Clinical Trial Protocol

Trial Title:	**A Multicentre, Open-label, Single-group Maximal Use Trial, Evaluating the Safety and Pharmacokinetic Profile of the Active Ingredients and their Metabolites after application of MC2-01 Cream in Adolescent Subjects (age 12 to 16 years, 11 months) with Extensive Psoriasis Vulgaris**
Investigational product:	**MC2-01 (calcipotriol and betamethasone dipropionate, 50 micrograms/0.64 mg/g) Cream**
Protocol No:	**MC2-01-C6**
IND:	**127152**
EudraCT No:	**2018-000685-12**
Development phase:	**2**
Documents status:	**Final**
Document version:	**Version 5.0**
Document date:	**23 September 2018**
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 (calcipotriol/betamethasone dipropionate) cream

Protocol number: MC2-01-C6

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The following persons has approved this clinical trial protocol. Separate signature page is adjoined to this document.

Johan Selmer, MD, VP Medical Affairs, MC2 Therapeutics

Charlotte Hindsberger, Principal consultant, Biostatistics, S-cubed

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SIGNATURE PAGE FOR INVESTIGATOR(S)

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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
AR	Adverse Reaction
AUC_{0-t}	Area under the time-concentration curve from time zero to the last measurable concentration
AUC_{0-5}	Area under the time-concentration curve from time zero to 5 hours imputing the lower limit of quantification (LLoQ) for concentrations below LLoQ
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
CYP 3A4	Cytochrome P450 3A4
ECG	Electrocardiogram
eCRF	Electronic case report form
FDA	Food and Drug Administration
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
LLoQ	Lower Limit of Quantification
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MUsT	Maximal Usage Trial
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

Abbreviation	Definition
SAP	Statistical analysis plan
SD	Standard deviation
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
SV1, SV2	Screening Visit 1, Screening Visit 2
T_{max}	Time to maximum plasma drug concentration
UBC	United BioSource Corporation
US	United States
UVB	Ultraviolet B
WBC	White blood cell

1.0 SYNOPSIS

Trial Title:	A Multicentre, Open-label, Single-group Maximal Use Trial, Evaluating the Safety and Pharmacokinetic Profile of the Active Ingredients and their Metabolites after application of MC2-01 Cream in Adolescent Subjects (age 12 to 16 years, 11 months) with Extensive Psoriasis Vulgaris
Protocol Number:	MC2-01-C6
Sponsor:	Drug Delivery Solutions Ltd (part of MC2 Therapeutics)
Development Phase:	2
Trial Objectives:	The primary objectives are 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. The secondary objective is to evaluate the pharmacokinetic profile of the active ingredients and their main metabolites following once daily topical application of MC2-01 cream under maximum-use conditions in adolescent subjects (age 12 to 16 years, 11 months) with extensive psoriasis vulgaris.
Trial Design:	This is a phase 2, open-label, single-group, multicentre trial in which the investigational product, MC2-01 cream, is investigated in adolescent subjects (age 12 to 16 years, 11 months) with clinically diagnosed extensive psoriasis vulgaris. After written informed assent/consent is obtained the subjects will undergo screening procedures. For subjects requiring a washout period, informed assent/ consent must be completed prior to washout. Subjects that fulfil the inclusion and exclusion criteria will be treated with the MC2-01 cream once-daily for 8 weeks. At Week 4 and Week 8, the effect of once-daily use of MC2-01 cream on the HPA axis and the calcium metabolism will be evaluated. Other assessments (local skin reactions, AEs, laboratory tests, electrocardiogram (ECG), vital signs and physical examination) and efficacy assessments are also performed. At Week 4, the pharmacokinetic (PK) profile of calcipotriol (CAL), betamethasone dipropionate (BDP) and their main metabolites MC1080 and betamethasone 17-propionate, respectively, will be assessed. The maximum trial duration for each subject will be approximately 18 weeks and includes a screening period of up to 6 weeks (if washout of medication is required), a treatment period of 8 weeks, and a follow-up period of up to 4 weeks.

Planned Sample Size:	It is planned to enrol approximately 30 subjects. The choice of sample size in this trial is based on regulatory considerations with respect to common practice in maximum use studies. For the PK population, the aim is to have at least 20 subjects included that have at least completed Week 4 (Visit 3).
Trial Population:	Generally healthy males or non-pregnant females, between 12 to 16 years, 11-month-old, 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 scalp and body (trunk and/or limbs) and a treatment area between 10% and 30% of the body surface area (BSA), excluding psoriatic lesions on the face, genitals, and intertriginous areas.
Investigational Product(s):	MC2-01 cream (CAL and BDP, 50 micrograms/0.64 mg/g).
Reference Product(s):	Not applicable.
Pharmacokinetics Evaluation Criteria:	Blood samples for PK assessments will be collected at • SV2: single time point • Week 2 visit: single time point before IP application • Week 4 visit: before the planned IP application at the visit and then at 1, 3, and 5 hours after the application • Week 8 visit: single time point. Subject should not apply IP on the day of the Week 8 visit 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:	The endpoint for the HPA axis evaluation will be a serum cortisol level of less than 18 µg/dL at 30 minutes after Adrenocorticotropic hormone (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; • Ratio of urinary calcium to creatinine.
Other Safety Evaluation Criteria	Adverse event incidence and severity, laboratory test results (haematology, clinical chemistry), vital signs, ECG, local skin reactions, physical examination.
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: HPA axis suppression: The proportion of subjects with HPA-axis suppression at Week 4 and Week 8 will be summarised using frequency counts. Calcium metabolism: 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 – Ratio of urinary calcium to creatinine (spot analysis, second morning urine sample) Secondary Endpoints: Plasma PK parameters (AUC_{0-t}, AUC_{0-5}, C_{max}, and T_{max}) will be calculated at Week 4. The PK parameters AUC_{0-5} and C_{max} will be calculated using standard formulas inserting the lower limit of quantification for non-quantifiable levels of the analyte; therefore, AUC_{0-5} 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} and T_{max} will be calculated if at least one time-point shows a quantifiable level of the analyte. The PK parameters will be summarised using appropriate descriptive statistics including median, lower and upper quartiles, minimum and maximum. A parametric model will be applied to estimate the geometric mean of Cmax and AUC0-5, respectively. The log-transformed values of the PK parameters will be assumed to be normally distributed. The mean of this normal distribution will be estimated taking the potential censoring of the values into account. The mean will then be back-transformed to the original scale as the geometric mean. 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). Other safety endpoints: Adverse events will be presented in data listings and summarised by frequency and severity. Laboratory, ECG, and vital sign data will be presented in data listings. Abnormal ECG and laboratory findings will be presented
Trial Sites:	Approximately 12 sites in Europe
Planned Dates of Trial:	Q4 2018 – Q4 2020

2.0 INTRODUCTION

2.1 Background

Psoriasis is a common condition that affects about 3.5% of the US population (1) and 2.5% of the German population (2). Epidemiological studies from other countries have presented prevalence data that have been much higher or lower, but the very different methodologies used in published studies makes it difficult to compare or draw conclusions about any geographical differences (3). Several prevalence studies have demonstrated that approximately one-third of psoriatic patients develop their symptoms sometimes during childhood (4, 0).

A recent, thorough epidemiological study by Tollefson et al. (6) has demonstrated that the incidence of psoriasis increases steadily with age until approximately the 7th decade of life, with a more rapid increase in the incidence until age 30-35. Furthermore, an increase in incidence of psoriasis was observed throughout the study period from 1970 to 2000. Overall annual incidence in the pediatric population was 29.6 per 100.000 in 1970-1974, 42.6 per 100.000 in 1985-1989, and 62.7 per 100.000 in 1995-1999. This temporal trend is very similar to the trend seen in adults during the same time period (7). The prevalence of adolescents diagnosed with psoriasis in the age group 12-17 years can be calculated to up to 0.72% (age and sex adjusted to the 2000 US population) from incidence data presented by Tollefson (6).

Plaque psoriasis with its variants is the most frequent type, also in infants and childhood. In a large series of more than 1200 Australian patients, 34% of the children presented this type of psoriasis manifestation (8). Lesions typically consist of well-defined, erythematous papules and scales of varying size with silvery scales. The lesions have close resemblance to those seen in adult patients (4, 0).

It is well known that psoriasis in adults often are associated with comorbidities resulting in high cardiovascular morbidity (10-12). Also, children suffering from psoriasis seem to have a higher prevalence of comorbidities, including obesity, hyperlipidaemia, diabetes mellitus, hypertension, rheumatoid arthritis, and Crohn's disease (2, 13-16)). In addition to comorbidities with effect on cardiovascular disease, pediatric patients with psoriasis have also reported to have an increased risk of anxiety, depression, and other psychiatric disorders (17). Because of the burden of disease and the associated comorbidities, early diagnosis and management in children are essential.

Considering the many similarities – both related to pathophysiology, clinical presentation, and concomitant diseases – it is not surprising that most therapeutics effective in adult psoriasis are equally effective in pediatric psoriasis. Despite this, treatment of childhood psoriasis is often considered a therapeutic challenge. Various therapies are available, but only a limited number of trials have studied the use of anti-psoriatic agents in children. Furthermore, many treatments are not approved for use in children and guidelines are often missing for children and adolescents.

There is no cure for psoriasis. The goal of treatment of both adult and childhood psoriasis is to reduce or eliminate its signs and symptoms. Mild to moderate disease is often treated with topical therapies. Among topical therapies, a combination treatment of a Vitamin D analog and a topical glucocorticosteroid has become especially popular. Several studies show that the combination of Calcipotriol (CAL) and Betamethasone dipropionate (BDP) is superior to each of the single agents (18,19). There is strong scientific rationale for the combination of vitamin D and glucocorticosteroids both with respect to efficacy and safety (20-22), and combination treatment with a Vitamin D analog and a topical corticosteroid is recommended in both American and European guidelines (23-26). The CAL/BDP products Taclonex® Ointment and Taclonex® scalp solution is approved for use in the age group 12-17 years in the US. The CAL/BDP products are marketed as Daivobet® Ointment and Gel respectively in the EU. Clinical trials with combinations of CAL and BDP are not possible in children below the age of 12, due to the BDP component.

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

Sponsor (referred to as MC2 in remainder of the protocol) has developed the MC2-01 cream containing the fixed dose combination 50 micrograms CAL (as anhydrate) and 0.64 mg/g BDP using the proprietary PAD™ Technology which protects the drug substances from degradation during storage. The MC2-01 cream is easy to apply, and the cosmetic appearance is that of a white, easily-spreadable cream that absorbs completely into the skin a few minutes after application and it is expected that MC2-01 cream will differentiate from marketed formulations of CAL/BDP by patient preference for the cream.

2.2 Rationale of the Trial

MC2-01 cream is investigated following once daily topical application under maximum-use conditions in Adolescent Subjects (age 12 to 16 years, 11 months) with clinically diagnosed extensive psoriasis vulgaris of at least moderate disease severity.

Subjects in this trial will have psoriasis on the body (trunk and/or limbs), and with or without scalp involvement that is at least moderate in severity according to PGA and involves 10-30% of BSA, excluding face, genitals and intrigenous areas. This disease extent is at the limit where topical treatment would be used, and systemic therapy or phototherapy would be considered.

At Week 4, the PK profile of CAL, BDP and their main metabolites MC1080 and betamethasone 17-propionate, respectively, will be assessed. Blood samples will be taken at selected intervals after topical dosing of each trial medication. The following PK parameters will be calculated: area under the concentration-time curve (AUC) from time zero to the planned last PK blood sampling time point of 5 hours (AUC0-5), maximum plasma drug concentration (Cmax), and time to maximum plasma drug concentration (Tmax).

At Week 4 and Week 8, the effect of once-daily use of MC2-01 cream on the HPA axis and the calcium metabolism will be evaluated. 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.

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 trial, enrolled subjects will be subjected to an ACTH-challenge test before and after 4 and 8-week treatment.

It is well known that safety analysis of oral or topical medication containing vitamin D or analogues hereof include an evaluation of effect on calcium metabolism. Generally, analysis of calcium in a 24-h urine collection is considered to be the most reliable method for evaluation of changes in calcium homeostasis. This method is not well accepted by many patients, and the low adherence to 24-h urine collection means that results of this test often are unreliable (27). A number of papers have presented data to suggest that a spot calcium/creatinine test may substitute for 24-hour urine calcium collection (28-30) Spot calcium/creatinine tests may be done on random urine samples, first morning urine, or second morning urine. For this trial, second morning urine is preferred, both because it is convenient in relation to time of visit, and because reference ranges of this test for adolescent is well documented. Both the 24-h urine sample collection and calcium/creatinine spot testing suffer from high intra-patient variability, and repeated samples is often recommended to improve accuracy of either test (31). For this reason, subjects with second morning calcium/creatinine spot test above the upper reference value at week 4 or week 8 must have this test repeated at the following visit. Moreover, if the calcium-creatinine ratio is above the reference range at two consecutive visits during the trial, 24-hour urine collection will be performed.

It is well-established that there is a relationship between dietary calcium intake and the urinary calcium excretion in adults (32). The urinary excretion of calcium has been reported to increase by 6-19 mg with each additional 100 mg of calcium intake (32, 33). Subjects will not be asked to change their diet during the trial, 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 4 days prior to each second morning urine collection. Considering that dairy products account for the majority of the 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 within 4 weeks prior to Visit 1/Day 0 in this trial with the exception of stable doses of oral vitamin D (up to 400 IU/day) at baseline with no dose adjustment during the trial period. Systemic safety of MC2-01 cream on calcium metabolism and HPA axis will be assessed at Week 4 and Week 8.

2.3 Benefit-risk Assessment

The subject population will be composed of adolescent subjects (age 12 to 16 years, 11 months) with psoriasis on the body (trunk and/or limbs), and with or without scalp involvement. The psoriasis disease intensity should be at least moderate in severity according to PGA and involve 10-30% of BSA, excluding face, genitals and intertriginous areas, in order to evaluate the trial medication under maximum use conditions.

Topical treatment with CAL/BDP is a well-known topical treatment for psoriasis. Daivobet® Ointment was approved in adults more than 15 years ago. Three different topical CAL/BDP formulations are approved in EU today for use in adults – all showing similar safety profiles with very limited systemic exposure

According to the SmPC for Daivobet® Gel, the common adverse reaction (AR)E (>1%) is pruritus. Uncommon (i.e., ≥0.1% and <1%) ARs are folliculitis, skin infections, exacerbation of psoriasis, dermatitis, erythema, rash, skin irritation, skin burning sensation, application site pain, as well as eye irritation (probably related to use on scalp). Rare ARs (≤0.1%) are skin striae, skin exfoliations, hypersensitivity, and rebound effect. The ARs for Daivobet® Ointment are remarkably like what has been observed with Daivobet® gel. In the US both the Ointment and Gel of CAL/BDP are approved for use in adolescents; Taclonex® Ointment (body psoriasis) for 4 weeks and Taclonex® Topical Suspension (scalp psoriasis) for 8 weeks, and the US prescribing information does not distinguish between ARs seen in adults and adolescents.

The description of the AR profile in the US prescribing information for Taclonex® Ointment and Taclonex® Topical Suspension does not differ from the description in the SmPCs for Daivobet® Ointment and Gel.

The systemic safety (HPA and calcium metabolism) of Daivobet® Ointment in body psoriasis has been evaluation a 4-week uncontrolled maximal usage trial clinical trial in the pediatric population age 12 to 17 years, as well as in two uncontrolled open 8-week trials with Daivobet® Gel including in total 109 adolescents aged 12-17 years with scalp psoriasis. The ARs seen in these trials were few and mild and did not differ from what is described from studies in adults.

The benign safety profiles observed in these trials are not surprising. There is no indication that children are more sensitive to HPA axis suppression than adults and there is no increased sensitivity of Vitamin D in children. Furthermore, based on considerations on skin penetration (34) and BSA to body mass ratio in adolescent (35), treatment of adolescents with topical therapies will only result in marginal increases in systemic exposure compared to what is seen in adults.

The fact that the AR profiles for Daivobet® Ointment and Gel are so similar despite treatment periods of 4 and 8 weeks, respectively, suggest that the nature of the ARs are independent of the length of treatment. This fact is underscored by the ARs in a trial where subjects were treated with the ointment for up to 52 weeks (36). Despite the prolonged treatment regime, there were no ARs not already mentioned for trials of shorter duration.

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

3.0 TRIAL OBJECTIVES AND PURPOSE

The primary objectives are to evaluate the effect of MC2-01 cream on the HPA axis and calcium metabolism following once daily topical application under maximum-use conditions in subjects with extensive psoriasis vulgaris.

The secondary objective is to evaluate the pharmacokinetic profile of the active ingredients and their main metabolites following once daily topical application of MC2-01 cream under maximum-use conditions in adolescent subjects (age 12 to 16 years, 11 months) with extensive psoriasis vulgaris.

4.0 TRIAL DESIGN

4.1 Overall Trial Design

This is a phase 2, open-label, single-group, multicentre trial in which the investigational product (IP), MC2-01 cream, is investigated in adolescent subjects (age 12 to 16 years, 11 months) with clinically diagnosed extensive psoriasis vulgaris of at least moderate disease severity (according to the Physician's Global Assessment of Disease Severity; PGA) on body (trunk and/or limbs), and with or without scalp involvement.

After written informed assent is provided by the subject and written informed consent is provided by the parent(s) or legal guardian(s) and the consent document is signed by the investigator or designee the subjects will undergo screening procedures. For subjects requiring a washout period, informed assent/informed consent must be completed prior to washout. Prior to Screening Visit 2

(SV2) the subject (or the parent(s) or legal guardian(s)) is instructed to keep a diary for a 4-day registration of the daily intake of calcium-rich nutrients. At SV2, a second morning urine sample will be collected at the site for analysis of the urinary calcium excretion. Subjects will have their HPA axis function assessed and a baseline PK sample is collected along with other baseline assessments to confirm the subject's eligibility before Day 0/Visit 1.

Subjects who fulfil all inclusion and exclusion criteria at Day 0/Visit 1 are enrolled in the trial and will apply one dose of trial medication topically once daily for 8 weeks.

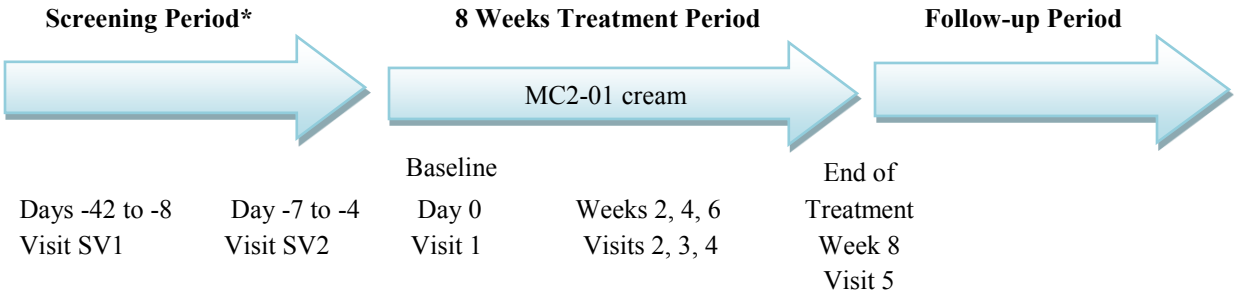
Please refer to Figure 4-1 for an overview of the trial design.

Trial subjects will be enrolled at approximately 12 sites in Europe.

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

The maximum trial duration for each subject will be approximately 18 weeks and includes a screening period of up to 6 weeks (if washout of medication is required), a treatment period of 8 weeks, and a follow-up period of up to 4 weeks. After Week 8 (Visit 5) a follow-up visit is required for all subjects. The end of trial is defined as last subject last visit.

Figure 4-1 Trial Design



*There should be at least four days between SV1 and SV2 in order to keep the food diary for 4 days prior to SV2.

4.2 Trial Endpoints

Primary Endpoints

HPA axis
Subjects with serum cortisol level of less than 18 µg/dL at 30 minutes after ACTH challenge test at Week 4 and Week 8.

Calcium metabolism
Changes from Baseline to Week 4 and Week 8 in:

- Albumin-corrected serum calcium;
- Ratio of urinary calcium to creatinine*.

*Spot analysis, second morning urine sample

Secondary Endpoints

Plasma PK parameters (AUC_{0-t}, AUC_{0-5}, C_{max} and T_{max}) will be calculated at Week 4. The PK parameters AUC_{0-5} and C_{max} will be calculated using standard formulas inserting the lower limit of quantification (LLOQ) for non-quantifiable levels of the analyte; therefore, AUC_{0-5} 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} and T_{max} will be calculated if at least one time-point shows a quantifiable level of the analyte. The PK parameters will be summarised using appropriate descriptive statistics including median, lower and upper quartiles, minimum and maximum.

Blood samples for PK assessments will be collected at

- SV2 (baseline sample)
- Week 2 (single time point before application of IP)
- Week 4; before application of IP and then at 1, 3, and 5 hours after the application.
- Week 8; (single time point. Subject should not apply IP on the day of the Week 8 visit)

The samples will be assayed for concentrations of the active ingredients (BDP and CAL) and for their main metabolites; MC1080 and betamethasone 17-propionate, respectively.

Safety Endpoints

Safety endpoints include the following:

- Adverse events (AEs) and serious adverse events (SAEs);
- Local skin reaction;

- Changes in safety laboratory test results;
- Changes in ECGs;
- Changes in vital signs and physical examinations

Other Endpoints

- The proportion of subjects with treatment success, defined as a minimum 2-point decrease from baseline in the PGA on the body (trunk and/or limbs), and with or without scalp at Week 4 and Week 8.
- Subject assessment of treatment convenience at Week 8 using a Psoriasis Treatment Convenience Scale.

5.0 SELECTION OF TRIAL POPULATION

5.1 Subject Population

It is planned to enroll approximately 30 subjects. The choice of sample size in this trial is based on regulatory considerations with respect to common practice in maximum use studies. For the PK population, the aim is to have at least 20 subjects included that have at least completed Week 4 (Visit 3).

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.

A written informed assent will be signed and dated by the subject and an informed consent document (ICF) will be signed and dated by the parent(s) or legal guardian(s) 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. The parent(s), or legal guardian(s) (according to national law) have provided written informed consent following their receipt of verbal and written information about the trial;
2. The subject (according to national law) has provided written assent to the trial following their receipt of verbal and written information about the trial;
3. Generally healthy males or non-pregnant females, of any race or ethnicity, who are between 12 to 16 years, 11-month-old at SV1;
4. At Visit 1/Day 0, have a clinical diagnosis of plaque psoriasis (psoriasis vulgaris) of at least 6 months duration involving body (trunk and/or limbs), with or without scalp;

5. Have a treatment area between 10% and 30% of the BSA on the body (trunk and/or limbs) and scalp, excluding psoriatic lesions on the face, genitals, and intertrigenous areas, at Visit 1/Day 0;
6. Have a PGA of at least moderate severity on the treatment area;
7. A normal HPA axis function including a serum cortisol concentration above 4.5mcg/dl (160nmol/l) before ACTH-challenge and equal or above 18 mcg/dl (500 nmol/l) 30 minutes after ACTH challenge, at SV2;
8. A serum albumin-corrected calcium below the upper reference limit at SV2;
9. Female subjects must have a negative urine pregnancy test result at SV1, and if sexually active they must agree to use a highly effective method of contraception (i.e. a method with a failure rate of less than 1% per year when used consistently and correctly) for two months prior to Visit 1 and until the follow-up visit has been performed. Highly effective contraception allowed in this trial is defined as follows:
    - intrauterine device (IUD)
    - bilateral tubal occlusion
    - vasectomised partner (provided that is the sole sexual partner of the subject and that the vasectomised partner has received medical assessment of the surgical success.)
    - sexual abstinence (if in line with the preferred and usual lifestyle of the subject and defined as refraining from heterosexual intercourse during the entire period of the trial. Periodic methods of abstinence (e.g. calendar, ovulation, sympto-thermal, post-ovulation methods) are not accepted methods of contraception.)

5.3 Exclusion Criteria

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

1. 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 infections in the treatment area (e.g. skin infection with bacteria (including tuberculosis), viruses, parasites or fungi) or skin manifestations of atrophic skin, atrophic striae, skin vein fragility, ichthyosis, acne vulgaris, acne rosacea, rosacea, ulcers and wounds in the treatment area.
4. Presence of pigmentation, extensive scarring, pigmented lesions or sunburn in the treatment areas, which could interfere with the rating of efficacy parameters;
5. Planned excessive or prolonged exposure to either natural or artificial sunlight, including tanning booths, sun lamps, etc;

6. Use of phototherapy (psoralen + ultraviolet A radiation [PUVA] and ultraviolet B radiation [UVB]) within 4 weeks prior to SV2 and during the trial;
7. Current or past history of disorders of calcium metabolism associated with hypercalcemia, vitamin D toxicity, severe renal insufficiency, or severe hepatic disorders;
8. Oral calcium supplements, vitamin D supplements, bisphosphonates or calcitonin within 4 weeks prior to SV2.
   Note: Stable doses of oral vitamin D supplementation ≤400 IU/day is permitted provided there are no dose adjustments during the trial period;
9. 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;
10. Use or planned initiation of estrogen and/or progestogen therapy (e.g. hormonal contraception) during the trial;
11. Strong systemic cytochrome P450 3A4 (CYP 3A4) inhibitors or inducers (e.g., clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir, rifampicin, phenobarbital, phenytoin) within 4 weeks prior to SV2 and during the trial period;
12. 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 SV2 and during the trial period;
13. Systemic treatment with biological therapies, whether marketed or not, with a possible effect on psoriasis vulgaris within the following time period prior to SV2 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)

    In general, subjects who are candidates for biological or other systemic therapy are excluded from the trial.
14. 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;
15. Any of the following conditions, whether known or suspected:

- Clinically diagnosed depression where the subject is in current treatment with medication approved for treatment of depression
- Endocrine disorders (e.g. Cushing's disease or Addison's disease) known to affect cortisol levels or HPA axis integrity.
- Non-nocturnal sleep patterns (e.g. irregular sleep patterns)

16. 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 SV2 and during the trial period;
17. Use of live vaccines 4 weeks before SV2 and during the trial period;
18. Known human immunodeficiency virus (HIV) infection, active hepatitis B or hepatitis C;
19. Known or suspected of hypersensitivity to any component of the test product;
20. Known allergic asthma, serious allergies or allergies where recurrent acute or chronic treatment is necessary (excluding hay fever);
21. Have any chronic or acute medical condition that, in the opinion of the investigator, may pose a risk to the safety of the subject, or may interfere with the assessment of safety or efficacy in this trial;
22. 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 IP or will interfere with the interpretation of the trial results;
23. Females who are pregnant, breast feeding, or planning a pregnancy;
24. Subject with known abnormal reduction in muscle mass, as judged by the investigator;
25. Participation in another clinical trial or received an IP or non-marketed drug substance within 30 days prior to SV2;
26. Previously enrolled in this trial;
27. 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 Harmonisation (ICH) – Good Clinical Practice (GCP) guidelines, every subject has the right to refuse further participation in this trial at any time and without providing reasons (see also Section 9.2). A subject's participation is to be terminated immediately upon his/her request. The investigator should seek to obtain the reason and record this on the electronic case report form (eCRF) whenever possible. If,

at the time of refusal, a trial product has already been administered, the subject should also be advised to have an Early Termination visit performed (see section 7.13 Early Termination) and follow up on treatment related AEs.

In 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. Examples of SAEs that do not necessarily require discontinuation of treatment include but are not limited to a hospitalisation that is not related to the IP, for example removal of tonsils or polyps.

The reasons for discontinuation of treatment may be among others;

- HPA axis suppression is noted at Week 4
- inconsistency with inclusion / exclusion criteria
- intake of a prohibited medication(s)
- AE / SAE
- investigator's discretion

Subjects discontinued treatment due to a treatment-related AE will be monitored until the AE is resolved or until the medical condition of the subject is stable.

In case the treatment is discontinued all efforts should be made to have the subject completing the trial, or at least come in for the Week 8 visit, even if not being on treatment anymore.

Reasons for discontinuation of the trial may be among others;

- lost to follow-up,
- withdrawal of informed consent / informed assent
- pregnancy
- investigator's discretion
- sponsor's decision to terminate or suspend the trial
- termination of the trial by the Regulatory Authority.

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 approximately 20 subjects are included in the PK population at Week 4.

6.0 TRIAL TREATMENTS

6.1 Investigational Product

MC2-01 cream is a combination product, calcipotriol and betamethasone dipropionate, administered as a cream formulation for topical administration. The MC2-01 cream is currently not a marketed product, which means that the product is still being tested and is not approved for sale. One concentration of the trial product will be studied: calcipotriol (50 micrograms) and betamethasone (0.64 mg/g, as dipropionate). The list of inactive ingredients present in MC2-01 cream is presented in the Investigator Brochure (37).

6.2 Dosing Regimen

Subjects are to apply the IP topically once daily, preferably in the evening, for 8 weeks. The subject should apply enough IP to treat the entire affected areas and rub in gently to ensure that the plaques are saturated with the medication. Up to 3 tubes of 60 gram will be dispensed for a treatment period of two weeks including the allowed visit window of 2 days.

The IP is applied to affected areas on the:

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

Only affected areas are to be treated. The subjects should therefore not continue treatment on a skin area which has been cleared but treatment may be restarted in case of recurrence at the subjects discretion (Section 6.3).

The face, genitals, and intertriginous areas should not be treated with the IP. The first application is done at Day 0 under the supervision and instruction of the trial staff. Subsequent applications will be applied by the subject or by the parent(s) or legal guardian(s).

All subjects are instructed to apply IP in the morning on the day before the Week 2, Week 4 and Week 8 visits. On the day of these visits, the subjects should not apply any IP before the visit.

Subjects are to record the date and time of application in the subject dosing diary (with the assistance of the parent(s) or legal guardian(s), as needed). The treated area should not exceed 30% of the BSA.

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

Detailed application instructions will be provided in the subject instructions.

6.3 Dose Modification

Dose modification can only occur after Week 4.

Subjects classified as clear at any of the on-treatment visits may stop the IP treatment at the investigator's discretion. They should remain in the trial and attend all visits up to and including the follow-up visit. The IP will continue to be dispensed to the subject, and IP 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 IP treatment on the advice of the investigator at a scheduled visit.

6.4 Packaging, Labeling, Storage and Destruction

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

The IP will be supplied by MC2s 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 pharmacy/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.

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

6.5 Assignment to Treatment

This is an open-label trial. All subjects who fulfil the trial eligibility requirements will be assigned to treatment with MC2-01. Hence, neither randomisation nor blinding will be performed.

6.6 Prior, Concomitant, and Prohibited Therapy

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

6.6.1 Washout of prohibited medications prior to enrolment

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

6.6.2 Prohibited medications during the trial

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

- Use of biological psoriasis therapies;
- Use of oral systemic treatments with a possible effect on psoriasis (e.g., methotrexate, apremilast, retinoids, PDE4 inhibitors, corticosteroids, and other immunosuppressants).
- Use of phototherapy (PUVA and UVB).
- Use of topical treatments with a possible effect on psoriasis (e.g., corticosteroids, vitamin D analogs, retinoids, PDE4 inhibitors, salicylic acid, pimecrolimus, tacrolimus, anthralin, tar, 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 or initiation of estrogen and/or progestogen therapy (e.g. hormonal contraception).
- Use of strong systemic 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.

6.6.3 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.

6.7 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 (with assistance from the parent(s) or legal guardian(s), if needed) 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 will be weighed to determine the amount of the IP used per treatment phase.

7.0 VISIT SCHEDULE AND ASSESSMENTS

Table 7-1 Visit Schedule and Assessments

	SV 1 [a]	SV 2	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Follow-up Visit [b]
			Day 0	Week 2	Week 4	Week 6	Week 8	FU
Examination	Day - 42 to Day - 8	Day -7 to - 4	Day 0	Day 14 ± 2	Day 28 ± 2	Day 42 ± 2	Day 56 ± 2	Day 70-84 ± 2
Informed assent/Informed consent [c]	X							
Inclusion/exclusion criteria	(X)		X					
Urine pregnancy test[d]	X		X					
Serum pregnancy test[d]		X			X		X	
Demographics, medical history	X							
Prior and concomitant medication	X	X	X	X	X	X	X	
Physical examination	X		X		X		X	X
PGA	(X)	(X)	X	X	X	X	X	
Body Surface Area (BSA) involvement	(X)	(X)	X		X		X	
Vital signs			X	X	X	X	X	
Laboratory assessments		X			X	(X)[e]	X	(X)
ACTH challenge test[f]		X			X		X	(X)
Morning urine assessment (second morning urine)	Instruct	X		Instruct	Instruct X	Instruct (X)[g]	Instruct X	(X)
Review food diary	Instruct	X		Instruct	Instruct X	Instruct (X)[g]	Instruct X	(X)
PK pre-dose blood sample (Single)		X	Instruct	X		Instruct	X	
PK serial blood samples[h]				Instruct	X			
12-Lead ECG		X			X		X	
Psoriasis Treatment Convenience Scale				X	X		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)[i]		X	X	X	X	X	X	X
Local Skin Reactions			X	X	X	X	X	

a) A washout period of up to 6 weeks must be completed if the subject has been treated with anti-psoriatic treatments or other relevant medication, as defined by exclusion criteria. There should be at least four days between SV1 and SV2 in order to keep the food diary for 4 days prior to SV2. 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) Follow-up visit is required 2 weeks after the Week 8 visit. For subject with HPA axis suppression at Week 8 the follow-up visit should be 4 weeks after the Week 8 visit.
If the albumin-corrected serum calcium or the urinary calcium creatinine ratio is elevated at Week 8 a repeat test should be performed. In case of a repeat of the urinary calcium creatinine ratio the subject should be instructed to record the calcium intake 4 days prior to the visit.
For Czech Republic and Hungary: if an on-site visit is not required the follow-up visit can be a telephone call 2 weeks after Week 8 to ask for the wellbeing of the subject. In Germany an on-site follow-up visit is mandatory.
In addition, subjects discontinued due to a treatment-related AE will be monitored until the AE is resolved or until the medical condition of the subject is stable.
c) Written informed assent must be provided by the subject and written informed consent must be provided by the parent(s), legal guardian(s) and the consent documents signed by the investigator or designee before any trial related procedures are carried out. For subjects requiring a washout period, informed assent/informed consent must be completed prior to washout.
d) All female subjects.
e) If serum albumin-corrected serum calcium is above the reference range at Week 4 a repeat test should be performed at Week 6.
f) The ACTH challenge test must be performed between 7 and 9 am
g) If the urinary calcium:creatinine ratio is above the reference range at Week 4, a repeat test should be performed, and the food diary filled in at Week 6. If the repeat test is also above the reference range, 24-hour urine collection must be performed.
h) Blood samples for PK analysis are drawn before IP application (pre-dose sample) and 1, 3, and 5 hours after IP application.
i) AEs are to be collected from the date of signing informed assent/informed consent and first trial-related activity is performed.

Instruct: At the indicated visits (Table 7-1), instruct the parent(s), legal guardian(s) or the subjects as to appropriate trial procedures as specified below:

- **Food diary:** instruct the parent(s), legal guardian(s) or subjects on how to use the food diary, especially recording their intake of calcium-rich nutrients. Consumption of calcium-rich foods should be kept constant during 4 days prior to each morning urine collection.
- **Second morning urine samples:** Second morning urine samples must be collected at the site on specific visits as specified in the visit schedule (Table 7-1).
  Food diary and morning urine sampling before Week 6 and Follow-up Visit is only relevant if urinary calcium:creatinine ratio is above the reference range at previous visit. Inform by telephone call a few days before the scheduled visit whether applicable or not.
- **IP application and PK blood samples:** instruct the parent(s), legal guardian(s) or subjects to apply the IP in the morning on the day before the Week 2, Week 4 and Week 8 visits. On the day of these visits, the subjects should not apply any IP before the visit. A reminder to the parent(s), legal guardian(s) or subjects may be needed a few days before the scheduled visit. If the subject has applied the IP in the morning prior to the visit, the visit must be rescheduled.

7.1 Demographics and Medical History

The following demographic and medical history must be collected:

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

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

Table 7-2 Fitzpatrick Skin Type Classification

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

7.2 Prior and Concomitant Medication

Review and record prior medication and concomitant medication.

All medications, including OTC drugs, herbals, vitamins, dietary supplements etc., taken within 30 days prior to the start of the trial will be recorded at Screening (SV1 and/or SV2). Thereafter, a record of all medications and supportive therapy taken during the trial will be made. Information regarding the total daily dose, route of administration, start and discontinuation dates, and indication are to be recorded on the subject's eCRF.

7.3 Physical Examination

An abbreviated physical examination including general appearance, regional lymph nodes and a complete dermatological examination of the skin must be performed, including height and

weight. without shoes, as specified in the visit schedule (Table 7-1).

7.4 Vital Signs

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

7.5 Pregnancy Test

All female subjects will undergo a routine urine pregnancy test at SV1 and V1 (Day 0) and a serum pregnancy test at SV2, Week 4 & Week 8 as specified in the visit schedule (Table 7-1). Instruct all sexually active female subjects to use approved form(s) of contraception.

7.6 Laboratory Assessments

All clinical laboratory specimens will be analysed by a central licensed and accredited laboratory facility according to the laboratory's standard operating procedures (SOPs).

7.6.1 Hematology and biochemistry

The planned maximum amount of blood drawn at each visit and for each subject is:

Visit	Maximum amount of blood drawn
Screening Visit 2 (SV2)	17 ml
Week 2	8 ml
Week 4	41 ml
Week 6	4 ml (only if albumin-corrected serum calcium is above the reference range at Week 4 and repeat test is required)
Week 8	17 ml
Follow-up Visit	9 ml (blood draw at the follow-up visit is only required if albumin-corrected serum calcium is above the reference range or HPA axis suppression is noted at Week 8)

To avoid too many venipunctures and thereby to cause as little pain, discomfort, fear and any other foreseeable risk as possible, it is recommended to use butterfly needles. This applies especially at the Week 4 visit where blood draw for the PK analysis will be repeated 4 times. In the event that butterfly needles cannot be used, it is important to minimize the number of attempts and it should

be assessed individually in each situation and should always be in agreement with the individual subject.

The following tests will be performed as specified in Table 7-1:

- 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, only at SV2

Week 4: If albumin-corrected serum calcium is above the reference range at Week 4, a repeat test should be performed at Week 6.

Week 8: If the albumin-corrected serum calcium is above the reference range at Week 8, a repeat test is required 14 days (± 2 days) after at a follow-up visit (see Section 7.12).

7.6.2 HPA axis suppression/ ACTH challenge test

Adrenal function will be assessed in a challenge test with an intravenous dose of 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 SV2, Week 4 and Week 8 visits. The test consists of blood sampling starting between 7 and 9 am. 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 following criterion will define an adrenal suppression:

- the 30-minute post-stimulation level below18 µg/dL (500 nmol/l).

Week 4: If HPA axis suppression is noted at Week 4, 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 ACTH challenge test has to be repeated at a follow-up visit 28 days (± 2 days) after the Week 8 visit (see Section 7.12).

7.6.3 Food diary: calcium-rich nutrients

All subjects should record their consumption of calcium-rich nutrients (mainly milk, other dairy products, calcium-fortified products) four days before each second morning urine collection (see Table 7-1).

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

7.6.4 Analysis of Morning Urine Spot Samples

All subjects are to collect second morning urine spot samples at the visits indicated in Table 7-1.

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.

The following provisions will apply for subjects with hypercalciuria, defined as a morning urinary calcium:creatinine ratio above the reference range (as defined in the laboratory manual):

Week 4: If the morning urinary calcium:creatinine ratio is above the reference range at Week 4, a repeat test should be performed at Week 6.

Week 8: If the urinary calcium:creatinine ratio is above the reference range at Week 8, a repeat test is required at a follow-up visit 14 days (± 2 days) after Week 8 (see 7.12).

If the calcium-creatinine ratio is above the reference range at two consecutive visits during the trial, 24-hour urine collection must be performed.

7.6.5 Pharmacokinetics

Samples for PK analysis will be collected though an untreated area of the skin, at the following time points:

- SV2: single time point
- Week 2 visit: single time point before IP application
- Week 4 visit: before the planned IP application at the visit and then at 1, 3, and 5 hours after the application
- Week 8 visit: single time point. Subject should not apply IP on the day of the Week 8 visit

Subjects are to be instructed to apply their daily dose of IP in the morning on the day before the Week 2, Week 4 and Week 8 visits. On the day of these visits, the subjects should not apply any IP before 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)

7.7 Electrocardiogram

A 12-lead ECG will be recorded at visits indicated in Table 7-1. 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 judgement of the investigator.

Clinically significant findings will be reported as medical history if detected at SV2. 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.

7.8 The Psoriasis Treatment Convenience Scale

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

The aim of the Psoriasis Treatment Convenience Scale is to assess the impact and convenience of psoriasis treatment. The scale has been tested for content validity through focus group interview with 20 patients and adapted based on the responses. The scale consists of 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 greasy did your skin feel after applying the treatment?
5. How much did treating your skin disrupt your daily routine?
6. Overall, how satisfied were you with the medical treatment?

7.9 Investigator Assessments

The investigator assessments are to be performed by a dermatologist, a physician or a pediatrician with at least 1 year of experience in dermatology. For physicians and pediatricians who do not fulfill the requirement regarding dermatological experience with at least 1 year of experience in dermatology, the person must be preapproved by MC2. The assessments are to be performed as specified in the visit schedule (see Table 7-1).

7.9.1 Physician's global assessment of psoriasis severity

The 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 7-3. The PGA assessment will represent the *average* lesion severity on the trunk, limbs, and/or scalp. The assessments will be based on the condition of the disease at the time of evaluation, and not in relation to the condition at a previous visit.

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

Score	Grade	Definition
0	Clear	Plaque thickening = no elevation or thickening of normal skin 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 colouration

7.9.2 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) as specified in the visit schedule (see Table 7-1).

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.

7.9.3 Local skin reactions

The local skin reaction assessment involves signs assessed by the investigator or designee and symptoms 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 7-4. 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 7-4 and the subject will tell which one to mark.

Table 7-4 Local Skin Reaction Scores

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

7.10 Adverse Events

7.10.1 Adverse events assessments

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

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

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

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

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

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

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

7.10.2 Timing

AEs will be collected/assessed from the time of the signature of the informed assent/informed consent form by the subject/parent(s) or legal guardian(s) and first trial-related activity performed.

7.10.3 Severity of adverse events

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

- Mild – The subject was aware of the signs and symptoms, but the signs and symptoms were easily tolerated and 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).

7.10.4 Relationship of an adverse event to trial treatment

The investigator is responsible for assessing 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 IP 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 IP are temporally related, and the AE is more likely explained by IP administration than by other causes
Definitely Related	The AE and IP administration are related in time, and a direct association can be demonstrated. Concomitant medication, therapeutics interventions, or underlying conditions do not provide a sufficient explanation for the observed AE

7.10.5 Unexpected adverse events

Any AE assessed 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 (37).

"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 IP but are not specifically mentioned as occurring with the particular IP under investigation.

7.10.6 IP overdose

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

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

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

7.10.7 Pregnancy

Any pregnancy occurring from date of the informed assent/informed consent signature until trial completion must be reported immediately to MC2 or designee as soon as it becomes known to the investigator and not later than within 24 hours of his/her knowledge of the occurrence of the pregnancy (see Section 13.2).

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

7.10.8 Serious adverse event

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

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

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

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

Any pre-planned hospitalisations that are known at the time of signing the 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 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.

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

A suspected unexpected serious adverse reaction (SUSAR) is an SAE that is both unexpected (not consistent with the current Investigator's Brochure (37), and for which there is evidence to suggest a causal relationship between the IP 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.

7.11 Unscheduled Visit

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

7.12 Follow-up Visit/ Follow-up Telephone Call

A follow-up visit is required for all subjects to ensure capturing of safety signals 2 weeks after Week 8, except for subjects where HPA axis suppression is noted at Week 8.

In case HPA axis suppression at Week 8 has been noted, the follow-up visit including an ACTH challenge test should be performed 28 days (± 2 days) after Week 8.

Physical examination and AE Assessment will be mandatory for all subjects. Other assessments will be performed depending on the results received at Week 8.

Additional laboratory assessments will be performed for the following reasons:

- If the albumin-corrected serum calcium was above the normal reference range at the Week 8 visit a repeat test should be done 14 days (± 2 days) after.
- If the urinary calcium:creatinine ratio is above the reference range at Week 8, a repeat test should be done 14 days (± 2 days) after.

For Czech Republic and Hungary: if an on-site visit is not required the follow up visit can be a telephone call 2 weeks after Week 8 to ask for the wellbeing of the subject. In Germany an on-site follow-up visit is mandatory.

Subjects discontinued due to a treatment-related AE will be monitored until the AE is resolved or until the medical condition of the subject is stable.

7.13 Early Termination

If a subject withdraws from the trial 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 serum pregnancy test for females
- ECG
- Haematology and biochemistry.
- 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.

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 visit and have had at least one blood draw for PK assessment at Week 4.
- **Safety population:** all subjects who are enrolled in the trial and dispensed the trial medication at Visit 1/Day 0, excluding subjects who return all of the trial medication unused. 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 show normal HPA function at SV2. 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 enrolled 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 enrolled 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_{0-5}, C_{max}, and T_{max}) will be calculated at Week 4. The PK parameters AUC_{0-5} and C_{max} will be calculated using standard formulas inserting the LLOQ for non-quantifiable levels of the analyte; therefore, AUC_{0-5} 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} and T_{max} will be calculated if at least one time-point shows a quantifiable level of the analyte. The PK parameters will be summarised using appropriate descriptive statistics including median, lower and upper quartiles, minimum and maximum.

A parametric model will be applied to estimate the geometric mean of C_{max} and AUC_{0-5}, respectively. The log-transformed values of the PK parameters will be assumed to be normally distributed. The mean of this normal distribution will be estimated taking the potential censoring of the values into account. The mean will then be back-transformed to the original scale as the geometric mean.

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 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. Adverse events will be presented in data listings and summarised by frequency and severity. 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 proportion of subjects with HPA-axis suppression at Week 4 and Week 8 will be summarised using frequency counts.

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
- 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 AEs will be summarised 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 AE 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 summarised by presenting shift tables using extended normal ranges (baseline to most extreme post-baseline value), by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations (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. 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 will be summarised.

8.9.2 Psoriasis treatment convenience scale

Subject assessment of treatment convenience at Week 4 using a Psoriasis Treatment Convenience Scale will be summarized.

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

10.0 DATA HANDLING AND RECORD KEEPING

10.1 Recording of Data

10.1.1 Source documents

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

Trial data collection procedures must ensure that each data element can be traced with a high level of confidence from its originator or recorder to its representation in the trial database and then to its place in the analysis and report of trial results. Once recorded, the trial data must be protected from unauthorised modification or deletion, and all authorised modifications and deletions must be securely linked in the permanent record with their author, time of change, and reason for change (i.e., the audit trail must be maintained).

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

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

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

10.1.2 Case report forms

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

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

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

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

10.2 Retention of Documents

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

11.0 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Direct Access to Source Documents

As specified in the investigator's agreement, the investigator agrees to allow trial-related monitoring, audit(s), IRB/IEC review(s) and regulatory inspection(s), with direct access to all the required source records, and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues.

11.2 Monitoring Procedures

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

11.3 Audit and Inspection

The investigator will make all the trial-related source data and records available to a quality assurance auditor mandated by the sponsor, or to domestic or foreign regulatory inspectors, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and

well-being of the subjects have been adequately protected, and that all data relevant for the evaluation of the IP have been processed and reported in compliance with GCP/ICH and applicable regulatory requirements.

The investigator is to notify 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 assent/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 has provided informed assent and each parent(s) or legal guardian(s) (according to national law) have provided written informed consent following their receipt of verbal and written information about the trial to participate in the trial. No trial-specific procedures will be performed before a subject’s informed assent/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 assent/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 assent/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 immediately as it becomes known to the investigator (and not later than within 24 hours of his/her knowledge of the occurrence of an SAE) electronically to the UBC using the SAE Reporting Email address or fax number.

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.clinical trial.gov and in accordance with applicable regulations.

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

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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)
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("MC2")

Protocol Authors

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Johan Selmer, MD, VP Medical Affairs, MC2 Therapeutics
Birgitte Vestbjerg, Director Clinical Operation, MC2 Therapeutics
Charlotte Hindsberger, Principal consultant, Biostatistics, S-cubed

17.2 Appendix 2 Vendors

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

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

Responsible for all services related to packaging, labeling, distribution and destruction of the investigational medical products:
Rachel Hopkins BPharm (Hons), MRPharmS, PhD
Director and Pharmacist, IMP Pharmaceutical Services Ltd.

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

Responsible for ECG services:
ERT, Peterborough Business Park, Lynch Wood, Peterborough, PE2 6FZ, UK.

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

Responsible for PK analysis, as specified in the contract:
ICON Laboratory Services Inc., 8282 Halsey Road, Whitesboro, NY 13492 USA.