# Clinical Trial Protocol

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| **Trial Title:** | **A Randomised, Multicentre, Investigator-Blind, Parallel-Group Trial to Evaluate the Efficacy and Safety of MC2-01 Cream Compared to Vehicle and Active Comparator in Subjects with Mild-to-Moderate Psoriasis Vulgaris** |
| **Investigational product:** | **MC2-01 (calcipotriol/betamethasone dipropionate, 0.05/0.64 mg/g) cream** |
| **Active Comparator:** | **Calcipotriol/betamethasone (calcipotriol/betamethasone dipropionate, 0.05/0.64 mg/g) gel** |
| **Protocol No:** | **MC2-01-C7** |
| **IND number:** | **127152** |
| **EudraCT number:** | **2018-001970-66** |
| **Development phase:** | **3** |
| **Documents status:** | **Final** |
| **Document version:** | **Version 2.0** |
| **Document date:** | **16 October 2018** |
| **Sponsor:** | **Drug Delivery Solutions Ltd (part of MC2 Therapeutics)**<br>**c/o Agern Alle 24-26**<br>**2970 Hoersholm**<br>**Denmark**<br>**("MC2")** |

## CLINICAL TRIAL PROTOCOL APPROVAL

**Product:** MC2-01 (calcipotriol/betamethasone dipropionate) cream

**Protocol number:** MC2-01-C7

**Protocol title:** A Randomised, Multicentre, Investigator-Blind, Parallel-Group Trial to Evaluate the Efficacy and Safety of MC2-01 Cream Compared to Vehicle and Active Comparator in Subjects with Mild-to-Moderate Psoriasis Vulgaris

The following persons have approved this clinical trial protocol, which are separate documents adjoined to this document:

Johan Selmer, MD, VP Medical Affairs, MC2 Therapeutics

Charlotte Hindsberger, Principal consultant, Biostatistics, S-cubed

Matthias Augustin, Prof. Dr. med, International Coordinating Investigator, University Medical Center Hamburg-Eppendorf

## SIGNATURE PAGE FOR INVESTIGATOR(S)

**Product:** MC2-01 (calcipotriol/betamethasone dipropionate; 0.05/0.64 mg/g) cream

**Protocol number:** MC2-01-C7

**Version:** 2

**Protocol title:** A Randomised, Multicentre, Investigator-Blind, Parallel-Group Trial to Evaluate the Efficacy and Safety of MC2-01 Cream Compared to Vehicle and Active Comparator in Subjects with Mild-to-Moderate Psoriasis Vulgaris.

The signature of the trial investigator below constitutes his/her approval of this protocol and provides the necessary assurances that this trial will be conducted according to all stipulations, clinical and administrative, as detailed in the protocol. The trial will not be initiated without the approval of an appropriate Institutional Review Board or Ethics Review Committee.

_____
Principal investigator's printed name

_____ _____
Principal investigator's signature Date

TABLE OF CONTENTS

## LIST OF TABLES



## LIST OF FIGURES

List of Abbreviations and Definition of Terms

| Abbreviation | Definition |
|---|---|
| ACE | Angiotensin converting enzyme |
| AE | Adverse event |
| ANCOVA | Analysis of covariance |
| BDP | Betamethasone dipropionate |
| BSA | Body surface area |
| CAL | Calcipotriene (United States term) / Calcipotriol (European Union term) |
| CRO | Contract Research Organisation |
| DLQI | Dermatology Life Quality Index |
| eCRF | Electronic case report form |
| EQ-5D | EuroQOL five dimensions |
| EU | European Union |
| FDA | Food and Drug Administration |
| HIV | Human immunodeficiency virus |
| ICF | Informed consent form |
| ICH-GCP | International Conference on Harmonisation-Good Clinical Practice |
| IEC | Independent Ethics Committee |
| IP | Investigational product |
| IRB | Institutional Review Board |
| ITT | Intent to treat |
| IUD | Intrauterine device |
| IUS | Intrauterine hormone-releasing system |
| IWRS | Interactive web response system |
| LOCF | Last-observation-carried forward |
| LSR | Local skin reaction |
| MCMC | Markov Chain Monte Carlo |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | Multiple imputation |
| mPASI | Modified Psoriasis Area and Severity Index |
| NRI | Non-responder imputation |
| OTC | Over the counter |
| PGA | Physician's Global Assessment |
| PP | Per protocol |
| PRO | Patient reported outcome |
| PTCS | Psoriasis Treatment Convenience Scale |
| PUVA | Psoralen + ultraviolet A |

| Abbreviation | Definition |
|---|---|
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SD | Standard deviation |
| SGA | Subject global assessment of disease severity |
| SUSAR | Suspected unexpected serious adverse reaction |
| UBC | United BioSource Corporation |
| UPT | Urine pregnancy test |
| US | United States |
| UVA / UVB | Ultraviolet A / ultraviolet B |

## 1.0 SYNOPSIS

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| Trial Title: | A Randomised, Multicentre, Investigator-Blind, Parallel-Group Trial to Evaluate the Efficacy and Safety of MC2-01 Cream Compared to Vehicle and Active Comparator in Subjects with Mild-to-Moderate Psoriasis Vulgaris |
| Protocol Number: | MC2-01-C7 |
| Sponsor: | Drug Delivery Solutions Ltd (part of MC2 Therapeutics |
| Development Phase: | 3 |
| Primary Objective: | To evaluate the efficacy of MC2-01 cream compared to active comparator in subjects with psoriasis vulgaris. |
| Secondary Objective: | To characterise the safety profile of MC2-01 cream in subjects with psoriasis vulgaris. |
| Trial Design: | Randomised, investigator-blind, multicentre, vehicle and comparator-controlled, parallel-group, 3-arm trial. The trial will include a maximum 30-day screening period, an 8-week treatment period, and a 2-week post-treatment follow-up period. |
| Planned Sample Size: | A total of 476 subjects is planned to be randomised in a 3:1:3 ratio (MC2-01 cream: MC2-01 cream vehicle: active comparator).<br><br>Under the assumptions of the trial and a sample size of N=204 per active treatment group, the power for each of the superiority comparisons of MC2-01 cream and active comparator to MC2-01 cream vehicle with respect to Modified Psoriasis Area and Severity Index (mPASI) is more than 99%. Assuming that 30% of subjects treated with either MC2-01 cream or active comparator respectively, 11% of subjects treated with MC2-01 cream vehicle will have Physician's Global Assessment (PGA) success, the power for the each of the superiority comparisons with respect to PGA success is 90.4%. |

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| Trial Population: | Generally healthy males or non-pregnant females, at least 18 years of age, with a clinical diagnosis of plaque psoriasis (psoriasis vulgaris) of at least 6 months duration that involves non-scalp regions of the body (trunk and/or limbs), with a PGA of disease severity of mild or moderate on the body (trunk and/or limbs) and an mPASI score of at least 3. |
| Investigational Product(s): | MC2-01 cream (calcipotriene (CAL) and betamethasone dipropionate (BPD), w/w 0.005%/0.064%).<br><br>MC2-01 cream vehicle. |
| Reference Product(s): | Calcipotriene/betamethasone dipropionate gel/topical suspension, 50 micrograms/g CAL (as monohydrate)/0.50 mg/g betamethasone (as dipropionate, equivalent to 0.64 mg/g BDP), approved in the European Union (EU) as Dovobet® Gel/Daivobet® Gel and in the US as Taclonex® Topical Suspension. For this phase 3 trial, the reference product will be sourced in EU as Daivobet® / Dovobet® Gel. |
| Primary Endpoint: | Percentage change from baseline in mPASI on the body (trunk and/or limbs) at Week 8. |
| Secondary Endpoints: | • PGA success on the body (trunk and/or limbs) at Week 8<br>• Subject assessment of treatment convenience at Week 8 using the Psoriasis Treatment Convenience Scale (PTCS) Analysis of secondary endpoints |
| Safety Endpoints | • Local skin reaction;<br>• AEs and serious adverse events (SAEs);<br>• Changes in safety laboratory test results;<br>• Changes in vital signs and physical examinations |

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| PRO Endpoints: | • Subject assessment of treatment convenience at Week 4 using the PTCS.<br>• Change from Baseline in DLQI score at Week 4 and Week 8;<br>• Change from Baseline in EQ-5D score at Week 4 and Week 8; |
| Other Endpoints: | • Percentage change from Baseline in mPASI on the body (trunk and/or limbs) at Week 4;<br>• mPASI 75 (at least 75% reduction in mPASI from baseline) on the body (trunk and/or limbs) at Week 4 and Week 8;<br>• Change from baseline in Subject global assessment of disease severity (SGA) at Week 4 and Week 8;<br>• Change from baseline in PGA for the scalp at Week 4 and Week 8; |

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| Statistical Methods: | **Primary endpoint**<br><br>The primary efficacy endpoint is the percentage change in mPASI the body (trunk and/or limbs) from baseline to Week 8.<br><br><u>Superiority analysis</u><br><br>First the percentage change in mPASI from baseline to Week 8 for MC2-01 cream and the active comparator will be compared with that of MC2-01 cream vehicle for a superiority evaluation using the treatment-policy estimand for the Intent to treat (ITT) population and imputing missing data using multiple imputation (MI).<br><br>The comparison will be done using an ANCOVA model including treatment, site, and baseline PGA as factors, and baseline mPASI as covariate. The estimated differences between MC2-01 cream and MC2-01 cream vehicle, and between active comparator and MC2-01 cream vehicle, will be reported together with the associated standard error, the 95% confidence interval, and a test corresponding to no difference between treatments.<br><br><u>Non-inferiority analysis</u><br><br>Next, if and only if superiority to MC2-01 cream vehicle can be claimed for both MC2-01 cream and active comparator on the 5% significance level, MC2-01 cream will be compared to active comparator for a non-inferiority evaluation using the treatment-regimen estimand for the ITT population and imputing missing data using MI.<br><br>Percentage change in mPASI from baseline to Week 8 will be compared between MC2-01 cream and active comparator for a non-inferiority evaluation using the -12 percentage points non-inferiority margin. The comparison will be done using the same model as applied for the analysis of superiority vs. vehicle as described above: an ANCOVA model including treatment, site, and baseline PGA as factors, and baseline mPASI as covariate. The estimated difference between MC2-01 cream and active comparator will be reported together with the associated standard |

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| | error, and the 95% confidence interval. If the lower limit of the 95% confidence interval is above -12 percentage points, non-inferiority is demonstrated.<br><br>Sensitivity analyses<br><br>For the superiority analyses of MC2-01 cream and active comparator to MC2-01 cream vehicle, as well as for the non-inferiority analysis of MC2-01 cream to active comparator, the below sensitivity analyses will be performed.<br><br>Internal validity<br><br>The primary analysis using MI assumes that data are missing at random within each treatment arm. For each hypothesis, the sensitivity of this assumption is investigated using a so-called tipping point analysis; a penalty (a number) is added to all imputed Week 8 values in the MC2-01 treatment group or (when testing superiority of active comparator vs. vehicle) in the active comparator group, and the analysis is repeated on the ITT population for the treatment-regimen estimand. The penalty d is gradually increased until the point, the tipping point, where the conclusion (superiority or non-inferiority depending on the analysis) no longer is demonstrated. If the tipping point is considered a clinical plausible difference, the tipping-point analysis does not support the primary analysis.<br><br>External validity<br><br>• The primary analysis is repeated using the hypothetical-strategy estimand based on the ITT population and imputing missing data using MI.<br><br>• The primary analysis using the treatment-policy estimand and imputing missing data using MI is repeated based on the PP population.<br><br>Secondary Efficacy Endpoints<br><br>The secondary efficacy endpoints are:<br><br>• PGA success the body (trunk and/or limbs) at Week 8 |

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| | • Subject assessment of treatment convenience at Week 8 using the PTCS<br><br>Analyses of secondary endpoints<br><br>To control the global Type-I error, the secondary endpoints will be tested in hierarchical order, if and only if non-inferiority can be demonstrated for the primary endpoint. The endpoints will be analyzed using the treatment-regimen policy estimand for the ITT population.<br><br>For PGA success, missing PGA values will be imputed using MI considering PGA as a continuous endpoint.<br><br>• PGA success: PGA success of both MC2-01 cream and active comparator will be compared with that of MC2-01 vehicle for a superiority evaluation. The comparison will be done using a logistic model with treatment, baseline PGA, and site as factors.<br><br>• PGA success: Non-inferiority of MC2-01 cream versus active comparator. PGA success will be compared between MC2-01 cream and active comparator for a non-inferiority evaluation using a -10 percentage points non-inferiority margin, as -10 percentage point is considered the largest clinically acceptable loss of effect. This non-inferiority margin was also used in the MC2-01-C2 phase 3 clinical trial: A randomised, multicentre, investigator-blind, parallel-group trial to evaluate the efficacy and safety of MC2-01 cream compared to MC2-01 cream vehicle and active comparator in subjects with mild-to-moderate psoriasis vulgaris (1). The percentage of subjects in each group with treatment success will be calculated along with its 95% confidence interval (CI) using normal approximation. A 95%, 2-sided CI for PM-PA, where PM and PA is the PGA treatment success rate at Week 8 for MC2-01 cream and active comparator respectively, will be computed using normal approximation using Proc FREQ with RISKDIFF option. MC2-01 will be considered non-inferior to active comparator if the lower bound of the 2-sided 95% CI is ≥ -10% points. |

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| | • PCTS: Superiority of MC2-01 cream versus active comparator. A PCTS score is considered invalid, if subject has discontinued study medication more than 7 days prior to the day of assessment. Missing and invalid PTCS scores will be imputed using the last valid measure prior to the visit (LOCF). This approach corresponds to a "PCTS while on treatment" estimand. The PCTS score will be compared between MC2-01 cream and active comparator using an ANCOVA model with treatment, baseline PGA, and site as factors.<br><br>• mPASI: In analogy with the analysis of the primary endpoint, superiority of MC2-01 cream versus active comparator will be evaluated using an ANCOVA model including treatment, site, and baseline PGA as factors, and baseline mPASI as covariate. Missing mPASI values will be imputed using MI.<br><br>• PGA: Superiority of MC2-01 cream versus active comparator. PGA success will be compared between MC2-01 cream and active comparator using a logistic model with treatment, baseline PGA, and site as factors.<br><br><u>Sensitivity analyses</u><br><br>• For PGA success, a sensitivity analysis will be performed where missing values are imputed as non-responders (NRI). Another sensitivity analysis will be performed repeating the primary analysis for the hypothetical-strategy estimand based on the ITT population and imputing missing data using MI.<br><br>• For PCTS the analysis will repeated for the PP population instead of the ITT population with the same imputation (LOCF).<br><br>• For mPASI the same sensitivity analyses as for the primary endpoint will be performed. |
| Trial Sites: | Approximately 34 trial sites in EU |
| Planned Dates of Trial: | Trial initiation Q4, 2018 |

# 2.0 INTRODUCTION

## 2.1 Background

Psoriasis is a common, immune-mediated, inflammatory skin disease that is found world-wide. The prevalence of diagnosed psoriasis in the United States (US) is approximately 3%(2) whereas the prevalence in Europe varies anywhere from 0.6 to 6.5%(3) with an average of approximately 3% (4). The clinical course is unpredictable but, in most cases, psoriasis is a chronically remitting and relapsing disease. Chronic stable plaque psoriasis (psoriasis vulgaris) is the most common form of the disease, accounting for 85-90 % of cases(5). Plaque-type psoriasis or psoriasis vulgaris is the most common form of the disease, and manifests as raised, red, scaly patches with silver scales. The lesions are usually distributed symmetrically and occur most commonly on the extensor parts of elbows and knees; scalp, lumbosacral region and umbilicus(6). Patients with psoriasis have reduced quality of life with reduced levels of employment and income(7), and studies have shown that patients with psoriasis are emotionally and physically impaired by their disease comparable to that seen with cancer, heart disease, rheumatoid arthritis, diabetes or depression(8, 9).

Individuals with psoriasis appear to be at an elevated risk of developing other chronic and serious health conditions, such as metabolic syndrome/type 2 diabetes, cardiovascular disease, psoriatric arthritis and other chronic inflammatory diseases(10, 11).

There is no cure for psoriasis. The goal of treatment is to reduce or eliminate its signs and symptoms. Mild to moderate disease is often treated with topical therapies. Among topical therapies, a combination treatment of a Vitamin D analog and a topical glucocorticosteroid has become especially popular. Several studies show that the combination of calcipotriol (CAL) and betamethasone dipropionate (BDP) is superior to each of the single agents(12-14).There is strong scientific rationale for the combination of vitamin D and glucocorticosteroids both with respect to efficacy and safety(15-17), and combination treatment with a Vitamin D analog and a topical corticosteroid is recommended in both European and American guidelines(18-20).

CAL and BDP are incompatible in an aqueous environment, since CAL requires basic conditions to maintain stability while betamethasone requires acidic conditions. Currently marketed products are therefore restricted to non-aqueous, oil-based formulations.

Sponsor has developed the MC2-01 cream containing the fixed dose combination 0.005 w/w% CAL (as anhydrate) and 0.064 w/w% BDP using the proprietary PAD™ Technology which protects the drug substances from degradation during storage. The MC2-01 cream is easy to apply, and the cosmetic appearance is that of a white, easily-spreadable cream that absorbs completely into the skin a few minutes after application and it is expected that MC2-01 cream will differentiate from marketed formulations of CAL/BDP by patient preference for the cream.

## 2.2 Rationale of the Trial

In this trial, the MC2-01 cream will be compared with MC2-01 cream vehicle and the marketed product CAL/BDP combination gel/topical suspension, which is marketed under the brand name Dovobet® Gel/Daivobet® Gel in the EU and as Taclonex® Topical Suspension in the US. For this trial, the active comparator is sourced in the European Union (EU) as Daivobet® / Dovobet® Gel. This product is a liquid oil that contains the active ingredients CAL/BDP (calcipotriol/betamethasone dipropionate, 0.05/0.64 mg/g). This corresponds to 0.005% w/w calcipotriol and 0.064 % w/w (or 0.64 mg/g) betamethasone diproprionate, i.e. the same concentrations as in MC2-01 cream.

The currently marketed CAL/BDP products are restricted to non-aqueous oil-based formulations that are sticky and inconvenient to many patients(21). The MC2-01 cream possesses superior cosmetic properties to most other topical formulations, and the purpose of the trial is to compare the clinical efficacy, safety, and convenience of the MC2-01 cream to the Daivobet ® / Dovobet® Gel. Treatment convenience evaluated using the Psoriasis Treatment Convenience Scale will be included as a secondary endpoint.

The primary focus of this trial is psoriasis on the body (trunk and/or limbs). The rationale for including subject with psoriasis involving the scalp is to explore the efficacy of MC2-01 cream in scalp psoriasis. Psoriasis on scalp and body, respectively, are to be regarded as two separate treatment indications and the treatment effect are expected to differ.

## 2.3 Benefit-risk Assessment

The subject population will be composed of subjects with mild to moderate psoriasis; their psoriasis is expected to be manageable with topical therapy.

The active ingredients in the investigational products (CAL and BDP) are known to be effective for the treatment of psoriasis. The safety and efficacy profiles for marketed products with these ingredients (formulated as ointment, gel/topical suspension and more recently aerosol foam) are well known. A cream formulation of CAL and BDP may benefit subjects by providing improved convenience and ease of use resulting in increased patient adherence to therapy which will improve real-life treatment outcome (22).

According to the SmPC for Daivobet gel, the common AE (>1%) is pruritus. Uncommon (i.e. ≥0.1% and < 1%) AEs are folliculitis, skin infections, exacerbation of psoriasis, dermatitis, erythema, rash, skin irritation, skin burning sensation, application site pain, as well as eye irritation (probably related to use on scalp).

The available data on MC2-01 cream suggest that MC2-01 cream will display a similar safety profile as the approved CAL/BDP topical products. A Phase 3 trial with MC2-01 cream and a maximal usage trial in adults have completed enrolment. As of the cut-off date of this clinical trial

protocol, the adverse event reported is as expected and no serious unexpected serious adverse reactions (SUSARs) have been reported.

A subset of subjects will receive a cream vehicle. There is a risk that psoriasis symptoms may worsen in these vehicle-treated subjects; while an exacerbation of psoriasis may be inconvenient, it would not put the subjects at undue risk. In case of inadequate efficacy, the subject can decide to withdraw and then receive alternative therapy according to her/his choice.

## 3.0 TRIAL OBJECTIVES AND PURPOSE

The primary objective is to evaluate the efficacy of MC2-01 cream compared to active comparator in subjects with psoriasis vulgaris.

The secondary objective is to characterise the safety profile of MC2-01 cream in subjects with psoriasis vulgaris.

## 4.0 TRIAL DESIGN

### 4.1 Overall Trial Design

This is a randomised, investigator-blind, multicentre, vehicle and comparator-controlled, parallel-group, 3-arm trial. The trial will include a maximum 30-day screening period, an 8-week treatment period, and a 2-week post-treatment follow-up period.

Trial subjects will be enrolled at approximately 34 investigative sites in the EU. Approximately 476 subjects who meet the trial entry criteria will be randomly assigned in a 3:1:3 ratio to receive either MC2-01 cream, MC2-01 cream vehicle or active comparator. Subjects will apply trial medication to affected areas of the body (trunk and/or limbs) and, if applicable, scalp once daily for 8 weeks.

The maximum trial duration for each subject will be approximately 14 weeks and includes a screening period of up to 30 days (if washout of prohibited medications is required), an 8-week treatment period, and a follow-up period of 2 weeks. The end of trial is defined as last subject last visit.

After having provided written informed consent, the subject will undergo screening procedures. At the end of the screening period, eligible subjects will be randomly assigned to one of the trial treatment groups on Day 0 (Visit 1/Baseline) of the treatment period.

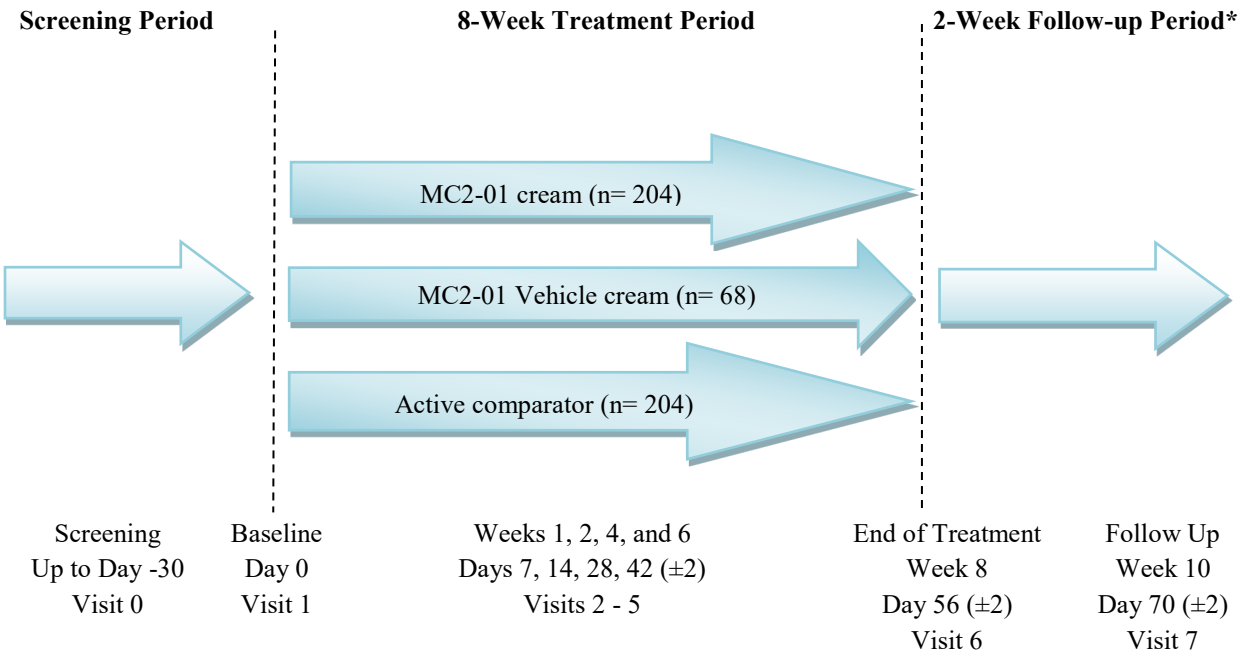
During the treatment period, subjects will return to the trial site according to the trial schedule for interim efficacy assessments, and assessment of compliance with the treatment regimen, concomitant medications, and adverse events (AEs).

The investigator will score the disease severity of the subject using mPASI, PGA, and body surface area (BSA) involvement; and the subject will perform a disease assessment using SGA. The

subjects will be asked to complete the Dermatology Life Quality Index (DLQI), EuroQOL five dimensions (EQ-5D), and the Psoriasis Treatment Convenience Scale questionnaires. Safety assessments (local skin reaction, AEs, laboratory tests, vital signs and physical examination) will be performed.

The trial design is summarised in Figure 4-1.

**Figure 4-1 Trial Design**




*Follow-up visits will be required for subjects who have treatment related unresolved AEs or elevated albumin corrected serum calcium levels at Week 8. For all other subjects, telephone call 2 weeks after the Week 8 visit is sufficient.

## 4.2 Trial Endpoints

### Primary Endpoint

- Percentage change from Baseline in mPASI on the body (trunk and/or limbs) at Week 8

### Secondary Endpoints

- PGA success at Week 8, defined as a minimum 2-point decrease from Baseline to Week 8 on the PGA of disease severity on the body (trunk and/or limbs); i.e., a score of 0 (clear) or 1 (almost clear) for subjects with moderate disease at Baseline; or a score of 0 (clear) for subjects with mild disease at Baseline.
- Subject assessment of treatment convenience at Week 8 using the PTCS.

**Safety Endpoints**

Safety endpoints include the following:

- Local skin reaction;
- AEs and serious adverse events (SAEs);
- Changes in safety laboratory test results;
- Changes in vital signs and physical examinations.

**Other Endpoints**

Efficacy

- Percentage change from Baseline in mPASI score on the body (trunk and/or limbs) at Week 4;
- At least 75% reduction in mPASI from Baseline (mPASI 75) on the body (trunk and/or limbs) at Week 4 and Week 8;
- PGA success at Week 4, defined as a minimum 2-point decrease from Baseline to Week 4 on the PGA of disease severity on the body (trunk and/or limbs); i.e., a score of 0 (clear) or 1 (almost clear) disease for subjects with moderate disease at Baseline; or a score of 0 (clear) for subjects with mild disease at Baseline.
- Change from baseline in PGA on the scalp at Week 4 and Week 8
- Change from Baseline in SGA at Week 4 and Week 8.

Patient reported outcome

- Subject assessment of treatment convenience at Week 4 using the PTCS.
- Change from Baseline in DLQI score at Week 4 and Week 8;
- Change from Baseline in EQ-5D score at Week 4 and Week 8;

# 5.0 SELECTION OF TRIAL POPULATION

## 5.1 Subject Population

A total of 476 subjects will be enrolled. An individual subject will be allowed to participate in the trial one time only. A rationale for the choice of sample size is provided in Section 8.2 of this protocol.

Each potential subject will sign and date an informed consent document before any trial-specified procedures are performed. Subjects will provide authorisation for use of their personal data in accordance with the applicable regulations regarding privacy and data protection.

## 5.2 Inclusion Criteria

Subjects must meet all the following criteria to be eligible for participation in the trial:

1. Have provided written informed consent.
2. Generally healthy males or non-pregnant females, of any race or ethnicity, who are at least 18 years of age at the time of screening;
3. Have a clinical diagnosis of plaque psoriasis (psoriasis vulgaris) of at least 6 months duration that involves the body (trunk and/or limbs) that is amenable to topical treatment with a maximum of 15 g of trial medication per day.
4. Have a PGA of disease severity of mild or moderate on the body (trunk and/or limbs);
5. Have an mPASI score of at least 3;
6. Have a treatment area involving 2−30% of the body (trunk and/or limbs). For subjects with scalp psoriasis included in the treatment area, the total treatment area on body and scalp must not exceed 30%;
7. Female subjects must be of either:
   - Non-childbearing potential, i.e., post-menopausal for at least 1 year or have a confirmed clinical history of sterility (e.g., hysterectomy or tubal ligation) or,
   - Childbearing potential with a negative urine pregnancy test prior to initiation of trial treatment, to rule out pregnancy.
8. Female subjects of childbearing potential must have a negative urine pregnancy test result at Screening, and if sexually active they must agree to use a highly effective method of contraception (i.e. a method with a failure rate of less than 1% per year when used consistently and correctly) for one month prior to Visit 1 and until the follow-up visit has been performed. Highly effective contraception is defined as follows:
   - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
     - oral
     - intravaginal
     - transdermal
   - progestogen-only hormonal contraception associated with inhibition of ovulation:
     - oral
     - injectable

- implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner (provided that is the sole sexual partner of the subject and that the vasectomised partner has received medical assessment of the surgical success.)
- sexual abstinence (if in line with the preferred and usual lifestyle of the subject and defined as refraining from heterosexual intercourse during the entire period of the trial. Periodic methods of abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) are not accepted methods of contraception.)

### 5.3 Exclusion Criteria

Subjects who fulfil any of the following criteria will be ineligible to participate in the trial:

1. Current diagnosis of unstable forms of psoriasis, including guttate, erythrodermic or pustular psoriasis;
2. Other inflammatory skin disease in the treatment area that may confound the evaluation of the psoriasis vulgaris (e.g., atopic dermatitis, contact dermatitis, tinea corporis);
3. Presence of pigmentation, extensive scarring, pigmented lesions or sunburn in the treatment areas, which could interfere with the rating of efficacy parameters;
4. Planned excessive or prolonged exposure to either natural or artificial sunlight, including tanning booths, sun lamps, etc;
5. History of hypersensitivity to any component of the test product or reference product;
6. Current or past history of hypercalcemia, vitamin D toxicity, severe renal insufficiency, or severe hepatic disorders;
7. Females who are pregnant, breast feeding, or planning a pregnancy;
8. Systemic treatment with biological therapies, whether marketed or not, with a possible effect on psoriasis vulgaris within the following time periods prior to Visit 1/Baseline and during the trial:
   - Etanercept – within 4 weeks prior to Visit 1/Baseline,
   - Adalimumab, Alefacept, Infliximab – within 8 weeks prior to Visit 1/Baseline,
   - Ustekinumab – within 16 weeks prior to Visit 1/Baseline,
   - Other products – within 4 weeks/5 half-lives prior to Visit 1/Baseline (whichever was longer).

   In general, patients who are candidates for biological or other systemic therapy are excluded from the trial.

9. Use of systemic treatments that suppress the immune system (fumaric acid, methotrexate, retinoids, PDE4 inhibitors, corticosteroids (excluding inhaled, nasal, auricular or ocular corticosteroids), ciclosporin (cyclosporine), and other systemic chemotherapeutic antineoplastic therapy) within 4 weeks prior to Visit 1/Baseline and during the trial;
10. Use of phototherapy (psoralen + ultraviolet A radiation [PUVA] and ultraviolet B radiation [UVB]) within 4 weeks prior to Visit 1/Baseline and during the trial;
11. Use of topical treatments (e.g., corticosteroids (Class 1, 2 and 3), vitamin D analogs, retinoids, PDE4 inhibitors, salicylic acid, pimecrolimus, tacrolimus, anthralin, tar), except for emollients and non-medicated shampoos, with a possible effect on psoriasis within 2 weeks prior to Visit 1/Baseline.
Glucocorticoids Class 4 (e.g. clobetasol propionate) are prohibited within 4 weeks prior to Visit 1/baseline. Subjects using glucocorticoids Class 4 may have their treatment switched to glucocorticoids Class 1-3. However, the treatment must be stopped at least 2 weeks prior to Visit 1/Baseline (refer to Appendix 3
Classification of Topical Corticosteroids).
12. Presence of infections in the treatment area (e.g. skin infection with bacteria (including tuberculosis), viruses, parasites or fungi) or skin manifestations of atrophic skin, atrophic striae, skin vein fragility, ichthyosis, acne vulgaris, acne rosacea, rosacea, ulcers and wound in the treatment;
13. Known Human Immunodeficiency Virus (HIV) infection
14. Have any chronic or acute medical condition that, in the opinion of the investigator, may pose a risk to the safety of the subject, or may interfere with the assessment of safety or efficacy in this trial;
15. Require the use of any concomitant medication that, in the investigator's opinion, has the potential to cause an adverse effect when given with the investigational product (IP) or will interfere with the interpretation of the trial results;
16. Initiation of, or expected changes to, concomitant medication that may affect psoriasis (e.g., beta-blockers, chloroquines, lithium, and angiotensin converting enzyme [ACE] inhibitors);
17. Participation in another clinical trial or received an investigational product or non-marketed drug substances within 30 days prior to screening.
18. In the opinion of the investigator, the subject is unlikely to comply with the clinical trial protocol

## 5.4 Withdrawals and Discontinuation of Treatment

In accordance with legal requirements and International Conference on Harmonisation (ICH) – Good Clinical Practice (GCP) guidelines, every subject has the right to refuse further participation in this trial at any time and without providing reasons (see also Section 9.2). A subject's participation is to be terminated immediately upon his/her request. The investigator should seek to obtain the reason and record this on the electronic case report form (eCRF) whenever possible.

If, at the time of refusal, a trial product has already been administered, the subject should be advised to have an Early Termination visit performed and follow up on treatment related AEs.

If a subject wants to discontinue from the trial, for example due to lack of time, efforts will be made to complete a final evaluation at Week 8 if possible.

The reasons for discontinuation of treatment may be among others:

- Inconsistency with inclusion/ exclusion criteria.
  The investigator should use his/her discretion to determine if there is a safety concern related to continued treatment with trial medication, or if the subject may continue treatment. For example, if a subject incorrectly is enrolled in the trial with a mPSAI of 1,8, the treatment with the IP should not be discontinued. This event should be reported as a Protocol Deviation
- Intake of a prohibited medication(s).
  The investigator should use his/her discretion to determine if there is a safety concern with the combined treatment or the subject may continue treatment with the IP. For example, if the subject has applied salicylic acid cream on the treatment area, the treatment with the IP should not be discontinued. The subject should be advised to stop the treatment and the event should be reported as a Protocol Deviation.
- AE/SAE. The investigator should use his/her discretion to determine if the subject should continue treatment with the IP.
  Subjects discontinued treatment due to a treatment-related AE will be monitored until the AE is resolved or until the medical condition of the subject is stable.
- Pregnancy
- Investigator's discretion
- Lost to follow-up

If the IP application is discontinued, the subject should be encourage to continue in the trial or at least come for the Week 8 visit.

In addition, Regulatory Authority and MC2 reserves the right to end or suspend the trial at any time (see Section 9.2).

### 5.5 Replacement Policy

Subjects who prematurely discontinue the trial after randomisation will not be replaced.

# 6.0 TRIAL TREATMENTS

## 6.1 Investigational Product

### 6.1.1 MC2-01 cream

MC2-01 cream is a combination product, CAL and BDP, administered as a cream formulation for topical administration. The MC2-01 cream is currently not a marketed product, which means that the product is still being tested and is not approved for sale. One concentration of the trial product will be studied: calcipotriol (50 micrograms) and betamethasone (0.64 mg/g). The list of inactive ingredients present in MC2-01 cream is presented in the Investigator Brochure(23).

### 6.1.2 MC2-01 cream vehicle

The MC2-01 vehicle cream will contain the same ingredients as the active formulation without the active ingredients(23).

### 6.1.3 Active Comparator Product

The active comparator is a marketed CAL/BDP gel/topical suspension, 50 micrograms/g CAL (as monohydrate)/0.50 mg/g betamethasone (as dipropionate, equivalent to 0.64 mg/g BDP), approved in the EU as Dovobet® Gel/Daivobet® Gel(24) and in the US as Taclonex® Topical Suspension(25). For this phase 3 trial, the reference product will be sourced in Europe as Daivobet® / Dovobet® Gel.

The CAL/BDP gel/topical suspension contains the following inactive ingredients: Paraffin, liquid; polyoxypropylene stearyl ether; castor oil, hydrogenated; butylhydroxytoluene (E321); All-rac-alpha-tocopherol.

## 6.2 Dosing Regimen

Subjects must apply the trial product topically once daily preferable in the evening for 8 weeks to affected areas on the following body locations:

- trunk (including the neck)
- limbs, i.e., arms (including the back of the hands)
- legs (including the buttocks and the top of the feet) and
- scalp.

The face, genitals and intertriginous areas should not be treated with the IP.

Only affected areas are to be treated.

Subjects are to record the date and time of application in the subject diary.

The subject should apply enough IP to treat the entire affected areas and rub in gently to ensure that the plaques are saturated with the medication. Up to 4 tubes/bottles of 60 gram will be dispensed for a treatment period of 2 weeks including the allowed visit window of 2 days. The weekly dose is not to exceed 100 g, and the treated area should not exceed 30% of the BSA. Subjects will be instructed that preferably no trial product should be applied within 4 hours of on-treatment trial visits.

In case an AE reported in one area of the body lead the investigator to the decision to discontinue treatment this will apply for treatment in general and not only to the area for which the AE was reported.

Detailed application instructions will be provided in the subject instructions.

### 6.3 Dose Modification

Subjects classified as clear at any of the on-treatment visits may stop the IP treatment at the investigator's discretion. They should remain in the trial and attend all visits up to and including the follow-up visit. The IPs will continue to be dispensed to the subject, and IP treatment may be restarted at the subject's discretion. The subjects should not discontinue IP treatment themselves between visits but is only allowed to stop using the IP treatment on the advice of the investigator at a scheduled visit.

### 6.4 Packaging, Labeling, Storage and Destruction

Medication labels for the IPs will comply with the legal requirements of the country where the trial is performed and be printed in the local language.

The IPs will be supplied by the MC2's designated vendor and stored securely at the site under the control of the investigator. The temperature will be monitored and documented.

The MC2-01 cream and MC2-01 cream vehicle will be supplied to the pharmacy/clinical site(s) as tubes containing 60 g of product. The MC2-01 cream and MC2-01 cream vehicle is to be protected from light and stored at a temperature of 2°- 8°C at the site. After dispensing to the subject, the MC2-01 cream can be stored for up to 8 weeks below 25°C.

All medication – unused and used - will be returned for reconciliation and destruction.

The active comparator will be supplied to the clinical site(s) as bottles containing 60 g of product. The active comparator is to be protected from light and stored below 25°C, however the product must not be refrigerated.

## 6.5 Assignment to Treatment

### 6.5.1 Randomisation

Randomisation will be performed using a validated system that automates the random assignment of treatment groups to randomisation numbers. Treatment assignment will be via a central interactive web response system (IWRS) in accordance with a pre-planned computer-generated randomisation schedule in a 3:1:3 ratio (MC2-01 cream; MC2-01 vehicle; active comparator). Randomisation will be stratified by trial site to ensure a proper distribution into the three treatment arms. Furthermore, on a country level, it will be ensured that up to 30 % of the population can be subjects with mild disease (based on the PGA), as monitored by data management.

Randomisation data will be kept strictly confidential, accessible only to authorised persons not otherwise involved in the conduct of the trial, until the time of un-blinding.

A subject who fulfils the trial eligibility requirements will be randomly assigned to treatment.

### 6.5.2 Blinding

Due to difference in formulation and packaging, it is not possible to double blind the IPs. However, several precautions will be taken to maintain the blind to the extent possible. To keep the trial investigator blinded, packing and labelling of the outer box will be identical for all IPs. Due to different formulations, the IPs will be either packed in bottles (active comparator) or in tubes (MC2-01 cream and MC2-01 cream vehicle). Handling of individual bottles/tubes of IPs (e.g., dispensing, returning, drug accountability and weighing) will therefore be handled by a designated third person. Individual bottles/tubes of IPs will be inaccessible to the investigator(s) and other trial staff involved in the evaluation of subjects. Subjects will be instructed not to reveal the formulation of the IPs to the trial investigator.

For details of the procedure for un-blinding of individual subjects in cases of emergency see Section 13.1.

## 6.6 Prior, Concomitant, and Prohibited Therapy

All medications, including over-the-counter (OTC) drugs and vitamins, herbal and dietary supplements, taken within 30 days prior to the start of the trial will be recorded at Screening. Thereafter, a record of all medications and supportive therapy taken during the course of the trial will be made. Information regarding the total daily dose, route of administration, start and discontinuation dates, and indication are to be recorded on the subject's eCRF.

### 6.6.1 Washout of prohibited medications prior to enrolment

If a washout period is necessary due to treatment with any medication specified in the exclusion criteria (see Section 5.3), the washout period must be completed within 30 days prior to baseline.

### 6.6.2 Prohibited medications during the trial

Use of any medication that would exclude the subject from participation in the trial (as specified in Section 5.3 Exclusion Criteria) is also prohibited during the treatment and follow-up periods, which includes medications in the following categories:

- Use of biological therapies with, whether marketed or not, with a possible effect on psoriasis;
- Use of systemic treatments with a possible effect on psoriasis (e.g., fumaric acid, methotrexate, retinoids, PDE4 inhibitors, corticosteroids (excluding inhaled, nasal, auricular or ocular corticosteroids), ciclosporin (cyclosporine), and other systemic chemotherapeutic antineoplastic therapy).
- Use of phototherapy (PUVA and UVB).
- Use of topical treatments with a possible effect on psoriasis (e.g., corticosteroids, vitamin D analogs, retinoids, PDE4 inhibitors, salicylic acid, pimecrolimus, tacrolimus, anthralin, tar).
- Initiation of dosing or changes in dosage of drugs that are known to have an effect on psoriasis should be avoided. This includes, but is not limited to, beta-blockers, chloroquines, lithium, and ACE inhibitors.
- Emollients on the psoriasis affected areas on body (trunk and/or limps) and scalp

### 6.6.3 Allowed treatment outside the treatment area

Subjects may receive laser treatment and use an emollient on the face, skin folds, and genital skin. Topical products (incl. products containing urea) that do not contain medication with antipsoriasis effect (e.g. vitamin D, glucocorticoids or calcineurins) are allowed on skin areas but not within 2 cm of skin areas treated with trial medication.

## 6.7 Treatment Compliance

Records of trial product used, and dosages administered will be kept during the trial.

At all on-treatment visits, the subject will be asked if he/she has used the medication as prescribed. If this is not the case, the degree and nature of noncompliance will be collected in the CRF. In addition, subjects will be asked to complete a dosing diary during the treatment period as a measure of treatment compliance. Subjects who are noncompliant will be counseled.

Subjects will be asked to return all used and unused tubes/bottles in the outer box at each visit. All returned tubes/bottles that had been dispensed to a subject and are returned with a broken seal will be weighed to determine the amount of the IP used per treatment phase.

## 7.0 VISIT SCHEDULE AND ASSESSMENTS

### Table 7-1 Visit Schedule

| Visit | Screening/ Visit 0[a] | Visit 1 | Visit 2 | TC (Visit 3) | Visit 4 | Visit 5 | Visit 6 /ET[b] | Follow Up, Visit 7[c] |
|---|---|---|---|---|---|---|---|---|
| | | Week 0 | Week 1 | Week 2 | Week 4 | Week 6 | Week 8 | Week 10 |
| | Up to Day -30 | Day 0 | Day 7±2 | Day 14±2 | Day 28±2 | Day 42±2 | Day 56±2 | Day 70±2 |
| Informed consent[d] | X | | | | | | | |
| Inclusion/exclusion criteria | [X] | X | | | | | | |
| Demographics, medical history | X | | | | | | | |
| Prior and concomitant medication | X | X | X | | X | X | X | X |
| Concurrent diagnoses | X | | | | | | | |
| Physical Examination | X | X | | | X | | X | |
| Vital signs | | X | | | X | | X | |
| Urine pregnancy test[e] | X | X | | | X | | X | |
| Laboratory assessments | | X[f] | | | X[f] | | X[f] | X[f] |
| SGA | | X | X | | X | X | X | |
| DLQI questionnaire | | X | X | | X | | X | |
| EQ-5D questionnaire | | X | | | X | | X | |
| Psoriasis Treatment Convenience Scale | | | X | | X | | X | |
| PGA scoring | [X] | X | X | | X | X | X | |
| mPASI scoring | [X] | X | X | | X | X | X | |
| BSA | [X] | X | | | X | | X | |
| Randomisation | | X | | | | | | |
| Dispensing of IP and Diary | | X | X | | X | X | | |
| Return of IP and Diary | | | X | | X | X | X | |
| Compliance | | | X | X | X | X | X | |
| Local skin reactions | | X | X | | X | X | X | |
| Photographs | | X | X | | X | X | X | |
| AE(s)[g] | | X | X | X | X | X | X | X |

TC = telephone call; ET = early termination; PGA = physician's global assessment; mPASI = modified Psoriasis Area and Severity Index; BSA= Body Surface Area; SGA = subject's global assessment; DLQI= Dermatology Life Quality Index; EQ-5D = EuroQOL five dimensions questionnaire, IP = investigational product; AE = adverse event.

a) A washout period of up to 30 days must be completed if the subject has been treated with anti-psoriatic treatments or other relevant medication, as defined by exclusion criteria. Items denoted in **[brackets]** must be reviewed at Visit 0/Screening prior to commencing a washout, to assess if the subject is otherwise eligible. Such items must be checked for any change in eligibility status at Visit 1/Baseline after the washout is completed. In case no washout is needed, the Screening Visit and Visit 1 may be performed on the same day.
b) Procedures for subjects who withdraw from the trial before Visit 6/Week 8.
c) An on-site follow-up visit after Week 8 is required to check: abnormal, elevated albumin corrected serum calcium or unresolved treatment related AEs. Treatment-related AEs will be monitored until the AE is resolved or until the medical condition of the subject is stable. For all other subject's telephone call 2 weeks after the Week-8 visit to follow-up is sufficient.
d) Informed consent must be signed both by subject and investigator before any trial related procedures are carried out. For subjects requiring a washout period, informed consent must be completed prior to washout.
e) For female subjects of childbearing potential. If there is a suspicion of pregnancy at any time during the trial, a urine sample will be obtained and tested.
f) If a laboratory result is abnormal and judged as clinically significant, the investigator must follow-up as clinically appropriate (this may involve requesting repeat samples).
g) AEs are to be collected from the date of signing the informed consent, i.e. also during the washout period.

## 7.1 Demographics and Medical History

The following demographic and medical history must be collected:

- Year of birth
- Sex
- Race
- Ethic origin
- Complete skin disease history
- The year diagnosed with psoriasis vulgaris. If diagnosis is within the ongoing and preceding year, also month should be collected
- All other current and past medical/surgical conditions within the previous 12 months.

The Fitzpatrick skin type will be assessed according to the classification scheme in Table 7-2.

**Table 7-2 Fitzpatrick Skin Type Classification**

| | | |
|---|---|---|
| I | Pale white skin, blue/hazel eyes, blond/red hair | Always burns\does not tan |
| II | Fair skin, blue eyes | Burns easily, tans poorly |
| III | Darker white skin | Tans after initial burn |
| IV | Light brown skin | Burns minimally, tans easily |
| V | Brown skin | Rarely burns, tans darkly easily |
| VI | Dark brown or black skin | Never burns, always tans darkly |

## 7.2 Prior and Concomitant Medication

Review and record prior medication and concomitant medication.

All medications, including OTC drugs, herbals, vitamins, dietary supplements etc., taken within 30 days prior to the start of the trial will be recorded at Screening. Thereafter, a record of all medications and supportive therapy taken during the trial will be made. Information regarding the total daily dose, route of administration, start and discontinuation dates, and indication are to be recorded on the subject's eCRF.

## 7.3 Concurrent diagnoses

Concurrent diagnoses must be collected as specified in the visit schedule (Table 7-1).

### 7.4 Physical Examination

An abbreviated physical examination including general appearance, regional lymph nodes and a complete dermatological examination of the skin must be performed, including height and weight at Visit 1/Day 0. The height and weight can be self-reported.

### 7.5 Vital Signs

Blood pressure and pulse rate will be taken with the subject in the sitting position with approximately 5 minutes rest prior to measurement. Body temperature (oral or ear) will be also be measured.

### 7.6 Pregnancy Test

Female subjects of child-bearing potential will undergo a routine urine pregnancy test (UPT) at the Visit 0/Screening before any trial-specific procedures are performed. The pregnancy test will be performed at the site using a urine dipsticks analysis. If the UPT is positive, the subject will not be permitted to enroll in the trial.

During the course of the trial, urine pregnancy tests will be performed as specified in the visit schedule (Table 7-1). At the investigator's discretion, additional testing for pregnancy may be performed for verification purposes. If there is a suspicion of pregnancy at any time during the trial, a urine sample will be obtained and tested. Should a subject become pregnant during the trial, treatment must be discontinued. Refer to Section 7.10.7 for additional information.

Instruct all female subjects of childbearing potential to use approved form(s) of contraception.

### 7.7 Laboratory Assessments

Blood and urine samples will be collected for routine safety laboratory tests as specified in the visit schedule (Table 7-1). Clinical laboratory specimens will be analyzed by a central licensed and accredited laboratory facility according to the laboratory's standard operating procedures.

#### 7.7.1 Biochemistry and Urinalysis

For all subjects, the following tests will be performed as specified in the visit schedule (Table 7-1):

- Serum biochemistry: serum calcium (albumin corrected), serum albumin, serum alkaline phosphatase, serum phosphate, plasma parathyroid hormone. 25-OH Vitamin D, only at Visit 1.
- Urinalysis: urinary calcium, urinary phosphate, urinary calcium:creatinine ratio.
- Pregnancy testing: all female subjects of child-bearing potential will undergo urine pregnancy testing as specified in Section 7.6.

The investigator may collect additional blood samples to repeat any laboratory test that is abnormal post-dosing and is considered clinically significant. Abnormal laboratory results at the last

scheduled visit may require additional collection of samples on an "as needed" basis until: a) the values return to the baseline value, b) the values are within normal limits, c) the values are clinically stable, or d) the investigator determines that further follow-up is unnecessary. The investigator will record the date and time of all additional samples collected. If the investigator establishes a clear explanation for the laboratory abnormality, he or she will record this explanation in the eCRF.

Abnormal clinically significant findings as determined by the Investigator will be reported as medical history if detected at Visit 1. At subsequent visits, any new abnormal clinically significant finding as determined by the Investigator will be reported as an AE.

If albumin-corrected serum calcium is above the reference range at the last on-treatment visit, a follow-up test must be performed.

## 7.8 Investigator Assessments

The investigator assessments are to be performed by a dermatologist or a physician with at least 1 year of experience in dermatology. For physicians who do not fulfill the requirement regarding dermatological experience, the person must be preapproved by the sponsor. Preferably the same investigator will assess the subject throughout the trial. The assessments are to be performed as specified in the visit schedule Table 7-1.

### 7.8.1 Body surface area (BSA) involvement of psoriasis vulgaris on the body

The total psoriatic involvement on the body and scalp will be recorded as a percentage of the total BSA, estimating that the surface of the subject's full, flat palm (including the five digits) correlates to approximately 1% of the total BSA.

The investigator will assess:

- the extent of the subject's psoriatic involvement on the body (excluding scalp, face, genitals, and intertriginous areas).
- the extent of the subject's psoriatic involvement on the scalp.

### 7.8.2 Modified Psoriasis Area and Severity Index (mPASI)

At all on site visits, the investigator will assess the extent and severity of the subjects' psoriasis on the body (trunk and/or limbs) (i.e. the scalp is not involved in this assessment) using an mPASI scoring system.

The extent of psoriatic involvement (extent (E)) will be recorded for each of the 3 areas (arms, trunk, and legs) using the following scale:

0 = no involvement
1 = < 10%
2 = 10% - 29%
3 = 30% - 49%
4 = 50% - 69%
5 = 70% - 89%
6 = 90% - 100%

The severity of the psoriatic lesions in each of the 3 areas will be recorded for each of the signs of redness, thickness, and scaliness. For each clinical sign, a single score, reflecting the average severity of all psoriatic lesions on given body region, will be determined according to the scale below:

Redness
0 = none (no erythema)
1 = mild (faint erythema, pink to very light red)
2 = moderate (definite light red erythema)
3 = severe (dark red erythema)
4 = very severe (very dark red erythema)

Thickness
0 = none (no plaque elevation)
1 = mild (slight, barely perceptible elevation)
2 = moderate (definite elevation but not thick)
3 = severe (definite elevation, thick plaque with sharp edge)
4 = very severe (very thick plaque with sharp edge)

Scaliness
0 = none (no scaling)
1 = mild (sparse, fine-scale lesions, only partially covered)
2 = moderate (coarser scales, most of lesions covered)
3 = severe (entire lesion covered with coarse scales)
4 = very severe (very thick coarse scales, possibly fissured)

The m-PASI is calculated from the scores given by the (sub)investigator during their assessment of the extent and severity of the disease by use of the following equation:

Arms $0.2 (R + T + S) E = X$

Trunk $0.3 (R + T + S) E = Y$

Legs $0.4 (R + T + S) E = Z$

Where: R = score for redness; T = score for thickness; S = score for scaliness; E = score for extent.

The sum of $X + Y + Z$ equals the m-PASI score resulting in a minimum score of 0 and a maximum score of 64.8.

### 7.8.3 Physician's global assessment of psoriasis severity

The Physician's Global Assessment (PGA) measures the investigator's impression of the disease at a single point using a defined, 5-point, static PGA scale (clear, almost clear, mild, moderate or severe); see Table 7-3.

The PGA assessment should be made separately for the body (trunk and/or limbs) and the scalp.

The PGA assessment will represent the *average* lesion severity on the two body locations. The assessments will be based on the condition of the disease at the time of evaluation, and not in relation to the condition at a previous visit.

**Table 7-3 Physician's Global Assessment (PGA)**

| Score | Grade | Definition |
|---|---|---|
| 0 | Clear | Plaque thickening = no elevation or thickening of normal skin<br>Scaling = no evidence of scaling<br>Erythema = none (no residual red colouration but post-inflammatory<br>hypo or hyperpigmentation may be present) |
| 1 | Almost clear | Plaque thickening = none or possible thickening but difficult to ascertain<br>whether there is a slight elevation above normal skin level<br>Scaling = none or residual surface dryness and scaling<br>Erythema = light pink colouration |
| 2 | Mild | Plaque thickening = slight but definite elevation<br>Scaling = fine thin scales partially or mostly covering lesions<br>Erythema = light red colouration |
| 3 | Moderate | Plaque thickening = moderate elevation with rounded or sloped edges<br>Scaling = coarse scale layer at least partially covering most lesions<br>Erythema = definite red colouration |
| 4 | Severe | Plaque thickening = marked or very marked elevation typically with hard or sharp edges<br>Scaling = non-tenacious or thick tenacious scale predominates, covering most or all of the<br>lesions<br>Erythema = very bright red colouration, extreme red coloration or deep red coloration |

### 7.8.4 Local skin reactions

The local skin reaction assessment involves signs assessed by the investigator.

The investigator will assess the treatment area and/or immediate surrounding for the following identified signs:

- Perilesional erythema, scaling, edema, atrophy, vesicles and erosion/ulceration;
- Lesional vesicles, and erosion/ulceration.

The intensity of each local skin reaction category is to be graded according to the scale in Table 7-4. The most severe intensity observed for each category of the local skin reaction assessment is to be recorded.

**Table 7-4 Local Skin Reaction Scores**

| **Investigator assessment of the lesional area** | | | | |
|---|---|---|---|---|
| | **0 (absent)** | **1 (Mild)** | **2 (Moderate)** | **3 (Severe)** |
| **Erosion/ulceration** in lesional area | None | Barely visible erosion | Distinct erosion | Ulceration |
| **Vesicles** in lesional area | None | Barely visible vesicles | Distinct vesicles | Bullae |
| **Investigator assessment of the perilesional area** | | | | |
| | **0=absent** | **1 (Mild)** | **2 (Moderate)** | **3 (Severe)** |
| **Erythema** in perilesional area | None | Barely visible erythema | Distinct erythema | Dark red erythema |
| **Scaling** in the perilesional area | None | Barely visible scaling | Distinct scaling | Gross scales |
| **Edema** in perilesional area | None | barely palpable swelling | Easily palpable swelling | Gross swelling |
| **Atrophy** in perilesional area | None | Barely visible thinning | Distinct thinning | Striae |
| **Vesicles** in perilesional area | None | Barely visible vesicles | Distinct vesicles | Bullae |
| **Erosion/ulceration** in perilesional area | None | Barely visible erosion | Distinct erosion | Ulceration |

## 7.9 Patient Reported Outcomes (PROs)

The PRO instruments must be completed by the subjects before any other assessments are performed. The PRO assessments are to be performed as specified in the visit schedule (Table 7-1).

### 7.9.1 Subject Global Assessment of disease severity (SGA)

Subjects will grade the overall severity of their symptoms according to the following 5-point scale:

0 = Clear; no psoriasis symptoms at all.

1 = Very mild; very slight psoriasis symptoms that do not interfere with daily life.

2 = Mild; slight psoriasis symptoms that interfere with daily life only occasionally.

3 = Moderate; definite psoriasis symptoms that interfere with daily life frequently.

4 = Severe; intense psoriasis symptoms that interfere or restrict daily life very frequently.

### 7.9.2 Dermatology Life Quality Index (DLQI)

The DLQI(26) is a validated questionnaire consisting of 10 questions relating to the degree to which the subject's skin condition affected their daily activities.

### 7.9.3 EuroQOL five dimensions questionnaire (EQ-5D)

The EQ-5D is one of the most commonly used generic questionnaires to measure health-related quality of life (QOL)(27). It consists of a questionnaire and a visual analog scale (EQ-VAS). The EQ-VAS records the subject's perceptions of their own current overall health and can be used to monitor changes over time. The self-assessment questionnaire is a self-reported description of the subject's current health in 5 dimensions i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

### 7.9.4 The Psoriasis Treatment Convenience Scale

The Psoriasis Treatment Convenience Scale must be completed by the subjects before any other assessments are performed. The assessments are to be performed as specified in the visit schedule (see Table 7-1).

The aim of the Psoriasis Treatment Convenience Scale is to assess the impact and convenience of psoriasis treatment. The scale has been tested for content validity through focus group interview with 20 patients and adapted based on the responses. The scale consists of 6 disease-specific, self-report questions with a recall period of 1 week and rated on a 1-10 point scale.

1. How easy was the treatment to apply to the skin?
2. How greasy was the treatment when applying it to the skin?
3. How moisturised did your skin feel after applying the treatment?
4. How greasy did your skin feel after applying the treatment?

5. How much did treating your skin disrupt your daily routine?
6. Overall, how satisfied were you with the medical treatment?

### 7.9.5 Photography

Colour photographs of the treatment area should be taken as specified in the visit schedule (see Table 7-1).

MC2 may at its discretion use the photographs in publication or similar types of information material for health care professionals. The photographs can also be part of the training material used for training and educational purposes. Use of photographs for these purposes is optional and requires prior consent by the subject.

MC2 will ensure that all necessary steps to ensure the anonymity of the subject are taken (e.g. masking of face, no photos of characteristic details on the body, etc.

## 7.10 Adverse Events

### 7.10.1 Adverse events assessments

The investigator is responsible for obtaining, assessing, and documenting all AEs during the trial. Adverse Events information will be collected from the time of the signature of the informed consent form and first trial-related activity performed until the end of the trial. An AE is an untoward medical occurrence in any subject during the trial which does not necessarily have a causal relationship with the IP.

All AEs will be documented in the eCRF, including a description of each AE, AE relationship to IP administration, start and stop dates, seriousness, severity, action taken and outcome.

Any AE that meet the serious criteria must be reported on the eCRF and on a separate SAEs report form. SAEs must be reported immediately to MC2 or designee as soon as it becomes known to the investigator and not later than within 24 hours of his/her knowledge of the occurrence of an SAE.

Throughout the trial, the occurrence of AEs should be sought by nondirective questioning of the subject at each visit during the trial. Information on AEs can also be obtained from signs and symptoms detected during examination, observations made by the trial site personnel, or spontaneous reports from subjects. Pre-existing conditions that worsen during the trial should also be recorded as AEs. This will also include worsening of the psoriasis vulgaris as judged by the investigator.

AEs requiring therapy must be treated with recognised standards of medical care to protect the health and well-being of the subject. Treatment due to an AE will be recorded in the subject's records and on the appropriate eCRF.

Any AE that is considered related to the IP must be followed by the investigator until it is resolved or until the medical condition of the subject is stable; all relevant follow-up information will be reported to MC2 or designee.

The outcome of an AE will be classified as recovered, recovered with sequelae, recovering/resolving, ongoing, or death.

### 7.10.2 Timing

AEs will be collected during the period from the time of the signature of the informed consent form and first trial-related activity performed until the end of the trial.

### 7.10.3 Severity of adverse events

The investigator is to classify the severity (intensity) of an AE according to the following definitions:

- Mild – The subject was aware of the signs and symptoms, but the signs and symptoms were easily tolerated and do not interfere with daily activity.
- Moderate – The signs and symptoms were sufficient to restrict, but did not prevent, usual daily activity for the subject. The subject is still able to function.
- Severe – The subject was unable to perform usual daily activity.

The maximum intensity of an AE (mild, moderate, or severe) will be assessed taking into account the possible range of intensity of the symptom(s).

### 7.10.4 Relationship of an adverse event to trial treatment

The investigator is responsible to assess the relationship of an AE to the IP treatment using good clinical judgment and the following definitions:

| | |
|---|---|
| Not Related | The AE is clearly explained by another cause not related to the IP administration; the temporal relationship of the AE to IP administration makes a causal relationship unlikely, or, concomitant medication, therapeutics interventions, or underlying condition provide a sufficient explanation for the observed AE |
| Possibly Related | The AE and administration of IP are temporally related, but the AE can be explained equally well by causes other than the IP administration |
| Probably Related | The AE and use of IP are temporally related, and the AE is more likely explained by IP administration than by other causes |

| | |
|---|---|
| Definitely Related | The AE and IP administration are related in time, and a direct association can be demonstrated. Concomitant medication, therapeutics interventions, or underlying conditions do not provide a sufficient explanation for the observed AE |

### 7.10.5 Unexpected adverse events

Any AE assessed at least as possibly related to the IP will be assessed for expectedness by the sponsor or designee. An AE is considered "unexpected" if its nature or severity is not consistent with information in the MC2-01 Investigator's Brochure(23) (for MC2-01 cream) or Daivobet® / Dovobet®Gel Summary of Product Characteristics (SmPC)(24) (for active comparator).

"Unexpected" as used in this definition, also refers to AEs that are mentioned in the Investigator's Brochure or SmPC as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

### 7.10.6 Trial medication overdose

An overdose of the IP, i.e., a dose that is higher than the highest dose under clinical investigation or the known therapeutic dose, will be fully documented even if no toxic effects were observed and will be considered an AE.

The application should only be done once daily, and the treated area should not be >30% of the body surface area.

Use of MC2-01 cream in excessive amounts may cause elevated serum calcium, which should rapidly subside when treatment is discontinued. Excessive prolonged use of topical corticosteroids may suppress the pituitary-adrenal functions, resulting in secondary adrenal insufficiency that is usually reversible. In such cases, symptomatic treatment is indicated.

### 7.10.7 Pregnancy

Any pregnancy occurring from date of the Informed Consent signature until trial completion must be reported immediately to MC2 or designee as soon as it becomes known to the investigator and not later than within 24 hours of his/her knowledge of the occurrence of the pregnancy (see Section 7.10.9).

All pregnancies should be actively followed through to resolution (i.e., delivery, miscarriage, or abortion). The corresponding report(s) should be submitted within the same timelines as mentioned above. A pregnancy per se is not considered an SAE.

### 7.10.8 Serious adverse event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect, or is an important medical event
- Other serious or important medical event

The death of a subject enrolled in a trial is per se not an event, but an outcome. Any event resulting in a fatal outcome must be fully documented and reported, regardless of the causality relationship to the IP.

Any medical important events that may not result in death, be life-threatening, or require hospitalisation may be considered an SAE when, based on appropriate medical judgment, they may jeopardise the subject or the subject may require medical or surgical intervention to prevent one of the outcomes listed in the above definitions.

Any pre-planned hospitalisations that are known at the time of signing the informed consent form (ICF) will not be recorded as SAEs, however they will be recorded as AEs only.

Any SAE, whether or not deemed drug-related or expected, must be reported immediately to the MC2 or designee as soon as it becomes known to the investigator and not later than within 24 hours of his/her knowledge of the occurrence of an SAE (see Section 7.10.9). The investigator will document such events in the best possible detail on the SAE Report Form.

If the investigator becomes aware of an SAE after the end of the clinical trial that is possibly related to the IP, he/she must inform the sponsor immediately.

A SUSAR is an SAE that is both unexpected (not consistent with the current Investigator's Brochure(23) or Daivobet® / Dovobet® Gel SmPC(24) (for active comparator), and for which there is evidence to suggest a causal relationship between the drug and the SAE. The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be informed of SUSARS according to local requirements. All investigators participating in the trial will also be notified of unexpected SAEs. The sponsor will report SAEs and other events requiring expedited reporting to regulatory authorities as required.

Investigator instructions for reporting SAEs are provided in Section 7.10.9.

### 7.10.9 Reporting of Serious Adverse Events and Pregnancies

#### 7.10.9.1 Contact person(s) and number(s)

SAEs and pregnancies must be reported immediately (i.e., not later than 24 hours after first knowledge). The SAE or pregnancy report should be e-mailed or faxed to United BioSource Corporation (UBC) using the following e-mail or fax-number:

Email: EUSafety@ubc.com
Fax number: +41 225 964 446

#### 7.10.9.2 Reporting procedures

**Serious adverse events**

For each SAE, the investigator will complete a Serious Adverse Event Report Form and assess the relationship of each SAE to trial treatment. The completed form(s) should be sent immediately (and not later than within 24 hours of first knowledge of the SAE) electronically to the UBC using the SAE Reporting by email or fax.

Follow-up reports regarding the status of the SAE and the subject's subsequent course should be submitted until the SAE has subsided, the condition stabilised (in the case of persistent impairment), the subject receives alternative therapy, or the subject dies. The form and fax confirmation will be retained. Contacts for reporting SAEs, pregnancies and other safety concerns are provided to each site.

### 7.11 Unscheduled Visit

An unscheduled visit may be performed at any time during the trial if judged necessary by the investigator, such as for a severe reaction, suspected pregnancy, clinically significant AE, or clinically significant local skin reaction result. Details of the event are to be recorded in the subject's records.

### 7.12 Follow-up Visit

An on-site follow-up visit is required for the following reasons:

- Unresolved treatment-related AEs.
- If the albumin-corrected serum calcium was above the normal reference range at the Week 8 visit a repeat test should be done 14 days (± 2 days) after.

A telephone call will be made 2 weeks after the Week 8 visit as follow-up for all subjects without unresolved treatment-related AEs or abnormal, elevated albumin-corrected serum calcium to ask for the wellbeing of the subject.

## 7.13 Early Termination

The subjects are free to withdraw at any time if they choose without providing reasons. All efforts will be made, however, to encourage the subject to continue in the trial or at least come for the Week 8 visit. This also is applicable in case administration of the IP has been terminated.

If the subject is considered non-compliant with protocol procedures, for example started prohibited medication, all efforts will be made to encourage the subject to continue on treatment (if no safety concerns) or at least come for the Week 8 visit.

The following procedures should be performed at the early termination visit:

- Collect all trial materials from the subject.
- Assess compliance
- Review any concomitant medication used since the previous trial visit.
- Record any AEs.
- Physical examination and vital signs
- Perform a urine pregnancy test for females of childbearing potential.
- Biochemistry and urinalysis.
- PGA
- mPASI
- BSA
- SGA
- DLQI
- EQ-5D
- Psoriasis Treatment Convenience Scale
- Local Skin Reactions

# 8.0 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE STATISTICAL AND ANALYTICAL PLANS

## 8.1 General Considerations for Data Analysis

The methodology presented below represents a brief overview of the statistical methods that will be fully detailed in the statistical analysis plan (SAP). The SAP will be finalised before the database is locked. Any changes to the methods described in the final SAP will be described and justified in the clinical trial report. All statistical analyses will be performed using SAS® statistical software (Version 9.2 or higher). Statistical significance will be tested at the 2-sided 5% level unless otherwise specified.

Subjects will be randomised in a 3:1:3 ratio (MC2-01 cream: MC2-01 cream vehicle: active comparator), stratifying by trial site. The aim is to randomise 14 subjects or more at each site. Furthermore, on a country level, it will be ensured that up to 30 % of the population can be subjects with mild disease (based on the PGA performed at Baseline), as monitored by data management. It is planned that the data from trial sites that participate in this trial will be combined so that an adequate number of subjects will be available for analysis. Trial sites yielding fewer than 14 subjects overall will be combined in order of geographical proximity. The exact composition of these "analysis sites" will be determined and documented prior to breaking the trial blind. In statistical models, site will refer to trial site or analysis site, if combination of trial sites is needed.

## 8.2 Sample Size and Power Considerations

The primary endpoint is percentage change from baseline in mPASI at Week 8. The primary endpoint will be used for superiority evaluations of MC2-01 cream and active comparator versus vehicle, and the non-inferiority evaluation of MC2-01 cream versus active comparator. The primary endpoint has been chosen as percentage change from baseline instead of absolute change, as this was the endpoint in the studies used to determine the non-inferiority margin.

The sample size calculation is based on the non-inferiority margin for the treatment difference in percentage change from baseline in mPASI at Week 8.

Non-inferiority margin:

According to information from experienced dermatologists as well as data from an observational study (28, 29), the two marketed products, Daivobet® Gel and Daivobet® Ointment, appear to be equally effective. The summary of mean reductions in mPASI in randomized trials with Daivobet® Gel and Daivobet® Ointment is shown below (Table 8-1 and Table 8-2).

**Table 8-1 Published mean reduction of PASI for active treatment from baseline to 8-weeks reported in CAL/BDP Gel phase 2/3 trials**

| Reference | Patients N | mPASI Baseline (mean) | PASI mean reduction from Baseline to Week 8 (%) | SD |
|---|---|---|---|---|
| Menter 2013 (30) | 482 | 7.9 | -55.8 | 34.4 |
| Langley 2011(31) | 183 | 9.39 | -57.0 | 29.6 |
| Fleming 2010 (12) | 162 | 7.7 | -55.3 | 33.3 |

**Table 8-2 Published mean reduction of PASI for active treatment from baseline to 8-weeks reported in CAL/BDP Ointment phase 3 trials**

| Reference | Patients N | mPASI Baseline (mean) | PASI mean reduction from Baseline to Week 8 (%) | 95% CI | 95% CI |
|---|---|---|---|---|---|
| Guenther 2002 (32) | 150 | 9.9 | -68.6 | -64.8 | -72.4 |
| Kaufmann 2002 (13) | 490 | 9.9 | -71.3 | -69.1 | -73.6 |
| Kragballe 2004; (33)<br>Kragballe 2006 (34) | 645 | 10.4 | -68.7 | -66.9 | -70.5 |
| Ortonne 2004 (35) | 249 | 9.7 | -65.0 | -61.4 | -68.6 |

CI: Confidence interval

Based on these trials, a random-effects meta-analysis of mean reduction in mPASI at end of trials shows an estimated difference of 12.71 percentage points [95% CI 8.00 to 17.41] between Daivobet® Gel and Daivobet® Ointment, suggesting that –12 percentage points is a clinically acceptable margin for non-inferiority. Therefore, the non-inferiority limit is set to –12 percentage points.

Assumptions for sample size calculation:

- The common standard deviation is assumed to be 38 (based on the assumption of an SD of 35 in the active treatment arms (see above Daivobet® Gel studies), 50 in the vehicle arm (found to be the largest SD in the above Daivobet® Gel studies), and the 3:1:3 ratio)
- The error probability is set to 0.05 for a 2-sided test

Under these assumptions, a sample size of N=204 per active treatment group for the non-inferiority evaluation, assuming 0 difference, results in a power of 88.9%. Thus, a total of 476 subjects should be randomised in a 3:1:3 ratio (MC2-01 cream: MC2-01 cream vehicle: active comparator).

With 476 subjects randomised 3:1:3, and the assumption that the effect of both active treatments is -56 percentage points (the average effect found in the gel studies), and the effect of MC2-01 cream vehicle is -27 percentage points (the largest effect found for the ointment, found in the MCB-9905 INT study), the power for each of the superiority comparisons of MC2-01 cream and active comparator to MC2-01 cream vehicle with respect to mPASI is more than 99%. If 30% of subjects treated with either MC2-01 cream or active comparator respectively 11% of subjects treated with MC2-01 cream vehicle will have PGA success, the power for the each of the superiority comparisons with respect to PGA success is 90.4%.

### 8.3 Analysis Populations

The analysis populations are defined as follows:

- **Intent To Treat (ITT) population:** all randomised subjects
- **Per Protocol (PP) population:** all subjects in the ITT population who complete the trial without any major protocol violations. The PP population will be determined and documented in blind review of the database conducted prior to un-blinding the trial database. Subjects may be excluded from the PP population if any of the following criteria are met:
    - Failure to meet key Inclusion/Exclusion criteria; i.e. violation of inclusion/exclusion criteria that according to medical judgement may impact the primary endpoint analysis
    - Usage of restricted medications/treatments; i.e. medications/treatments that according to medical judgement may impact the primary endpoint analysis
    - Nonadherence to the visit schedule at Week 8: -7/+10 days
    - Noncompliance with the trial treatment regimen; adherence to the treatment schedule defined as application of IP as specified by the investigator for at least 80% of the days from Day 1 to Week 8 visit, and at least 80% of the days from Week 4 visit to Week 8 visit
- **Safety population:** all randomised subjects who are dispensed the trial medication, excluding subjects who return all the trial medication unused.

Subjects in the ITT and PP populations will be analyzed as randomized, and subjects in the Safety population will be analysed as treated.

The ITT population will be used for the analyses of efficacy and other endpoints, while the Safety population will be used for all safety analyses. The PP population will be used in sensitivity analyses for the non-inferiority evaluations, and in a sensitivity analysis for the PCTS score evaluation.

## 8.4 Estimands

The efficacy endpoints will be analyzed focusing on two different estimands:

Primary estimand (treatment-policy): the effect of initiating the treatment regimen in subjects with mild-to-moderate psoriasis, with or without any other psoriasis treatment, and whether or not the subject adhered to the treatment regimen.

Thus, for the treatment-policy estimand all available data will be used.

Secondary estimand (hypothetical-strategy): the expected effect in subjects with mild-to-moderate psoriasis if all subjects adhered to the treatment regimen and did not take any other psoriasis treatment (=treatment that according to medical judgement may improve psoriasis).

This is interpreted in the sense that subjects did not initiate other treatment that according to medical judgement may improve psoriasis, and for visits after baseline adhered to the treatment schedule defined as application of IP as specified by the investigator at the previous site visit for at least 70% of the days from baseline visit to Week 4, Week 4 to Week 6 and Week 6 to Week 8. For example, applying IP for 10 out of 14 days is considered adherence, while 9 out of 14 days is not. Thus, for the hypothetical-strategy estimand, only data at or prior to use of other treatment that may improve psoriasis according to medical judgement, and prior to non-adherence to treatment schedule is used. Missing data, data after use of other psoriasis treatment, and data after non-adherence is imputed.

## 8.5 Handling of Missing Data

For analyses using the PP population, no imputations will be made for missing data.

For analyses using the ITT population, both multiple imputation (MI), last-observation-carried forward (LOCF), and non-responder imputation (NRI) will be used. MI will be the primary imputation method and is described below, and sensitivity analyses utilizing LOCF and NRI will be performed to assess the robustness of the imputation assumptions of MI.

**Multiple imputation** (for continuous endpoints):

Post-baseline missing efficacy data will be multiple imputed separately for each treatment group using a Markov Chain Monte Carlo (MCMC) method to obtain a monotone missing data pattern, after which imputation is done using a monotone regression method. In more detail the process is as follows:

Impute to get a monotone missing data pattern: Intermittent missing values are imputed using MCMC separately for each treatment group to obtain 100 copies of the original dataset with a monotone missing data pattern.

Impute Week 1 data: For each of the 100 datasets and each treatment group separately, an analysis of covariance (ANCOVA) model is fitted to the endpoint measured at Week 1. The ANCOVA model will include the effects of site and baseline PGA as factors and baseline value of the endpoint as a covariate. For each treatment group and each dataset, the estimated parameters and their variances are used to impute the endpoint at Week 1 for the missing values.

Repeat stepwise imputation: For each of the 100 datasets and each treatment group separately, missing values at Week 4 are imputed in the same way as for Week 1 using a similar ANCOVA model but including also the (possibly imputed) endpoint at Week 1 as an additional covariate. For each dataset and each treatment group, the estimated parameters and their variances are used to impute the missing values at Week 4 in the dataset. This stepwise procedure is repeated sequentially for Week 6 and Week 8, including in the ANCOVA models the additional covariate (possibly imputed) endpoint at Week 4, and, for the imputation for Week 8, also the covariate (possibly imputed) endpoint at Week 6.

**Data analysis using MI,** continuous endpoint:

Use MI. For each of the 100 complete, imputed datasets, the endpoint at Week 8 will be analysed using an ANCOVA model with effects of treatment, site, and baseline PGA as factors and the baseline value of the endpoint as a covariate. The estimated differences between the treatments at Week 8 will be derived together with the associated standard error. The estimates and standard errors from the 100 analyses are pooled to one estimate and associated standard error using Rubin's rule to draw inference. From these pooled results, the 95% CI for the treatment differences is calculated.

**Data analysis using MI,** for dichotomous endpoint:

Use MI for the underlying quantitative variable, prior to dichotomizing the endpoint. For each of the 100 complete, imputed datasets, dichotomize the endpoint at Week 8. Then analyze using a logistic model with effects of treatment, site, baseline PGA as factors, and if applicable the baseline value of the endpoint as a covariate. The estimated log odds ratios between the treatments at Week 8 will be derived together with the associated standard error. The estimates and standard errors from the 100 analyses are pooled to one estimate and associated standard error using Rubin's rule to draw inference. From these pooled results, the 95% CI for the odds ratios between treatments are calculated.

## 8.6 Analyses of Efficacy

All efficacy endpoints will be described using summary statistics for each treatment group by visit.

For mPASI absolute values, absolute reduction, and percentage reduction from baseline will be summarized using mean, median, SD, quartiles and ranges. Frequency counts and percentages for

PGA, SGA, and PGA for scalp, will be provided. For PGA success and mPASI 75, frequency counts and percentages will be provided.

The efficacy endpoints will primarily be analyzed using the treatment-regimen policy estimand for the ITT population and imputing missing data using MI.

### 8.6.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the percentage change in mPASI on the body (trunk and/or limbs) from baseline to Week 8.

#### 8.6.1.1 Analysis of primary endpoint

Superiority analysis

First the percentage change in mPASI from baseline to Week 8 for MC2-01 cream and the active comparator will be compared with that of MC2-01 cream vehicle for a superiority evaluation using the treatment-policy estimand for the ITT population and imputing missing data using MI.

The comparison will be done using an ANCOVA model including treatment, site, and baseline PGA as factors, and baseline mPASI as covariate. The estimated differences between MC2-01 cream and MC2-01 cream vehicle, and between active comparator and MC2-01 cream vehicle, will be reported together with the associated standard error, the 95% confidence interval, and a test corresponding to no difference between treatments.

Non-inferiority analysis

Next, if and only if superiority to MC2-01 cream vehicle can be claimed for both MC2-01 cream and active comparator on the 5% significance level, MC2-01 cream will be compared to active comparator for a non-inferiority evaluation using the treatment-regimen estimand for the ITT population and imputing missing data using MI.

Percentage change in mPASI from baseline to Week 8 will be compared between MC2-01 cream and active comparator for a non-inferiority evaluation using the -12 percentage points non-inferiority margin. The comparison will be done using the same model as applied for the analysis of superiority vs. vehicle as described above: an ANCOVA model including treatment, site, and baseline PGA as factors, and baseline mPASI as covariate. The estimated difference between MC2-01 cream and active comparator will be reported together with the associated standard error, and the 95% confidence interval. If the lower limit of the 95% confidence interval is above -12 percentage points, non-inferiority is demonstrated.

#### 8.6.1.2 Sensitivity analyses

For the superiority analyses of MC2-01 cream and active comparator to MC2-01 cream vehicle, as well as for the non-inferiority analysis of MC2-01 cream to active comparator, the below sensitivity analyses will be performed.

Internal validity

The primary analysis using MI assumes that data are missing at random within each treatment arm. For each hypothesis, the sensitivity of this assumption is investigated using a so-called tipping point analysis; a penalty (a number) is added to all imputed Week 8 values in the MC2-01 treatment group or (when testing superiority of active comparator vs. vehicle) in the active comparator group, and the analysis is repeated on the ITT population for the treatment-regimen estimand. The penalty d is gradually increased until the point, the tipping point, where the conclusion (superiority or non-inferiority depending on the analysis) no longer is demonstrated. If the tipping point is considered a clinical plausible difference, the tipping-point analysis does not support the primary analysis.

External validity

- The primary analysis is repeated using the hypothetical-strategy estimand based on the ITT population and imputing missing data using MI.
- The primary analysis using the treatment-policy estimand and imputing missing data using MI is repeated based on the PP population.

### 8.6.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- PGA success on the body (trunk and/or limbs) at Week 8
- Subject assessment of treatment convenience at Week 8 using the PTCS Analysis of secondary endpoints

To control the global Type-I error, the secondary endpoints will be tested in hierarchical order, if and only if non-inferiority can be demonstrated for the primary endpoint. The endpoints will be analyzed using the treatment-regimen policy estimand for the ITT population.

For PGA success, missing PGA values will be imputed using MI considering PGA as a continuous endpoint.

- PGA success: PGA success of both MC2-01 cream and active comparator will be compared with that of MC2-01 vehicle for a superiority evaluation. The comparison will be done using a logistic model with treatment, baseline PGA, and site as factors.

- PGA success: Non-inferiority of MC2-01 cream versus active comparator. PGA success will be compared between MC2-01 cream and active comparator for a non-inferiority evaluation using a -10 percentage points non-inferiority margin, as -10 percentage point is considered the largest clinically acceptable loss of effect. This non-inferiority margin was also used in the MC2-01-C2 trial (1). The percentage of subjects in each group with treatment success will be calculated along with its 95% confidence interval (CI) using normal approximation. A 95%, 2-sided CI for PM-PA, where PM and PA are the PGA treatment success rate at Week 8 for MC2-01 cream and active comparator respectively, will be computed using normal approximation using Proc FREQ with RISKDIFF option. MC2-01 will be considered non-inferior to active comparator if the lower bound of the 2-sided 95% CI is ≥ -10% points.

- PCTS: Superiority of MC2-01 cream versus active comparator. A PCTS score is considered invalid, if subject has discontinued study medication more than 7 days prior to the day of assessment. Missing and invalid PTCS scores will be imputed using the last valid measure prior to the visit (LOCF). This approach corresponds to a "PCTS while on treatment" estimand. The PCTS score will be compared between MC2-01 cream and active comparator using an ANCOVA model with treatment, baseline PGA, and site as factors.

- mPASI: In analogy with the analysis of the primary endpoint, superiority of MC2-01 cream versus active comparator will be evaluated using an ANCOVA model including treatment, site, and baseline PGA as factors, and baseline mPASI as covariate. Missing mPASI values will be imputed using MI.

- PGA: Superiority of MC2-01 cream versus active comparator. PGA success will be compared between MC2-01 cream and active comparator using a logistic model with treatment, baseline PGA, and site as factors.

#### 8.6.2.1 Sensitivity analyses

- For PGA success, a sensitivity analysis will be performed where missing values are imputed as non-responders (NRI). Another sensitivity analysis will be performed repeating the primary analysis for the hypothetical-strategy estimand based on the ITT population and imputing missing data using MI.

- For PCTS the analysis will repeated for the PP population instead of the ITT population with the same imputation (LOCF).

- For mPASI the same sensitivity analyses as for the primary endpoint will be performed.

### 8.6.3 Other Endpoints

Efficacy

- Percentage change from Baseline in mPASI on the body (trunk and/or limbs) at Week 4;

- mPASI 75 (at least 75% reduction in mPASI from baseline) on the body (trunk and/or limbs) at Week 4 and Week 8;
- Change from baseline in SGA at Week 4 and Week 8;
- Change from baseline in PGA for the scalp at Week 4 and Week 8;

Patient reported outcome

- Subject assessment of treatment convenience at Week 4 using the PTCS;
- Change from baseline in DLQI score at Week 4 and Week 8;
- Change from baseline in EQ-5D score at Week 4 and Week 8;

#### 8.6.3.1 Analysis of other endpoints

The statistical analyses of other endpoints will be exploratory only, and no formal statistical testing will be conducted.

Efficacy

The efficacy endpoints will be analyzed using the treatment-regimen policy estimand for the ITT population and imputing missing data using MI. For the dichotomous endpoints based on mPASI, values of mPASI will be imputed, and then dichotomized.

- Percentage change from baseline in mPASI at Week 4 will be analyzed like the primary endpoint including the same sensitivity analyses
- mPASI 75 at Week 4 and Week 8, and PGA success at Week 4 will be analyzed like PGA success at Week 8 (secondary endpoint), with the analyses of mPASI 75 including mPASI at baseline as a covariate.
- Change from baseline in SGA at Week 4 and Week 8, and change from baseline in PGA for the scalp at Week 4 and Week 8 will be presented descriptively only

Patient reported outcome

- The PCTS score at Week 4 will be analyzed like the PCTS score at Week 8
- The DLQI score as well as the scores for the individual domains (symptoms and feelings, daily activities, leisure, work and school, and personal relationship) will be summarized by trial visit and treatment group. Missing values, if any, will be incorporated based on the developers scoring instructions. Missing domains will be imputed using MI and then combined to a total score. Change from baseline in DLQI score at Week 4 and Week 8 will be analyzed for the treatment-regimen estimand and the ITT population using an ANCOVA model with treatment, site, baseline PGA, and baseline DLQI as factors

- For the EQ-5D VAS score as well as the 5 dimensions mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, will be summarized by trial visit and treatment group. Change from baseline in EQ-VAS score at Week 4 and Week 8 will be analyzed for the treatment-regimen estimand and the ITT population imputing missing data using MI and using an ANCOVA model with treatment, site, baseline PGA, and baseline EQ-VAS as factors

## 8.7 Analysis of Safety

The assessment of safety will be based mainly on the frequency of AEs, on the number of laboratory values that fall outside of predetermined ranges, and on local skin reactions.

### 8.7.1 Adverse events

AEs will be summarised by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. The incidence of AEs (percent of subjects reporting the AE at least once) as well as the number of AEs will be tabulated separately for each treatment group by severity and relationship to drug.

### 8.7.2 Local Skin Reaction Assessment

Assessments of local skin reaction will be performed at all post-screening visits for all subjects in the trial. These local skin reaction assessments (LSRs) will be made by the investigator. The treatment area and the immediate surrounding area will be assessed.

The LSR sum score will be summarized by trial visit and treatment group. The LSR intensities, scored as 0=none, 1=mild, 2=moderate, or 3=severe, will be summarized by trial visit and treatment group for each of the LSR categories.

In addition, for each LSR category, the most intense reaction over the course of the trial will be determined for each subject, and the frequency distributions of these scores will be tabulated.

### 8.7.3 Other safety variables

Clinical laboratory values will be reported as complete listings of individual subject data. Laboratory parameters will include:

• Serum biochemistry: serum calcium (albumin corrected), serum albumin, serum alkaline phosphatase, serum phosphate, plasma parathyroid hormone. 25-OH Vitamin D (Assessed at Visit 1 and used to stratify patients and treatment effect on calcium metabolism).

• Urinalysis: urinary calcium, urinary phosphate, urinary calcium:creatinine ratio.

Clinical laboratory data will be summarised by presenting shift tables using extended normal ranges (baseline to most extreme post-baseline value), by presenting summary statistics of raw

data and change from baseline values (means, medians, standard deviations, ranges), and by the flagging of notable values in data listings.

Data from other tests (e.g., vital signs) will be considered as appropriate and listed. Notable values will be flagged, and any other information collected will be listed as appropriate. Any statistical tests performed to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

# 9.0 CHANGES IN THE PLANNED TRIAL

## 9.1 Protocol Amendments

Except for administrative changes, any changes or additions to this clinical trial protocol require a written protocol amendment that must be approved by the IRB before implementation.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or MC2 in the interests of preserving the safety of all subjects included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons, MC2 or designee should be notified and the IRB should be informed according to their reporting requirements.

## 9.2 Termination or Suspension of the Trial

MC2, the investigator, the IRB/IECs or competent authorities serves the right to terminate or suspend the trial, part of the trial or a trial site at any time, but agreement on procedures to be followed must be obtained. In case of premature termination or suspension of the trial, the contract research organization (CRO) project manager will promptly inform the investigators, regulatory authorities, and IRBs about the premature termination or suspension, including the reason for it. In terminating the trial, MC2 and the investigator will ensure that adequate consideration is given to the protection of the subjects' interests. The trial must be terminated if the perception of the benefit/risk ratio (judged from clinical signs and symptoms, (S)AEs and/or remarkable safety laboratory changes) becomes unfavorable for the continuation of the trial.

# 10.0 DATA HANDLING AND RECORD KEEPING

## 10.1 Recording of Data

### 10.1.1 Source documents

Source data are all the information in original records and copies of original records of clinical findings, observations, or other activities in the trial, which are necessary for the reconstruction and evaluation of the trial.

Trial data collection procedures must ensure that each data element can be traced with a high level of confidence from its originator or recorder to its representation in the trial database and then to its place in the analysis and report of trial results. Once recorded, the trial data must be protected

from unauthorised modification or deletion, and all authorised modifications and deletions must be securely linked in the permanent record with their author, time of change, and reason for change (i.e., the audit trail must be maintained).

The investigator will permit trial-related monitoring, audit(s), IRB/IEC review(s) and regulatory inspection(s), with direct access to all the required source records.

The principal investigator will certify the data to be accurate and complete and will release the data for transmittal to MC2 or designee.

Source records need to be preserved for the maximum period of time permitted by local requirements (see Section 10.2). For each subject enrolled, the investigator will indicate in the source record(s) that the subject participated in the trial.

### 10.1.2 Case report forms

The primary data collection tool for the trial is an eCRF designed specifically for the trial. For each subject enrolled in the trial, an eCRF will be completed by the trial coordinator and signed by the investigator or his/her designate.

The investigator will be responsible for ensuring the accuracy of all data entered in the eCRFs. All eCRFs are to be completed in a timely manner.

Errors occurring in the eCRFs will be queried. Queries raised by data reviewers must be addressed by site personnel.

On request, the investigator will provide the MC2 with additional data relating to the trial, or copies of relevant source records, duly anonymised (i.e., subject's name is redacted).

## 10.2 Retention of Documents

The investigator shall take responsibility for maintaining adequate and accurate source documents of all observations and data generated during this trial, including any data clarification forms received from the MC2 or designee. Such documentation is subject to inspection by the sponsor or its agents, the US Food and Drug Administration (FDA) and/or other regulatory agencies. The investigator is responsible for retention of essential documents including the Investigator Trial File until MC2 informs the investigator that the documents are no longer to be retained or longer if required by local regulations.

# 11.0 QUALITY CONTROL AND QUALITY ASSURANCE

## 11.1 Direct Access to Source Documents

As specified in the investigator's agreement, the investigator agrees to allow trial-related monitoring, audit(s), IRB/IEC review(s) and regulatory inspection(s), with direct access to all the

required source records, and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues.

### 11.2 Monitoring Procedures

The Clinical Trial Monitor will contact and/or visit the investigator site periodically to verify the adherence to the protocol, the maintenance of trial-related source records, and the completeness and accuracy of all eCRF entries compared to source data. The investigator will cooperate with the trial monitor to ensure that any discrepancies that may be identified are resolved.

### 11.3 Audit and Inspection

The investigator will make all the trial-related source data and records available to a quality assurance auditor mandated by the sponsor, or to domestic or foreign regulatory inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects have been adequately protected, and that all data relevant for the evaluation of the IP have been processed and reported in compliance with GCP/ICH and applicable regulatory requirements.

The investigator is to notify the MC2 or designee immediately of any inspection by regulatory authorities or IRBs.

## 12.0 ETHICS

### 12.1 Ethical Conduct of the Trial

This trial must be carried out in compliance with the protocol and the applicable laws and regulatory requirements of the appropriate regulatory agency. The trial must be conducted in accordance with the ethical principles originating from the Declaration of Helsinki and amendments and the ICH-GCP guidelines.

### 12.2 Institutional Review Board (IRB) or Independent Ethics Committee (IEC)

This protocol, the proposed informed consent form, and other information for subjects must be reviewed and approved by an IRB or IEC, before the start of the trial, in compliance with local regulations. This committee must also approve any amendments to the protocol, other than administrative ones, before initiation of the amendment procedures.

### 12.3 Subject Information and Consent

Before participation in the trial, each subject is required to provide written consent to participate in the trial. No trial-specific procedures will be performed before a subject’s informed consent is obtained.

### 12.4 Disclosure and Confidentiality

#### 12.4.1 Confidentiality of trial documentation

By signing the protocol, the investigator agrees to keep all information provided by the sponsor in strict confidence and to request similar confidentiality from his/her staff and the IRB or IEC. Trial documents provided by the trial sponsor (i.e., protocols, Investigators' Brochures, eCRFs and other material) will be stored appropriately to ensure their confidentiality. The information provided by the sponsor to the investigator may not be disclosed to others without direct written authorisation from the sponsor, except to the extent necessary to obtain informed consent from subjects who wish to participate in the trial.

#### 12.4.2 Privacy of individual health information

The investigator will undertake to protect the privacy of all individually identifiable health information except as specifically authorised by each individual subject through the written informed consent. The Informed Consent document will include a request of the subject's consent to release the collected data for research purposes in such a way that the individual's identity remains masked. While all data records will be identified by the corresponding subject number, the identity of the subject will be held in confidential source documents at the trial site. All trial personnel with access to this information are legally bound not to disclose such information.

## 13.0 EMERGENCY PROCEDURES

### 13.1 Emergency Unblinding

Un-blinding by trial personnel should be performed only in emergencies where knowledge of the subject's treatment assignment is essential for further management of the subject's medical care. Un-blinding a subject's treatment assignment under any other circumstances will be considered a protocol violation.

The investigator should assess the relationship of any AEs to administration of the IP prior to un-blinding.

The investigator is strongly encouraged to contact the trial Medical Expert before un-blinding any subject's treatment assignment but must do so within 1 working day after the un-blinding. The subject's treatment code should not be communicated to the Medical Expert. The un-blinding will be documented by the investigator.

If the blind is broken for any reason, the investigator must record the date and reason for breaking the blind on the appropriate trial documents.

## 14.0 INSURANCE

MC2 has taken out appropriate insurance policies covering the subjects in the clinical trial in accordance with applicable laws and regulations.

## 15.0 PUBLICATION POLICY

The clinical trial information will be posted on www.clinical trial.gov and in accordance with applicable regulations.

All publications (e.g., manuscripts, abstracts, oral/slide presentations, book chapters) based on this trial must be submitted to MC2 for review, as specified in the Clinical Trial Agreement between the institution, investigator and MC2 or its designee.

## 16.0 REFERENCES

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# 17.0 APPENDICES

## 17.1 Appendix 1
## Contact List of MC2 and Protocol Authors

Contact details for MC2 representatives are provided to the trial sites on a list outside the protocol, which is included in the clinical trial application.

**Sponsor**

Drug Delivery Solutions Ltd (part of MC2 Therapeutics)
c/o Agern Alle 24-26
2970 Hoersholm
DENMARK
("MC2")

**Protocol Author**

Marianne Thrane, Medical Writer, Altrapharma ApS
Johan Selmer, VP Medical Affairs, MC2 Therapeutics
Birgitte Vestbjerg, Director Clinical Operation, MC2 Therapeutics
Dorte Almstrup, Clinical Project Manager, MC2 Therapeutics
Charlotte Hindsberger, Principal consultant, Biostatistics, S-cubed

## 17.2 Appendix 2 Vendors

Responsible for all services related to the conduct of the trial:
Proinnovera GmbH; Contract Organization for Clinical Research and Development, Wienburgstraße 207; 48159 Münster, Germany.

Responsible for all services related to central laboratory analysis:
MLM Medical Labs GmbH, 41066 Moenchengladbach, Germany.

Responsible for all services related to packaging, labeling, distribution and destruction of the investigational medical products: IMP Pharmaceutical Services Ltd., Caerphilly, Wales NP12 2DG, United Kingdom.

Responsible for providing electronic data capture services: Data MATRIX Ltd., 14a Nekrasova Street, Let. A, 4th Floor, Saint-Petersburg, 191014, Russian Federation.

Responsible for services related to SAE reporting and tracking, as specified in the contract: United BioSource Corporation (UBC), Chemin des Coquelicots 16, CH-1214 Vernier Geneva, Switzerland.

## 17.3 Appendix 3
## Classification of Topical Corticosteroids - Examples

| Class | Generic name and strength | Brand name and formulation |
|---|---|---|
| Class I | Clobetasol Propionate 0.05% | Dermovate Cream / Ointment / Scalp Application |
| | Diflucortolone Valerate 0.3% | Nerisone Forte Oily Cream / Ointment |
| Class II | Beclometasone Dipropionate 0.025% | Generic Beclometasone Dipropionate Cream / Ointment |
| | Betamethasone Valerate 0.1% | Betnovate Cream / Ointment / Lotion / Scalp Application |
| | Betamethasone Dipropionate 0.05% | Diprosone Cream / Ointment / Lotion |
| | Diflucortolone Valerate 0.1% | Nerisone Cream / Oily Cream / Ointment |
| | Fluocinolone Acetonide 0.025% | Synalar Cream / Ointment / Gel |
| | Fluocinonide 0.05% | Metosyn FAPG Cream / Ointment |
| | Fluticasone Propionate 0.05% | Cutivate Cream |
| | Fluticasone Propionate 0.005% | Cutivate Ointment |
| | Hydrocortisone Butyrate 0.1% | Locoid Cream / Ointment / Scalp Lotion Locoid Crelo Emulsion |
| | Mometasone Furoate 0.1% | Elocon Cream / Ointment / Scalp Lotion |
| | Triamcinolone Acetonide 0.1% | Aureocort Ointment * |
| Class III | Alclometasone Dipropionate 0.05% | Modrasone Cream |
| | Betamethasone Valerate 0.025% | Betnovate-RD Cream / Ointment |
| | Clobetasone Butyrate 0.05% | Eumovate Cream / Ointment |
| | Fludroxycortide 0.0125% | Haelan Cream / Ointment |
| | Fluocinolone Acetonide 0.00625% | Synalar 1 in 4 Dilution Cream / Ointment |
| | Fluocortolone 0.25% | Ultralanum Plain Cream / Ointment |
| Class IV | Hydrocortisone 0.1-2.5% | Generic Hydrocortisone Cream / Ointment Dioderm Cream |
| | Fluocinolone Acetonide 0.0025% | Synalar 1 in 10 Dilution Cream |

* Compound preparation (also contains chlortetracycline hydrochloride 3%); List of brand names and formulation is not exhaustive.

# CLINICAL TRIAL PROTOCOL APPROVAL FORM

**Product:** MC2-01 (calcipotriene/betamethasone dipropionate) Cream

**Protocol number:** MC2-01-C7

**Protocol title:** A Randomised, Multicentre, Investigator-Blind, Parallel-Group Trial to Evaluate the Efficacy and Safety of MC2-01 Cream Compared to Vehicle and Active Comparator in Subjects with Mild-to-Moderate Psoriasis Vulgaris

**Version:** 2.0

**Date:** 16 October 2018

The following person has approved this clinical trial protocol:

Johan Selmer, MD
VP Medical Affairs
MC2 Therapeutics

18-OCT-2018

Signature and date

# CLINICAL TRIAL PROTOCOL APPROVAL FORM

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**Version:** 2.0

**Date:** 16 October 2018

The following person has approved this clinical trial protocol:

Charlotte Hindsberger,
Principal consultant,
Biostatistics,
S-cubed

Charlotte Hindsberger 21-Oct-2018
Signature and date

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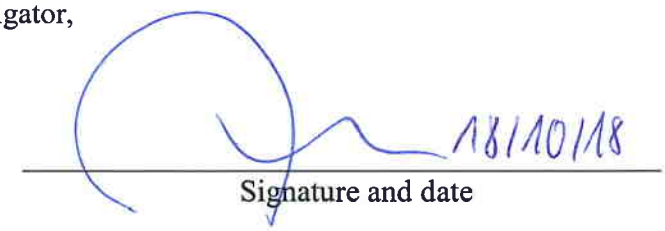
**Version:** 2.0

**Date:** 16 October 2018

The following person has approved this clinical trial protocol:

Matthias Augustin, Prof. Dr. med,
International Coordinating Investigator,
University Medical Center,
Hamburg-Eppendorf, Germany




Signature and date