Clinical Trial Protocol

Trial Title:	**A Randomised, Multicentre, Open-label, Parallel-group Maximal Use Trial, Evaluating the Pharmacokinetic Profile of the Active Ingredients and their Metabolites after application of MC2-01 Cream compared with Active Comparator in Subjects with Extensive Psoriasis Vulgaris**
Investigational product:	**MC2-01 (calcipotriene/betamethasone dipropionate, w/w 0.005%/0.064%) Cream**
Active Comparator:	**Taclonex® (calcipotriene and betamethasone dipropionate, w/w 005%/0.064%) Ointment**
Protocol No:	**MC2-01-C3**
IND:	**127152**
Development phase:	**2**
Documents status:	**Final**
Document version:	**Version 3.0**
Document date:	**20 December 2017**
Sponsor:	**Drug Delivery Solutions Ltd (part of MC2 Therapeutics)** **c/o Agern Alle 24-26** **2970 Hørsholm** **Denmark** **("MC2")**

CLINICAL TRIAL PROTOCOL APPROVAL

Product: MC2-01 (calcipotriene/betamethasone dipropionate) cream

Protocol number: MC2-01-C3

Protocol title: A Randomised, Multicentre, Open-label, Parallel-group Maximal Use Trial, Evaluating the Pharmacokinetic Profile of the Active Ingredients and their Metabolites after application of MC2-01 Cream compared with Active Comparator in Subjects with Extensive Psoriasis Vulgaris.

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

Johan Selmer, MD, VP Medical Affairs, MC2 Therapeutics

Carol Udell, Senior Director, Clinical Data Management and Biostatistics, Novella Clinical

George Han, MD, PhD, International Coordinating Investigator, Department of Dermatology, Mount Sinai Beth Israel

SIGNATURE PAGE FOR INVESTIGATOR(S)

Product: MC2-01 (calcipotriene/betamethasone dipropionate, w/w 0.005%/0.064%) cream

Protocol number: MC2-01-C3

Version: 3

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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

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ACE	Angiotensin converting enzyme
ACTH	Adrenocorticotropic hormone
AE	Adverse event
ALP	Alkaline phosphatase
AUC_{0-7}	Area under the time-concentration curve from time zero to 7 hours
AUC_{0-t}	Area under the time-concentration curve from time zero to the last measurable concentration
$AUC_{0-\infty}$	Area under the time-concentration curve from time zero to infinity
BDP	Betamethasone dipropionate
BSA	Body surface area
CAL	Calcipotriene (United States term) / Calcipotriol (European Union term)
C_{max}	Maximum plasma drug concentration
CRO	Contract Research Organisation
ECG	Electrocardiogram
eCRF	Electronic case report form
EU	European Union
FDA	Food and Drug Administration
FU1, FU2	Follow up visit 1, Follow up visit 2
HIV	Human immunodeficiency virus
HPA	Hypothalamic-pituitary-adrenal
ICF	Informed consent form
ICH-GCP	International Conference on Harmonisation-Good Clinical Practice
IEC	Independent Ethics Committee
IP	Investigational product
IRB	Institutional Review Board
IWR	Interactive web response
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
OTC	Over the counter
PGA	Physician's Global Assessment
PK	Pharmacokinetics
PTH	Parathyroid hormone
PUVA	Psoralen + ultraviolet A
RBC	Red blood cell
SAE	Serious adverse event
SAR	Suspected adverse reaction

Abbreviation	Definition
SD	Standard deviation
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
SV1, SV2	Screening Visit 1, Screening Visit 2
$T_{1/2}$	Elimination half-life
TH17	T helper 17 (cell)
T_{max}	Time to maximum plasma drug concentration
UBC	United BioSource Corporation
UPT	Urine pregnancy test
US	United States
UVA / UVB	Ultraviolet A / ultraviolet B
WBC	White blood cell

1.0 SYNOPSIS

Trial Title:	A Randomised, Multicentre, Open-label, Parallel-group Maximal Use Trial, Evaluating the Pharmacokinetic Profile of the Active Ingredients and their Metabolites after application of MC2-01 Cream compared with Active Comparator in Subjects with Extensive Psoriasis Vulgaris.
Protocol Number:	MC2-01-C3
Sponsor:	Drug Delivery Solutions Ltd (part of MC2 Therapeutics)
Development Phase:	2
Trial Objectives:	The primary objective is to evaluate the pharmacokinetic profile of the active ingredients and their main metabolites after application of MC2-01 cream, and compare with the active comparator following once daily topical application under maximum-use conditions in subjects with extensive psoriasis vulgaris. The secondary objective is to evaluate the effect of MC2-01 cream on the hypothalamic-pituitary-adrenal (HPA) axis and calcium metabolism following once daily topical application under maximum-use conditions in subjects with extensive psoriasis vulgaris.
Trial Design:	This is a Phase 2, randomised, open-label, parallel-group, multicentre trial in which the investigational product, MC2-01 cream, and calcipotriene/betamethasone ointment (comparator) is investigated in subjects with clinically diagnosed extensive psoriasis vulgaris. After having provided informed consent, the subjects will undergo screening procedure. Subjects that fulfil the inclusion and exclusion criteria are randomly assigned in a 1:1 ratio to receive the MC2-01 cream or the comparator. Subjects assigned to the MC2-01 cream will be treated once-daily for 8 weeks and the subjects assigned to the comparator will be treated once-daily for 4 weeks. At Week 4, the pharmacokinetic (PK) profile of calcipotriene (CAL), betamethasone dipropionate (BDP) and their main metabolites MC1080 and betamethasone 17-propionate, respectively, will be assessed for both treatment groups. At Week 8, the PK profile of calcipotriene, betamethasone and their main metabolites will be assessed for the MC2-01 cream treatment group only. The effect of use of MC2-01 cream on the hypothalamus-pituitary-adrenal (HPA) axis and calcium metabolism will be evaluated at week 4 and week 8. The maximum trial duration for each subject will be approximately 12 or 16 weeks and includes a screening period of up to 4 weeks (if washout of medication is required), a treatment period of 4 or 8 weeks, and a follow-up period of up to 4 weeks (if required for follow-up of adverse events, calcium concentrations, and/or HPA axis suppression).

Sample Size:	It is planned to enrol approximately 60 subjects with the aim to have 25 subjects included in the PK population after 4 weeks of treatment in each treatment arm. The choice of sample size in this trial is not based on statistical considerations, but rather on regulatory considerations with respect to common practice in maximum use studies evaluating pharmacokinetic profiles and evidence of HPA safety
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, with a Physician Global Assessment (PGA) of disease severity of at least moderate on the trunk, limbs and/or scalp and a treatment area between 20% and 30% of the BSA, excluding psoriatic lesions on the face, genitals, and intertriginous areas.
Investigational Product(s):	MC2-01 cream (CAL and BDP, w/w 0.005%/ 0.064%).
Reference Product(s):	CAL/BDP ointment (w/w 0.005%/0.064%). Approved in the United States (US) as Taclonex® Ointment and in rest of the world as Daivobet® Ointment/Dovobet® Ointment.
Pharmacokinetics Evaluation Criteria:	Blood samples for PK assessments will be collected at • SV2 (baseline sample) • Week 2 • Week 4 and for subjects assigned to the MC2-01 cream at Week 8; before application of trial medication and then at 0.5, 1, 2, 3, 5, and 7 hours after the application. The samples will be assayed for concentrations of the active ingredients (BDP and CAL) and for their main metabolites; betamethasone 17-propionate and MC1080, respectively.
HPA axis and calcium metabolism Evaluation Criteria:	For subjects assigned to the MC2-01 cream, the endpoint for the HPA axis evaluation will be a serum cortisol level of 18 µg/dL or less at 30 minutes after ACTH challenge at Week 4 and Week 8: The primary response criteria for calcium metabolism will be changes from Baseline to Week 4 and Week 8 in: • Albumin-corrected serum calcium; • 24-hour urinary calcium excretion; • Ratio of urinary calcium to creatinine.

Other Safety Evaluation Criteria	Adverse event incidence and severity, laboratory test results (haematology, clinical chemistry, urinalysis), vital signs, local skin reactions, physical examination. For subjects assigned to the MC2-01 cream electrocardiogram (ECG).
Statistical Methods:	It is planned to combine the data from all centres that participate in this protocol, in order to have an adequate number of subjects for analysis. No imputation will be made for missing data. **Primary endpoint:** Systemic PK profile of the active ingredients of the MC2-01 cream and their main metabolites following once daily topical application for 4 weeks. All available concentration results will be summarised using appropriate descriptive statistics for active ingredients (BDP and CAL) and for their major metabolites. Median and individual concentration versus time curves will be plotted (linear and semi-log plots). Plasma PK parameters (AUC_{0-t}, $AUC_{0-\infty}$, AUC_{0-7}, C_{max}, and T_{max}, and $T_{½}$) will be calculated. For a given analyte, the PK parameters AUC_{0-t}, $AUC_{0-\infty}$, T_{max}, and $T_{½}$ will be calculated if data allow. The PK parameters AUC_{0-7} and C_{max} will be calculated using standard formulas inserting the lower limit of quantification (LLoQ) in case of concentrations below the LLoQ, in which case the result is an upper limit for the PK parameter. The PK parameters will be summarised using appropriate descriptive statistics. The PK parameters AUC_{0-7} and C_{max} will be compared for the two treatment groups using analysis of variance for censored data. <u>Only for subjects assigned to the MC2-01 cream:</u> Systemic PK profile of the active ingredients of the MC2-01 cream and their main metabolites following once daily topical application for 8 weeks. The PK parameters AUC_{0-t}, $AUC_{0-\infty}$, AUC_{0-7}, C_{max}, T_{max}, and $T_{½}$ will be calculated and presented as described for Week 4. **Secondary endpoints for subjects assigned to the MC2-01 cream:** <u>HPA axis suppression</u> The proportion of subjects with HPA-axis suppression at Week 4 and at Week 8 will be summarised using frequency counts. <u>Calcium metabolism endpoints:</u> Summary statistics will be provided for the following: Observed values of and changes from Baseline (SV2) to Week 4 and Week 8 in: • Albumin-corrected serum calcium

	• 24 hours' urinary calcium excretion • Ratio of urinary calcium to creatinine. **Other safety endpoints:** Adverse events will be presented in data listings and summarised by frequency and severity for each treatment group. Laboratory, ECG, and vital sign data will be presented in data listings. Abnormal ECG and laboratory findings will be presented
Trial Sites:	10-15 sites in US
Planned Dates of Trial:	4th quarter, 2017 - 3nd quarter, 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 US is approximately 3%[1] whereas the prevalence in Europe varies anywhere from 0.6 to 6.5%[2] with an average of approximately 3%[3]. 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[4]. 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[5]. Patients with psoriasis have reduced quality of life with reduced levels of employment and income[6], 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[7;8].

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[9;10]

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 Calcipotriene (CAL) and betamethasone (BDP) is superior to each of the single agent[11-12].There is strong scientific rationale for the combination of vitamin D and glucocorticosteroids both with respect to efficacy and safety[13-15], and combination treatment with a Vitamin D analog and a topical corticosteroid is recommended in both American and European guidelines[16-19]

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.

The 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. 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

To increase the likelihood that adequate quantifiable systemic concentrations of CAL and BDP and their main metabolites under maximal use conditions to determine the pharmacokinetic parameters in sufficient numbers of patients, Taclonex® Ointment has been selected as the comparator. MC2-01 cream will be compared to Taclonex® Ointment following once daily topical application under maximal use conditions in subjects with extensive psoriasis on the scalp, trunk, and limbs. Dosages will be up to 100 g per week for 8 weeks for MC2-01 cream and for 4 weeks for Taclonex® Ointment.

At Week 4, blood samples will be taken at selected intervals after topical dosing of each trial medication. Upper limits will be calculated for the PK parameters, area under the concentration-time curve (AUC) from time zero to the planned last PK blood sampling time point of 7 hours (AUC_{0-7}) and maximum plasma drug concentration (C_{max}). To the extent the data allow to calculate the PK parameters, the following parameters will be calculated: AUC from time zero to the last quantifiable concentration (AUC_{0-t}), AUC from time zero to infinity ($AUC_{0-\infty}$), time to maximum plasma drug concentration (T_{max}), and elimination half-life ($T_{½}$).

Taclonex® Ointment is only approved for daily application for up to 4 weeks, whereas it is the intention that MC2-01 cream will be used daily for up to 8 weeks. The pharmacokinetic comparison between the two trial medications will be done at Week 4. Additional pharmacokinetic data at Week 8 will be obtained only from subjects receiving the MC2-01 cream.

Since MC2-01 cream is a combination of CAL and BDP, disturbance of calcium metabolism and adrenal function respectively could theoretically be the result if these two components are absorbed through the skin.

As the current trial is a MUsT trial only subjects with upper level of disease involvement will be included. Inclusion criteria will be subjects with extensive psoriasis covering between 20-30% of the BSA on trunk, limbs and/or scalp. The intent of the inclusion criteria is both to take into account the potential risk that patients may decide to apply MC2-01 cream on the scalp and also to take into account precedent from previous approved CAL/BPD products.

According to input from experienced investigators, subjects with extensive vulgaris psoriasis may have psoriasis elements of guttatae character. Considering that the histological characteristics of guttate psoriasis and the clinical response to Vitamin D and glucocorticoids are similar to what is observed in subject with psoriasis vulgaris, presence of psoriasis elements of guttate character will not be an exclusion criterium in this study.

To evaluate the safety of the MC2-01 cream, all adverse events (AEs), reported by the subject or observed by the investigator, are recorded. In addition, any effects resulting from systemic absorption of the active components, BDP and CAL, are evaluated by assessing adrenal function and calcium metabolism, respectively. Adrenal function can therefore be measured by injection of a synthetic subunit of ACTH into the subject, and then measuring the production of cortisol by the adrenal glands in response to this. In the present study, enrolled subjects in the MC2-01 arm of the study will be subjected to an ACTH-challenge test before and after 4 and 8 weeks' treatment.

Overdosage with topical CAL can cause hypercalcemia[20] due to the systemic absorption of CAL, which then affects calcium metabolism as it is a vitamin D analogue. However, extensive experience with topical use of CAL in psoriasis has demonstrated no significant impact on calcium metabolism, when used in the recommended amounts (maximum weekly dose in adults of 100 g of a 50 mcg/g concentration). Doses up to 300 g have been used with serum calcium remaining within the reference range[21]. Calcium metabolism will be evaluated in the present study by measurement of albumin corrected serum calcium, phosphate, alkaline phosphatase and plasma PTH before, during and after treatment. A 24-hour urine sample will be collected and the urinary calcium phosphate, sodium and creatinine will be measured and the urinary calcium:creatinine and phosphate:creatinine ratios will be calculated. It is well-established that there is a relationship between dietary calcium intake and the urinary calcium excretion in adults[22]. The urinary excretion of calcium has been reported to increase by 6-19 mg with each additional 100 mg of calcium intake[22;23]. Subjects will not be asked to change their diet during the study, but in order to limit diet-related variability in urinary calcium excretion, their normal consumption of calcium-rich foods will be reviewed and should be kept constant during 3 days prior to and during each 24-hour urinary collection. Considering that dairy products account for the majority of the of calcium absorption in most people, this protocol focusses on the intake of dairy products. The subjects will keep a diary of the daily intake of dairy products, calcium-fortified products (e.g. bread, cereals, orange juice or soy milk) and other specified calcium-rich products. The number of daily servings of calcium defined as 240 mL (one US cup) in dairy products such as milk or yoghurt or of a calcium-fortified product with corresponding calcium content (300 mg calcium per 240mL/one US cup) or 42g (1.5 ounces) of cheese. As an extreme calcium intake has been shown to significantly increase urinary excretion of calcium, subjects will be instructed not to consume more than five daily calcium servings (i.e. 1500 mg calcium). The combination of high calcium intake with vitamin D supplementation significantly increases urinary calcium. Hence the use of calcium or vitamin D supplements were excluded in this study with the exception of stable doses of oral vitamin D (up to 400 IU/day) at baseline with no dose adjustment during the study period. Systemic safety of MC2-01 cream on calcium metabolism and HPA axis will be assessed at Week 4 and Week 8. Experience with the current commercially available fixed-dose combinations of CAL and BDP has shown that effects on HPA axis suppression or calcium homeostasis are infrequent events. For this reason, post-Baseline HPA

axis suppression and calcium homeostasis testing will be performed only in subjects receiving the MC2-01 cream, without any comparison to the reference compound.

Data from this trial, together with the measurements of albumin-corrected serum calcium and the calcium:creatinine ratio in urine samples in the phase 3 trial with MC2-01 cream are expected to provide adequate information with respect to the systemic safety of the MC2-01 cream.

2.3 Benefit-risk Assessment

The subject population will be composed of subjects with psoriasis that is at least moderate in severity according to PGA and involves 20-30% of body surface area (BSA), excluding face, genitals and intrigenous areas, in order to evaluate the trial medication under maximum use conditions.

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.

MC2-01 cream contains the same active ingredients at identical concentrations of CAL and BDP as the marketed products (w/w 0.005%/0.064%) but in a novel cream formulation that is expected to provide better cosmetic acceptability to patients than the currently available formulations.

The side effects reported with CAL/BDP topical formulations are mild and reversible upon stopping therapy. It is therefore not considered necessary to have analysis of calcium homeostasis prior to initiation of treatment. Subjects in this trial will be monitored for both systemic and local safety during the trial.

Clinical signs or symptoms of systemic safety (e.g., hypercalcemia, HPA axis suppression, or cardiac safety) will be part of the periodic assessment of subjects throughout this trial. In addition, for subjects assigned to the MC2-01 Cream, an ACTH challenge test supplemented with measurement of albumin corrected calcium, and total calcium excretion will be performed at Week 4 and Week 8.

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[24].

3.0 TRIAL OBJECTIVES AND PURPOSE

The primary objective is to evaluate the pharmacokinetic profile of the active ingredients after application of MC2-01 cream and their main metabolites, and compare with the active

comparator following once daily topical application under maximum-use conditions in subjects with extensive psoriasis vulgaris.

The secondary objective is to evaluate the effect of MC2-01 cream on the hypothalamic-pituitary-adrenal (HPA) axis and calcium metabolism following once daily topical application under maximum-use conditions in subjects with extensive psoriasis vulgaris.

4.0 TRIAL DESIGN

4.1 Overall Trial Design

This is a Phase 2, randomised, open-label, parallel-group, multicentre trial in which the investigational product, MC2-01 cream, and CAL/BDP ointment (comparator) are investigated in subjects with clinically diagnosed extensive psoriasis vulgaris.

After having provided written informed consent, the subject will undergo screening procedures. Subjects who meet the trial entry criteria will be randomly assigned in a 1:1 ratio to receive either MC2-01 cream or the comparator, CAL/BDP ointment. Subjects assigned to MC2-01 cream will apply 1 dose of trial medication topically once daily for 8 weeks and the subjects assigned to the comparator will apply 1 dose of trial medication topically once daily for 4 weeks.

Please refer to Figure 4-1 for an overview of the trial design for subjects assigned to the MC2-01 cream and refer to Figure 4-2 for an overview of the trial design for subjects assigned to the active comparator.

Trial subjects will be enrolled at approximately 10-15 sites in US.

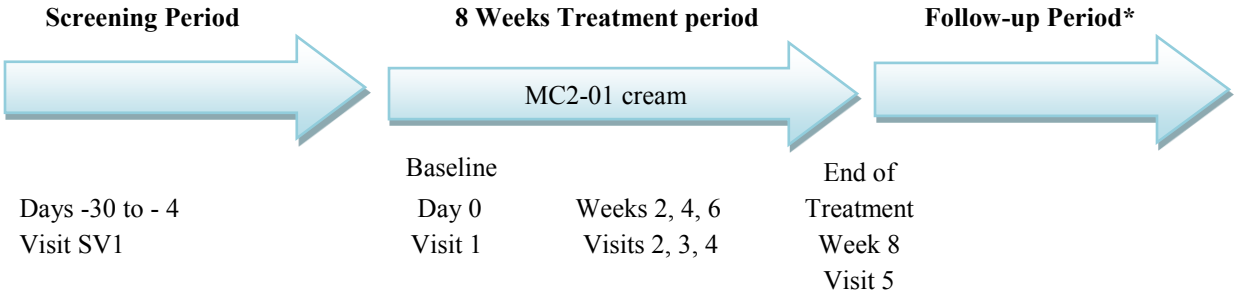
At Week 4, the pharmacokinetic (PK) profile of calcipotriene (CAL), betamethasone dipropionate (BDP) and their main metabolites MC1080 and betamethasone 17-propionate, respectively, will be assessed for both treatment groups. At Week 8, the PK profile of CAL, BDP and their main metabolites will be assessed for the MC2-01 cream treatment group only. At Week 4 and Week 8, the effect of once-daily use of MC2-01 cream on the HPA axis and calcium metabolism will be evaluated for MC2-01 cream treatment group. Other safety assessments (local skin reactions, AEs, laboratory tests, electrocardiogram (ECG)), vital signs and physical examinations) and efficacy assessments are also performed.

The maximum trial duration for each subject will be approximately 12 or 16 weeks and includes a screening period of up to 4 weeks (if washout of medication is required), a treatment period of 4 or 8 weeks, and a follow-up period of up to 4 weeks (if required for follow-up of adverse events, calcium concentrations, and/or HPA axis suppression).

During the trial, the effect of once-daily use of MC2-01 cream on the HPA axis and calcium metabolism will be evaluated for subjects assigned to the MC2-01 cream. Systemic exposure will be assessed for both treatment groups at Week 4, and additionally at Week 8 for the subjects

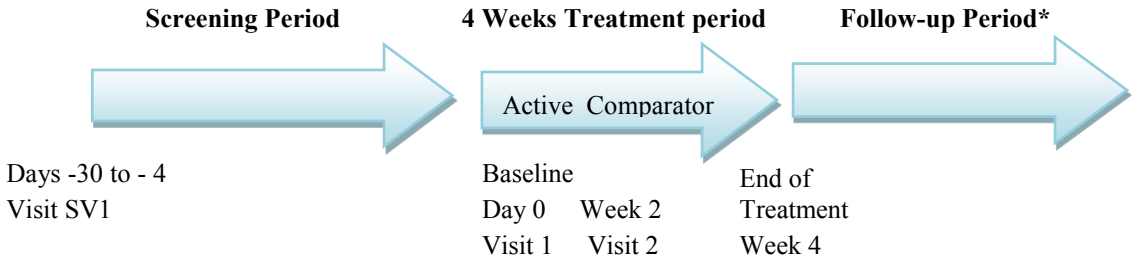
assigned to the MC2-01 cream. Other safety assessments (local skin reaction, AEs, laboratory tests, electrocardiogram (ECG), vital signs and physical examinations) and efficacy assessments are also performed.

Figure 4-1 Trial Design for Subjects Assigned to the MC2-01 Cream



*Follow-up visits will be required only for subjects who have unresolved AEs or whose calcium levels have not returned to pre-treatment levels at the End of Treatment visit.

Figure 4-2 Trial Design for Subjects Assigned to the Active Comparator



*Follow-up visits will be required only for subjects who have unresolved AEs at the End of Treatment visit.

4.2 Trial Endpoints

Primary Endpoints

For all subjects:

Pharmacokinetic (PK) parameters (AUC_{0-t}, $AUC_{0-\infty}$, AUC_{0-7}, C_{max}, T_{max}, and $T_{½}$) of active ingredients and their main metabolites at Week 4. For a given analyte, the PK parameters AUC_{0-t}, $AUC_{0-\infty}$, T_{max}, and $T_{½}$ will be calculated if data allow. The PK parameters AUC_{0-7} and C_{max} will be calculated for all subjects; AUC_{0-7} will be an upper limit in case at least one time point shows a non-quantifiable level of the analyte, and C_{max} will be an upper limit in case all

time points show non-quantifiable levels of the analyte. T_{max} will be calculated in case at least one time point shows quantifiable levels of the analyte.

For subjects assigned to the MC2-01 cream:
PK parameters (AUC_{0-t}, $AUC_{0-\infty}$, AUC_{0-7}, C_{max}, T_{max}, and $T_{½}$) of active ingredients and their main metabolites at Week 8. For a given analyte, PK parameters will be calculated under similar conditions as described for Week 4.

Secondary Endpoints

HPA axis evaluation for subjects assigned to the MC2-01 cream:

The number of subjects with a serum cortisol level of 18 µg/dL or less at 30 minutes after ACTH challenge at Week 4 or Week 8.

Calcium metabolism evaluation for subjects assigned to the MC2-01 cream:

Changes from Baseline to Week 4 or Week 8 in:

- Albumin-corrected serum calcium;
- 24-hour urinary calcium excretion;
- Ratio of urinary calcium to creatinine.

Safety Endpoints

Safety endpoints include the following:

- Local skin reaction;
- Adverse events (AEs) and serious adverse events (SAEs);
- Changes in safety laboratory test results;
- Changes in ECGs (Only for subjects assigned to the MC2-01 cream);
- Changes in vital signs and physical examinations.

Other Endpoints

- For all subjects:
  The proportion of subjects with treatment success, defined as a minimum 2-point decrease from Baseline in the physician's global assessment (PGA) on the scalp, trunk, and limbs at Week 4.

- For subjects assigned to the MC2-01 cream:
  The proportion of subjects with treatment success, defined as a minimum 2-point decrease from Baseline in the PGA on the trunk, limbs, and scalp at Week 8.

- For all subjects:
  Subject assessment of treatment convenience at Week 4 using a Psoriasis Treatment Convenience Scale.

5.0 SELECTION OF TRIAL POPULATION

5.1 Subject Population

A sufficient number of subjects will be enrolled in order to provide 25 subjects in each treatment arm, who are included in the PK analysis at Week 4. 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 (ICF) 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. At Visit 1/Day 0, have a clinical diagnosis of plaque psoriasis (psoriasis vulgaris) of at least 6 months duration involving trunk, limbs and/or scalp that is amenable to topical treatment with a maximum of 100 g of trial medication per week.
4. Have a PGA of severity of at least moderate on the trunk, limbs and/or scalp, excluding psoriatic lesions on the face, genitals, and intertriginous areas, at Visit 1/Day 0.
5. Have a treatment area between 20% and 30% of the BSA on the trunk, limbs and/or scalp, excluding psoriatic lesions on the face, genitals, and intertriginous areas, at Visit 1/Day 0.
6. Female subjects must be of either:
   - Non-childbearing potential, i.e., post-menopausal for a least 1 year or have a 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.

7. Female subjects of childbearing potential must be willing to use effective contraception at trial entry and until completion. Effective contraception is defined as follows:

   - Oral/implant/injectable/transdermal/estrogenic vaginal ring contraceptives, intrauterine device, condom with spermicide, diaphragm with spermicide.
   - Abstinence or partner's vasectomy are acceptable if the female agrees to implement one of the other acceptable methods of birth control if these conditions do not any longer apply.

5.3 Exclusion Criteria

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

1. Have a current diagnosis of unstable forms of psoriasis, including 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. 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;
6. Current or past history of disorders of calcium metabolism associated with hypercalcemia, vitamin D toxicity, severe renal insufficiency, or severe hepatic disorders;
7. Oral calcium supplements, vitamin D supplements, bisphosphonates or calcitonin within 4 weeks prior to Visit 1/Day 0 during the trial period.
   Note: Stable doses of oral vitamin D supplementation ≤400 IU/day are permitted provided there are no dose adjustments during the trial period;
8. Planned initiation of, or changes to concomitant medication that could affect calcium metabolism (e.g., antacids, thiazide and/or loop diuretics, antiepileptics) during the trial;
9. Planned initiation of, or changes to, concomitant estrogen therapy during the trial;
10. Strong systemic cytochrome P450 3A4 (CYP 3A4) inhibitors (e.g., clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir) within 4 weeks prior to Vist 1/Day 0 and during the trial period;
11. Use of topical treatments (eg, corticosteroids, 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/Day 0 and during the trial period;

12. Systemic treatment with biological therapies (whether marketed or not marketed), with a possible effect on psoriasis vulgaris within the following time period prior to Visit 1/Day 0 and during the trial period;
    - etanercept – within 4 weeks
    - adalimumab, alefacept, infliximab – within 8 weeks
    - ustekinumab – within 16 weeks
    - other products – within 4 weeks/5 half-lives (whichever is longer)
13. Initiation of, or expected changes to, concomitant medication that may affect psoriasis (e.g., beta-blockers, chloroquines, lithium, and angiotensin converting enzyme [ACE] inhibitors) and during the trial period;
14. Any of the following conditions, whether known or suspected:
    - depression and endocrine disorders (e.g. Cushing's disease, Addison's disease, diabetes mellitus) known to affect cortisol levels or HPA axis integrity
    - Non-nocturnal sleep patterns (e.g. night shift workers);
15. Use of systemic medication that suppresses the immune system (e.g, 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 the Visit 1/Day 0 and during the trial period;
16. Have clinical signs of skin infection with bacteria, viruses, or fungi;
17. Known human immunodeficiency virus (HIV) infection;
18. Known or suspected of hypersensitivity to any component of the test product or reference product;
19. Have any chronic or acute medical condition that, in the option 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;
20. 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 or will interfere with the interpretation of the trial results;
21. Females who are pregnant, breast feeding, or planning a pregnancy;

22. Participation in another clinical trial or received an investigational product or non-marketed drug substances within 30 days;
23. Previously enrolled in this trial;
24. In the opinion of the (sub)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 Harmonization (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 on follow-up safety evaluations.

If HPA axis is suppressed at Visit 1/Day 0 or Week 4, the subject should be contacted and the application with the investigational product (IP) should be discontinued (see Section 7.9.2 and Section 7.16).

If albumin corrected serum calcium is above upper limit at Visit1/Day 0, the application with the investigational product (IP) should be discontinued (see Section 7.9.2).

In the case of an SAE or development of a condition that would have met the trial safety-related exclusion criteria, the subject should be evaluated by the investigator. The investigator should use his/her discretion to determine whether the subject should continue treatment with the IP.

A subject may be withdrawn from the trial at any time at the discretion of the investigator. The reasons for early termination are to be fully documented on the eCRF.

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

If a subject withdraws from the trial, all efforts will be made to complete a final evaluation if possible. Protocol-specified withdrawal procedures are defined in Section 7.16 Early Termination.

Subjects discontinued for an AE will be monitored until the AE is resolved, a reasonable explanation is provided for the event, or the subject is referred to his/her own primary medical doctor. The specific AE in question will be recorded on the appropriate eCRF.

5.5 Replacement Policy

After trial enrolment, has been completed, subjects who prematurely discontinue the trial after randomisation can be replaced if necessary to ensure 25 subjects in both treatment arms are included in the PK population at Week 4.

6.0 TRIAL TREATMENTS

6.1 Investigational Product

MC2-01 cream is a combination product, calcipotriene and betamethasone dipropionate, administered as a cream formulation for topical administration. One concentration of the trial product will be studied: calcipotriene (w/w 0.005%) and betamethasone (w/w 0.064%, as dipropionate). The list of inactive ingredients present in MC2-01 cream is presented in the Investigator Brochure.

6.2 Active Comparator

The active comparator is CAL and BDP Ointment, 0.005%/0.064%, approved in the US as Taclonex Ointment and in the rest of the world as Daivobet® Ointment/Dovobet® Ointment.

Taclonex® Ointment contain the following inactive ingredients:

- mineral oil,
- polyoxypropylene stearyl ether
- all-rac-alpha-tocopherol
- butylhydroxytoluene
- white petrolatum

6.3 Dosing Regimen

Subjects are to apply the trial product topically once daily, preferably in the evening, to affected areas on the scalp and the trunk (including the neck) and/or limbs, i.e., arms (including the back of the hands) and/or legs (including the buttocks and the top of the feet). The face, genitals, and intertriginous areas should not be treated with the investigational product. The first application is done under the supervision and instruction of the trial staff.

All subjects are instructed to apply the dose of trial medication in the morning on the day before the Week 2, Week 4 and for subjects assigned to the MC2-01 cream also at the Week 8 visit. On the day of the visit, the subjects should not apply any investigational product before the visit

Subjects are to record the date and time of application in the subject dosing diary. The weekly dose is not to exceed 100 g for the MC2-01 cream or for the comparator. The treated area should not exceed 30% of the BSA.

Detailed application instructions will be provided in the subject instructions.

6.4 Dose Modification

Until Week 4:
Subjects classified as clear at the Week 2 visit are to continue use of the treatment unless investigator finds further treatments unacceptable.

After Week 4:
Subjects classified as clear at any of the on-treatment visits may stop the 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 treatment may be restarted at the subject's discretion. The subject should not discontinue treatment themselves between visits, but is only allowed to stop using the treatment on the advice of the investigator at a scheduled visit.

6.5 Packaging, Labeling and Storage

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

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

The MC2-01 cream will be supplied to the clinical site(s) as tubes containing 60 g of product. The MC2-01 cream is to be stored at a temperature of 2°- 8°C (35°- 46°F) at the site, and below 25°C (below 77°F) after dispensing to the subject. At all times, the MC2-01 cream should be protected from light.

The active comparator will be supplied to the clinical sites as tubes containing 60 g of product. The active comparator is to be stored at 20°- 25°C (68° -77°F).

6.6 Assignment to Treatment

6.6.1 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 (IWR) system in accordance with a pre-planned computer-generated randomisation schedule in a 1:1 ratio.

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

6.6.2 Blinding

This is an open-label trial with the treatment assignment known by the subjects, the investigators and their staff, and the clinical research team. No blinding will be performed.

6.7 Prior, Concomitant, and Prohibited Therapy

All medications, including over-the-counter (OTC) drugs, 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.

6.7.1 Washout of prohibited medications prior to enrolment

A washout period must be completed if the subject has been treated with any medication as specified in the exclusion criteria (Section 5.3).

6.7.2 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 psoriasis therapies;
- Use of oral systemic treatments with a possible effect on psoriasis (eg, methotrexate, retinoids, PDE4 inhibitors, corticosteroids, and other immunosuppressants).
- Use of phototherapy (PUVA and UVB).
- Use of topical treatments with a possible effect on psoriasis (eg, corticosteroids, vitamin D analogs, retinoids, PDE4 inhibitors, salicylic acid, pimecrolimus, tacrolimus, anthralin, tar, etc.).
- 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.
- Use of strong systemic cytochrome P450 3A4 (CYP 3A4) inhibitors (e.g., clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir.
- Emollients on the psoriasis affected areas.
- Any medications with proven or purported activity against psoriasis (including OTC medications) should be discussed with the Investigator prior to use.

6.7.3 Allowed treatment on the face, skin folds, and genital skin only

Subjects may receive laser treatment and use an emollient on the face, skin folds, and genital skin.

6.8 Treatment Compliance

Records of trial product used and dosages administered will be kept during the trial. The trial monitor will note product accountability during site visits and at the completion of 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 specified. In addition, subjects will be asked to complete a dosing diary during the treatment period as a measure of treatment compliance. Subjects who are consistently noncompliant will be counseled.

Subjects will be asked to return all used and unused tubes in the outer box at each visit. All returned tubes that had been dispensed to a subject and have broken seals will be weighed to determine the amount of the investigational product used per treatment phase.

7.0 VISIT SCHEDULE AND ASSESSMENTS

7.1 Visit Schedule for Screening and until Randomisation

Table 7-1 Visit Schedule for Screening until Randomisation

	Screening Visit 1[a]	**Visit 1**
	Screening 1	**Day 0**
Examination	**Day –30 to – 4**	**Day 0**
Informed consent[b]	X	
Inclusion/exclusion criteria	[X]	X
Urine pregnancy test (UPT)[c]	[X]	X
Demographics, medical history	[X]	X
Prior and concomitant medication	[X]	X
Physical examination	[X]	X[d]
PGA	[X]	X
Body Surface Area (BSA) involvement	[X]	X
Vital signs	[X]	X
Laboratory assessments		X
Review food diary	Instruct	X
24-h urine collection	Instruct	X
Randomisation		X
Adverse event(s)[e]		X
Local Skin Reactions		X

a) A washout period of up to 4 weeks 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 during screening, to assess if the subject is otherwise eligible. Such items must be checked for any change in eligibility status at Visit 1/Day 0 after the washout is completed.
b) Informed consent must be signed both by subject and investigator or designee before any trial related procedures are carried out. For subjects requiring a washout period, informed consent must be completed prior to washout.
c) For female subjects of childbearing potential.
d) Including height and weight
e) AEs are to be collected from the date of signing informed consent, i.e., during the washout period.

Instruct: At the indicated visits, instruct the subjects as to appropriate trial procedures as specified below:

- **Food diary:** instruct the subjects on how to use the food diary, especially recording their intake of calcium-rich nutrients
- **24-hour urine collection:** instruct the subjects on how to perform the 24-hour urine collection.

7.2 Visit Schedule and Assessment for Subjects Assigned the MC2-01 Cream

Table 7-2 Visit Schedule for Subjects Assigned to the MC2-01 Cream

	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Follow-up Visit** [a]
	Day 0	**Week 2**	**Week 4**	**Week 6**	**Week 8**	
Examination	**Day 0**	**Day 14 ± 2**	**Day 28 ± 2**	**Day 42 ± 2**	**Day 56 ± 2**	
Inclusion/exclusion criteria	X					
Urine pregnancy test (UPT)[b]	X		X		X	
Demographics, medical history	X					
Prior and concomitant medication	X	X	X	X	X	
Physical examination	X[c]		X		X	
PGA	X	X	X	X	X	
Body Surface Area (BSA) involvement	X		X		X	
Vital signs	X	X	X	X	X	
Laboratory assessments	X		X	(X)[d]	X	X
Review food diary	X		X		X	
24-h urine collection	X	Instruct	X	Instruct	X	
Randomisation	X					
PK pre-dose blood sample (Single)	X Instruct	X				
PK serial blood samples[e]		Instruct	X	Instruct	X	
12-Lead ECG	X		X		X	
ACTH challenge test [f]	X		X		X	X
Psoriasis Treatment Convenience Scale			X			
Dispense IP and diary for compliance	X	X	X	X		
Collect IP		X	X	X	X	
Compliance		X	X	X	X	
Adverse event(s)[g]	X	X	X	X	X	X
Local Skin Reactions	X	X	X	X	X	

a) A follow-up visit is required to check: abnormal albumin-corrected serum calcium, HPA axis suppression, or unsolved treatment-related AEs at Week 8.
b) For female subjects of childbearing potential.
c) Including height and weight
d) If serum albumin-corrected serum calcium is above the reference range at Week 4, a repeat test should be performed at Week 6.
e) Blood samples for PK analysis are drawn before IP application (pre-dose sample) and 0.5, 1, 2, 3, 5 and 7 hours after IP application.
f) The ACTH challenge test must be performed at 8 am (±30 minutes) before application of the IP.
g) AEs are to be collected from the date of signing informed consent, i.e., during the washout period.

Instruct: At the indicated visits, instruct the subjects as to appropriate trial procedures as specified below:

- **Food diary:** instruct the subjects on how to use the food diary, especially recording their intake of calcium-rich nutrients
- **24-hour urine collection:** instruct the subjects on how to perform the 24-hour urine collection. Consumption of calcium-rich foods should be kept constant during and 3 days prior to each 24 hour urine collection.
- **PK blood samples:** instruct the subjects that the day before the Week 2, Week 4, and Week 8 visits, they should apply the trial drug in the morning. On the day of the visit, the subjects should not apply any investigational product before the visit, but will apply the IP after the pre-dosing PK sample has been drawn. A reminder to the subjects may be needed a few days before the scheduled visit. If the subject has applied the investigational product in the morning prior to the visit, the visit must be rescheduled.

7.3 Visit Schedule and Assessments for Subjects Assigned the Comparator

Table 7-3 Visit Schedule for Subjects Assigned to the Comparator

	Visit 1	**Visit 2**	**Visit 3**	**Follow-up Visit[a]**
	Day 0	**Week 2**	**Week 4**	
Examination	**Day 0**	**Day 14 ± 2**	**Day 28 ± 2**	
Inclusion/exclusion criteria	X			
Urine pregnancy test (UPT)[b]	X		X	
Demographics, medical history	X			
Prior and concomitant medication	X	X	X	
Physical examination	X[c]		X	
PGA	X	X	X	
Body Surface Area (BSA) involvement	X		X	
Vital signs	X	X	X	
Laboratory assessments	X		X	
Review food diary	X			
24-h urine collection	X			
PK pre-dose blood sample (Single)	X Instruct	X		
PK serial blood samples[d]		Instruct	X	
Randomisation	X			
Psoriasis Treatment Convenience Scale			X	
Dispense IP and diary for compliance	X	X	X	
Collect IP		X	X	
Compliance		X	X	
Adverse event(s)[e]	X	X	X	X
Local Skin Reactions	X	X	X	

a) A follow-up visit is required to check unsolved treatment-related AEs at Week 4
b) For female subjects of childbearing potential.
c) Including height and weight.
d) Blood samples for PK analysis are drawn before IP application (pre-dose sample) and 0.5, 1, 2, 3, 5 and 7 hours after IP application
e) AEs are to be collected from the date of signing informed consent, i.e., during the washout period.

Instruct: At the indicated visits, instruct the subjects as to appropriate trial procedures as specified below:

- **Food diary:** instruct the subjects on how to use the food diary, especially recording their intake of calcium-rich nutrients.
- **24-hour urine collection:** instruct the subjects on how to perform the 24-hour urine collection. Consumption of calcium-rich foods should be kept constant during and 3 days prior to each 24 hour urine collection.
- **PK blood samples:** instruct the subjects that the day before the Week 2 and Week 4 visits, they should apply the trial drug in the morning. On the day of the visit, the subjects should not apply any investigational product before the visit, but will apply the IP after the pre-dosing PK sample has been drawn. A reminder to the subjects may be needed a few days before the scheduled visit. If the subject has applied the investigational product on the day of the visit before the visit, the visit should be rescheduled.

7.4 Demographics and Medical History

The following demographic and medical history must be collected:

- Date of birth
- Sex
- Race
- Ethic origin
- Complete skin disease history
- All other current and past medical/surgical conditions within the last 12 months
- The year diagnosed with psoriasis vulgaris

The Fitzpatrick skin type will be assessed according to the classification scheme in Table 7-4.

Table 7-4 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

7.5 Prior and Concomitant Medication

Review and record prior medication and concomitant medication.

All medications, including OTC drugs, 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.

7.6 Physical Examination

An abbreviated physical examination and 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.

7.7 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.

7.8 Urine Pregnancy Test

Female subjects of child-bearing potential will undergo a routine urine pregnancy test at SV, Visit 1/Day 0, Week 4 visit and for the subjects assigned to the MC2-01 cream at the Week 8 visit. Instruct all female subjects to use approved form(s) of contraception.

7.9 Laboratory Assessments

Clinical laboratory specimens will be analyzed by a central licensed and accredited laboratory facility according to the laboratory's standard operating procedures.

7.9.1 Hematology, biochemistry and urinalysis

For all subjects the following tests will be performed at Visit 1/Day 0 and the Week 4 visit and for subject assigned to the MC2-01 cream at the Week 8 visit:

- Hematology: hemoglobin, hematocrit, red blood cell (RBC) count, mean corpuscular volume (MCV), white blood cell (WBC) count, including differential count and platelet count.
- Serum biochemistry: cortisol, urea, glucose, creatinine, calcium, albumin, calcium (albumin corrected), sodium, potassium, chloride, calcium, phosphate, alkaline phosphatase (ALP), plasma parathyroid hormone (PTH).
  25-OH Vitamin D (Visit 1 only)

Visit 1/Day 0: If serum albumin-corrected serum calcium is above the reference range at Visit 1/Day 0, the application with the investigational product (IP) should be discontinued and an Early Termination visit should be performed (see Section 7.9.2).

Week 4: If serum albumin-corrected serum calcium is above the reference range at Week 4, a repeat test should be performed at Week 6. If the serum albumin-corrected serum calcium is above the reference range at Week 8, a follow-up visit is required (see Section 7.15).

7.9.2 HPA axis suppression/ ACTH challenge test

For subjects assigned to the MC2-01 cream, adrenal function will be assessed in a challenge test with an intravenous dose of adrenocorticotropic hormone (ACTH) (cosyntropin). Measurement of serum cortisol levels pre- and post- stimulation with cosyntropin 0.25 mg is the accepted standard method used to evaluate adrenal suppression. The ACTH challenge test will be performed at Visit 1/Day 0, Week 4 and Week 8 visits. The test consists of blood sampling starting at 8 am (± 30 minutes). Following the blood sample, an intravenous bolus injection of 0.25 mg cosyntropin is given at time zero (t=0 minutes). Serum cortisol concentration at t=30 minutes will reflect

stimulation of the adrenal glands induced by cosyntropin. The ACTH challenge test must be performed before application of the IP.

Since many people do not respond to the degree expected with cosyntropin stimulation, the following criteria[25] have been established to denote a normal response:

1. pre-stimulation cortisol levels >5 µg/dL will be considered normal,
2. the 30-minute post-stimulation level should show an increment of ≥7 µg/dL above the basal level, and
3. the 30-minute post-stimulation level should exceed 18 µg/dL.

Therefore, a basal serum cortisol level ≤5 µg/dL, or a 30-minute post-stimulation level ≤18 µg/dL, or a post-stimulation increase (over basal) <7 µg/dL constitutes the definition of HPA axis suppression in the trial.

Visit 1/Day 0: If HPA axis is suppressed at Visit 1/Day 0, the subject should be contacted because the application with the investigational product (IP) should be discontinued and an Early Termination visit should be performed (see Section 7.16).

Week 4: If HPA axis is suppressed at Week 4, the subject should be contacted and the application with the MC2-01 cream should be discontinued. The subject should continue in the trial and the ACTH challenge test is repeated at the Week 8 visit. If HPA axis suppression is noted at Week 8, the subject must return for a follow-up visit (see Section 7.15).

7.9.3 Food diary: calcium-rich nutrients

All subjects should record their consumption of calcium-rich nutrients (mainly milk, other dairy products, calcium-fortified products) three days before and during the 24-hour urine collection prior to Visit 1/Day 0.

For subjects assigned to the MC2-01 cream, the same procedure will be followed before the Week 4 and Week 8 visits.

Based on the diary entries, the number of daily calcium servings should be calculated for each day and recorded in the eCRF.

7.9.4 24-hour urinalysis

All subjects are to collect urine for 24 hours before Visit 1/Day 0. Subjects assigned to the MC2-01 cream should collect urine for 24 hours before the Week 4 and Week 8 visits.

The following urine analyses will be performed:

- Calcium, phosphate, creatinine, volume, total calcium excretion, total phosphate excretion, total creatinine excretion, urinary calcium:creatinine ratio, urinary phosphate:creatinine ratio.

For follow-up on urine analysis only spot samples are performed.

7.9.5 Pharmacokinetics

For all subjects, samples for PK testing will be collected though an untreated area of the skin, at the following time points:

- SV2/baseline visit: single time point
- Week 2 visit: single time point
- Week 4 visit: before application of IP at the visit and then at 0.5, 1, 2, 3, 5, and 7 hours after the end of the application

For subjects assigned to the MC2-01 cream, samples for PK testing will be collected at the following time points:

- Week 8 visit: before application of trial medication at the visit and then at 0.5, 1, 2, 3, 5, and 7 hours after the end of the application.

Subjects are to be instructed to apply their daily dose of trial medication in the morning on the day before the visit and not before the visit on the day of the visit. A reminder to the subject may be needed a few days before the scheduled visit.
The samples will be assayed for concentrations of the active ingredients (BDP and CAL) and for their major metabolites (betamethasone 17-propionate and MC180, respectively)

7.10 Electrocardiogram

For all subjects assigned to the MC2-01 cream, a 12-lead ECG will be recorded at Visit 1/Day 0, Week 4 and Week 8 visits. Recording will take place after 5 minutes' rest in supine position.

Recordings will be promptly transmitted to the central ECG vendor for interpretation. Additional (unscheduled) ECGs can be recorded for safety reasons at any time based on the judgment of the investigator.

Clinically significant findings will be reported as medical history if detected at Visit 1/Day 0. At subsequent visits, any new clinically significant finding will be reported as an AE. Any ECG abnormalities will be carefully monitored and if necessary the subject will be withdrawn from the trial.

7.11 The Psoriasis Treatment Convenience Scale

The Psoriasis Treatment Convenience Scale 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 (see Table 7-2, and Table 7-3).

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 5 disease-specific, self-report questions with a recall period of 1 week and rated on a 1-10 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 much did treating your skin disrupt your daily routine?
5. Overall, how satisfied were you with the medical treatment?

7.12 Investigator Assessments

The investigator assessments are to be performed by a dermatologist, a physician with at least 1 year of experience in dermatology, or a Nurse Practitioner or Physician Assistant with at least 2 years of experience in dermatology. For physicians, Nurse Practitioners and Physician Assistants who do not fulfill the requirement regarding dermatological experience, the person must be preapproved by the sponsor. The assessments are to be performed as specified in the visit schedule Table 7-1, Table 7-2 and Table 7-3.

7.12.1 Physician's global assessment of psoriasis severity

The Physician's Global Assessment (PGA) measures the investigator's or designee'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 7-5. The PGA assessment will represent the *average* lesion severity on scalp, trunk and limbs (excluding face, genitals, and intertriginous areas). 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 7-5 Physician's Global Assessment (PGA)

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

7.12.2 Body surface area involvement of psoriasis vulgaris

The investigator or designee will assess the extent of the subject's psoriatic involvement on the scalp, trunk and limbs (excluding face, genitals, and intertriginous areas).

The total psoriatic involvement on the scalp, trunk and limbs 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. If the subject has psoriasis of guttatae character, these elements will be part of the estimation of total psoriatic involvement. The purpose of this is to obtain an estimate of the area on the trunk and limbs to be treated with trial medication.

7.12.3 Local skin reactions

The local skin reaction assessment involves signs assessed by the investigator or designee and symptom reported by the subject.

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 7-6. The most severe intensity observed for each category of the local skin reaction assessment is to be recorded.

The subject will assess burning and pain after application. The investigator or designee will explain the scores in Table 7-6 and the subject will tell which one to mark.

Signs and symptoms fulfilling the adverse advent definition should be reported as adverse events.

Table 7-6 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
Subject Assessment				
	0 (absent)	**1 (Mild)**	**2 (Moderate)**	**3 (Severe)**
Burning or pain after application	None	Barely present and disappears within few minutes	Distinct and lasts for up to an hour	Pronounced and lasts for several hours

7.13 Adverse Events

7.13.1 Adverse events assessments

The investigator or designee is responsible for obtaining, assessing, and documenting all AEs during the study. 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 study. An

AE is an untoward medical occurrence in any subject during the trial which does not necessarily have a causal relationship with the trial drug treatment.

All AEs will be documented in the eCRF, including a description of each AE, AE relationship to trial product 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 to the United BioSource Corporation (UBC) within 24 hours of awareness.

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.

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 trial product 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 the MC2 or designee.

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

7.13.2 Timing

AEs will be collected/assessed during the period from the time of the signature of the informed consent form by the subject and first trial-related activity performed.

7.13.3 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 does 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).

7.13.4 Relationship of an adverse event to trial treatment

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

Not Related	The AE is clearly explained by another cause not related to the trial product 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 trial product are temporally related, but the AE can be explained equally well by causes other than the trial product administration
Probably Related	The AE and use of trial product are temporally related, and the AE is more likely explained by trial product administration than by other causes
Definitely Related	The AE and trial product 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

7.13.5 Unexpected adverse events

Any AE assessed as 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 (for MC2-01 cream)[26] or Taclonex® Ointment prescribing information[27] (for active comparator).

"Unexpected" as used in this definition, also refers to AEs that are mentioned in the Investigator's Brochure or product prescribing information 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.

7.13.6 Trial medication overdose

An overdose of the investigational product, 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 maximum weekly dose of the MC2-01 cream and the comparator is 100 g. The treated area should not be >30% of the body surface area.

Use above the recommended dose 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.

7.13.7 Pregnancy

Any pregnancy occurring from date of the Informed Consent signature until study completion 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 the pregnancy (see Section 13.2).

Investigator must actively follow-up, document and report to MC2 or designee the progress of the pregnancy until outcome is reached.

7.13.8 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 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 13.2). The investigator will document such events in the best possible detail on the SAE Report Form.

A suspected unexpected serious adverse reaction (SUSAR) is an SAE that is both unexpected (not consistent with the current Investigator's Brochure[1] or Taclonex® Ointment prescribing information,[3], 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 13.2.

7.14 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.

7.15 Follow-up Visit

A follow-up visit is required for the following reasons:

- Unresolved related AEs.

For subjects assigned to the MC2-01 cream:

- If the albumin-corrected serum calcium was above the normal reference range at Week 4 and Week 8 a repeat should be done 14 days (± 2 days) after.
- If the HPA axis suppression is noted at Week 8 an ACTH challenge test should be performed 28 days (± 2 days) after.

7.16 Early Termination

If a subject withdraws from the trial prior to Week 4 and for subjects assigned to the MC2-01 cream prior to Week 8, the subject is to return to the site for an unscheduled visit. The following procedures should be performed:

- 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 UPT for females of childbearing potential.
- ECG (only for subjects assigned to the MC2-01 cream)
- Haematology, biochemistry, and urinalysis.
- PGA
- BSA
- Psoriasis Treatment Convenience Scale (Only if before Week 4)

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).

It is planned that the data from all centres that participate in this protocol will be combined so that an adequate number of subjects will be available for analysis. No imputation will be made for missing data.

8.2 Sample Size and Power Considerations

The choice of sample size in this trial is not based on statistical considerations, but rather on regulatory considerations with respect to common practice in maximum use studies evaluating pharmacokinetic profiles and evidence of HPA safety. The chosen number of approximately 25 subjects included in the PK population at Week 4 in each treatment arm is considered sufficient to compare the PK properties corresponding to the two treatments.

8.3 Analysis Populations

The analysis populations are defined as follows:

- **PK population:** all subjects in the Safety population who have received the planned application of treatment at the Week 4 or Week 8 visit, respectively, and have had at least one post-application blood draw for PK assessment at the corresponding visit.

- **Safety population:** all subjects who are randomized and have been dispensed the trial medication at Randomisation/Day 0, excluding subjects who return all of the trial medication unopened. The Safety population will be used for all safety analyses other than evaluation of the HPA-axis.

- **HPA population:** all subjects in the Safety population that are assigned to MC2-01 cream and who show normal HPA function at Baseline. Since the objective of the analysis is to estimate the risk to subjects with normal HPA function of HPA-axis suppression following treatment, subjects who meet the definition of HPA-axis suppression at Baseline will be excluded from the analysis. The HPA population will be used for the HPA axis suppression analysis.

8.4 Background and Demographic Characteristics

Descriptive statistics will be used to summarise demographic characteristics (age, sex, and race) and background characteristics for the Safety population. Past/coexistent medical history information, physical examination observations, and vital signs information for all randomised subjects will be presented in a by-subject listing.

8.5 Trial Medication/Exposure

Descriptive statistics will be used to summarise trial medication exposure for the Safety population. Measures of trial medication exposure will include the total duration of treatment, the total weight of trial medication used, and the total number of applications.

8.6 Prior and Concomitant Therapy

Prior and concomitant medication information for all randomised subjects will be presented in a by-subject listing.

8.7 Analysis of Pharmacokinetics

All available concentration results will be summarised using appropriate descriptive statistics for active ingredients (BDP and CAL) and for their major metabolites. Median and individual concentration versus time curves will be plotted (linear and semi-log plots).

Plasma PK parameters (AUC_{0-t}, $AUC_{0-\infty}$, AUC_{0-7}, C_{max}, T_{max}, and $T_{½}$) will be calculated at Week 4 and Week 8 (subjects randomised to MC2-01 cream only). The PK parameters AUC_{0-7} and C_{max} will be calculated using standard formulas inserting the lower limit of quantification for non-quantifiable levels of the analyte; therefore, AUC_{0-7} will be an upper limit in case at least one time point shows a non-quantifiable level of the analyte, and C_{max} will be an upper limit in case all time points show non-quantifiable levels of the analyte. For a given analyte, the PK parameters AUC_{0-t}, $AUC_{0-\infty}$, T_{max}, and $T_{½}$ will be calculated if data allow. The PK parameters will be summarised using appropriate descriptive statistics including median, lower and upper quartiles, minimum and maximum.

Assessment of systemic exposure (Week 4)

Assessment of relative systemic exposure in the two treatment arms will be performed for AUC_{0-7} and C_{max} at Week 4. It will be based on an analysis of variance for censored data for each parameter, assuming a log-normal distribution of the PK parameter. Geometric mean ratio and associated 90% confidence interval will be presented.

8.8 Analysis of Safety

The assessment of HPA axis suppression (using pre- and post-stimulation cortisol levels) and of changes in calcium metabolism are the primary safety endpoints in this trial.

Other assessments of safety will be based mainly on the frequency of AEs and on the number of laboratory values that fall outside of predetermined ranges, presented for the two periods, Weeks 1 to 4 and Weeks 5 to 8, separately. Adverse events will be presented in data listings and summarized by frequency and severity for each treatment group for each period. Laboratory and vital sign data will be presented in data listings. Abnormal laboratory findings will be presented. The analysis of safety will be described in the SAP.

8.8.1 HPA-axis suppression

The number and proportion of subjects with HPA-axis suppression at Week 4 and Week 8 will be summarised.

8.8.2 Calcium metabolism endpoints

Summary statistics will be provided for the following:

Observed values of and changes from Baseline to Week 4 and Week 8 in:

- Albumin-corrected serum calcium
- 24 hours urinary calcium excretion
- Ratio of urinary calcium to creatinine

8.8.3 Adverse events

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology. Treatment-emergent adverse events will be summarized by the overall incidence of at least one event, incidence by body system, and incidence by body system and preferred term. Each subject will contribute only once (e.g., the first occurrence) to each of the rates, regardless of the number of occurrences (events) the subject experiences. Treatment-emergent AEs will be summarised by severity (mild, moderate, or severe), and by relationship to trial product (none, unlikely, possible, probable, or definite). An adverse event is treatment-emergent if its date of onset is Day 1 (Baseline) or later.

Discontinuations from the trial due to AEs and SAEs will be listed by subject.

8.8.4 Other safety variables

Clinical laboratory values will be reported as complete listings of individual subject data.

Clinical laboratory data will be summarized 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, SDs, ranges), and by the flagging of notable values in data listings.

Data from other tests (e.g., vital signs, ECG results) 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.

Vital signs will be summarised at each visit, both as absolute values and as change from Baseline, with descriptive statistics.

8.9 Analysis of Other Endpoints

8.9.1 Physician global assessment

Investigator ratings of disease severity will be summarised by trial visit using frequency counts for each treatment. The proportion of subjects with treatment success, defined as a minimum 2-point decrease from Baseline in the physician's global assessment (PGA) on the trunk, limbs, and scalp will be summarized.

8.9.2 Psoriasis treatment convenience scale

Subject assessment of treatment convenience at Week 4 using a Psoriasis Treatment Convenience Scale will be summarized and further compared between MC2-01 cream and the active comparator using mixed effect model with treatment as a systematic effect and study site as a random effect.

8.10 Quality of Life Analysis (Not Applicable)

Not applicable.

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 reserves the right to terminate or suspend the trial at any time. 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.

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. The identification of any data to be recorded directly on the eCRFs is to be considered source data.

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 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 or guardian 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 (Not Applicable)

This is an open-label trial.

13.2 Reporting of Serious Adverse Events and Pregnancies

13.2.1 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 UBC using the following e-mail or fax-number:

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

13.2.2 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 electronically to the UBC using the SAE Reporting fax number within 24 hours of first knowledge of the SAE.

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.

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.clinicaltrials.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.

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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

Barbara Liptak, Medical Writer, Novella Clinical, 350 West Passaic Street, Suite 550, Rochelle Park, NJ 07662.
Johan Selmer, VP Medical Affairs, MC2 Therapeutics
Birgitte Vestbjerg, Director Clinical Operation, MC2 Therapeutics
Carol Udell, Senior Director, Clinical Data, Management and Biostatistics, Novella Clinical, 350 West Passaic Street, Suite 550, Rochelle Park, NJ 07662.

17.2 Appendix 2
Vendors

Novella Clinical, a Quintiles Company, 365 W. Passaic St, Suite 550, Rochelle Park, NJ 07662, United States. Novella Clinical will be responsible for all services related protocol writing and the conduct of the trial, as specified in the contract.

ACM Global Central Laboratory, 160 Elmgrove Park Rochester, New York. ACM will be responsible for all services related to central laboratory analysis, as specified in the contract.

Clinical Materials Services Unit (CMSU), 77 Ridgeland Rd. Rochester, NY, United States. CMSU will be responsible for all services related to packaging, labeling, distribution and destruction of the investigational medical products, as specified in the contract.

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

DSG Inc, 325 Technology Drive, Malvern, Pennsylvania 19355, United States. DSG will be responsible for providing electronic data capture and IWRS services as specified in the contract.

BioTelemetry Research, One Preserve Parkway, Suite 600, Rockville, Maryland 20852, United States. BioTelemetry Research will be responsible for the ECG services as specified in the contract.

ICON Laboratory Services Inc., 8282 Halsey Road, Whitesboro, NY 13492 USA. ICON will be responsible for the PK analysis.

CLINICAL TRIAL PROTOCOL APPROVAL FORM

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

Protocol number: MC2-01-C3

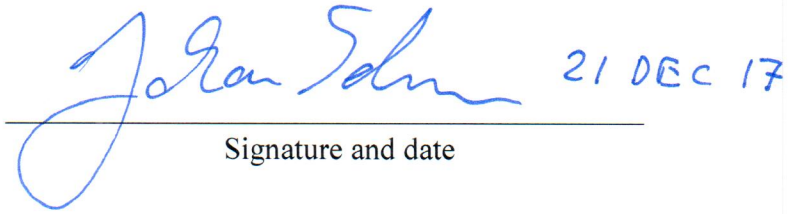
Protocol title: A Randomised, Multicentre, Open-label, Parallel-group Maximal Use Trial, Evaluating the Pharmacokinetic Profile of the Active Ingredients and their Metabolites after application of MC2-01 Cream compared with Active Comparator in Subjects with Extensive Psoriasis Vulgaris

Version: 3.0

Date: 20 October 2017

The following person has approved this clinical trial protocol:

Johan Selmer, MD
VP Medical Affairs
MC2 Therapeutics



Signature and date

CLINICAL TRIAL PROTOCOL APPROVAL FORM

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

Protocol number: MC2-01-C2

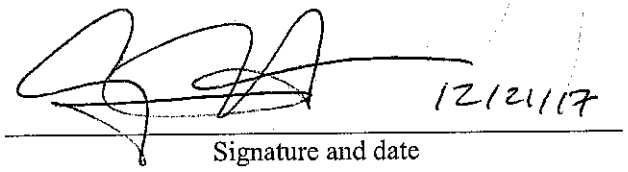
Protocol title: A Randomised, Multicentre, Open-label, Parallel-group Maximal Use Trial, Evaluating the Pharmacokinetic Profile of the Active Ingredients and their Metabolites after application of MC2-01 Cream compared with Active Comparator in Subjects with Extensive Psoriasis Vulgaris

Version: 3.0

Date: 20 December 2017

The following person has approved this clinical trial protocol:

George Han, MD, PhD,
International Coordinating Investigator,
Department of Dermatology,
Mount Sinai Beth Israel



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Carol Udell
Senior Director, Clinical Data Management and Biostatistics
Novella

DocuSigned by:
Carol Udell
Signer Name: Carol Udell
Signing Reason: I approve this document
Signing Time: 12/21/2017 7:36:12 AM PST
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21-Dec-2017 | 10:36:14 EST

Signature and date