic potency of anti-TNF- α and anti-IL-17 biologics is evidence of immune modulation's potential to reduce disease severity [1].

However, antibody-based biologics therapies are not optimal therapies for life-long treatment of psoriasis, due to decreasing efficacy over time and relatively high costs. Furthermore, the use of immune-suppressive drugs, such as methotrexate, cyclosporine, or anti-TNF-α/IL-12/IL-17/ IL-23 biologics increases the risk of opportunistic infections and/or requires regular laboratory checks on blood and liver function [1].

MP1032 has been shown to reduce TNF-α and IL-6 levels *in vitro* (human peripheral blood mononuclear cells and differentiated human promyelocytic leukemia cells), and *in vivo*, and its anti-inflammatory potential has been shown in mouse and rat arthritis models. Other anti-inflammatory compounds usually exhibit immune-suppressive effects resulting in an increased vulnerability to infections. MP1032, on the other hand, has shown an anti-infective potential in animal infection models.

The mechanism of action is thought to be mediated by MP1032's partial inhibition of the enzyme poly(adenosine diphosphate [ADP]-ribose) polymerase 1 (PARP-1), the kinases human Aurora-B, human Aurora-C, serine / threonine-protein kinase (SGK-2), tyrosine kinase (colony-stimulating factor-1 receptor [c-fms / FMS], and the metalloprotease TNF-α converting enzyme (TACE, also known as ADAM17).

As a multi-target small-molecule macrophage modulator, MP1032 seems to avoid the problems of tolerance and reduced long-term efficacy that biologics have. An important potential safety advantage of MP1032 lies in the observation from animal models that the compound reduces rather than increases susceptibility to bacterial and viral infections. This may be due to the fact that MP1032 is reducing – rather than completely suppressing – TNF-α and IL-6 levels.

MetrioPharm considers these molecular and safety characteristics along with the ease of an oral therapy over topical therapies as strong arguments for MP1032 to become an effective therapy option in moderate-to-severe psoriasis, where topical agents are not effective enough or too tedious for patients to apply them regularly.

MP1032 has been assessed in a phase I first-in-man clinical trial. In part 1 of this trial (single-ascending doses), 12 volunteers were administered 50 to 600 mg MP1032. One mild adverse drug reaction (ADR) of “headache” was classified as related to the investigational medicinal product (IMP) and was reported after treatment with 50 mg MP1032. In part 2 of the clinical trial, general safety and tolerability of MP1032 were assessed in multiple ascending doses. No ADRs were reported in part 2, in which the volunteers received 2 × 100 mg per day and 2 × 300 mg per day at 12-hour intervals for 7 consecutive days.

Subsequently, an exploratory, double-blind, parallel phase IIa trial to evaluate the safety, pharmacokinetics and efficacy of orally administered MP1032 in patients with moderate to severe chronic plaque psoriasis was performed. A total of 44 patients were randomized with a 1:1 ratio to either receiving 100 mg MP1032 twice daily or placebo for 42 days. The findings of that trial shows that after only six weeks of treatment, there is a clinically meaningful response in patients who entered the trial with a PASI score of 10-20 and achieved appropriate MP1032 exposure values. 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.

Further details can be found in the Investigator's Brochure (Edition 5, September 2017), which contains comprehensive information on the IMP [3]. See Section 5.1 for details concerning the design of the current trial and section 5.2 for justification of the design of this trial.

3. Risk-benefit evaluation

3.1 Stress/risks due to trial procedures

The noninvasive procedures (clinical assessments and photographic documentation) do not pose a risk or stress for the patients.

The blood sampling procedure poses the same very small risk as normally associated with this procedure (e.g. infection, bleeding into the surrounding tissue, and very rarely inflammation of the vein or formation of blood clots). Therefore blood withdrawal will only be conducted by qualified medical personnel.

3.2 Stress/risks due to the investigational medicinal product (IMP)

General safety and tolerability of MP1032 has been assessed in one phase 1 first-in-man clinical trial. In the single ascending doses part of this trial, twelve volunteers were administered 50 to 600 mg MP1032. One mild ADR ("headache") was reported once after treatment with 50 mg MP1032 in one volunteer. No ADRs were reported in the multiple ascending doses part where volunteers received 2×100 mg per day and 2×300 mg per day at 12-hour intervals for seven consecutive days.

In a previous IIa trial following TEAEs were observed: In summary the number of patients with TEAEs was 14 (60.87%, 27 TEAEs) in the MP1032 group and 15 (65.22%, 32 TEAEs) in the placebo group. The most commonly reported TEAEs were in the SOC categories of infections and infestations (5 patients [21.74%] in the MP1032 group and 8 patients [34.78%] in the placebo group) and nervous system disorders (7 patients [30.43%] in the MP1032 group and 3 patients [13.04%] in the placebo group). No clinically important differences were seen between the two treatment groups with regard to the number and overall pattern of patients reporting TEAEs by System Organ Class (SOC).

A positive phototoxic signal detected in non-clinical studies could be indicative of a likely clinical phototoxic risk of MP1032, although the risk for the patients seems to be unlikely and no associated TEAEs were seen in the previous clinical trials. Nevertheless, psoriasis patients participating in this trial should be advised to minimize sun exposure (sun bathing) and strong UV exposure (see also inclusion criterion No. 9). Furthermore, the use of sunscreen will be recommended when spending an extended period of time outdoors. The latter requirement will be valid during the whole 12 weeks of treatment duration plus the 4 weeks of follow up period.

Women of childbearing potential (WCBP) must agree to use a highly effective contraceptive method (Pearl-Index < 1%) starting at screening and continuing throughout the clinical trial period and for 28 days after final IMP administration.

Highly effective forms of birth control (according to International Conference on Harmonization [ICH] M3) have low failure rates (i.e. less than 1% per year) when used consistently and correctly, and include the following:

- The male partner of a female patient has undergone effective surgical sterilization.
- A female patient can use an established oral contraceptive, injected or implanted hormonal methods of contraception or an established intrauterine device or intrauterine system.

True sexual abstinence as a form of birth control will be allowed in the trial when this is in accordance with a patient's preferred and common lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception. Patients who use abstinence as a form of birth control must agree to abstain from heterosexual intercourse from the month prior to screening until 28 days after the last dose of IMP (or longer if required by local regulations). Study personnel must confirm the continued use of abstinence is still in accordance with the patient's lifestyle at regular intervals during the trial.

Post-menopausal is defined as 12 months of spontaneous amenorrhea. Females who have been sterilized, or had a hysterectomy, may be included.

A **sterile** woman is defined by either of the following medical interventions performed before intake of IMP

- Tubal ligation, or
- Bilateral oophorectomy, or
- Total hysterectomy.

If documented, women with one of these conditions are not required to use additional contraception.

Male patients who are sexually active with a female partner and are not surgically sterile (vasectomy performed at least six months prior to treatment) must agree to inform their female sexual partner about his trial participation and to use an acceptable form of birth control as described in the informed consent form. Prior to trial enrollment, patients must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The patient must sign an informed consent form documenting this discussion.

Against these minimal risks stands the benefit of information on the efficacy and safety of a promising new substance which is intended to be used in the oral administration in patients with psoriasis vulgaris.

Taking into account these risks and benefits, the performance of the trial can be considered ethically sound since the expected benefits of the IMPs appear greater at present than the risks for the patients. The clinical trial protocol will be submitted to the responsible ethics committee(s) for approval.

4. Trial objectives/endpoints

The trial is designed with two primary endpoints as described in the EMA guideline [2].

Table 1: Objectives and endpoints:

Primary objective	Primary endpoint
The primary objective of this trial is to evaluate the clinical efficacy and safety of two oral doses of MP1032 (150 mg bid and 300 mg bid) when taken for 12 weeks by patients with moderate-to-severe chronic plaque psoriasis.	Efficacy: MP1032 300 mg bid vs. placebo 1. Percentage of patients who achieve a 75% improvement (response) in their PASI score (PASI 75) at Week 12 (Day 84) compared to baseline treated with 300 mg bid of MP1032 compared to placebo 2. Improvement (1 or more points on a 7 Point Scale) in PGA at Week 12 (Day 84) compared to baseline treated with 300 mg bid of MP1032 compared to placebo Efficacy: MP1032 150 mg bid vs. placebo 3. Percentage of patients who achieve a 75% improvement (response) in their PASI score (PASI 75) at Week 12 (Day 84) compared to baseline treated with 150 mg bid of MP1032 compared to placebo 4. Improvement (1 or more points on a 7 Point Scale) in PGA Score at Week 12 (Day 84) compared to baseline treated with 150 mg bid of MP1032 compared to placebo Safety: 5. Incidence of adverse events

Secondary objectives	Secondary endpoints
To evaluate the effect of each oral doses of MP1032 (150 mg bid and 300 mg bid) compared to placebo on the PASI score	• Percentage of patients who achieve a 50% improvement (response) in their PASI score (PASI 50) at Week 12 (Day 84) compared to baseline treated with 300 mg bid of MP1032 compared to placebo • Percentage of patients who achieve a 50% improvement (response) in their PASI score (PASI 50) at Week 12 (Day 84) compared to baseline treated with 150 mg bid of MP1032 compared to placebo • Mean PASI score and change to baseline at Week 4 (Day 28), 8 (Day 56), 12 (Day 84) and week 16 (Day 112) • Time to achieve PASI 50 and PASI 75 • Mean PASI score and change from Baseline at Week 4 (Day 28), 8 (Day 56), 12 (Day 84) and 16 (Day 112)
To evaluate the effect of each oral dose of MP1032 (150 mg bid and 300 mg bid) compared to placebo on the PGA score	Mean score and change from Baseline at Week 4 (Day 28), 8 (Day 56), 12 (Day 84) and 16 (Day 112) in the PGA
To evaluate the effect of each oral dose of MP1032 (150 mg bid and 300 mg bid) compared to placebo on the BSA score	Mean score and change from Baseline at Week 4 (Day 28), 8 (Day 56), 12 (Day 84) and 16 (Day 112) in the BSA
To evaluate systemic exposure of two oral doses of MP1032 (150 mg bid and 300 mg bid) when taken for 12 weeks by patients with moderate-to-severe chronic plaque psoriasis	PK data analysis

5. Investigational plan

5.1 Overall trial design and plan - description

This trial is 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 consists of a 28-day screening period, a 12-week treatment period, and subsequently a 28-day follow-up period. Each patient will have 6 visits and unscheduled visits as needed.

Approximately 150 patients (2 × 50 patients MP1032 and 50 patients placebo) who meet the entry criteria will be randomized on Day 1 to receive either 150 mg MP1032, 300 mg MP1032 or placebo orally twice daily for 12 weeks. The administration of IMP will stop after end of study (in max. 13 weeks). Recruitment will be competitive between the sites but enrollment will be limited to 12 patients per site. A recruitment of more than 12 patients may be allowed after sponsor approval.

Safety parameter will be monitored from the signing of the informed consent form (ICF) until the last follow-up visit.

Efficacy and safety will be assessed as outlined in the trial flow chart.

5.2 Discussion of trial design, including the choice of control groups

Pre-clinical toxicology studies, a Phase I single plus multiple ascending dose trial, as well as an exploratory Phase IIa pilot trial of oral MP1032 have indicated a higher degree of safety and tolerability of the IMP compared to all currently used systemic psoriasis treatments. Moreover, a first assessment of oral MP1032's clinical efficacy in moderate-to-severe psoriasis in the preceding Phase IIa trial has shown clinically meaningful response in patients who entered the trial with a PASI score of 10-20 during six-week treatment period.

In several animal models of chronic, immune-mediated inflammatory diseases, MP1032 has been shown to have a pronounced anti-inflammatory effect.

The primary objective - to evaluate clinical efficacy and safety of MP1032 in patients with psoriasis during the 12-week treatment period and a 4-week follow up - will provide an opportunity to perform oral MP1032's clinical efficacy in moderate-to-severe psoriasis when taken for twice as long as done in Phase IIa.

On the basis of pre-clinical, Phase I and Phase IIa data, the current trial was also designed to assess the safety and tolerability of oral MP1032 over a period of 12 weeks, trying to reproduce the excellent tolerability and safety profile that was seen in Phase I and Phase IIa (up to 7 days and 6 weeks, respectively), over a longer period of time.

The extension of treatment to 12 weeks and a 4-week follow-up observation period will give the opportunity to obtain even more meaningful safety data and more comprehensive data on efficacy.

To evaluate systemic concentrations of MP1032 PK samples will be analyzed in a subgroup.

The photographic documentation will only be used for visual demonstration of efficacy. No assessments will be performed using this data.

Patients will be randomized to one of three treatment arms (MP1032 600mg, MP1032 300mg or placebo) in a blinded manner. The treatment allocation will be on a 1:1:1 ratio (50:50:50 patients). Recruitment will be competitive between the sites but enrollment per site will be limited to 12 patients (more than 12 patients needs to be approved by the sponsor).

5.3 Selection and discontinuation/withdrawal of patients

5.3.1 Selection of patients

The selection of patients is in accordance with the requirements of the national laws as well as the recommendations of the currently valid revision of the Helsinki Declaration [4] and the ICH GCP guideline [5]. Advertisement (e.g. newspaper, online portal, bus or metro) will be used only after positive approval by the responsible EC.

The trial population will consist of approx. 150 patients (planned 75 Germany and 75 Poland) with moderate-to-severe chronic plaque psoriasis. Patients must be able to provide written consent and meet all the inclusion criteria and none of the exclusion criteria.

A gender specific subdivision into groups is not necessary in this clinical trial. Male or female patients between 18 years and 70 years are eligible for this clinical trial insofar that they suffer from moderate-to-severe-psoriasis. The antipsoriatic efficacy is likewise detectable in men and women.

5.3.2 Inclusion criteria

All of the following criteria have to be met for inclusion of a patient in this trial:

1. Participants legally competent to sign and give informed consent.
2. Adult male and female patients between 18 years and 70 years with moderate-to-severe chronic plaque psoriasis (diagnosed by Investigator):
   a) PASI score ≥10 - ≤20 at baseline
   b) BSA score: > 10%
   c) Stable disease duration of ≥ 6 months at the initiation of IMP.
   d) topical therapy fails to control the disease
3. Body Mass Index (BMI) between 18.5 and 34.9 kg/m^2.
4. Women of childbearing potential (WCBP) must have a negative serum pregnancy test at Screening (Visit 1). In addition, sexually active WCBP must agree to use adequate contraception throughout the trial (see Section 3.2 for more details on adequate contraception):
   a) A method with less than 1% failure rate OR
   b) Abstinence
5. Post-menopausal women with spontaneous amenorrhea for at least 12 months and women on hormonal replacement therapy (HRT). The use of hormonal replacement therapy (HRT) during the trial is permitted, however for these patients an appropriate contraception method according to Inclusion Criterion 4 must be ensured. Sterilized women may be included (see Section 3.2 for more details on sterile definition)
6. Male patients who are sexually active with a female partner and are not surgically sterile (vasectomy performed at least six months prior to treatment) must agree to inform their female sexual partner to use an acceptable form of birth control as described in the informed consent form. For females, an acceptable method (Pearl Index < 1%) would be to use implants, injectable, combined oral contraceptives, some intrauterine devices, or be postmenopausal, be surgically sterile (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy)
7. In good health as judged by the investigator, based on medical history, physical examination, serum chemistry, hematology and urinalysis
8. Patients must meet the following clinical laboratory criteria:

- White blood cell count ≥3.5 × 109/L
- Platelet count ≥100 × 109/L
- Serum creatinine ≤1.5 × upper limit of normal (ULN); estimated glomerular filtration rate >60 mL/min
- Total bilirubin ≤1.5 × ULN
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN
- Hemoglobin ≥ lower limit of normal as per central laboratory reference ranges for women and men accordingly
- No coagulopathy (International Normalized Ratio [INR] <1.5)

9. Patients agree to minimize normal sun exposure during the course of the trial
10. Patients are considered reliable and capable of adhering to the protocol (e.g. able to understand the patient information and complete diaries), visit schedule, or medication intake according to the judgment of the Investigator.

5.3.3 Exclusion criteria

Patients are to be excluded from the trial, when one or more of the following conditions are met:

1. Patients with non-plaque form of psoriasis (erythrodermic, guttate, pustular form of psoriasis). Associated psoriasis arthritis is allowed provided no other in-/exclusion criteria are influenced, no forbidden concomitant therapy is required for the well-being of the patient and there is no impact on trial objectives as determined by the Investigator.
2. Treatment with concomitant medication that may affect and provoke or aggravate psoriasis, e.g. antimalarial drugs, beta-blockers or ACE inhibitors unless on a stable dose for 3 months before IMP intake.
3. Evidence of skin conditions at the time of Screening Visit other than psoriasis that would interfere with evaluations of the effect of the IMP on psoriasis.
4. Patients with any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the patient from signing the ICF, as assessed by the investigator.
5. Pregnant or lactating women or women planning to become pregnant during the trial and / or within 28 days following the last dose of IMP.

6. Male patients planning a partner pregnancy or sperm donation during the trial including follow up period.
7. Known allergies to any ingredient of the IMP e.g. mannitol, macrophage modulators, or gelatin.
8. History or symptoms of a clinically significant illness in the four weeks before first treatment and during the trial that in the opinion of the investigator may place the patient at risk by trial participation or influence the outcome of the trial. Well controlled diseases such as hypertension, hyperlipidemia, diabetes or hypothyroidism are permitted.
9. Patients with active malignancy or history of malignancy, except for basal cell and actinic keratosis. Basal cell carcinoma of the skin or *in situ* cervical carcinoma that have been fully treated and show no evidence of recurrence are allowed.
10. Positive HIV-Antibody, HBs-Antigen or HCV-Antibody-Test at screening.
11. Previous strong sun exposure (e.g. sea holiday) within 28 days or UV treatment within 24 weeks before IMP initiation.
12. Known photo allergy and / or experienced drug-induced photo toxicity.
13. Elective (planned) hospitalization or medical intervention preventing patient from following the protocol requirements.
14. Prior treatment not adhering to Table 2.

Table 2: Prohibited medication:

Drug Class	**Last Dose Prior to IMP Initiation** (Washout Period)
Topical psoriasis medications (including, but not limited to corticosteroids, calcipotriene, topical vitamin D derivates, retinoids, coal tar) shampoos for scalp psoriasis containing tar	14 days
Topical immunosuppressive drugs (tacrolimus, pimecrolimus, or anthralin)	14 days
(Exception: Non-medicated emollients, moisturizers and sunscreens will be allowed)	
Systemic treatments (non-biologics): Systemic immunosuppressant agents (e.g.: methotrexate, cyclosporine, azathioprine)	28 days

Drug Class	Last Dose Prior to IMP Initiation (Washout Period)
Systemic fumarate Systemic corticosteroids	
Phototherapy or photochemotherapy / photosensitizing drugs **UVA phototherapy with or without psoralen, excimer laser**	28 days 24 weeks
Systemic retinoids	12 weeks
Investigational drugs	24 weeks (systemic); 4 weeks (topical)
Anti-tumor necrosis factor (TNF) drugs: Adalimumab, Infliximab, brodalumab, Ixekizumab, etanercept,	8 weeks
Guselkumab, certolizumab pegol, golimumab,	12 weeks
Other biologics and other systemic therapies:	8 weeks
apremilast	12 weeks
Ustekinumab, alefacept, secukinumab	24 weeks
Rituximab	12 months

15. Planned use of any ultraviolet (UV) phototherapy or photochemotherapy / photosensitizing drugs during the course of the trial and within 28 days/24 weeks following the last dose of the IMP.
16. Patients with a history of chronic alcohol or drug abuse within 6 months of IMP initiation.
17. Patients with a blood pressure outside the given range of 160 mm Hg (systolic) and 95 mm Hg (diastolic)
18. Patients who are employed by MetrioPharm, contract research organization (CRO) or clinical site involved in the clinical trial.
19. Vulnerable patients (e.g. patients kept in detention).
20. Patients who are unable to communicate, read or understand the local language, or who display another condition, which, in the Investigator's opinion, makes them unsuitable for clinical trial participation.
21. Patient is institutionalized because of legal or regulatory order.

5.3.4 Restrictions during the clinical trial

A positive phototoxic signal detected in non-clinical studies could be indicative of a likely clinical phototoxic risk of MP1032, although the risk for the patients seems to be unlikely. Nevertheless, psoriasis patients participating in this trial should be advised to avoid strong sun exposure (sun bathing) and strong UV exposure (see inclusion criterion no. 9). Furthermore, the use of sunscreen will be recommended when spending an extended period of time outdoors. During the trial patients should adhere to their standard skin care regimen and may use their standard emollients/moisturizers as symptoms require but may not use treatments as precluded by the exclusion criteria. The latter requirement will be valid during the whole 12 weeks of trial duration plus the 4 weeks of follow up period.

5.3.5 Removal of patients from therapy or assessment

5.3.5.1 Criteria for discontinuing the whole clinical trial

Premature termination of a clinical trial may occur upon decision of the Sponsor, upon decision of the Investigator, by request of an authority, or because of withdrawal of positive vote by the responsible IEC. If the Investigator, the Sponsor, or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to patients, if the trial continues, the trial may be terminated after appropriate consultation between the relevant parties. The trial may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination of the trial as a whole include, but are not limited to:

- Concerns for safety that arise within this trial or in any other trial with the IMP;
- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the trial;
- Failure to enroll patients at an acceptable rate;
- Ethical issues;
- Severe non-compliance;
- A decision on the part of the Sponsor to suspend or discontinue development of the drug.

5.3.5.2 Criteria for discontinuing in the case of individual patients

Patients may withdraw from the entire trial including follow-up at any time without penalty and for any reason without prejudice to his or her future medical care.

The following criteria must lead to discontinuation from the clinical trial in individual patients:

- Patient withdraws informed consent

- Pregnancy (see section 7.4)
- Severe protocol violations that result in a significant risk to the patient's safety
- Emergence of the following AEs including:

  a) Patient reports symptoms which are considered unacceptable by the patient or the Investigator or if any serious AE occurs that is judged as at least possibly related to the IMP by the Investigator

  b) Abnormal laboratory value(s) confirmed by repeat measurements:

    - Elevated liver transaminases (AST/ALT) ≥3 × ULN AND elevated bilirubin total bilirubin ≥ 2 × ULN
    - Elevated serum creatinine ≥2 × ULN

The following criteria may lead to discontinuation from the clinical trial in individual patients:

- Use of prohibited concomitant medication as defined in section 5.4.5.

In all cases, the reason(s) for withdrawal, and the primary reason, must be recorded on the electronic data capture (EDC) system / electronic case report form (eCRF). If a patient is prematurely withdrawn from the IMP for any reason, the Investigator must make every effort to perform the evaluations described for the End of Treatment and Follow-up Visits. The Investigator should contact the Medical Monitor, whenever possible, to approve withdrawal of patients in advance.

If a patient withdraws consent and still agrees to undergo a final examination, it will be documented on the eCRF and the patient record.

A patient may also be withdrawn from the IMP by the Sponsor, Regulatory Authorities, or Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs).

Patients who are withdrawn from the trial will be not replaced.

Protocol violation, failure to comply with the trial stipulations/poor compliance may lead to discontinuation from the clinical trial in individual patients.

5.3.6 Definition of end of trial

The end of the trial is defined as the last visit of the last patient completing the trial (including follow-up visits).

5.4 Treatments

The IMP will be packed in kits, 1 kit per patient per week. One kit contains 14 blisters and one blister contains six, 50 mg, hard gelatin capsules of MP1032 and/or placebo (described below). IMP will be packaged and labelled by CCI [redacted] according to all local legal requirements. IMP will be labelled in accordance with applicable regulatory requirements.

All IMP supplies must be stored at room temperature (15 - 25°C) and protected from light, in accordance with the manufacturer's instructions. Until dispensed to the patients, the IMP will be stored in a securely locked area, accessible to authorized personnel only.

5.4.1 Treatments to be administered (manner and dose selection)

Once patients have met the trial entry criteria, completed the screening procedures and run-in period, and completed the pre-dose procedures and assessments, they will be randomly assigned as described in Section 5.4.3 above to one of the three treatment groups described below. They will receive total daily doses of 300 mg or 600 mg MP1032 (IMP) or placebo (IMP placebo) as follows (1:1:1):

- Treatment A: 3 × 50 mg (150 mg) MP1032 plus 3 × placebo hard gelatin capsules (per dosage) twice daily for 84 days
- Treatment B: 6 × 50 mg (300 mg) MP1032 hard gelatin capsules (per dosage) twice daily for 84 days
- Treatment C: 6 × placebo hard gelatin capsules (per dosage) twice daily for 84 days.

All administrations will take place with at least 8 hours between the dosings.

5.4.2 Identity of investigational medicinal products

Details of the IMPs are given in the table 3.

Table 3:Identity of investigational medicinal products:

Generic name/brand name/INN	Verum	Placebo
Formulation	Hard gelatin capsules, size 3 The mixture (995 parts mannitol and 5 parts colloidal anhydrous silica) is well known and described in compendia (German: Neues Rezepturformularium, Monographie Nr. S. p. 38.). At least 25% of the mass of the contents are active ingredient. Placebo capsules constituted only of the excipients described above.	
Active ingredient	MP1032 5-Amino-1,4-dioxo-1,2,3,4-tetrahydrophthalazine-3-id, sodium salt	n.a.
Amount per unit	containing 50 mg MP1032 for oral administration	n.a.
Primary packaging	Blister	Blister
Storage	room temperature (15 – 25 °C)	room temperature (15 – 25 °C)
Manufacturers	CCI [redacted]	CCI [redacted]

All IMPs will be labeled according to the requirements of local law and legislation. A copy of the labels will be filed in the trial master file (TMF).

All IMPs used during the trial will be stored at the trial center in accordance with instructions given, and will be inaccessible to unauthorized personnel.

Missing a treatment

If the patient misses a dose, and remembers the dose within 6 hours of scheduled dosing, he/she may take it. If it has been more than 6 hours since the planned dose time, the patient should skip the dose. All missing doses should be documented by the patient in the diary. However, all administrations will take place with at least 8 hours between the dosings.

Overdose

The risk of overdosing in general in this trial is considered to be low due to the maximum dose that each patient can receive via six capsules being 150 mg, 300 mg MP1032 or Placebo. Nevertheless, unintentional administration of any dose that deviates from the scheduled regimen will be documented and reported by site staff via eCRF. In case of overdose symptomatic

treatment should be provided as indicated and a safety blood analysis should be performed. The Sponsor should be informed immediately.

5.4.3 Assignment of treatments and randomization

Patient Identification

Upon signature of informed consent (screening period) each patient receives a 5-digit **patient identification number**, which is composed of:

Digits 1 and 2:	trial center (01, 02, 03, etc.) 01 – 10 for German sites and 11 – 20 for Polish sites
Digits 3, 4 and 5:	individual screening number within the center (consecutively in the order of screening within the center: 001, 002, etc.)

Treatment Assignment

Patients will be randomized on a 1:1:1 basis to one of three treatment groups:

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

The trial will use a block randomization scheme. Enrollment will be performed competitively between all 14 centers (Germany and Poland) until approximately 150 patients are enrolled in the trial in order to have 120 evaluable patients.

Patients who are eligible for enrollment into the trial will be randomized at Visit 2/Day 1 and will be assigned the lowest random number available at the site. Patient kits will be dispensed according to the kit number assigned by the IWRS. The kit numbers will be assigned to the treatment kits by a simple randomization.

The treatment group designation will remain blinded until the final database is locked.

The random list, assigning the randomization number to the treatment groups, and the kit number list, assigning the kit number to the treatment groups will be generated by psy consult scientific services.

5.4.4 Blinding and Breaking the Blind

The trial will be performed in a double-blind manner. All IMPs will be supplied in identical form and will be similar in color, smell, taste, and appearance.

The IMPs will be blinded by CCI [redacted].

The trial blind should not be broken except in case of a medical emergency (where knowledge of the IMP received would affect the treatment of the emergency) or regulatory requirement (e.g. for SUSAR [in Germany]).

If the blind is broken via IWRS, the date, time, person who broke the blind and the reason must be recorded in the patient's eCRF, and any associated AE report.

The treatment code will only be broken after all the clinical database is locked.

5.4.5 Prior and concomitant therapy

Any medication the patient takes other than the IMP, including herbal and other non-traditional remedies, is considered a concomitant medication. All concomitant medications taken in the 6 weeks before the first dose must be recorded in the eCRF. The following information must be recorded in the eCRF for each concomitant medication: brand name, route of administration, start date, stop date, dosage, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRF.

At Screening, patients will be asked which psoriatic treatment they have previously taken (last 6 weeks) and which other concomitant medications they have taken in the last 6 weeks. At each subsequent trial visit, patients will be asked which concomitant medications they are currently taking and have taken since the previous site visit.

For a detailed list of forbidden medication see exclusion criterion 14.

Medication allowed during the course of the trial:

- Topical moisturizers or emollients, UVA/UVB sunscreens, shampoos for scalp psoriasis (without tar), as needed.
- Contraceptives (see section 3.2)
- Any concomitant medication to treat stable diseases (such as well-controlled hypertension, hyperlipidemia, etc.)

Prohibited medication:

- All treatment as specified in exclusion criteria.

Concomitant medications should be kept to a minimum during the clinical trial. However, if these are considered necessary for the patient's welfare and are unlikely to interfere with the clinical trial objectives, they may be allowed at the discretion of the investigator. For a detailed list of forbidden medication see exclusion criterion 14.

5.4.6 Treatment compliance

All treatment administrations (except first for the PK subgroup and last treatment for all patients) will be taken by the patients at home. All treatment administrations will be documented in a diary. All missing treatment administrations documented in the diary will be counted and documented in the eCRF.

All dispensed kits and blisters (used and unused) will be collected at each visit and capsules will be counted at each visit during the treatment period. The results will be documented in the eCRF.

In case of inadequate usage the patient will be instructed again on application use.

5.5 Efficacy and safety variable(s)

5.5.1 Procedures

Screening period

Day -28 to -3 (visit 1)

Within the 28 days prior to the first IMP administration the volunteer will come to the trial centers for the initial screening (including documentation of demographic data). Screening assessments will be performed after the volunteer has agreed to participate and has signed and dated the informed consent form.

At screening a serum pregnancy test will be carried out in all female patients.

The following examinations will be performed:

- Obtain written informed consent
- Documentation of relevant medical and relevant surgical history (last 5 years)
- Documentation of demographic data
- Documentation of Smoking history/ alcohol consumption
- Documentation of relevant previous medication (last 6 weeks)
- Serum pregnancy test and urinalysis (see section 5.5.2)
- Start check in-/exclusion criteria (see section 5.3.2 and 5.3.3)
- Physical examination (see section 5.5.5)
- Height, body weight and BMI
- Record vital signs (see section 5.5.3)
- PASI (see section 5.5.1.1)
- PGA (see section 5.5.1.2)
- BSA (see section 5.5.1.3)

- Collection of samples for determination of laboratory parameters (serology, hematological status, clinical chemistry, see section 5.5.2).

Note: Adverse events before start of treatment (i.e. occurring after signature on consent form).

Patients who have abnormal test results during the screening period may be re-screened if the Medical Monitor agrees.

Experimental phase

Trial Day 1 (baseline, week 1, visit 2)

- Re-check of in-/exclusion criteria (see section 5.3.2)
- Randomization
- Physical examination (see section 5.5.5)
- Record vital signs (see section 5.5.3)
- Urine pregnancy test and urinalysis (see section 5.5.2)
- Record concomitant medications
- Record adverse events occurring from the time of informed consent signature
- *Localization of photographic documentation test field only for a subgroup (see section 5.5.1.4)*
- *Photographic documentation only for a subgroup (see section 5.5.1.4)*
- Collection of samples for determination of laboratory parameters (hematological status, clinical chemistry, see section 5.5.2)
- PASI (see section 5.5.1.1)
- PGA (see section 5.5.1.2)
- BSA (see section 5.5.1.3)
- Dispensing diary
- *Start of PK samples only for a subgroup (see section 5.5.1.5)*
- Dispensing IMP
- *Administration of IMP at site (PK subgroup only)*

Trial Day 28 (week 4, visit 3) and Day 56 (week 8, visit 4)

- Check concomitant therapy and adverse events
- Record vital signs
- Drug return / accountability and re-dispensation of unused kits/blister
- Diary collected and checked
- *Photographic documentation only for a subgroup (see section 5.5.1.4)*
- Urinalysis (see section 5.5.2)
- Collection of samples for determination of laboratory parameters (hematological status, clinical chemistry, urinalysis, see section 5.5.2)
- PASI (see section 5.5.1.1)

- PGA (see section 5.5.1.2)
- BSA (see section 5.5.1.3)
- Dispensing of IMP and diary

Trial Day 84 (week 12, visit 5) (EoT)

- Check concomitant therapy and adverse events
- Physical examination (see section 5.5.5)
- Record vital signs (see section 5.5.3)
- Urine pregnancy test and urinalysis (see section 5.5.2)
- *Photographic documentation only for a subgroup (see section 5.5.1.4)*
- Collection of samples for determination of laboratory parameters (hematological status, clinical chemistry, see section 5.5.2)
- *PK samples only for a subgroup (see section 5.5.1.5)*
- Last IMP administration at site for all patients
- Drug return / accountability
- Diary collected and checked
- PASI (see section 5.5.1.1)
- PGA (see section 5.5.1.2)
- BSA (see section 5.5.1.3)

Trial Day 112 (week 16, visit 6, Follow-up) (End of Study, EoS)

- *Photographic documentation only for a subgroup (see section 5.5.1.4)*
- Check concomitant therapy and adverse events
- Physical examination (see section 5.5.5)
- Record vital signs (see section 5.5.3)
- Urinalysis(see section 5.5.2)
- Collection of samples for determination of laboratory parameters (hematological status, clinical chemistry, see section 5.5.2)
- PASI (see section 5.5.1.1)
- PGA (see section 5.5.1.2)
- BSA (see section 5.5.1.3)

The patients must be present at site for approximately 60 minutes on Screening and Day 1, 45 minutes on Day 28 and 56, 60 minutes on Day 84 and 45 minutes on Day 112.

The above mentioned time will be extended for 15 minutes for patients with photographic documentation on each visit.

The above mentioned time will be extended on Day 1 and Day 84 for 120 minutes for patients with PK sampling.

Early Termination Visit

Patients who discontinue early from the trial should, if possible, have an Early Termination Visit. This visit should take place as soon as possible after the patient stops taking IMP. The observations and procedures scheduled for Visit 5 (End of Treatment) should be performed at the Early Termination Visit.

A schedule of trial procedures is provided in appendix A to this trial protocol.

Unscheduled visit

The patient may return to the clinic at the discretion of the investigator.

At this visit, the investigator or designee will:

• Query the patient about any changes in health status or concomitant medications and therapies since the previous visit, and document the findings respectively (AE/concomitant medications)

• Perform assessments which are relevant to the reason for the unscheduled visit (e.g. Photographic documentation, Lab analysis, PASI, PGA, BSA, etc.)

• Confirm the next visit

5.5.1.1 Psoriasis Area Severity Index (PASI)

The PASI is the most commonly used and validated assessment for grading the severity of psoriasis in clinical studies [2]. The PASI is a physician's assessment of psoriasis that is a therapeutic standard in clinical studies for this disease (appendix B). The PASI quantifies the severity and extent of the disease and weighs these with the body surface area involvement. It involves the assessment of erythema, infiltration, desquamation, and body surface area involvement over 4 body regions: head, trunk, upper and lower extremities.

The Investigator assesses the redness, thickness, and scaliness of lesions on a 5-point scale (from 0 = none, through 4 = severe). The percentage of skin involved is scored and transferred to a grade (graded 0 to 6; 0 = 0% involved area, 6 = 90%-100% involved area). In addition, the percentage of involved body surface area is estimated across 4 body areas, head (10%), upper extremities (20%), trunk (30%), and lower extremities (40%). The sum of all 3 severity parameters is then calculated for each of the 4 sections of skin, multiplied by the area score for that area, and multiplied by the weight of the respective section to give a PASI score, which ranges from 0 to 72, with a higher score indicating increased disease severity. The PASI will be completed by the

Investigator or designee at the time points prior to and following IMP administration as defined in the trial schedule. See appendix B for details of calculation.

If possible, the same investigator should complete the evaluations for a given patient throughout the trial. Initials of the assessor will be documented in the eCRF.

5.5.1.2 Physician`s Global Assessment (PGA)

The PGA provides an overall evaluation of the severity of the disease [6]. The PGA is a 7-point physician's assessment of psoriasis that is a therapeutic standard in clinical studies for this disease.

The Investigator or designee will complete a PGA form to evaluate the disease severity at a single time point. Scoring is on a 7-point scale: 0 = clear; 1 = almost clear; 2 = mild; 3 = mild to moderate; 4 = moderate; 5 = moderate to severe, and 6 = severe. The PGA will be completed by the Investigator (or designee) at the time points specified.

If possible, the same investigator should complete the evaluations for a given patient throughout the trial. Initials of the assessor will be documented in the eCRF.

5.5.1.3 Assessment of body surface area (BSA)

The total surface area of the body affected with psoriasis plaques will be determined by the Investigator at V2 (Wk0-D1), V3 (Wk4-D28), V4 (Wk8-D56), V5 (Wk12-D84), and V6 (Wk16-D112). Calculation should include psoriasis on the palms of the hands and soles of the feet as well as on the face and scalp. The investigator will calculate the approximate BSA by assuming that 1% BSA is approximately equal to the surface area of one outstretched hand (with fingers) of the patient [2].

The assessment of BSA by the Investigator serves to describe the change in % BSA affected by psoriasis after 12 weeks of treatment.

If possible, the same investigator should complete the evaluations for a given patient throughout the trial.

5.5.1.4 Photographic documentation

At all visits photographic documentation of one affected area (from trunk, arms or legs) will be performed in a patient subgroup at two selected trial sites (one site in Germany and one in Poland; approximately 30 patients in total). The target plaque for the photographic documentation will be defined before first treatment on Day 1 and should mirror the actual individual psoriasis grade of

the patient. The procedure will be described in a separate photographic method manual. Steps will be taken to ensure that the identity of the patient is protected to the extent possible. Additional consent will be undertaken with regard to collection, transmission, storage and use of images.

No efficacy or safety assessment will be made using these images. The images will be taken for educational and marketing purposes only and might be used in scientific publications.

5.5.1.5 PK samples

To evaluate systemic concentrations of MP1032 PK samples will be analyzed in a subgroup at two selected trial sites (one in Germany and one in Poland; approximately 30 patients in total). 4.9 mL blood must be collected before morning dose and 15, 30, 60 and 120 minutes after morning dose at visit 2 (baseline, week 1) and at visit 5 (EoT, week 12). In total 49.0 mL blood will be collected per patient.

The date and time of the last application of IMP prior to the PK sample be taken and the date and time of the PK sample must be documented in the eCRF.

Collection, handling and shipment instructions for PK samples will be provided in a separate laboratory manual.

Samples will be analyzed at:

CCI, PPD

5.5.1.6 Diary

The diaries will include instructions on the use of the IMP. Patients will be instructed to complete the diary after intake of each IMP dose. Date/time of intake of IMP will be recorded twice daily.

At each visit at the site, the number of dose recorded on the diary will be reviewed and transcribed to the eCRF. Diary cards will be retained by trial sites as part of the source documentation and new diary cards will be dispensed.

At subsequent visits, trial personnel will review, collect and dispense a new diary and determine whether the patient requires counseling for dosage compliance. In addition, each patient will be reminded to return completed diary at the next visit.

5.5.2 Measurement of safety parameters

Relevant medical history of the past five years and adverse events will be recorded.
The following laboratory parameters will be collected at every visit (except serology):

Table 4: Laboratory Parameter per visit:

Parameter	Screening	Day 1	Day 28 / 56	Day 84 (EoT)	Day 112 (FU)
Serology					
Hepatitis A IgG-antibody-test	X	--	--	--	--
Hepatitis A IgM-antibody-test	X	--	--	--	--
Hepatitis B core antibody-test	X	--	--	--	--
Hepatitis B surface antibody-test	X	--	--	--	--
Hepatitis B surface antigen-test	X	--	--	--	--
Hepatitis C virus antibody-test	X	--	--	--	--
HIV-1 antibody-test	X	--	--	--	--
HIV-2 antibody-test	X	--	--	--	--
Hematology					
RBC	X	X	X	X	X
WBC* including differential	X	X	X	X	X
Hemoglobin	X	X	X	X	X
Hematocrit	X	X	X	X	X
MCH	X	X	X	X	X
MCV	X	X	X	X	X
MCHC	X	X	X	X	X
Platelets	X	X	X	X	X
Clinical Chemistry					
AST (GOT)	X	X	X	X	X

Parameter	Screening	Day 1	Day 28 / 56	Day 84 (EoT)	Day 112 (FU)
ALT (GPT)	X	X	X	X	X
γGT	X	X	X	X	X
AP	X	X	X	X	X
Creatinine	X	X	X	X	X
Total bilirubin	X	X	X	X	X
CRP	X	X	X	X	X
hCG serum	X	--	--	--	--
Urine					
Urine dip stick test**	X	X	X	X	X

* including lymphocyte, neutrophils count, and eosinophils

** leukocytes, nitrite, pH, protein, glucose, ketones, urobilinogen, bilirubin, blood/hemoglobin

Hematological status, serology and clinical chemical parameters will be determined by LKF, Lise-Meitner-Str. 25 – 29, 24223 Schwentinental, Germany. Urinalyses will be performed at the sites using a dipstick test (Medi-Test®, Combi 10L, Macherey-Nagel, Dueren, Germany). Approximately 19.2 ml of blood will be withdrawn at each visit with laboratory analysis (in total approximately 116 mL per patient). For the PK subgroup additional 24.5 mL will be withdrawn on day 1 and day 84 (in total 49 mL per patient).

Spontaneously noted complaints will be recorded with duration, intensity and probability of a correlation with the IMP (see section 7.3., evaluation of adverse events).

5.5.3 Vital signs

Blood pressure and pulse rate will be measured at all visits after at least 5 minutes in a seated position. The following ranges for vital signs are given in table 5.

Table 5: Vital signs ranges

Variable	Units	Acceptable limit
Systolic blood pressure	mm Hg	80 - 150
Diastolic blood pressure	mm Hg	60 - 95
Heart rate	beats/min	50 – 100

Values outside 160 mm Hg / 95 mm Hg will not be randomized.

5.5.4 Smoking and alcohol consumption

Information on smoking and alcohol consumption will be documented at screening.

5.5.5 Physical examination

The physical examination comprises a routine medical examination including gross neurological assessments. The following body systems will be examined: basic status of the main organ systems (ENT, heart, lungs, abdomen, neurological status) as well as physical examination of the skin.

5.5.6 Appropriateness of assessments

PASI, PGA, BSA are widely used, non-invasive methods for examining overall psoriasis severity and coverage.

These methods are described in the EMA guideline [2] for evaluation of product efficacy.

Assessments should be conducted by investigators who are experienced and have been trained on the use of these evaluation tools. If possible, the same investigator should complete the evaluations for a given patient throughout the trial.

5.5.7 Primary efficacy/tolerability variable(s)

Primary variable:

The primary efficacy variables are:

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 are:

1. 50% improvement (response) in their PASI score (PASI 50)
2. Mean PASI score and change to baseline
3. Time to achieve PASI 50 and PASI 75
4. Mean score and change from baseline in the PGA
5. Mean score and change from baseline in the BSA
6. PK data

The primary variables are choose in accordance to the EMA guideline http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003329.pdf (4)

6. Data analysis and statistics

The statistical evaluation will be performed at bioskin using the software program SAS® (Statistical Analysis System, SAS, Cary, NC), Version 9.3 or higher.

A formal statistical analysis plan (SAP), providing a complete description of the methodology of the planned statistical analyses, will be written, finalized, and signed prior to breaking the trial blind. Any changes in the statistical methods described in this protocol that occur prior to database lock will be documented in the SAP and will not require a protocol amendment.

6.1 Generation of data base

In general, data from the source documents will be captured in an eCRF by a software package that can be customized for remote data entry procedure and that maintains an electronic audit trail. The eCRFs will be developed in the EDC system in accordance with bioskin SOPs under supervision and in agreement with the sponsor. The database structure will be validated.

Only authorized site personnel will be able to enter/modify/correct data to the eCRF. The investigator/coordinator or designee must enter the information required by the protocol as soon as possible after the visit into the eCRF.

The data will be checked for consistency. Queries for discrepant data may be generated automatically by the system upon entry or generated manually by the monitor or the trial data manager. All queries, whether generated by the system or by a user, will be in an electronic format. Once all the queries are closed and data have been verified by the CRA, the eCRF will be signed (eSignature) by the investigator and the database will be locked.

All data management procedures will be detailed in a separate, specifically identified file that collectively will be referenced as the (DMP).

Adverse events and medical history will be coded with Medical Dictionary for Regulatory Activities (MedDRA) mapping system, previous and concomitant therapy will be coded according to WHO-DD.

Patient data in PDF files generated from the eCRF will be provided to the site at the end of the trial.

6.2 Analysis sets and type of analysis

The safety-evaluation-set (SES) will include all patients who received any trial medication at least once; all safety analyses will be based on the SES.

The full-analysis-set (FAS) will include all randomized patient who received at least one dose of IMP, and had at least one post-baseline assessment. The intention-to-treat (ITT) analysis will be based on the FAS.

The valid-cases-set (VCS) will include all patient from the FAS, without any protocol violation interfering with the trial aims and with sufficient exposure to IMP. The per-protocol (PP) analysis will be based on the VCS.

6.3 Hypotheses

Since this is an exploratory trial no formal hypotheses are postulated. The data will be evaluated descriptively.

6.4 Rationale for the sample size

It is planned to recruit approximately 150 patients for this clinical trial in Germany and Poland (each country approximately 75 patients) to achieve 120 evaluable patients.

No formal sample size calculations were performed for this explorative trial. A sample size of 40 in each group is adequate to detect a difference in rates of at least 0,274, with 80% power, using a two group χ^2 test with a 0,100 two-sided significance level.

6.5 Statistical methods

Statistical analyses will be performed using two-sided tests, without adjustment for multiplicity. All p-values will be interpreted descriptively.

Data will be summarized by treatment group (and by visit when applicable), with respect to demographic and baseline characteristics, efficacy variables, and safety variables.

Summary statistics will include the mean, number of non-missing cases (n), standard deviation, median, minimum, and maximum values for continuous variables, and frequencies and percentages for categorical variables.

Categorical efficacy variables will be analyzed using the Cochran-Mantel-Haenszel (CMH) test with stratification by (pooled) analysis center and the Fisher's exact test in case of analyses without stratification (mainly for safety assessment).

Selected scores will be analyzed using an analysis of covariance (ANCOVA) model, with treatment group and (pooled) analysis center as factors and baseline outcome as covariate.

Time to event data will be analyzed using the Kaplan-Meier method, and treatment group differences will be tested by the log-rank test.

Unless otherwise specified, baseline is defined as the latest non-missing observation prior to first treatment with IMP.

Details of the model and the analyses will be specified in the SAP.

6.5.1. Efficacy analyses

Primary efficacy endpoints

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

Secondary efficacy endpoints

Secondary efficacy endpoints will be evaluated descriptively. The methodology outlined in section 6.5 will be applied for pairwise treatment comparisons vs. placebo.

Responder rates will be evaluated as the primary efficacy endpoint.

The change in the PASI score from baseline to each post baseline visit, respectively, will be evaluated using an analysis of covariance (ANCOVA) model, with treatment group and (pooled) analysis center as factors and baseline outcome as covariate.

The time to achievement of PASI 50 and PASI 75, respectively, will be evaluated using the Kaplan-Meier method. Pairwise treatment group differences will be tested by the log-rank test.

Descriptive summaries will be provided for each parameter by treatment group and by visit, if applicable. Percentages will be provided based on the number of non-missing cases, if not otherwise stated.

6.5.2. Safety analyses

All AEs reported during the trial will be listed, documenting course, severity, investigator assessment of the relationship to the IMPs, and outcome. AEs will be coded using the MedDRA mapping system for preferred terms (PTs) and system organ class (SOC).

Treatment-emergent adverse events (TEAEs), i.e. AEs with an onset or worsening on or after the time of the first IMP application will be summarized by the number of patients reporting TEAEs, primary system organ class (SOC), preferred term (PT), severity, and relationship to IMP.

Listings of serious adverse events (SAE) and patients who prematurely discontinued treatment due to AEs will be given.

Safety laboratory parameters (hematology, clinical chemistry) and vital signs will be summarized descriptively, including changes from baseline. Urinalysis outcomes will be summarized by frequency counts.

6.5.3. Other analyses

Blood MP1032 concentration-time data will be listed 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 will be provided.

Statistical analyses will be performed using non-compartmental analysis (NCA) methods, as appropriate, providing C_{max}, t_{max} and $AUC_{(0,t)}$. Listings and summary statistics of NCA parameters will be provided.

6.6 Handling of dropouts and missing data

For the evaluation of success rates of the primary efficacy variables PASI and PGA missing PGA assessments and/or any parts of the PASI assessments will be evaluated as failure to achieve improvement. For descriptive analyses of PASI, PGA and BSA the last observation carried forward (LOCF) principle will be applied to impute the missing assessments, up to the Day 84 visit. Follow-up assessments will not be imputed.

Sensitivity of the primary efficacy analyses will be evaluated applying PP analyses.

Handling of missing AE data, will be detailed in the SAP.

6.7 Identification of source data

For the following source data should be available:

- patients identification incl. age, height and weight
- relevant previous and concomitant therapies
- up-to-date relevant medical history (last 5 years)
- findings at physical examination
- pregnancy test results

- date of entry into the trial/visit dates
- vital signs
- adverse events
- laboratory results
- photographic documentation (at the selected sites)
- assessment scores PASI, PGA and BSA
- PK sampling (at the selected sites)
- Randomization number
- date and time of assessments
- IMP return / accountability and administration
- Missing treatment (diary)

7. Adverse events

7.1 Evaluation of adverse events

An adverse event (AE) is any untoward medical occurrence in a patient or clinical trial subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

The period of observation for adverse events extends from the time the patient gives informed consent until the trial is completed. Adverse events that are still present after the last patient's scheduled visit will be followed up 28 days of receiving the last IMP dose by means of a visit. After that time point the need for additional follow-up of ongoing AEs/SAEs will be discussed between the investigator and the sponsor, although in the event of discrepancies the investigator's criteria will prevail. Adverse events occurring after the end of the clinical trial must be reported if the investigator considers there is a causal relationship with the investigational product.

The investigator will be responsible for the necessary acute medical treatment of any adverse event required during the trial and will ensure that appropriate medical care will be maintained thereafter, if necessary.

All patients experiencing adverse events - whether considered related with the use of the IMP or not - will be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report will be supplied, if possible. "Related" means a reasonable

possibility that the event may have been caused by the IMP. All findings will be reported on an "adverse event"/“serious adverse event“ page in the case report form.

All adverse events, including intercurrent illnesses, will be reported and documented as described below.

Adverse events are divided into the categories "serious" and "nonserious". This determines the procedure which will be used to report/document the adverse event (see below).

Surgical procedures themselves are not adverse events; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required is an adverse event, if it occurs or is detected during the trial period. Planned surgical measures permitted by the clinical trial protocol and the condition(s) leading to these measures are not adverse events, if the condition(s) was (were) known before the start of treatment with investigational product. In the latter case the condition should be reported as medical history.

7.2 Definition of serious and nonserious adverse events

A serious adverse event is any untoward medical occurrence that at any dose:

- results in death or is life-threatening;
- results in permanent or significant disability/incapacity;
- requires inpatient hospitalization* or prolongation of hospitalization;
- results in a congenital abnormality/birth defect.

Medical and scientific judgment will be exercised in classification of other important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Adverse events which do not fall into these categories are defined as nonserious.

*Hospitalization solely for the purpose of diagnostic tests, even if related to an adverse event, elective hospitalization for an intervention which was already planned before the inclusion of the patient in the clinical trial, and admission to a day-care facility may not themselves constitute sufficient grounds to be considered as a serious adverse event.

7.3 Reporting/documentation of adverse events

7.3.1 Reporting of adverse events

Adverse events either reported by the patient, or observed by the investigator **must be recorded on the adverse event page of the eCRF** and should be described in the following manner:

The **nature** of the event will be described in precise, standard medical terminology (i.e. not necessarily the exact words used by the patient). If known, a specific diagnosis should be stated (e.g., allergic contact dermatitis).

The **intensity** of the adverse event will be described in terms of mild, moderate or severe according to the investigator's clinical judgment.

- **Mild**: The adverse event does not interfere in a significant manner with the patient's normal functioning level, but may be an annoyance.
- **Moderate**: The adverse event produces some impairment of functioning but is not hazardous to health, but is uncomfortable and/or an embarrassment.
- **Severe:** The adverse event produces significant impairment of functioning or incapacitation and is a hazard to the patient.

The **duration** of the event will be described by the start date and end date.

The **causal relationship** of the event to use of the IMP will be described in terms of:

Certain: the adverse event

- occurs in a plausible time relationship to IMP administration, and cannot be explained by concurrent disease or other drugs or chemicals, and
- follows a clinically plausible response to withdrawal of the IMP, and
- is definitive based on recognized pharmacological or other parameter associated with the IMP, and
- is confirmed by rechallenge procedure, if performed.

Probable: the adverse event

- follows a reasonable temporal sequence from administration of the IMP, and
- is unlikely to be attributed to a disease or other drug/s, and
- disappears or decreases on withdrawal of the IMP

Possible: the adverse event

- follows a reasonable temporal sequence from administration of the IMP, but
- can also be explained by disease or other drugs, and
- information on drug withdrawal may be lacking or unclear.

Unlikely: the adverse event

- does not follow a reasonable temporal sequence from administration of the IMP, and
- can be reasonably explained by disease or other drug/s, and
- does not follow a known pattern of response to the IMP, and
- does not reappear or worsen upon re-challenge, if performed.

Not related: the adverse event

- The event is either a pre-dose event or is definitely due to causes separate from the administration of the IMP, i.e.
  - documented pre-existing condition
  - technical and manual procedural problems
  - concomitant medication
  - patient's clinical state

The **outcome** of the event will be described in terms of:

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

It will also be recorded if the IMP use is continued, interrupted or discontinued.

Note: Insofar as possible all serious adverse events should be followed-up to determine the final outcome of the event. Details of follow-up should be given (e.g. discontinuation of IMP, if specific treatment is required, if hospitalization is required, FU by PharmaLex, FU by Investigator etc.).

For the purpose of expedited reporting for the causality assessment (i.e. relationship of the adverse event to IMP) the terms “probable” and “possible” describe a relationship to IMP treatment, whereas the terms “unlikely” and “not related” classify the event as being not related to IMP treatment.

7.3.2 Reporting of serious adverse events

The investigator shall report all serious adverse events immediately (within 24 hours after he becomes aware of the event) by fax or e-mail to PharmaLex. General information on the patient (pseudonymed), the randomization number, and screening identification number event term (diagnosis) and measures already taken are to be reported. The immediate report shall be followed by detailed, written reports. The investigator is obliged to completely document the course of the event and the measures taken, if possible including the original findings and using the form for serious adverse events. Additional documentation is carried out on the case report forms.

SAE reports should be emailed/faxed to the Pharmacovigilance unit of the PV vendor:

CCI, PPD
[redacted]

For reported deaths of a patient, the investigator shall supply the sponsor and the ethics committee with any additional information requested.

The sponsor/PharmaLex shall ensure that all relevant information about suspected unexpected serious adverse reactions (SUSAR) that are fatal or life-threatening is recorded and reported as soon as possible to the competent authorities in all the member states concerned, and to the ethics committee, and in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

All other SUSARs shall be reported to the competent authorities concerned and to the ethics committee concerned as soon as possible but within a maximum of fifteen days of first knowledge by the sponsor accordingly.

PharmaLex shall also inform all investigators.

7.4 Pregnancies

Pregnancies occurring during a patient's participation in a clinical trial, although not typically considered an SAE, must be notified to the sponsor within the same timelines as an SAE (within 24 hours after being made aware of the pregnancy) on a pregnancy notification form. The pregnant trial patient should be withdrawn immediately from the trial.

Pregnancy reports should be emailed/faxed to the Pharmacovigilance unit of the PV vendor:

CCI, PPD
[redacted]

Any pregnancy occurring in the trial should be followed up until outcome. If relevant, the development of the newborn has to be monitored for an appropriate time post-delivery.

8. Case report form (CRF), documentation and archiving

- The CRFs will be drawn up by bioskin in agreement with the sponsor.
- All trial documents, in particular the eCRFs, must be continually filled out. The eCRF is validated system which automatically creates an audit trail for all changes.
- The documentation will be kept in such a way, that it is possible to easily reconstruct the course of the trial at a later date (in accordance with the details given in the clinical trial protocol). All documents will be filed in the TMF or the investigator file, respectively.
- Following the specific patient information, consent forms will be signed by the patient and the physician responsible for supplying information twice. One will be filed in the investigator file. And one will be given to the patient.
- Electronic data media are to be clearly marked with the trial number/data type/date/hard- and software information (readability).
- All trial documents drawn up or available in paper form (e.g. raw data on data forms, CRFs, informal papers, printouts, etc.) are to be uniformly labeled with the trial number/screening number/data type/measurement time point and/or time/date/initials of the staff member.
- Clinical research associate (CRA) will verify all data entered into eCRFs for completeness and accuracy with reference to the source documents and records and will issue manual

data queries to correct missing data or discrepancies found against the source within the EDC system.

- Data validation will consist of automated and manual edit checks that are created directly in EDC. Automated edit checks will be executed on all data points defined and documented by the trial team and data management.
- Any changes from the clinical trial protocol in trial planning or execution after submission of the final version of the clinical trial protocol that have ethical or medical implications are to be documented as a „Substantial amendment to clinical trial protocol," including cause, content, grounds, consequences, date and the signature of the sponsor and investigator. Such an amendment must be submitted to the appropriate ethics committee(s)/competent authority(ies) for approval. All staff involved in the trial will be informed by the clinical trial manager and investigator. Changes in the clinical trial protocol are only allowed after prior consultation with the person in charge of the trial at the sponsor (clinical trial manager). Changes without ethical or medical implications are to be documented as non-substantial amendments or file notes including date and signature of the sponsor and the responsible person at bioskin.
- After all data have been verified by the CRA, an investigator or sub-investigator is required to review and approve all eCRFs prior to database lock and breaking of the blind.
- After database lock, each site will be provided with the eCRF data from their site for local archival purposes.
- After the conclusion of the trial, the original trial documents (TMF, CRFs) are to be submitted to the sponsor according to the agreements made.
- Currently the statutory period for archiving the documents after conclusion of the trial is at least 15 years.

8.1 Primary source documents

The investigator must maintain primary source documents supporting significant data for each patient's medical notes.

All applicable trial data collected on each patient will be recorded by trained site personnel into the source data record and the eCRF. Only authorized site personnel will be able to enter/modify/correct data to the eCRF.

Source documents such as the medical records are to be maintained separately from the eCRF to allow data verification. Because of the potential for errors, inaccuracies, and illegibility in transcribing data onto eCRFs, originals of laboratory and other test results must be kept on file

with the patient's source documentation. The investigator must also retain all patient-specific printouts/reports of tests and procedures performed as a requirement of the trial. During monitoring visits the monitor will validate eCRF entries against these sources of data.

eCRFs, source documents, and copies of test results must be available at all times for inspection by the trial monitor, auditors, or regulatory inspectors. The following should also be available for review

- Patient screening log, which should reflect the reason any patient screened for the trial was found to be ineligible;
- Site personnel and delegation log, which will list all site personnel with their responsibilities as delegated by the investigator and their signatures. This log will be maintained at the site throughout the trial;
- Monitoring visit log, which will list the date and purpose of all monitoring visits by the sponsor or designee;
- Enrollment log, which will list patient initials and start and end dates for all enrolled patients;
- Drug inventory/Packing slip, which will list the total amount of drug shipped to the site and received and signed for by the investigator;
- IMP dispensing log, which will list the total amount of IMP dispensed to and returned by each patient;
- ICF which must be available for each patient and be verified for proper documentation. Following the specific patient information, consent forms will be signed by the patient and the physician responsible for supplying information twice. One will be filed in the investigator file. And one will be given to the patient;
- All correspondence.

9. Statutory regulations and GCP

This clinical trial will be conducted in compliance with the protocol. Planning and execution of this clinical trial are subject to globally accepted standards of good clinical practice (as defined in the ICH E6 (R2) guideline for good clinical practice, November 2016), in agreement with the Declaration of Helsinki and in keeping with local regulations.

9.1 Ethics committee/competent authorities

Before the start of the trial, the clinical trial protocol, informed consent document, and other appropriate documents will be submitted to the appropriate ethics committees (ECs) and competent authorities (CAs). The trial must not start before approval has been granted by the appropriate EC and no grounds for non-acceptance have been issued by the CA concerned.

9.2 Insurance

Insurance policy will be provided for each country participating in the study in accordance with local regulations.

In Germany every patient participating in the clinical trial will be insured in accordance with § 40 paragraph 3 of the German drug law against injuries to health which may occur during the trial.

Excluded from this however are injuries to health and deteriorations of illnesses already in existence which would have occurred or continued to exist even if the patient had not taken part in the clinical trial.

The insurance cover is jeopardized if the patient fails to report immediately to the investigator or responsible physician any injury to health which might have resulted from participation in the clinical trial, or if he/she undergoes any other medical treatment without their consent before the clinical trial has been completely finished - insofar as the individual patient is concerned.

Any injury to health which might have occurred as a result of participation in the clinical trial must be reported by the patient to the insurer without delay. The investigator is obliged to make such a report in any case.

The patient insurance will be arranged by bioskin GmbH on the basis of the final version of the patient information and informed consent form. The patient insurer is CCI [redacted].
The insurance policy number is CCI [redacted].

9.3 Patient instruction and consent forms

Every patient will receive a complete and comprehensive explanation of the significance, nature, extent and possible risks of the trial. To this end a detailed, written patient information sheet will be made available. In addition a physician will carry out an oral information session during which the patients will be given sufficient time and opportunity to clarify remaining questions. Two identical forms for written informed consent will be given to the patients for signature. One copy of the signed forms will be archived in the investigator file and the other retained by the patient.

The investigator will acknowledge instruction of every patient in accordance with the clinical trial protocol and the existence of a signed consent form.

9.4 Data protection

During the clinical trial medical and personal information (like age, gender, racial, and ethnic origin) will be collected at the site and documented in the personal file or electronically saved. In addition, important data for the clinical trial (including photos and PK data of the subgroups) will be saved pseudonymized, transferred, and evaluated.

If necessary, the collected and saved data (including the photos and PK data) during the clinical trial will be held for inspection by the supervisory authority or by people charged by the sponsor who check that the trial is done properly. If needed, the related data will be shared pseudonymized to:

- The sponsor or sponsor-appointed party for the purpose of scientific analysis;
- The applicant and the authority responsible for marketing authorization, in case that application for marketing authorization is requested;
- Sponsor and the responsible competent authority, which will also forward the data to the European database, in case of adverse events of the trial drug;
- Parties in Europe and in non-European foreign countries which are affiliates of the Sponsor and as well forwarded to the responsible authorities in charge of marketing authorization by the latter.

Personal and medical data collected during the trial may be moved, stored and used in the EU or another country where the sponsor or those working with the sponsor located. Data – including trial results – might be published in Scientific Journals, Conference abstract, etc. The trial and trial data will be published in clinicaltrials.gov.

9.5 Termination of participation

Every patient has the right to refuse further participation in the trial at any point in time and without giving reasons. Nonetheless, efforts should be made to find out the cause and to document it on the case report form. If the administration of the investigational product has already taken place at the time of refusal, the patient should be convinced to consent to a complete final examination as planned in the protocol in his/her own interest. This has to be documented on the corresponding pages of the eCRF.

9.6 Quality control (Trial monitoring)

According to bioskin quality management procedures internal quality control will be applied to all steps of the trial e.g. planning, conduct, analysis and reporting.

A representative of sponsor or bioskin will monitor the trial progress as regularly as necessary during the conduct of the trial until the last case report forms have been completed and all queries have been resolved.

The trial and site activities will be monitored according to the ICH-GCP guidelines for:

- Protocol adherence (trial is conducted in accordance with the currently approved protocol and any other trial agreements)
- Quality of data (data are authentic, accurate, and complete)
- Drug accountability
- Protection of safety and rights of patients
- Compliance with regulatory requirements (trial is conducted in accordance with GCP, and all applicable regulatory requirements)
- Adequacy of the facilities (unchanged high qualification of the site and site staff)

The investigators and the head of the medical institutions (where applicable) agree to allow the monitor direct access to all relevant documents.

9.7 Quality assurance

To ensure compliance with GCP and all applicable regulatory requirements Sponsor may conduct a quality assurance assessment and/or audit of the site records at any time during or after completion of the trial.

Auditing will be performed by or on behalf of Quality Assurance MetrioPharm in accordance with the requirements of Note for Guidance on Good Clinical Practice, the clinical trial protocol, applicable standard operating procedures and according to the agreed audit plan.

All audit activities in the course of MP1032-CT04 will be documented and archived.

Independent of any sponsor audit the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the trial.

In the event of an assessment, audit or inspection, the investigators (and institutions) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the trial, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

9.8 Handling of investigational medicinal products

The investigator or his representative confirms receipt of the IMPs in writing and will only use them within the framework of this clinical trial and in accordance with the existing clinical trial protocol. All containers opened, together with remaining contents and unopened containers will be returned to the manufacturer at the end of the trial.

Delivery, consumption and return must be completely documented.

A written explanation must be compiled on any containers/investigational products which are missing. The investigational products will be stored in a safe place according to the manufacturer's instructions for storage.

The investigator is responsible for ensuring appropriate storage and control of the IMPs. Storage records, including temperature records should be maintained and be available for inspection during the course of the trial.

Deviations in storage requirements should be reported to the CRA, the bioskin CTM and to the sponsor and may require that the IMP is quarantined during the review of the deviation.

10. Trial administrative structure/responsibilities

Any change of the following responsible persons will not be considered as an amendment.

Table 6: Trial administrative structure/responsibilities

Function	Name / contact data
International coordinating investigator	CCI, PPD [redacted]
Sponsor project manager(s)	
Sponsor's responsible physician	
Randomization	
Data management	
Statistics (including PK)	
Responsible for pharmacovigilance/ Drug safety physician (sponsor representative)	
Medical monitor	
Clinical trial manager at bioskin	
Central Lab	
PK Lab	
Affiliated regional CRO	
Clinical supplies – packaging, distribution	
Lead CRA	

11. Literature

[1] Nast A. Boehncke WH. Mrowietz U et al. S3-Leitlinie zur Therapie der Psoriasis vulgaris Update 2011. JDDG; 2011; 9 (Suppl. 2):S1-S104.

[2] EMA Guideline on Psoriasis. Guideline on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis. Issued by the European Medicines Agency, London,18 November 2004. Accessed 27 Jan 2016.

[3] MetrioPharmAG. Investigator's Brochure MP1032. Edition No. 5. 18. Sep 2017.

[4] World Health Association Declaration of Helsinki. Ethical Principles for Medical Research involving Human Patients. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996.

[5] Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95). The European Agency for the Evaluation of Medicinal Products (EMEA) 2002;1-59.

[6] Grekin SJ, Ellis CN. Evaluating the severity of dermatologic disorders. Dermatol Ther 2009;22(3);191-198.

Appendix A
Trial flow chart

Trial flow chart

Trial Period	Screening	Treatment phase				Follow-up	Unscheduled visit
Day	(Day - 28 to -3)	Day 1	Day 28 (±2 days)	Day 56 (±2 days)	Day 84 (+5 days)	Day 112 (±2 days)	
Visit Number	1	2	3	4	5	6	unscheduled
Procedure							
Informed consent	X						
In-/exclusion criteria	X	X					
Demographics/medical history	X						
Physical examination	X	X			X	X	
Height, body weight, BMI	X						
Smoking history/ alcohol consumption	X						
Vital signs	X	X	X	X	X	X	
Pregnancy test in female patients [a]	X	X[b]			X		
Safety laboratory, incl. urine dipstick	X	X	X	X	X	X	X
HIV, Hepatitis	X						
Randomization		X					
Localization of photographic documentation test field[c]		X					
Photographic documentation [c]		X	X	X	X	X	
PK sample [d]		X			X		
PASI	X	X	X	X	X	X	
PGA	X	X	X	X	X	X	
BSA	X	X	X	X	X	X	
Dispensing of IMP		X	X	X			
IMP administration [e]		X	X	X	X		
Diary dispensing		X	X	X			
Drug return / accountability			X	X	X		
Diary return and check			X	X	X		
Prior and concomitant therapy	X	X	X	X	X	X	X
Adverse events [f]	X	X	X	X	X	X	X

a) A serum pregnancy test will be done for all women at screening and urine test for all other visits.
b) A urine pregnancy test on Day 1 will be performed prior to the first administration of IMP for all

women.

c) Only performed in a subgroup of approx. 2 sites (approx. 30 patients); on Day 1 Photographic documentation will be performed prior to the first administration of IMP

d) Only performed in a subgroup of approx. 2 sites (approx. 30 patients); on Day 1 and Day 84 first PK sample will be performed prior to the first administration of IMP. PK samples will be collected before IMP administration, and 15, 30, 60 and 120 minutes after administration of IMP.

e) IMP administration will start on Day 1 after randomization and will continue as self-administration by trial patients at home until Day 84. Patients included in the PK analysis will administrate the first treatment (Day 1) at the site. All patients will administrate the last treatment (Day 84) at the sites.

f) AE reporting starts after the signature of informed consent form and finishes at the End of Study Follow-Up Visit.

Appendix B
PASI

Appendix B Psoriasis Area Severity Index (PASI)

Shown below is the original description of the PASI (Fredriksson T, Pettersson U. Dermatologica 1978;157:238-44) which involves the assessment of erythema (E), infiltration (I), and desquamation (D), and body surface area involvement (A) over 4 body regions (head (h), trunk (t), upper (u) and lower (l) extremities).

Degree of severity (per body region)	Value given
No symptoms	0
Slight	1
Moderate	2
Marked	3
Very marked	4

Surface involved (per body region)	Value given
<10%	1
10-29%	2
30-49%	3
50-69%	4
70-89%	5
90-100%	6

Because the head, upper extremities, trunk, and lower extremities correspond to approximately 10, 20, 30, and 40% of body surface area, respectively, the PASI score is calculated by the formula:

PASI = $0.1(Eh + Ih + Dh)Ah + 0.2(Eu + Iu + Du)Au + 0.3(Et + It + Dt)At + 0.4(El + Il + Dl)Al$

Amendment 1

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.

Amendment 1 to clinical trial protocol version 1 from 22SEP2017

Confidential

bioskin GmbH
Burchardstrasse 17 • 20095 Hamburg, Germany

The protocol amendment 1 contains the following modifications to the original trial design:

Change and rationale:

Changes due to recruitment of subjects of PK samples

- In section 5.5.1.5 (PK samples) the number of PK sites has been changed from 2 (one in each country) to approximately 4 (two in each country).

Changes due to administrative reasons:

- On page 09 (signatures) the name o PPD [redacted] has been changed to PPD [redacted].
- In section 5.5.1.5 (PK samples) the address of the PK laboratory has been changed since the laborytory has been moved within the city.
- Both Medical Monitors are mentioned in table 6.

Changes to the protocol text due to conditions noted by the ethics committee

The following text changes will be implemented:

Page: 9

Responsible person for SAE notifications:

Old text:

CCI, PPD [redacted]

New text:

CCI, PPD [redacted]

Page: 38

5.5.1.5 PK samples

Old text:

To evaluate systemic concentrations of MP1032 PK samples will be analyzed in a subgroup at two selected trial sites (one in Germany and one in Poland; approximately 30 patients in total).

New text:

To evaluate systemic concentrations of MP1032 PK samples will be analyzed in a subgroup at selected trial sites (approximately two in Germany and two in Poland; approximately 30 patients in total).

Page: 38

Old text

Samples will be analyzed at:

CCI, PPD

New text

Samples will be analyzed at:

CCI, PPD

Page: 50

Old text:

SAE reports should be emailed/faxed to the Pharmacovigilance unit of the PV vendor:

CCI, PPD

New text:

SAE reports should be emailed/faxed to the Pharmacovigilance unit of the PV vendor:

CCI, PPD

Page: 51

Old text:

SAE reports should be emailed/faxed to the Pharmacovigilance unit of the PV vendor:

CCI, PPD
[redacted]

New text:

SAE reports should be emailed/faxed to the Pharmacovigilance unit of the PV vendor:

CCI, PPD
[redacted]

Page 58:

Old text:

Trial administrative structure/responsibilities

Any change of the following responsible persons will not be considered as an amendment.

Table 6: Trial administrative structure/responsibilities

Function	Name / contact data
International coordinating investigator	PPD, CCI [redacted]
Sponsor project manager(s)	
Sponsor's responsible physician	
Randomization	
Data management	
Statistics (including PK)	
Responsible for pharmacovigilance/ Drug safety physician (sponsor representative)	
Medical monitor	
Clinical trial manager at bioskin	
Central Lab	
PK Lab	
Affiliated regional CRO	
Clinical supplies – packaging, distribution	
Lead CRA	

New text:

Trial administrative structure/responsibilities

Any change of the following responsible persons will not be considered as an amendment.

Table 6: Trial administrative structure/responsibilities

Function	Name / contact data
International coordinating investigator	PPD, CCI [redacted]
Sponsor project manager(s)	
Sponsor's responsible physician	
Randomization	
Data management	
Statistics (including PK)	
Responsible for pharmacovigilance/ Drug safety physician (sponsor representative)	
Medical Monitor	
Medical Monitor (back-up)	
Clinical trial manager at bioskin	
Central Lab	
PK Lab	
Affiliated regional CRO	
Clinical supplies – packaging, distribution	
Lead CRA	

Appendix A Trial Flow chart

Old text:

d) Only performed in a subgroup of approx. 2 sites (approx. 30 patients); on Day 1 and Day 84 first PK sample will be performed prior to the first administration of IMP. PK samples will be collected before IMP administration, and 15, 30, 60 and 120 minutes after administration of IMP.

New text:

d) Only performed in a subgroup of approx. 4 sites (approx. 30 patients); on Day 1 and Day 84 first PK sample will be performed prior to the first administration of IMP. PK samples will be collected before IMP administration, and 15, 30, 60 and 120 minutes after administration of IMP.

Clinical Trial Protocol

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.

Confidential

bioskin GmbH
Burchardstrasse 17 • 20095 Hamburg, Germany

Synopsis

Sponsor	MetrioPharm AG Bleicherweg 45 8002 Zurich Switzerland
Sponsor's EU Representative	MetrioPharm Deutschland GmbH Am Borsigturm 100 13507 Berlin Germany
Trial no.	**MP1032-CT04 / 370205BS**
EudraCT-no.	2017-003484-36
Title	A Phase II, Multicenter, Double-blind, Placebo-controlled, Efficacy and Safety Trial of Two Oral Doses (150 mg bid / 300 mg bid) of MP1032 in Male and Female Patients with Moderate-to-Severe Chronic Plaque Psoriasis.
Title lay people	Study to evaluate efficacy and safety of MP1032 after oral administration in patients with moderate-to-severe chronic plaque psoriasis
Phase	II (POC)
Coordinating/ Investigator	PPD [redacted]
Trial center(s)	Multicenter Europe, approximately 17 centers Germany (8) and Poland (9). Site numbers may be revised to accommodate recruitment.
Trial period (planned)	January 2018 to March 2019 The duration of patient participation is approximately 16 weeks (12 weeks treatment phase and 4 weeks follow-up) and will require up to 6 visits with unscheduled visits, as needed
Objective(s)	The primary objective of this trial is to evaluate the clinical efficacy and safety of two oral doses of MP1032 (150 mg bid and 300 mg bid) when taken for 12 weeks by patients with moderate-to-severe chronic plaque psoriasis
Trial design	Three-arm randomized, double-blind, placebo-controlled, parallel group phase II multi-center trial
Number of patients (planned)	Planned number of patients: approx. 150 (120 + 30), ratio 1:1:1 • 150 mg bid arm: approx. 50 patients • 300 mg bid arm: approx. 50 patients • Placebo bid arm: approx. 50 patients

(continued…)

Synopsis (continued)

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 - ≤20 at baseline, BSA score > 10%
Investigational medicinal product (IMP)	MP1032 will be supplied as 50 mg capsules. Identical appearing placebo capsules will be provided.
Dose	MP1032 50 mg capsules or placebo will be administered orally as follows in a blinded version bid for 84 days: • 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)
Duration of treatment	12 weeks (84 days)
Mode of administration	Oral treatment (6 capsules), twice daily administered by the patient at home (last day at site), patients of the PK subgroup will administrate the first and last treatment at the site.
Efficacy assessments	Psoriasis Area Severity Index (PASI) The PASI is the most commonly used and validated assessment for grading the severity of psoriasis in clinical studies. The PASI is a physician's assessment of psoriasis that is a therapeutic standard in clinical studies for this disease. The PASI quantifies the severity and extent of the disease and weighs these with the body surface area involvement. It involves the assessment of erythema, infiltration, desquamation, and body surface area involvement over 4 body regions: head, trunk, upper and lower extremities. The Investigator assesses the redness, thickness, and scaliness of lesions on a 5-point scale (from 0 = none, through 4 = severe). The PASI score ranges from 0 to 72, with a higher score indicating increased disease severity. The PASI will be completed by the Investigator or designee at the time points prior to and following IMP administration as defined in the trial schedule. Physician`s Global Assessment (PGA) The PGA provides an overall evaluation of the severity of the disease. The PGA is a 7-point physician's assessment of psoriasis that is a therapeutic standard in clinical studies for this disease. The Investigator or designee will complete a PGA form to evaluate the disease severity at a single time point. Scoring is on a 7-point scale: 0 = clear; 1 = almost clear; 2 = mild; 3 = mild to moderate; 4 = moderate; 5 = moderate to severe, and 6 = severe.

(continued…)

Synopsis (continued)

Efficacy assessments	Assessment of body surface area (BSA) The total surface area of the body affected with psoriasis plaques will be determined by the Investigator. Calculation should include psoriasis on the palms of the hands and soles of the feet as well as on the face and scalp. The investigator will calculate the approximate BSA by assuming that 1% BSA is approximately equal to the surface area of one outstretched hand (with fingers) of the patient.
Baseline and safety parameters	Medical history including psoriasis history, physical examination focusing on the skin, demographic data, previous and concomitant medication, vital signs, recording of adverse events, serum pregnancy test at screening, safety laboratory scheduled at all visits (except serology), extent of exposure.
Rationale for sample size	It is planned to recruit approximately 150 patients for this clinical trial in Germany and Poland (each country approximately 75 patients) to achieve 120 evaluable patients. No formal sample size calculations were performed for this explorative trial. A sample size of 40 in each group is adequate to detect a difference in rates of at least 0,274, with 80% power, using a two group χ^2 test with a 0,100 two-sided significance level.
Statistical methods	Hypotheses: Since this is an exploratory trial no formal hypotheses are postulated. The data will be evaluated descriptively. Primary efficacy endpoints Two primary co-parameters will be analyzed as described in the EMA Guideline. The comparisons of the treatment groups MP1032 300 mg bid and MP1032 150 mg bid, each vs. the placebo treatment, with respect to each, the PASI 75 rate and PGA improvement rate, at Week 12 (Day 84) will be evaluated by the CMH test stratified by (pooled) analysis center. The common odds-ratio with 95% confidence interval will be provided. The homogeneity of the individual odds-ratios will be assessed by the Breslow-Day test. Secondary efficacy endpoints Secondary efficacy endpoints will be evaluated descriptively. The change in the PASI score from baseline to each post baseline visit, respectively, will be evaluated using an analysis of covariance (ANCOVA) model, with treatment group and (pooled) analysis center as factors and baseline outcome as covariate.

(continued…)

Synopsis (continued)

Statistical methods	The time to achievement of PASI 50 and PASI 75, respectively, will be evaluated using the Kaplan-Meier method. Pairwise treatment group differences will be tested by the log-rank test. Descriptive summaries will be provided for each parameter by treatment group and by visit, if applicable. Percentages will be provided based on the number of non-missing cases, if not otherwise stated. **Other endpoints:** Blood MP1032 concentration-time data will be listed 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 will be provided. Statistical analyses will be performed using non-compartmental analysis (NCA) methods, as appropriate, providing Cmax, tmax and AUC(0,t). Listings and summary statistics of NCA parameters will be provided. **Safety analysis:** All AEs reported during the trial will be listed, documenting course, severity, investigator assessment of the relationship to the IMPs, and outcome. AEs will be coded using the MedDRA mapping system for preferred terms (PTs) and system organ class (SOC). Treatment-emergent adverse events (TEAEs), i.e. AEs with an onset or worsening on or after the time of the first IMP application, will be summarized by the number of patients reporting TEAEs, primary system organ class (SOC), preferred term (PT), severity, and relationship to IMP. Listings of serious adverse events (SAE) and patients who prematurely discontinued treatment due to AEs will be given. Safety laboratory parameter (hematology, clinical chemistry) and vital signs will be summarized descriptively, including changes from baseline. Urinalysis outcomes will be summarized by frequency counts.
Date of issue	October 19, 2018

Signatures of sponsor

This clinical trial protocol was subject to critical review and has been approved by the sponsor. The information it contains is consistent with:

- the current risk-benefit evaluation of the investigational product
- the moral, ethical, and scientific principles governing clinical research as set out in the currently valid revision of the Declaration of Helsinki and the principles of GCP as described in ICH GCP.

The investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

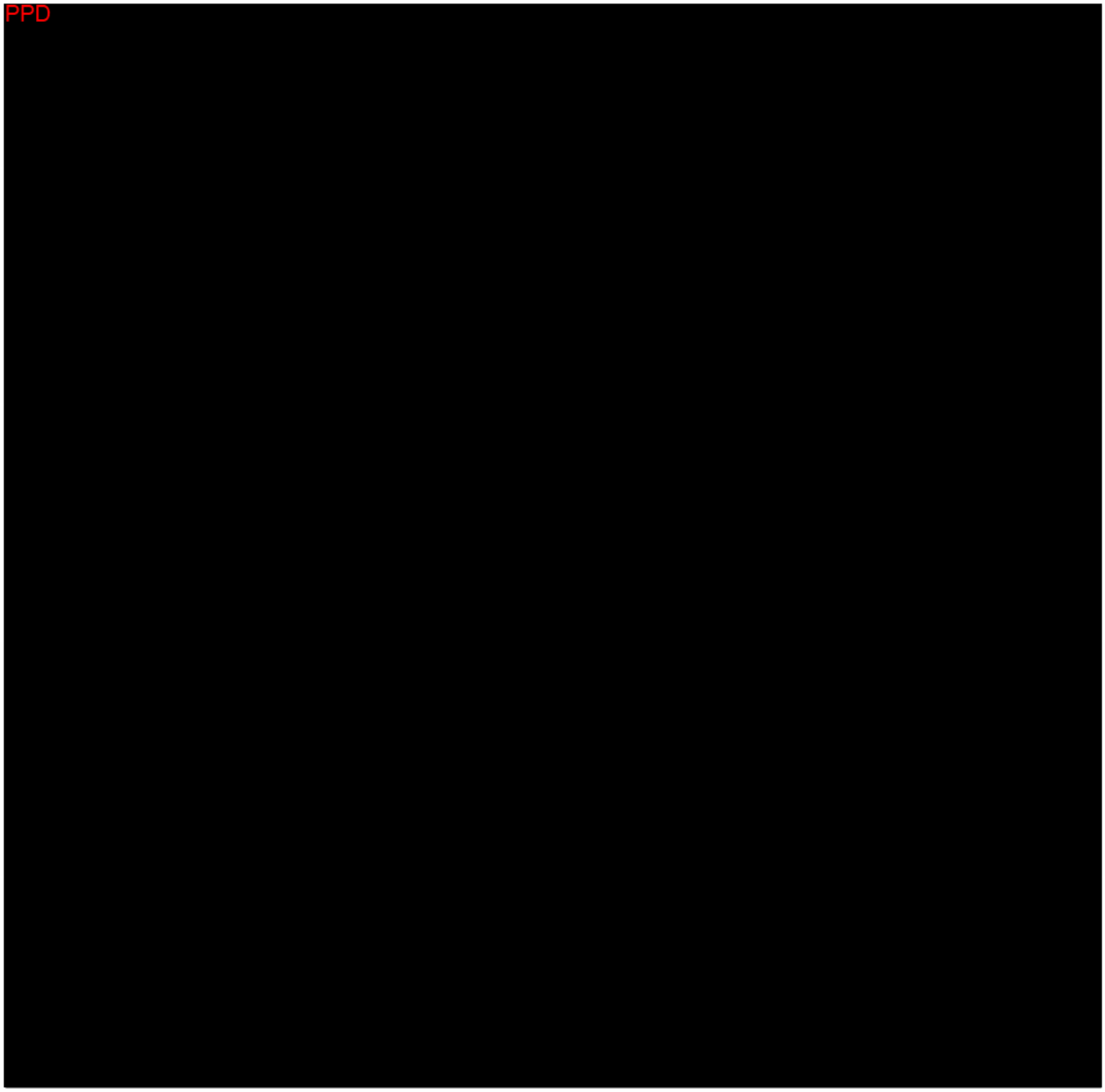
PPD

Signatures of bioskin

The undersigned hereby declare their consent to performance of the clinical trial in compliance with regulations as laid down in this clinical trial protocol, in the currently valid revision of the Declaration of Helsinki and in the ICH-GCP guideline and applicable national laws and regulations. Changes to this protocol require written agreement of both investigator and sponsor.

The investigator has acquainted himself with the results of the pharmacological and toxicological trials of the investigational product and the results of other trials as described in the investigator's brochure or other appropriate information.

PPD



Signature of International Coordinating Investigator

The undersigned hereby declare their consent to performance of the clinical trial in compliance with regulations as laid down in this clinical trial protocol, in the currently valid revision of the Declaration of Helsinki and in the ICH-GCP guideline and applicable national laws and regulations. Changes to this protocol require written agreement of both investigator and sponsor.

The investigator has acquainted himself with the results of the pharmacological and toxicological trials of the investigational product and the results of other trials as described in the investigator's brochure or other appropriate information.

PPD

Responsible person for SAE notifications:

CCI, PPD
[redacted]

SAE reporting to:

CCI
[redacted]

Table of Content

Tables

1. Abbreviations

ADP	Adenosine diphosphate ribose
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AMG	German drug law (Arzneimittelgesetz)
AST	aspartate aminotransferase
AUC	area under the curve
BfArM	Federal institute for drugs and medical devices (Bundesinstitut fuer Arzneimittel und Medizinprodukte)
BMI	body mass index
CA	competent authority
CMH	Cochran-Mantel-Haenszel
CRF	case report form
EC	ethics committee
ENT	Ear nose throat
EoS	End of study
EoT	end of treatment
FAS	full analysis set
(c)-fms	colony-stimulating factor-1 receptor
GCP	good clinical practice
GMP	good manufacturing practice
GOT	glutamic oxaloacetic transaminase
GPT	glutamic pyruvic transaminase
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	investigator's brochure
ICH	international conference on harmonisation
IL-6	interleukin-6
IMP	investigational medicinal product
IMPD	investigational medicinal product dossier
ITT	intent-to-treat
IWRS	Interactive Web Response Systems
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	medical dictionary for regulatory activities
PARP-1	poly(adenosine diphosphate [ADP]-ribose) polymerase 1
PP	per-protocol
PT	preferred term
PV	Pharmacovigilance
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis system
SES	safety evaluation set
SGK-2	serine / threonine-protein kinase
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction

TACE	metalloprotease TNF-α converting enzyme
TEAE	treatment emergent adverse event
TMF	trial master file
TNF-α	Tumor Necrosis Factor α
VCS	valid cases set
WBC	white blood cell
WCBP	women of childbearing potential
WHO	world health organization

2. Introduction

MP1032 is a small-molecule macrophage modulator currently not available as a registered or approved medicinal product within the borders of the European economic area, the United States, or Japan. Experimental data have shown that MP1032 can inhibit inflammation by reducing Tumor Necrosis Factor α (TNF-α) and Interleukin-6 (IL-6) [1]. MetrioPharm AG is developing MP1032 as an anti-inflammatory compound. The first target indication is psoriasis.

Psoriasis is a relatively common skin condition, affecting 1.5 to 3% of the general population in Europe [2]. Psoriasis can have a particularly negative effect on quality of life, affecting a sufferer's physical, social, and psychological functioning so the need for effective therapies is high. Psoriasis is characterized by outbreaks of skin inflammation interspersed by varying periods of remission. The underlying mechanisms of the inflammatory flares in psoriasis are poorly understood, but the therapeutic potency of anti-TNF- α and anti-IL-17 biologics is evidence of immune modulation's potential to reduce disease severity [1].

However, antibody-based biologics therapies are not optimal therapies for life-long treatment of psoriasis, due to decreasing efficacy over time and relatively high costs. Furthermore, the use of immune-suppressive drugs, such as methotrexate, cyclosporine, or anti-TNF-α/IL-12/IL-17/ IL-23 biologics increases the risk of opportunistic infections and/or requires regular laboratory checks on blood and liver function [1].

MP1032 has been shown to reduce TNF-α and IL-6 levels *in vitro* (human peripheral blood mononuclear cells and differentiated human promyelocytic leukemia cells), and *in vivo*, and its anti-inflammatory potential has been shown in mouse and rat arthritis models. Other anti-inflammatory compounds usually exhibit immune-suppressive effects resulting in an increased vulnerability to infections. MP1032, on the other hand, has shown an anti-infective potential in animal infection models.

The mechanism of action is thought to be mediated by MP1032's partial inhibition of the enzyme poly(adenosine diphosphate [ADP]-ribose) polymerase 1 (PARP-1), the kinases human Aurora-B, human Aurora-C, serine / threonine-protein kinase (SGK-2), tyrosine kinase (colony-stimulating factor-1 receptor [c-fms / FMS], and the metalloprotease TNF-α converting enzyme (TACE, also known as ADAM17).

As a multi-target small-molecule macrophage modulator, MP1032 seems to avoid the problems of tolerance and reduced long-term efficacy that biologics have. An important potential safety advantage of MP1032 lies in the observation from animal models that the compound reduces rather than increases susceptibility to bacterial and viral infections. This may be due to the fact that MP1032 is reducing – rather than completely suppressing – TNF-α and IL-6 levels.

MetrioPharm considers these molecular and safety characteristics along with the ease of an oral therapy over topical therapies as strong arguments for MP1032 to become an effective therapy option in moderate-to-severe psoriasis, where topical agents are not effective enough or too tedious for patients to apply them regularly.

MP1032 has been assessed in a phase I first-in-man clinical trial. In part 1 of this trial (single-ascending doses), 12 volunteers were administered 50 to 600 mg MP1032. One mild adverse drug reaction (ADR) of “headache” was classified as related to the investigational medicinal product (IMP) and was reported after treatment with 50 mg MP1032. In part 2 of the clinical trial, general safety and tolerability of MP1032 were assessed in multiple ascending doses. No ADRs were reported in part 2, in which the volunteers received 2 × 100 mg per day and 2 × 300 mg per day at 12-hour intervals for 7 consecutive days.

Subsequently, an exploratory, double-blind, parallel phase IIa trial to evaluate the safety, pharmacokinetics and efficacy of orally administered MP1032 in patients with moderate to severe chronic plaque psoriasis was performed. A total of 44 patients were randomized with a 1:1 ratio to either receiving 100 mg MP1032 twice daily or placebo for 42 days. The findings of that trial shows that after only six weeks of treatment, there is a clinically meaningful response in patients who entered the trial with a PASI score of 10-20 and achieved appropriate MP1032 exposure values. 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.

Further details can be found in the Investigator's Brochure (Edition 5, September 2017), which contains comprehensive information on the IMP [3]. See Section 5.1 for details concerning the design of the current trial and section 5.2 for justification of the design of this trial.

3. Risk-benefit evaluation

3.1 Stress/risks due to trial procedures

The noninvasive procedures (clinical assessments and photographic documentation) do not pose a risk or stress for the patients.

The blood sampling procedure poses the same very small risk as normally associated with this procedure (e.g. infection, bleeding into the surrounding tissue, and very rarely inflammation of the vein or formation of blood clots). Therefore blood withdrawal will only be conducted by qualified medical personnel.

3.2 Stress/risks due to the investigational medicinal product (IMP)

General safety and tolerability of MP1032 has been assessed in one phase 1 first-in-man clinical trial. In the single ascending doses part of this trial, twelve volunteers were administered 50 to 600 mg MP1032. One mild ADR ("headache") was reported once after treatment with 50 mg MP1032 in one volunteer. No ADRs were reported in the multiple ascending doses part where volunteers received 2×100 mg per day and 2×300 mg per day at 12-hour intervals for seven consecutive days.

In a previous IIa trial following TEAEs were observed: In summary the number of patients with TEAEs was 14 (60.87%, 27 TEAEs) in the MP1032 group and 15 (65.22%, 32 TEAEs) in the placebo group. The most commonly reported TEAEs were in the SOC categories of infections and infestations (5 patients [21.74%] in the MP1032 group and 8 patients [34.78%] in the placebo group) and nervous system disorders (7 patients [30.43%] in the MP1032 group and 3 patients [13.04%] in the placebo group). No clinically important differences were seen between the two treatment groups with regard to the number and overall pattern of patients reporting TEAEs by System Organ Class (SOC).

A positive phototoxic signal detected in non-clinical studies could be indicative of a likely clinical phototoxic risk of MP1032, although the risk for the patients seems to be unlikely and no associated TEAEs were seen in the previous clinical trials. Nevertheless, psoriasis patients participating in this trial should be advised to minimize sun exposure (sun bathing) and strong UV exposure (see also inclusion criterion No. 9). Furthermore, the use of sunscreen will be recommended when spending an extended period of time outdoors. The latter requirement will be valid during the whole 12 weeks of treatment duration plus the 4 weeks of follow up period.

Women of childbearing potential (WCBP) must agree to use a highly effective contraceptive method (Pearl-Index < 1%) starting at screening and continuing throughout the clinical trial period and for 28 days after final IMP administration.

Highly effective forms of birth control (according to International Conference on Harmonization [ICH] M3) have low failure rates (i.e. less than 1% per year) when used consistently and correctly, and include the following:

- The male partner of a female patient has undergone effective surgical sterilization.
- A female patient can use an established oral contraceptive, injected or implanted hormonal methods of contraception or an established intrauterine device or intrauterine system.

True sexual abstinence as a form of birth control will be allowed in the trial when this is in accordance with a patient's preferred and common lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception. Patients who use abstinence as a form of birth control must agree to abstain from heterosexual intercourse from the month prior to screening until 28 days after the last dose of IMP (or longer if required by local regulations). Study personnel must confirm the continued use of abstinence is still in accordance with the patient's lifestyle at regular intervals during the trial.

Post-menopausal is defined as 12 months of spontaneous amenorrhea. Females who have been sterilized, or had a hysterectomy, may be included.

A **sterile** woman is defined by either of the following medical interventions performed before intake of IMP

- Tubal ligation, or
- Bilateral oophorectomy, or
- Total hysterectomy.

If documented, women with one of these conditions are not required to use additional contraception.

Male patients who are sexually active with a female partner and are not surgically sterile (vasectomy performed at least six months prior to treatment) must agree to inform their female sexual partner about his trial participation and to use an acceptable form of birth control as described in the informed consent form. Prior to trial enrollment, patients must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. The patient must sign an informed consent form documenting this discussion.

Against these minimal risks stands the benefit of information on the efficacy and safety of a promising new substance which is intended to be used in the oral administration in patients with psoriasis vulgaris.

Taking into account these risks and benefits, the performance of the trial can be considered ethically sound since the expected benefits of the IMPs appear greater at present than the risks for the patients. The clinical trial protocol will be submitted to the responsible ethics committee(s) for approval.

4. Trial objectives/endpoints

The trial is designed with two primary endpoints as described in the EMA guideline [2].

Table 1: Objectives and endpoints:

Primary objective	Primary endpoint
The primary objective of this trial is to evaluate the clinical efficacy and safety of two oral doses of MP1032 (150 mg bid and 300 mg bid) when taken for 12 weeks by patients with moderate-to-severe chronic plaque psoriasis.	Efficacy: MP1032 300 mg bid vs. placebo 1. Percentage of patients who achieve a 75% improvement (response) in their PASI score (PASI 75) at Week 12 (Day 84) compared to baseline treated with 300 mg bid of MP1032 compared to placebo 2. Improvement (1 or more points on a 7 Point Scale) in PGA at Week 12 (Day 84) compared to baseline treated with 300 mg bid of MP1032 compared to placebo Efficacy: MP1032 150 mg bid vs. placebo 3. Percentage of patients who achieve a 75% improvement (response) in their PASI score (PASI 75) at Week 12 (Day 84) compared to baseline treated with 150 mg bid of MP1032 compared to placebo 4. Improvement (1 or more points on a 7 Point Scale) in PGA Score at Week 12 (Day 84) compared to baseline treated with 150 mg bid of MP1032 compared to placebo Safety: 5. Incidence of adverse events

Secondary objectives	Secondary endpoints
To evaluate the effect of each oral doses of MP1032 (150 mg bid and 300 mg bid) compared to placebo on the PASI score	• Percentage of patients who achieve a 50% improvement (response) in their PASI score (PASI 50) at Week 12 (Day 84) compared to baseline treated with 300 mg bid of MP1032 compared to placebo • Percentage of patients who achieve a 50% improvement (response) in their PASI score (PASI 50) at Week 12 (Day 84) compared to baseline treated with 150 mg bid of MP1032 compared to placebo • Mean PASI score and change to baseline at Week 4 (Day 28), 8 (Day 56), 12 (Day 84) and week 16 (Day 112) • Time to achieve PASI 50 and PASI 75 • Mean PASI score and change from Baseline at Week 4 (Day 28), 8 (Day 56), 12 (Day 84) and 16 (Day 112)
To evaluate the effect of each oral dose of MP1032 (150 mg bid and 300 mg bid) compared to placebo on the PGA score	Mean score and change from Baseline at Week 4 (Day 28), 8 (Day 56), 12 (Day 84) and 16 (Day 112) in the PGA
To evaluate the effect of each oral dose of MP1032 (150 mg bid and 300 mg bid) compared to placebo on the BSA score	Mean score and change from Baseline at Week 4 (Day 28), 8 (Day 56), 12 (Day 84) and 16 (Day 112) in the BSA
To evaluate systemic exposure of two oral doses of MP1032 (150 mg bid and 300 mg bid) when taken for 12 weeks by patients with moderate-to-severe chronic plaque psoriasis	PK data analysis

5. Investigational plan

5.1 Overall trial design and plan - description

This trial is 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 consists of a 28-day screening period, a 12-week treatment period, and subsequently a 28-day follow-up period. Each patient will have 6 visits and unscheduled visits as needed.

Approximately 150 patients (2 × 50 patients MP1032 and 50 patients placebo) who meet the entry criteria will be randomized on Day 1 to receive either 150 mg MP1032, 300 mg MP1032 or placebo orally twice daily for 12 weeks. The administration of IMP will stop after end of study (in max. 13 weeks). Recruitment will be competitive between the sites but enrollment will be limited to 12 patients per site. A recruitment of more than 12 patients may be allowed after sponsor approval.

Safety parameter will be monitored from the signing of the informed consent form (ICF) until the last follow-up visit.

Efficacy and safety will be assessed as outlined in the trial flow chart.

5.2 Discussion of trial design, including the choice of control groups

Pre-clinical toxicology studies, a Phase I single plus multiple ascending dose trial, as well as an exploratory Phase IIa pilot trial of oral MP1032 have indicated a higher degree of safety and tolerability of the IMP compared to all currently used systemic psoriasis treatments. Moreover, a first assessment of oral MP1032's clinical efficacy in moderate-to-severe psoriasis in the preceding Phase IIa trial has shown clinically meaningful response in patients who entered the trial with a PASI score of 10-20 during six-week treatment period.

In several animal models of chronic, immune-mediated inflammatory diseases, MP1032 has been shown to have a pronounced anti-inflammatory effect.

The primary objective - to evaluate clinical efficacy and safety of MP1032 in patients with psoriasis during the 12-week treatment period and a 4-week follow up - will provide an opportunity to perform oral MP1032's clinical efficacy in moderate-to-severe psoriasis when taken for twice as long as done in Phase IIa.

On the basis of pre-clinical, Phase I and Phase IIa data, the current trial was also designed to assess the safety and tolerability of oral MP1032 over a period of 12 weeks, trying to reproduce the excellent tolerability and safety profile that was seen in Phase I and Phase IIa (up to 7 days and 6 weeks, respectively), over a longer period of time.

The extension of treatment to 12 weeks and a 4-week follow-up observation period will give the opportunity to obtain even more meaningful safety data and more comprehensive data on efficacy.

To evaluate systemic concentrations of MP1032 PK samples will be analyzed in a subgroup.

The photographic documentation will only be used for visual demonstration of efficacy. No assessments will be performed using this data.

Patients will be randomized to one of three treatment arms (MP1032 600mg, MP1032 300mg or placebo) in a blinded manner. The treatment allocation will be on a 1:1:1 ratio (50:50:50 patients). Recruitment will be competitive between the sites but enrollment per site will be limited to 12 patients (more than 12 patients needs to be approved by the sponsor).

5.3 Selection and discontinuation/withdrawal of patients

5.3.1 Selection of patients

The selection of patients is in accordance with the requirements of the national laws as well as the recommendations of the currently valid revision of the Helsinki Declaration [4] and the ICH GCP guideline [5]. Advertisement (e.g. newspaper, online portal, bus or metro) will be used only after positive approval by the responsible EC.

The trial population will consist of approx. 150 patients (planned 75 Germany and 75 Poland) with moderate-to-severe chronic plaque psoriasis. Patients must be able to provide written consent and meet all the inclusion criteria and none of the exclusion criteria.

A gender specific subdivision into groups is not necessary in this clinical trial. Male or female patients between 18 years and 70 years are eligible for this clinical trial insofar that they suffer from moderate-to-severe-psoriasis. The antipsoriatic efficacy is likewise detectable in men and women.

5.3.2 Inclusion criteria

All of the following criteria have to be met for inclusion of a patient in this trial:

1. Participants legally competent to sign and give informed consent.
2. Adult male and female patients between 18 years and 70 years with moderate-to-severe chronic plaque psoriasis (diagnosed by Investigator):
   a) PASI score ≥10 - ≤20 at baseline
   b) BSA score: > 10%
   c) Stable disease duration of ≥ 6 months at the initiation of IMP.
   d) topical therapy fails to control the disease
3. Body Mass Index (BMI) between 18.5 and 34.9 kg/m^2.
4. Women of childbearing potential (WCBP) must have a negative serum pregnancy test at Screening (Visit 1). In addition, sexually active WCBP must agree to use adequate contraception throughout the trial (see Section 3.2 for more details on adequate contraception):
   a) A method with less than 1% failure rate OR
   b) Abstinence
5. Post-menopausal women with spontaneous amenorrhea for at least 12 months and women on hormonal replacement therapy (HRT). The use of hormonal replacement therapy (HRT) during the trial is permitted, however for these patients an appropriate contraception method according to Inclusion Criterion 4 must be ensured. Sterilized women may be included (see Section 3.2 for more details on sterile definition)
6. Male patients who are sexually active with a female partner and are not surgically sterile (vasectomy performed at least six months prior to treatment) must agree to inform their female sexual partner to use an acceptable form of birth control as described in the informed consent form. For females, an acceptable method (Pearl Index < 1%) would be to use implants, injectable, combined oral contraceptives, some intrauterine devices, or be postmenopausal, be surgically sterile (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy)
7. In good health as judged by the investigator, based on medical history, physical examination, serum chemistry, hematology and urinalysis
8. Patients must meet the following clinical laboratory criteria:

- White blood cell count ≥3.5 × 109/L
- Platelet count ≥100 × 109/L
- Serum creatinine ≤1.5 × upper limit of normal (ULN); estimated glomerular filtration rate >60 mL/min
- Total bilirubin ≤1.5 × ULN
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN
- Hemoglobin ≥ lower limit of normal as per central laboratory reference ranges for women and men accordingly
- No coagulopathy (International Normalized Ratio [INR] <1.5)

9. Patients agree to minimize normal sun exposure during the course of the trial
10. Patients are considered reliable and capable of adhering to the protocol (e.g. able to understand the patient information and complete diaries), visit schedule, or medication intake according to the judgment of the Investigator.

5.3.3 Exclusion criteria

Patients are to be excluded from the trial, when one or more of the following conditions are met:

1. Patients with non-plaque form of psoriasis (erythrodermic, guttate, pustular form of psoriasis). Associated psoriasis arthritis is allowed provided no other in-/exclusion criteria are influenced, no forbidden concomitant therapy is required for the well-being of the patient and there is no impact on trial objectives as determined by the Investigator.
2. Treatment with concomitant medication that may affect and provoke or aggravate psoriasis, e.g. antimalarial drugs, beta-blockers or ACE inhibitors unless on a stable dose for 3 months before IMP intake.
3. Evidence of skin conditions at the time of Screening Visit other than psoriasis that would interfere with evaluations of the effect of the IMP on psoriasis.
4. Patients with any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the patient from signing the ICF, as assessed by the investigator.
5. Pregnant or lactating women or women planning to become pregnant during the trial and / or within 28 days following the last dose of IMP.

6. Male patients planning a partner pregnancy or sperm donation during the trial including follow up period.
7. Known allergies to any ingredient of the IMP e.g. mannitol, macrophage modulators, or gelatin.
8. History or symptoms of a clinically significant illness in the four weeks before first treatment and during the trial that in the opinion of the investigator may place the patient at risk by trial participation or influence the outcome of the trial. Well controlled diseases such as hypertension, hyperlipidemia, diabetes or hypothyroidism are permitted.
9. Patients with active malignancy or history of malignancy, except for basal cell and actinic keratosis. Basal cell carcinoma of the skin or *in situ* cervical carcinoma that have been fully treated and show no evidence of recurrence are allowed.
10. Positive HIV-Antibody, HBs-Antigen or HCV-Antibody-Test at screening.
11. Previous strong sun exposure (e.g. sea holiday) within 28 days or UV treatment within 24 weeks before IMP initiation.
12. Known photo allergy and / or experienced drug-induced photo toxicity.
13. Elective (planned) hospitalization or medical intervention preventing patient from following the protocol requirements.
14. Prior treatment not adhering to Table 2.

Table 2: Prohibited medication:

Drug Class	**Last Dose Prior to IMP Initiation** (Washout Period)
Topical psoriasis medications (including, but not limited to corticosteroids, calcipotriene, topical vitamin D derivates, retinoids, coal tar) shampoos for scalp psoriasis containing tar	14 days
Topical immunosuppressive drugs (tacrolimus, pimecrolimus, or anthralin)	14 days
(Exception: Non-medicated emollients, moisturizers and sunscreens will be allowed)	
Systemic treatments (non-biologics): Systemic immunosuppressant agents (e.g.: methotrexate, cyclosporine, azathioprine)	28 days

Drug Class	Last Dose Prior to IMP Initiation (Washout Period)
Systemic fumarate Systemic corticosteroids	
Phototherapy or photochemotherapy / photosensitizing drugs **UVA phototherapy with or without psoralen, excimer laser**	28 days 24 weeks
Systemic retinoids	12 weeks
Investigational drugs	24 weeks (systemic); 4 weeks (topical)
Anti-tumor necrosis factor (TNF) drugs: Adalimumab, Infliximab, brodalumab, Ixekizumab, etanercept,	8 weeks
Guselkumab, certolizumab pegol, golimumab,	12 weeks
Other biologics and other systemic therapies:	8 weeks
apremilast	12 weeks
Ustekinumab, alefacept, secukinumab	24 weeks
Rituximab	12 months

15. Planned use of any ultraviolet (UV) phototherapy or photochemotherapy / photosensitizing drugs during the course of the trial and within 28 days/24 weeks following the last dose of the IMP.
16. Patients with a history of chronic alcohol or drug abuse within 6 months of IMP initiation.
17. Patients with a blood pressure outside the given range of 160 mm Hg (systolic) and 95 mm Hg (diastolic)
18. Patients who are employed by MetrioPharm, contract research organization (CRO) or clinical site involved in the clinical trial.
19. Vulnerable patients (e.g. patients kept in detention).
20. Patients who are unable to communicate, read or understand the local language, or who display another condition, which, in the Investigator's opinion, makes them unsuitable for clinical trial participation.
21. Patient is institutionalized because of legal or regulatory order.

5.3.4 Restrictions during the clinical trial

A positive phototoxic signal detected in non-clinical studies could be indicative of a likely clinical phototoxic risk of MP1032, although the risk for the patients seems to be unlikely. Nevertheless, psoriasis patients participating in this trial should be advised to avoid strong sun exposure (sun bathing) and strong UV exposure (see inclusion criterion no. 9). Furthermore, the use of sunscreen will be recommended when spending an extended period of time outdoors. During the trial patients should adhere to their standard skin care regimen and may use their standard emollients/moisturizers as symptoms require but may not use treatments as precluded by the exclusion criteria. The latter requirement will be valid during the whole 12 weeks of trial duration plus the 4 weeks of follow up period.

5.3.5 Removal of patients from therapy or assessment

5.3.5.1 Criteria for discontinuing the whole clinical trial

Premature termination of a clinical trial may occur upon decision of the Sponsor, upon decision of the Investigator, by request of an authority, or because of withdrawal of positive vote by the responsible IEC. If the Investigator, the Sponsor, or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to patients, if the trial continues, the trial may be terminated after appropriate consultation between the relevant parties. The trial may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination of the trial as a whole include, but are not limited to:

- Concerns for safety that arise within this trial or in any other trial with the IMP;
- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the trial;
- Failure to enroll patients at an acceptable rate;
- Ethical issues;
- Severe non-compliance;
- A decision on the part of the Sponsor to suspend or discontinue development of the drug.

5.3.5.2 Criteria for discontinuing in the case of individual patients

Patients may withdraw from the entire trial including follow-up at any time without penalty and for any reason without prejudice to his or her future medical care.

The following criteria must lead to discontinuation from the clinical trial in individual patients:

- Patient withdraws informed consent

- Pregnancy (see section 7.4)
- Severe protocol violations that result in a significant risk to the patient's safety
- Emergence of the following AEs including:

  a) Patient reports symptoms which are considered unacceptable by the patient or the Investigator or if any serious AE occurs that is judged as at least possibly related to the IMP by the Investigator

  b) Abnormal laboratory value(s) confirmed by repeat measurements:

    - Elevated liver transaminases (AST/ALT) ≥3 × ULN AND elevated bilirubin total bilirubin ≥ 2 × ULN
    - Elevated serum creatinine ≥2 × ULN

The following criteria may lead to discontinuation from the clinical trial in individual patients:

- Use of prohibited concomitant medication as defined in section 5.4.5.

In all cases, the reason(s) for withdrawal, and the primary reason, must be recorded on the electronic data capture (EDC) system / electronic case report form (eCRF). If a patient is prematurely withdrawn from the IMP for any reason, the Investigator must make every effort to perform the evaluations described for the End of Treatment and Follow-up Visits. The Investigator should contact the Medical Monitor, whenever possible, to approve withdrawal of patients in advance.

If a patient withdraws consent and still agrees to undergo a final examination, it will be documented on the eCRF and the patient record.

A patient may also be withdrawn from the IMP by the Sponsor, Regulatory Authorities, or Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs).

Patients who are withdrawn from the trial will be not replaced.

Protocol violation, failure to comply with the trial stipulations/poor compliance may lead to discontinuation from the clinical trial in individual patients.

5.3.6 Definition of end of trial

The end of the trial is defined as the last visit of the last patient completing the trial (including follow-up visits).

5.4 Treatments

The IMP will be packed in kits, 1 kit per patient per week. One kit contains 14 blisters and one blister contains six, 50 mg, hard gelatin capsules of MP1032 and/or placebo (described below). IMP will be packaged and labelled by CCI [redacted] according to all local legal requirements. IMP will be labelled in accordance with applicable regulatory requirements.

All IMP supplies must be stored at room temperature (15 - 25°C) and protected from light, in accordance with the manufacturer's instructions. Until dispensed to the patients, the IMP will be stored in a securely locked area, accessible to authorized personnel only.

5.4.1 Treatments to be administered (manner and dose selection)

Once patients have met the trial entry criteria, completed the screening procedures and run-in period, and completed the pre-dose procedures and assessments, they will be randomly assigned as described in Section 5.4.3 above to one of the three treatment groups described below. They will receive total daily doses of 300 mg or 600 mg MP1032 (IMP) or placebo (IMP placebo) as follows (1:1:1):

- Treatment A: 3 × 50 mg (150 mg) MP1032 plus 3 × placebo hard gelatin capsules (per dosage) twice daily for 84 days
- Treatment B: 6 × 50 mg (300 mg) MP1032 hard gelatin capsules (per dosage) twice daily for 84 days
- Treatment C: 6 × placebo hard gelatin capsules (per dosage) twice daily for 84 days.

All administrations will take place with at least 8 hours between the dosings.

5.4.2 Identity of investigational medicinal products

Details of the IMPs are given in the table 3.

Table 3:Identity of investigational medicinal products:

Generic name/brand name/INN	**Verum**	**Placebo**
Formulation	Hard gelatin capsules, size 3 The mixture (995 parts mannitol and 5 parts colloidal anhydrous silica) is well known and described in compendia (German: Neues Rezepturformularium, Monographie Nr. S. p. 38.). At least 25% of the mass of the contents are active ingredient. Placebo capsules constituted only of the excipients described above.	
Active ingredient	MP1032 5-Amino-1,4-dioxo-1,2,3,4-tetrahydrophthalazine-3-id, sodium salt	n.a.
Amount per unit	containing 50 mg MP1032 for oral administration	n.a.
Primary packaging	Blister	Blister
Storage	room temperature (15 – 25 °C)	room temperature (15 – 25 °C)
Manufacturers	CCI [redacted]	CCI [redacted]

All IMPs will be labeled according to the requirements of local law and legislation. A copy of the labels will be filed in the trial master file (TMF).

All IMPs used during the trial will be stored at the trial center in accordance with instructions given, and will be inaccessible to unauthorized personnel.

Missing a treatment

If the patient misses a dose, and remembers the dose within 6 hours of scheduled dosing, he/she may take it. If it has been more than 6 hours since the planned dose time, the patient should skip the dose. All missing doses should be documented by the patient in the diary. However, all administrations will take place with at least 8 hours between the dosings.

Overdose

The risk of overdosing in general in this trial is considered to be low due to the maximum dose that each patient can receive via six capsules being 150 mg, 300 mg MP1032 or Placebo. Nevertheless, unintentional administration of any dose that deviates from the scheduled regimen will be documented and reported by site staff via eCRF. In case of overdose symptomatic

treatment should be provided as indicated and a safety blood analysis should be performed. The Sponsor should be informed immediately.

5.4.3 Assignment of treatments and randomization

Patient Identification

Upon signature of informed consent (screening period) each patient receives a 5-digit **patient identification number**, which is composed of:

Digits 1 and 2: trial center (01, 02, 03, etc.) 01 – 10 for German sites and 11 – 20 for Polish sites

Digits 3, 4 and 5: individual screening number within the center (consecutively in the order of screening within the center: 001, 002, etc.)

Treatment Assignment

Patients will be randomized on a 1:1:1 basis to one of three treatment groups:

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

The trial will use a block randomization scheme. Enrollment will be performed competitively between all 14 centers (Germany and Poland) until approximately 150 patients are enrolled in the trial in order to have 120 evaluable patients.

Patients who are eligible for enrollment into the trial will be randomized at Visit 2/Day 1 and will be assigned the lowest random number available at the site. Patient kits will be dispensed according to the kit number assigned by the IWRS. The kit numbers will be assigned to the treatment kits by a simple randomization.

The treatment group designation will remain blinded until the final database is locked.

The random list, assigning the randomization number to the treatment groups, and the kit number list, assigning the kit number to the treatment groups will be generated by psy consult scientific services.

5.4.4 Blinding and Breaking the Blind

The trial will be performed in a double-blind manner. All IMPs will be supplied in identical form and will be similar in color, smell, taste, and appearance.

The IMPs will be blinded by CCI [redacted].

The trial blind should not be broken except in case of a medical emergency (where knowledge of the IMP received would affect the treatment of the emergency) or regulatory requirement (e.g. for SUSAR [in Germany]).

If the blind is broken via IWRS, the date, time, person who broke the blind and the reason must be recorded in the patient's eCRF, and any associated AE report.

The treatment code will only be broken after all the clinical database is locked.

5.4.5 Prior and concomitant therapy

Any medication the patient takes other than the IMP, including herbal and other non-traditional remedies, is considered a concomitant medication. All concomitant medications taken in the 6 weeks before the first dose must be recorded in the eCRF. The following information must be recorded in the eCRF for each concomitant medication: brand name, route of administration, start date, stop date, dosage, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRF.

At Screening, patients will be asked which psoriatic treatment they have previously taken (last 6 weeks) and which other concomitant medications they have taken in the last 6 weeks. At each subsequent trial visit, patients will be asked which concomitant medications they are currently taking and have taken since the previous site visit.

For a detailed list of forbidden medication see exclusion criterion 14.

Medication allowed during the course of the trial:

- Topical moisturizers or emollients, UVA/UVB sunscreens, shampoos for scalp psoriasis (without tar), as needed.
- Contraceptives (see section 3.2)
- Any concomitant medication to treat stable diseases (such as well-controlled hypertension, hyperlipidemia, etc.)

Prohibited medication:

- All treatment as specified in exclusion criteria.

Concomitant medications should be kept to a minimum during the clinical trial. However, if these are considered necessary for the patient's welfare and are unlikely to interfere with the clinical trial objectives, they may be allowed at the discretion of the investigator. For a detailed list of forbidden medication see exclusion criterion 14.

5.4.6 Treatment compliance

All treatment administrations (except first for the PK subgroup and last treatment for all patients) will be taken by the patients at home. All treatment administrations will be documented in a diary. All missing treatment administrations documented in the diary will be counted and documented in the eCRF.

All dispensed kits and blisters (used and unused) will be collected at each visit and capsules will be counted at each visit during the treatment period. The results will be documented in the eCRF.

In case of inadequate usage the patient will be instructed again on application use.

5.5 Efficacy and safety variable(s)

5.5.1 Procedures

Screening period

Day -28 to -3 (visit 1)

Within the 28 days prior to the first IMP administration the volunteer will come to the trial centers for the initial screening (including documentation of demographic data). Screening assessments will be performed after the volunteer has agreed to participate and has signed and dated the informed consent form.

At screening a serum pregnancy test will be carried out in all female patients.

The following examinations will be performed:

- Obtain written informed consent
- Documentation of relevant medical and relevant surgical history (last 5 years)
- Documentation of demographic data
- Documentation of Smoking history/ alcohol consumption
- Documentation of relevant previous medication (last 6 weeks)
- Serum pregnancy test and urinalysis (see section 5.5.2)
- Start check in-/exclusion criteria (see section 5.3.2 and 5.3.3)
- Physical examination (see section 5.5.5)
- Height, body weight and BMI
- Record vital signs (see section 5.5.3)
- PASI (see section 5.5.1.1)
- PGA (see section 5.5.1.2)
- BSA (see section 5.5.1.3)

- Collection of samples for determination of laboratory parameters (serology, hematological status, clinical chemistry, see section 5.5.2).

Note: Adverse events before start of treatment (i.e. occurring after signature on consent form).

Patients who have abnormal test results during the screening period may be re-screened if the Medical Monitor agrees.

Experimental phase

Trial Day 1 (baseline, week 1, visit 2)

- Re-check of in-/exclusion criteria (see section 5.3.2)
- Randomization
- Physical examination (see section 5.5.5)
- Record vital signs (see section 5.5.3)
- Urine pregnancy test and urinalysis (see section 5.5.2)
- Record concomitant medications
- Record adverse events occurring from the time of informed consent signature
- *Localization of photographic documentation test field only for a subgroup (see section 5.5.1.4)*
- *Photographic documentation only for a subgroup (see section 5.5.1.4)*
- Collection of samples for determination of laboratory parameters (hematological status, clinical chemistry, see section 5.5.2)
- PASI (see section 5.5.1.1)
- PGA (see section 5.5.1.2)
- BSA (see section 5.5.1.3)
- Dispensing diary
- *Start of PK samples only for a subgroup (see section 5.5.1.5)*
- Dispensing IMP
- *Administration of IMP at site (PK subgroup only)*

Trial Day 28 (week 4, visit 3) and Day 56 (week 8, visit 4)

- Check concomitant therapy and adverse events
- Record vital signs
- Drug return / accountability and re-dispensation of unused kits/blister
- Diary collected and checked
- *Photographic documentation only for a subgroup (see section 5.5.1.4)*
- Urinalysis (see section 5.5.2)
- Collection of samples for determination of laboratory parameters (hematological status, clinical chemistry, urinalysis, see section 5.5.2)
- PASI (see section 5.5.1.1)

- PGA (see section 5.5.1.2)
- BSA (see section 5.5.1.3)
- Dispensing of IMP and diary

Trial Day 84 (week 12, visit 5) (EoT)

- Check concomitant therapy and adverse events
- Physical examination (see section 5.5.5)
- Record vital signs (see section 5.5.3)
- Urine pregnancy test and urinalysis (see section 5.5.2)
- *Photographic documentation only for a subgroup (see section 5.5.1.4)*
- Collection of samples for determination of laboratory parameters (hematological status, clinical chemistry, see section 5.5.2)
- *PK samples only for a subgroup (see section 5.5.1.5)*
- Last IMP administration at site for all patients
- Drug return / accountability
- Diary collected and checked
- PASI (see section 5.5.1.1)
- PGA (see section 5.5.1.2)
- BSA (see section 5.5.1.3)

Trial Day 112 (week 16, visit 6, Follow-up) (End of Study, EoS)

- *Photographic documentation only for a subgroup (see section 5.5.1.4)*
- Check concomitant therapy and adverse events
- Physical examination (see section 5.5.5)
- Record vital signs (see section 5.5.3)
- Urinalysis(see section 5.5.2)
- Collection of samples for determination of laboratory parameters (hematological status, clinical chemistry, see section 5.5.2)
- PASI (see section 5.5.1.1)
- PGA (see section 5.5.1.2)
- BSA (see section 5.5.1.3)

The patients must be present at site for approximately 60 minutes on Screening and Day 1, 45 minutes on Day 28 and 56, 60 minutes on Day 84 and 45 minutes on Day 112.

The above mentioned time will be extended for 15 minutes for patients with photographic documentation on each visit.

The above mentioned time will be extended on Day 1 and Day 84 for 120 minutes for patients with PK sampling.

Early Termination Visit

Patients who discontinue early from the trial should, if possible, have an Early Termination Visit. This visit should take place as soon as possible after the patient stops taking IMP. The observations and procedures scheduled for Visit 5 (End of Treatment) should be performed at the Early Termination Visit.

A schedule of trial procedures is provided in appendix A to this trial protocol.

Unscheduled visit

The patient may return to the clinic at the discretion of the investigator.

At this visit, the investigator or designee will:

• Query the patient about any changes in health status or concomitant medications and therapies since the previous visit, and document the findings respectively (AE/concomitant medications)

• Perform assessments which are relevant to the reason for the unscheduled visit (e.g. Photographic documentation, Lab analysis, PASI, PGA, BSA, etc.)

• Confirm the next visit

5.5.1.1 Psoriasis Area Severity Index (PASI)

The PASI is the most commonly used and validated assessment for grading the severity of psoriasis in clinical studies [2]. The PASI is a physician's assessment of psoriasis that is a therapeutic standard in clinical studies for this disease (appendix B). The PASI quantifies the severity and extent of the disease and weighs these with the body surface area involvement. It involves the assessment of erythema, infiltration, desquamation, and body surface area involvement over 4 body regions: head, trunk, upper and lower extremities.

The Investigator assesses the redness, thickness, and scaliness of lesions on a 5-point scale (from 0 = none, through 4 = severe). The percentage of skin involved is scored and transferred to a grade (graded 0 to 6; 0 = 0% involved area, 6 = 90%-100% involved area). In addition, the percentage of involved body surface area is estimated across 4 body areas, head (10%), upper extremities (20%), trunk (30%), and lower extremities (40%). The sum of all 3 severity parameters is then calculated for each of the 4 sections of skin, multiplied by the area score for that area, and multiplied by the weight of the respective section to give a PASI score, which ranges from 0 to 72, with a higher score indicating increased disease severity. The PASI will be completed by the

Investigator or designee at the time points prior to and following IMP administration as defined in the trial schedule. See appendix B for details of calculation.

If possible, the same investigator should complete the evaluations for a given patient throughout the trial. Initials of the assessor will be documented in the eCRF.

5.5.1.2 Physician`s Global Assessment (PGA)

The PGA provides an overall evaluation of the severity of the disease [6]. The PGA is a 7-point physician's assessment of psoriasis that is a therapeutic standard in clinical studies for this disease.

The Investigator or designee will complete a PGA form to evaluate the disease severity at a single time point. Scoring is on a 7-point scale: 0 = clear; 1 = almost clear; 2 = mild; 3 = mild to moderate; 4 = moderate; 5 = moderate to severe, and 6 = severe. The PGA will be completed by the Investigator (or designee) at the time points specified.

If possible, the same investigator should complete the evaluations for a given patient throughout the trial. Initials of the assessor will be documented in the eCRF.

5.5.1.3 Assessment of body surface area (BSA)

The total surface area of the body affected with psoriasis plaques will be determined by the Investigator at V2 (Wk0-D1), V3 (Wk4-D28), V4 (Wk8-D56), V5 (Wk12-D84), and V6 (Wk16-D112). Calculation should include psoriasis on the palms of the hands and soles of the feet as well as on the face and scalp. The investigator will calculate the approximate BSA by assuming that 1% BSA is approximately equal to the surface area of one outstretched hand (with fingers) of the patient [2].

The assessment of BSA by the Investigator serves to describe the change in % BSA affected by psoriasis after 12 weeks of treatment.

If possible, the same investigator should complete the evaluations for a given patient throughout the trial.

5.5.1.4 Photographic documentation

At all visits photographic documentation of one affected area (from trunk, arms or legs) will be performed in a patient subgroup at two selected trial sites (one site in Germany and one in Poland; approximately 30 patients in total). The target plaque for the photographic documentation will be defined before first treatment on Day 1 and should mirror the actual individual psoriasis grade of

the patient. The procedure will be described in a separate photographic method manual. Steps will be taken to ensure that the identity of the patient is protected to the extent possible. Additional consent will be undertaken with regard to collection, transmission, storage and use of images.

No efficacy or safety assessment will be made using these images. The images will be taken for educational and marketing purposes only and might be used in scientific publications.

5.5.1.5 PK samples

To evaluate systemic concentrations of MP1032 PK samples will be analyzed in a subgroup at selected trial sites (approximately two in Germany and two in Poland; approximately 30 patients in total). 4.9 mL blood must be collected before morning dose and 15, 30, 60 and 120 minutes after morning dose at visit 2 (baseline, week 1) and at visit 5 (EoT, week 12). In total 49.0 mL blood will be collected per patient.

The date and time of the last application of IMP prior to the PK sample be taken and the date and time of the PK sample must be documented in the eCRF.

Collection, handling and shipment instructions for PK samples will be provided in a separate laboratory manual.

Samples will be analyzed at:

CCI, PPD [redacted]

5.5.1.6 Diary

The diaries will include instructions on the use of the IMP. Patients will be instructed to complete the diary after intake of each IMP dose. Date/time of intake of IMP will be recorded twice daily.

At each visit at the site, the number of dose recorded on the diary will be reviewed and transcribed to the eCRF. Diary cards will be retained by trial sites as part of the source documentation and new diary cards will be dispensed.

At subsequent visits, trial personnel will review, collect and dispense a new diary and determine whether the patient requires counseling for dosage compliance. In addition, each patient will be reminded to return completed diary at the next visit.

5.5.2 Measurement of safety parameters

Relevant medical history of the past five years and adverse events will be recorded.
The following laboratory parameters will be collected at every visit (except serology):

Table 4: Laboratory Parameter per visit:

Parameter	Screening	Day 1	Day 28 / 56	Day 84 (EoT)	Day 112 (FU)
Serology					
Hepatitis A IgG-antibody-test	X	--	--	--	--
Hepatitis A IgM-antibody-test	X	--	--	--	--
Hepatitis B core antibody-test	X	--	--	--	--
Hepatitis B surface antibody-test	X	--	--	--	--
Hepatitis B surface antigen-test	X	--	--	--	--
Hepatitis C virus antibody-test	X	--	--	--	--
HIV-1 antibody-test	X	--	--	--	--
HIV-2 antibody-test	X	--	--	--	--
Hematology					
RBC	X	X	X	X	X
WBC* including differential	X	X	X	X	X
Hemoglobin	X	X	X	X	X
Hematocrit	X	X	X	X	X
MCH	X	X	X	X	X
MCV	X	X	X	X	X
MCHC	X	X	X	X	X
Platelets	X	X	X	X	X
Clinical Chemistry					
AST (GOT)	X	X	X	X	X

Parameter	Screening	Day 1	Day 28 / 56	Day 84 (EoT)	Day 112 (FU)
ALT (GPT)	X	X	X	X	X
γGT	X	X	X	X	X
AP	X	X	X	X	X
Creatinine	X	X	X	X	X
Total bilirubin	X	X	X	X	X
CRP	X	X	X	X	X
hCG serum	X	--	--	--	--
Urine					
Urine dip stick test**	X	X	X	X	X

* including lymphocyte, neutrophils count, and eosinophils

** leukocytes, nitrite, pH, protein, glucose, ketones, urobilinogen, bilirubin, blood/hemoglobin

Hematological status, serology and clinical chemical parameters will be determined by LKF, Lise-Meitner-Str. 25 – 29, 24223 Schwentinental, Germany. Urinalyses will be performed at the sites using a dipstick test (Medi-Test®, Combi 10L, Macherey-Nagel, Dueren, Germany). Approximately 19.2 ml of blood will be withdrawn at each visit with laboratory analysis (in total approximately 116 mL per patient). For the PK subgroup additional 24.5 mL will be withdrawn on day 1 and day 84 (in total 49 mL per patient).

Spontaneously noted complaints will be recorded with duration, intensity and probability of a correlation with the IMP (see section 7.3., evaluation of adverse events).

5.5.3 Vital signs

Blood pressure and pulse rate will be measured at all visits after at least 5 minutes in a seated position. The following ranges for vital signs are given in table 5.

Table 5: Vital signs ranges

Variable	Units	Acceptable limit
Systolic blood pressure	mm Hg	80 - 150
Diastolic blood pressure	mm Hg	60 - 95
Heart rate	beats/min	50 – 100

Values outside 160 mm Hg / 95 mm Hg will not be randomized.

5.5.4 Smoking and alcohol consumption

Information on smoking and alcohol consumption will be documented at screening.

5.5.5 Physical examination

The physical examination comprises a routine medical examination including gross neurological assessments. The following body systems will be examined: basic status of the main organ systems (ENT, heart, lungs, abdomen, neurological status) as well as physical examination of the skin.

5.5.6 Appropriateness of assessments

PASI, PGA, BSA are widely used, non-invasive methods for examining overall psoriasis severity and coverage.

These methods are described in the EMA guideline [2] for evaluation of product efficacy.

Assessments should be conducted by investigators who are experienced and have been trained on the use of these evaluation tools. If possible, the same investigator should complete the evaluations for a given patient throughout the trial.

5.5.7 Primary efficacy/tolerability variable(s)

Primary variable:

The primary efficacy variables are:

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 are:

1. 50% improvement (response) in their PASI score (PASI 50)
2. Mean PASI score and change to baseline
3. Time to achieve PASI 50 and PASI 75
4. Mean score and change from baseline in the PGA
5. Mean score and change from baseline in the BSA
6. PK data

The primary variables are choose in accordance to the EMA guideline http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003329.pdf (4)

6. Data analysis and statistics

The statistical evaluation will be performed at bioskin using the software program SAS® (Statistical Analysis System, SAS, Cary, NC), Version 9.3 or higher.

A formal statistical analysis plan (SAP), providing a complete description of the methodology of the planned statistical analyses, will be written, finalized, and signed prior to breaking the trial blind. Any changes in the statistical methods described in this protocol that occur prior to database lock will be documented in the SAP and will not require a protocol amendment.

6.1 Generation of data base

In general, data from the source documents will be captured in an eCRF by a software package that can be customized for remote data entry procedure and that maintains an electronic audit trail. The eCRFs will be developed in the EDC system in accordance with bioskin SOPs under supervision and in agreement with the sponsor. The database structure will be validated.

Only authorized site personnel will be able to enter/modify/correct data to the eCRF. The investigator/coordinator or designee must enter the information required by the protocol as soon as possible after the visit into the eCRF.

The data will be checked for consistency. Queries for discrepant data may be generated automatically by the system upon entry or generated manually by the monitor or the trial data manager. All queries, whether generated by the system or by a user, will be in an electronic format. Once all the queries are closed and data have been verified by the CRA, the eCRF will be signed (eSignature) by the investigator and the database will be locked.

All data management procedures will be detailed in a separate, specifically identified file that collectively will be referenced as the (DMP).

Adverse events and medical history will be coded with Medical Dictionary for Regulatory Activities (MedDRA) mapping system, previous and concomitant therapy will be coded according to WHO-DD.

Patient data in PDF files generated from the eCRF will be provided to the site at the end of the trial.

6.2 Analysis sets and type of analysis

The safety-evaluation-set (SES) will include all patients who received any trial medication at least once; all safety analyses will be based on the SES.

The full-analysis-set (FAS) will include all randomized patient who received at least one dose of IMP, and had at least one post-baseline assessment. The intention-to-treat (ITT) analysis will be based on the FAS.

The valid-cases-set (VCS) will include all patient from the FAS, without any protocol violation interfering with the trial aims and with sufficient exposure to IMP. The per-protocol (PP) analysis will be based on the VCS.

6.3 Hypotheses

Since this is an exploratory trial no formal hypotheses are postulated. The data will be evaluated descriptively.

6.4 Rationale for the sample size

It is planned to recruit approximately 150 patients for this clinical trial in Germany and Poland (each country approximately 75 patients) to achieve 120 evaluable patients.

No formal sample size calculations were performed for this explorative trial. A sample size of 40 in each group is adequate to detect a difference in rates of at least 0,274, with 80% power, using a two group χ^2 test with a 0,100 two-sided significance level.

6.5 Statistical methods

Statistical analyses will be performed using two-sided tests, without adjustment for multiplicity. All p-values will be interpreted descriptively.

Data will be summarized by treatment group (and by visit when applicable), with respect to demographic and baseline characteristics, efficacy variables, and safety variables.

Summary statistics will include the mean, number of non-missing cases (n), standard deviation, median, minimum, and maximum values for continuous variables, and frequencies and percentages for categorical variables.

Categorical efficacy variables will be analyzed using the Cochran-Mantel-Haenszel (CMH) test with stratification by (pooled) analysis center and the Fisher's exact test in case of analyses without stratification (mainly for safety assessment).

Selected scores will be analyzed using an analysis of covariance (ANCOVA) model, with treatment group and (pooled) analysis center as factors and baseline outcome as covariate.

Time to event data will be analyzed using the Kaplan-Meier method, and treatment group differences will be tested by the log-rank test.

Unless otherwise specified, baseline is defined as the latest non-missing observation prior to first treatment with IMP.

Details of the model and the analyses will be specified in the SAP.

6.5.1. Efficacy analyses

Primary efficacy endpoints

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

Secondary efficacy endpoints

Secondary efficacy endpoints will be evaluated descriptively. The methodology outlined in section 6.5 will be applied for pairwise treatment comparisons vs. placebo.

Responder rates will be evaluated as the primary efficacy endpoint.

The change in the PASI score from baseline to each post baseline visit, respectively, will be evaluated using an analysis of covariance (ANCOVA) model, with treatment group and (pooled) analysis center as factors and baseline outcome as covariate.

The time to achievement of PASI 50 and PASI 75, respectively, will be evaluated using the Kaplan-Meier method. Pairwise treatment group differences will be tested by the log-rank test.

Descriptive summaries will be provided for each parameter by treatment group and by visit, if applicable. Percentages will be provided based on the number of non-missing cases, if not otherwise stated.

6.5.2. Safety analyses

All AEs reported during the trial will be listed, documenting course, severity, investigator assessment of the relationship to the IMPs, and outcome. AEs will be coded using the MedDRA mapping system for preferred terms (PTs) and system organ class (SOC).

Treatment-emergent adverse events (TEAEs), i.e. AEs with an onset or worsening on or after the time of the first IMP application will be summarized by the number of patients reporting TEAEs, primary system organ class (SOC), preferred term (PT), severity, and relationship to IMP.

Listings of serious adverse events (SAE) and patients who prematurely discontinued treatment due to AEs will be given.

Safety laboratory parameters (hematology, clinical chemistry) and vital signs will be summarized descriptively, including changes from baseline. Urinalysis outcomes will be summarized by frequency counts.

6.5.3. Other analyses

Blood MP1032 concentration-time data will be listed 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 will be provided.

Statistical analyses will be performed using non-compartmental analysis (NCA) methods, as appropriate, providing C_{max}, t_{max} and $AUC_{(0,t)}$. Listings and summary statistics of NCA parameters will be provided.

6.6 Handling of dropouts and missing data

For the evaluation of success rates of the primary efficacy variables PASI and PGA missing PGA assessments and/or any parts of the PASI assessments will be evaluated as failure to achieve improvement. For descriptive analyses of PASI, PGA and BSA the last observation carried forward (LOCF) principle will be applied to impute the missing assessments, up to the Day 84 visit. Follow-up assessments will not be imputed.

Sensitivity of the primary efficacy analyses will be evaluated applying PP analyses.

Handling of missing AE data, will be detailed in the SAP.

6.7 Identification of source data

For the following source data should be available:

- patients identification incl. age, height and weight
- relevant previous and concomitant therapies
- up-to-date relevant medical history (last 5 years)
- findings at physical examination
- pregnancy test results

- date of entry into the trial/visit dates
- vital signs
- adverse events
- laboratory results
- photographic documentation (at the selected sites)
- assessment scores PASI, PGA and BSA
- PK sampling (at the selected sites)
- Randomization number
- date and time of assessments
- IMP return / accountability and administration
- Missing treatment (diary)

7. Adverse events

7.1 Evaluation of adverse events

An adverse event (AE) is any untoward medical occurrence in a patient or clinical trial subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

The period of observation for adverse events extends from the time the patient gives informed consent until the trial is completed. Adverse events that are still present after the last patient's scheduled visit will be followed up 28 days of receiving the last IMP dose by means of a visit. After that time point the need for additional follow-up of ongoing AEs/SAEs will be discussed between the investigator and the sponsor, although in the event of discrepancies the investigator's criteria will prevail. Adverse events occurring after the end of the clinical trial must be reported if the investigator considers there is a causal relationship with the investigational product.

The investigator will be responsible for the necessary acute medical treatment of any adverse event required during the trial and will ensure that appropriate medical care will be maintained thereafter, if necessary.

All patients experiencing adverse events - whether considered related with the use of the IMP or not - will be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report will be supplied, if possible. "Related" means a reasonable

possibility that the event may have been caused by the IMP. All findings will be reported on an "adverse event"/“serious adverse event“ page in the case report form.

All adverse events, including intercurrent illnesses, will be reported and documented as described below.

Adverse events are divided into the categories "serious" and "nonserious". This determines the procedure which will be used to report/document the adverse event (see below).

Surgical procedures themselves are not adverse events; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required is an adverse event, if it occurs or is detected during the trial period. Planned surgical measures permitted by the clinical trial protocol and the condition(s) leading to these measures are not adverse events, if the condition(s) was (were) known before the start of treatment with investigational product. In the latter case the condition should be reported as medical history.

7.2 Definition of serious and nonserious adverse events

A serious adverse event is any untoward medical occurrence that at any dose:

- results in death or is life-threatening;
- results in permanent or significant disability/incapacity;
- requires inpatient hospitalization* or prolongation of hospitalization;
- results in a congenital abnormality/birth defect.

Medical and scientific judgment will be exercised in classification of other important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Adverse events which do not fall into these categories are defined as nonserious.

*Hospitalization solely for the purpose of diagnostic tests, even if related to an adverse event, elective hospitalization for an intervention which was already planned before the inclusion of the patient in the clinical trial, and admission to a day-care facility may not themselves constitute sufficient grounds to be considered as a serious adverse event.

7.3 Reporting/documentation of adverse events

7.3.1 Reporting of adverse events

Adverse events either reported by the patient, or observed by the investigator **must be recorded on the adverse event page of the eCRF** and should be described in the following manner:

The **nature** of the event will be described in precise, standard medical terminology (i.e. not necessarily the exact words used by the patient). If known, a specific diagnosis should be stated (e.g., allergic contact dermatitis).

The **intensity** of the adverse event will be described in terms of mild, moderate or severe according to the investigator's clinical judgment.

- **Mild**: The adverse event does not interfere in a significant manner with the patient's normal functioning level, but may be an annoyance.
- **Moderate**: The adverse event produces some impairment of functioning but is not hazardous to health, but is uncomfortable and/or an embarrassment.
- **Severe:** The adverse event produces significant impairment of functioning or incapacitation and is a hazard to the patient.

The **duration** of the event will be described by the start date and end date.

The **causal relationship** of the event to use of the IMP will be described in terms of:

Certain: the adverse event

- occurs in a plausible time relationship to IMP administration, and cannot be explained by concurrent disease or other drugs or chemicals, and
- follows a clinically plausible response to withdrawal of the IMP, and
- is definitive based on recognized pharmacological or other parameter associated with the IMP, and
- is confirmed by rechallenge procedure, if performed.

Probable: the adverse event

- follows a reasonable temporal sequence from administration of the IMP, and
- is unlikely to be attributed to a disease or other drug/s, and
- disappears or decreases on withdrawal of the IMP

Possible: the adverse event

- follows a reasonable temporal sequence from administration of the IMP, but
- can also be explained by disease or other drugs, and
- information on drug withdrawal may be lacking or unclear.

Unlikely: the adverse event

- does not follow a reasonable temporal sequence from administration of the IMP, and
- can be reasonably explained by disease or other drug/s, and
- does not follow a known pattern of response to the IMP, and
- does not reappear or worsen upon re-challenge, if performed.

Not related: the adverse event

- The event is either a pre-dose event or is definitely due to causes separate from the administration of the IMP, i.e.
  - documented pre-existing condition
  - technical and manual procedural problems
  - concomitant medication
  - patient's clinical state

The **outcome** of the event will be described in terms of:

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

It will also be recorded if the IMP use is continued, interrupted or discontinued.

Note: Insofar as possible all serious adverse events should be followed-up to determine the final outcome of the event. Details of follow-up should be given (e.g. discontinuation of IMP, if specific treatment is required, if hospitalization is required, FU by PharmaLex, FU by Investigator etc.).

For the purpose of expedited reporting for the causality assessment (i.e. relationship of the adverse event to IMP) the terms “probable” and “possible” describe a relationship to IMP treatment, whereas the terms “unlikely” and “not related” classify the event as being not related to IMP treatment.

7.3.2 Reporting of serious adverse events

The investigator shall report all serious adverse events immediately (within 24 hours after he becomes aware of the event) by fax or e-mail to PharmaLex. General information on the patient (pseudonymed), the randomization number, and screening identification number event term (diagnosis) and measures already taken are to be reported. The immediate report shall be followed by detailed, written reports. The investigator is obliged to completely document the course of the event and the measures taken, if possible including the original findings and using the form for serious adverse events. Additional documentation is carried out on the case report forms.

SAE reports should be emailed/faxed to the Pharmacovigilance unit of the PV vendor:

CCI, PPD [redacted]

For reported deaths of a patient, the investigator shall supply the sponsor and the ethics committee with any additional information requested.

The sponsor/PharmaLex shall ensure that all relevant information about suspected unexpected serious adverse reactions (SUSAR) that are fatal or life-threatening is recorded and reported as soon as possible to the competent authorities in all the member states concerned, and to the ethics committee, and in any case no later than seven days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

All other SUSARs shall be reported to the competent authorities concerned and to the ethics committee concerned as soon as possible but within a maximum of fifteen days of first knowledge by the sponsor accordingly.

PharmaLex shall also inform all investigators.

7.4 Pregnancies

Pregnancies occurring during a patient's participation in a clinical trial, although not typically considered an SAE, must be notified to the sponsor within the same timelines as an SAE (within 24 hours after being made aware of the pregnancy) on a pregnancy notification form. The pregnant trial patient should be withdrawn immediately from the trial.

Pregnancy reports should be emailed/faxed to the Pharmacovigilance unit of the PV vendor:

CCI, PPD [redacted]

Any pregnancy occurring in the trial should be followed up until outcome. If relevant, the development of the newborn has to be monitored for an appropriate time post-delivery.

8. Case report form (CRF), documentation and archiving

- The CRFs will be drawn up by bioskin in agreement with the sponsor.
- All trial documents, in particular the eCRFs, must be continually filled out. The eCRF is validated system which automatically creates an audit trail for all changes.
- The documentation will be kept in such a way, that it is possible to easily reconstruct the course of the trial at a later date (in accordance with the details given in the clinical trial protocol). All documents will be filed in the TMF or the investigator file, respectively.
- Following the specific patient information, consent forms will be signed by the patient and the physician responsible for supplying information twice. One will be filed in the investigator file. And one will be given to the patient.
- Electronic data media are to be clearly marked with the trial number/data type/date/hard- and software information (readability).
- All trial documents drawn up or available in paper form (e.g. raw data on data forms, CRFs, informal papers, printouts, etc.) are to be uniformly labeled with the trial number/screening number/data type/measurement time point and/or time/date/initials of the staff member.
- Clinical research associate (CRA) will verify all data entered into eCRFs for completeness and accuracy with reference to the source documents and records and will issue manual

data queries to correct missing data or discrepancies found against the source within the EDC system.

- Data validation will consist of automated and manual edit checks that are created directly in EDC. Automated edit checks will be executed on all data points defined and documented by the trial team and data management.
- Any changes from the clinical trial protocol in trial planning or execution after submission of the final version of the clinical trial protocol that have ethical or medical implications are to be documented as a „Substantial amendment to clinical trial protocol," including cause, content, grounds, consequences, date and the signature of the sponsor and investigator. Such an amendment must be submitted to the appropriate ethics committee(s)/competent authority(ies) for approval. All staff involved in the trial will be informed by the clinical trial manager and investigator. Changes in the clinical trial protocol are only allowed after prior consultation with the person in charge of the trial at the sponsor (clinical trial manager). Changes without ethical or medical implications are to be documented as non-substantial amendments or file notes including date and signature of the sponsor and the responsible person at bioskin.
- After all data have been verified by the CRA, an investigator or sub-investigator is required to review and approve all eCRFs prior to database lock and breaking of the blind.
- After database lock, each site will be provided with the eCRF data from their site for local archival purposes.
- After the conclusion of the trial, the original trial documents (TMF, CRFs) are to be submitted to the sponsor according to the agreements made.
- Currently the statutory period for archiving the documents after conclusion of the trial is at least 15 years.

8.1 Primary source documents

The investigator must maintain primary source documents supporting significant data for each patient's medical notes.

All applicable trial data collected on each patient will be recorded by trained site personnel into the source data record and the eCRF. Only authorized site personnel will be able to enter/modify/correct data to the eCRF.

Source documents such as the medical records are to be maintained separately from the eCRF to allow data verification. Because of the potential for errors, inaccuracies, and illegibility in transcribing data onto eCRFs, originals of laboratory and other test results must be kept on file

with the patient's source documentation. The investigator must also retain all patient-specific printouts/reports of tests and procedures performed as a requirement of the trial. During monitoring visits the monitor will validate eCRF entries against these sources of data.

eCRFs, source documents, and copies of test results must be available at all times for inspection by the trial monitor, auditors, or regulatory inspectors. The following should also be available for review

- Patient screening log, which should reflect the reason any patient screened for the trial was found to be ineligible;
- Site personnel and delegation log, which will list all site personnel with their responsibilities as delegated by the investigator and their signatures. This log will be maintained at the site throughout the trial;
- Monitoring visit log, which will list the date and purpose of all monitoring visits by the sponsor or designee;
- Enrollment log, which will list patient initials and start and end dates for all enrolled patients;
- Drug inventory/Packing slip, which will list the total amount of drug shipped to the site and received and signed for by the investigator;
- IMP dispensing log, which will list the total amount of IMP dispensed to and returned by each patient;
- ICF which must be available for each patient and be verified for proper documentation. Following the specific patient information, consent forms will be signed by the patient and the physician responsible for supplying information twice. One will be filed in the investigator file. And one will be given to the patient;
- All correspondence.

9. Statutory regulations and GCP

This clinical trial will be conducted in compliance with the protocol. Planning and execution of this clinical trial are subject to globally accepted standards of good clinical practice (as defined in the ICH E6 (R2) guideline for good clinical practice, November 2016), in agreement with the Declaration of Helsinki and in keeping with local regulations.

9.1 Ethics committee/competent authorities

Before the start of the trial, the clinical trial protocol, informed consent document, and other appropriate documents will be submitted to the appropriate ethics committees (ECs) and competent authorities (CAs). The trial must not start before approval has been granted by the appropriate EC and no grounds for non-acceptance have been issued by the CA concerned.

9.2 Insurance

Insurance policy will be provided for each country participating in the study in accordance with local regulations.

In Germany every patient participating in the clinical trial will be insured in accordance with § 40 paragraph 3 of the German drug law against injuries to health which may occur during the trial.

Excluded from this however are injuries to health and deteriorations of illnesses already in existence which would have occurred or continued to exist even if the patient had not taken part in the clinical trial.

The insurance cover is jeopardized if the patient fails to report immediately to the investigator or responsible physician any injury to health which might have resulted from participation in the clinical trial, or if he/she undergoes any other medical treatment without their consent before the clinical trial has been completely finished - insofar as the individual patient is concerned.

Any injury to health which might have occurred as a result of participation in the clinical trial must be reported by the patient to the insurer without delay. The investigator is obliged to make such a report in any case.

The patient insurance will be arranged by bioskin GmbH on the basis of the final version of the patient information and informed consent form. The patient insurer is CCI [redacted].
The insurance policy number is CCI [redacted].

9.3 Patient instruction and consent forms

Every patient will receive a complete and comprehensive explanation of the significance, nature, extent and possible risks of the trial. To this end a detailed, written patient information sheet will be made available. In addition a physician will carry out an oral information session during which the patients will be given sufficient time and opportunity to clarify remaining questions. Two identical forms for written informed consent will be given to the patients for signature. One copy of the signed forms will be archived in the investigator file and the other retained by the patient.

The investigator will acknowledge instruction of every patient in accordance with the clinical trial protocol and the existence of a signed consent form.

9.4 Data protection

During the clinical trial medical and personal information (like age, gender, racial, and ethnic origin) will be collected at the site and documented in the personal file or electronically saved. In addition, important data for the clinical trial (including photos and PK data of the subgroups) will be saved pseudonymized, transferred, and evaluated.

If necessary, the collected and saved data (including the photos and PK data) during the clinical trial will be held for inspection by the supervisory authority or by people charged by the sponsor who check that the trial is done properly. If needed, the related data will be shared pseudonymized to:

- The sponsor or sponsor-appointed party for the purpose of scientific analysis;
- The applicant and the authority responsible for marketing authorization, in case that application for marketing authorization is requested;
- Sponsor and the responsible competent authority, which will also forward the data to the European database, in case of adverse events of the trial drug;
- Parties in Europe and in non-European foreign countries which are affiliates of the Sponsor and as well forwarded to the responsible authorities in charge of marketing authorization by the latter.

Personal and medical data collected during the trial may be moved, stored and used in the EU or another country where the sponsor or those working with the sponsor located. Data – including trial results – might be published in Scientific Journals, Conference abstract, etc. The trial and trial data will be published in clinicaltrials.gov.

9.5 Termination of participation

Every patient has the right to refuse further participation in the trial at any point in time and without giving reasons. Nonetheless, efforts should be made to find out the cause and to document it on the case report form. If the administration of the investigational product has already taken place at the time of refusal, the patient should be convinced to consent to a complete final examination as planned in the protocol in his/her own interest. This has to be documented on the corresponding pages of the eCRF.

9.6 Quality control (Trial monitoring)

According to bioskin quality management procedures internal quality control will be applied to all steps of the trial e.g. planning, conduct, analysis and reporting.

A representative of sponsor or bioskin will monitor the trial progress as regularly as necessary during the conduct of the trial until the last case report forms have been completed and all queries have been resolved.

The trial and site activities will be monitored according to the ICH-GCP guidelines for:

- Protocol adherence (trial is conducted in accordance with the currently approved protocol and any other trial agreements)
- Quality of data (data are authentic, accurate, and complete)
- Drug accountability
- Protection of safety and rights of patients
- Compliance with regulatory requirements (trial is conducted in accordance with GCP, and all applicable regulatory requirements)
- Adequacy of the facilities (unchanged high qualification of the site and site staff)

The investigators and the head of the medical institutions (where applicable) agree to allow the monitor direct access to all relevant documents.

9.7 Quality assurance

To ensure compliance with GCP and all applicable regulatory requirements Sponsor may conduct a quality assurance assessment and/or audit of the site records at any time during or after completion of the trial.

Auditing will be performed by or on behalf of Quality Assurance MetrioPharm in accordance with the requirements of Note for Guidance on Good Clinical Practice, the clinical trial protocol, applicable standard operating procedures and according to the agreed audit plan.

All audit activities in the course of MP1032-CT04 will be documented and archived.

Independent of any sponsor audit the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the trial.

In the event of an assessment, audit or inspection, the investigators (and institutions) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the trial, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

9.8 Handling of investigational medicinal products

The investigator or his representative confirms receipt of the IMPs in writing and will only use them within the framework of this clinical trial and in accordance with the existing clinical trial protocol. All containers opened, together with remaining contents and unopened containers will be returned to the manufacturer at the end of the trial.

Delivery, consumption and return must be completely documented.

A written explanation must be compiled on any containers/investigational products which are missing. The investigational products will be stored in a safe place according to the manufacturer's instructions for storage.

The investigator is responsible for ensuring appropriate storage and control of the IMPs. Storage records, including temperature records should be maintained and be available for inspection during the course of the trial.

Deviations in storage requirements should be reported to the CRA, the bioskin CTM and to the sponsor and may require that the IMP is quarantined during the review of the deviation.

10. Trial administrative structure/responsibilities

Any change of the following responsible persons will not be considered as an amendment.

Table 6: Trial administrative structure/responsibilities

Function	Name / contact data
International coordinating investigator	PPD, CCI [redacted]
Sponsor project manager(s)	
Sponsor's responsible physician	
Randomization	
Data management	
Statistics (including PK)	
Responsible for pharmacovigilance/ Drug safety (sponsor representative)	
Medical Monitor	
Medical monitor (back-up)	
Clinical trial manager at bioskin	
Central Lab	
PK Lab	
Affiliated regional CRO	
Clinical supplies – packaging, distribution	
Lead CRA	

11. Literature

[1] Nast A. Boehncke WH. Mrowietz U et al. S3-Leitlinie zur Therapie der Psoriasis vulgaris Update 2011. JDDG; 2011; 9 (Suppl. 2):S1-S104.

[2] EMA Guideline on Psoriasis. Guideline on Clinical Investigation of Medicinal Products Indicated for the Treatment of Psoriasis. Issued by the European Medicines Agency, London,18 November 2004. Accessed 27 Jan 2016.

[3] MetrioPharmAG. Investigator's Brochure MP1032. Edition No. 5. 18. Sep 2017.

[4] World Health Association Declaration of Helsinki. Ethical Principles for Medical Research involving Human Patients. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996.

[5] Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95). The European Agency for the Evaluation of Medicinal Products (EMEA) 2002;1-59.

[6] Grekin SJ, Ellis CN. Evaluating the severity of dermatologic disorders. Dermatol Ther 2009;22(3);191-198.

Appendix A
Trial flow chart

Trial flow chart

Trial Period	Screening	Treatment phase				Follow-up	Unscheduled visit
Day	(Day - 28 to -3)	Day 1	Day 28 (±2 days)	Day 56 (±2 days)	Day 84 (+5 days)	Day 112 (±2 days)	
Visit Number	1	2	3	4	5	6	unscheduled
Procedure							
Informed consent	X						
In-/exclusion criteria	X	X					
Demographics/medical history	X						
Physical examination	X	X			X	X	
Height, body weight, BMI	X						
Smoking history/ alcohol consumption	X						
Vital signs	X	X	X	X	X	X	
Pregnancy test in female patients [a]	X	X[b]			X		
Safety laboratory, incl. urine dipstick	X	X	X	X	X	X	X
HIV, Hepatitis	X						
Randomization		X					
Localization of photographic documentation test field[c]		X					
Photographic documentation [c]		X	X	X	X	X	
PK sample [d]		X			X		
PASI	X	X	X	X	X	X	
PGA	X	X	X	X	X	X	
BSA	X	X	X	X	X	X	
Dispensing of IMP		X	X	X			
IMP administration [e]		X	X	X	X		
Diary dispensing		X	X	X			
Drug return / accountability			X	X	X		
Diary return and check			X	X	X		
Prior and concomitant therapy	X	X	X	X	X	X	X
Adverse events [f]	X	X	X	X	X	X	X

a) A serum pregnancy test will be done for all women at screening and urine test for all other visits.
b) A urine pregnancy test on Day 1 will be performed prior to the first administration of IMP for all women.
c) Only performed in a subgroup of approx. 2 sites (approx. 30 patients); on Day 1 Photographic

documentation will be performed prior to the first administration of IMP

d) Only performed in a subgroup of approx. 4 sites (approx. 30 patients); on Day 1 and Day 84 first PK sample will be performed prior to the first administration of IMP. PK samples will be collected before IMP administration, and 15, 30, 60 and 120 minutes after administration of IMP.

e) IMP administration will start on Day 1 after randomization and will continue as self-administration by trial patients at home until Day 84. Patients included in the PK analysis will administrate the first treatment (Day 1) at the site. All patients will administrate the last treatment (Day 84) at the sites.

f) AE reporting starts after the signature of informed consent form and finishes at the End of Study Follow-Up Visit.

Appendix B
PASI

Appendix B Psoriasis Area Severity Index (PASI)

Shown below is the original description of the PASI (Fredriksson T, Pettersson U. Dermatologica 1978;157:238-44) which involves the assessment of erythema (E), infiltration (I), and desquamation (D), and body surface area involvement (A) over 4 body regions (head (h), trunk (t), upper (u) and lower (l) extremities).

Degree of severity (per body region)	Value given
No symptoms	0
Slight	1
Moderate	2
Marked	3
Very marked	4

Surface involved (per body region)	Value given
<10%	1
10-29%	2
30-49%	3
50-69%	4
70-89%	5
90-100%	6

Because the head, upper extremities, trunk, and lower extremities correspond to approximately 10, 20, 30, and 40% of body surface area, respectively, the PASI score is calculated by the formula:

PASI = $0.1(Eh + Ih + Dh)Ah + 0.2(Eu + Iu + Du)Au + 0.3(Et + It + Dt)At + 0.4(El + Il + Dl)Al$