

Clinical Trial Protocol

Trial Title:	A Randomised, Multicentre, Investigator-Blind, Parallel-Group Trial to Evaluate the Efficacy and Safety of MC2-01 Cream Compared to MC2-01 Cream Vehicle and Active Comparator in Subjects with Mild-to-Moderate Psoriasis Vulgaris
Investigational product:	MC2-01 (calcipotriene/betamethasone dipropionate, w/w 0.005%/0.064%) cream
Active Comparator:	Calcipotriene/betamethasone (calcipotriene/betamethasone dipropionate, w/w 0.005%/0.064%) gel/topical suspension
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CLINICAL TRIAL PROTOCOL APPROVAL

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

Protocol number: MC2-01-C2

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

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SIGNATURE PAGE FOR INVESTIGATOR(S)**Product:** MC2-01 (calcipotriene/betamethasone dipropionate) Cream**Protocol number:** MC2-01-C2**Protocol Version:** 3.0**Protocol title:** A Randomised, Multicentre, Investigator-Blind, Parallel-Group Trial to Evaluate the Efficacy and Safety of MC2-01 Cream Compared to MC2-01 Cream Vehicle and Active Comparator in Subjects with Mild-to-Moderate Psoriasis Vulgaris

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, clinically and administratively, 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
AE	Adverse event
ANOVA	Analysis of variance
AUC	Area under the curve
BDP	Betamethasone dipropionate
BOCF	Baseline observation carried forward
BSA	Body surface area
CAL	Calcipotriene
CI	Confidence interval
CRO	Contract Research Organisation
DLQI	Dermatology Life Quality Index
ECG	Electrocardiogram
eCRF	Electronic case report form
EQ-5D	EuroQOL five dimensions questionnaire
EQ-VAS	EQ-5D visual analog scale
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IP	Investigational product
IRB	Institutional Review Board
ITT	Intent to treat
IWR	Interactive web response
LOCF	Last observation carried forward
MCMC	Markov Chain Monte Carlo
MI	Multiple imputation
mPASI	Modified Psoriasis Area and Severity Index
MedDRA	Medical Dictionary for Regulatory Activities
NI	Non-inferiority
NRI	Non-responder imputation
NRS	Numerical Rating Scale
OTC	Over the counter

Abbreviation	Definition
PASI	Psoriasis Area and Severity Index
PASI 75	75% reduction in mPASI
PASI 50	50% reduction in mPASI
PGA	Physician's global assessment
PP	Per protocol
PRO	Patient-reported outcome
PUVA	Psoralen + ultraviolet-A radiation
QOL	Quality of Life
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SGA	Subject's global assessment
SUSAR	Suspected unexpected serious adverse reaction
TC	Telephone call
UBC	United BioSource Corporation
UPT	Urine pregnancy test
US	United States
UVB	Ultraviolet B
VAS	Visual analog scale

1.0 SYNOPSIS

Trial Title:	A Randomised, Multicentre, Investigator-Blind, Parallel-Group Trial to Evaluate the Efficacy and Safety of MC2-01 Cream Compared to MC2-01 Cream Vehicle and Active Comparator in Subjects with Mild-to-Moderate Psoriasis Vulgaris
Protocol Number:	MC2-01-C2
Sponsor:	Drug Delivery Solutions Ltd (part of MC2 Therapeutics)
Development Phase:	3
Trial Objectives:	The primary objective is to show therapeutic non-inferiority of MC2-01 cream to active comparator, as well as to characterise the safety profile of MC2-01 cream in subjects with psoriasis vulgaris.
Trial Design:	Randomised, investigator-blind, multicentre, vehicle- and comparator-controlled, parallel-group, 3-arm trial. The trial will include a maximum 4-week screening period, an 8-week treatment period, and a 2-week post-treatment follow-up period.
Planned Sample Size:	<p>A total enrolment of approximately 791 subjects is planned in order to have approximately 712 completed subjects.</p> <p>Under the assumptions of the trial, a sample size of N=305 per active treatment group is calculated to satisfy the non-inferiority conditions with 90% power. Assuming 90% completion rate of the randomised subjects, a total sample size of N=339 per active treatment group is required to be randomised. Following a 3:1:3 randomisation ratio, 113 subjects will be randomised to receive the MC2-01 cream vehicle.</p>
Trial Population:	Generally healthy males or non-pregnant females, at least 18 years of age, with a clinical diagnosis of plaque psoriasis (psoriasis vulgaris) of at least 6 months duration that involves non-scalp regions of the body (trunk and/or limbs), with a Physician Global Assessment (PGA) of disease severity of mild or moderate on the body (trunk and/or limbs) and a minimum modified Psoriasis Area and Severity Index (mPASI) score of at least 2.
Investigational Product (IP):	<p>MC2-01 cream (calcipotriene (CAL) and betamethasone dipropionate (BPD), w/w 0.005%/0.064%).</p> <p>MC2-01 cream vehicle.</p>

Reference/Control Product(s):	Calcipotriene/betamethasone dipropionate gel/topical suspension, w/w 0.005%/0.064%, approved in the United States (US) as Taclonex [®] topical suspension and in the European Union (EU) as Dovobet [®] /Daivobet [®] gel.
Efficacy Evaluation Criteria:	Efficacy will be assessed by the investigator (PGA and mPASI), and by subject's global assessments (SGA) of disease severity, Dermatology Life Quality Index (DLQI) questionnaire, and EuroQOL five dimensions (EQ-5D) questionnaire.
Safety Evaluation Criteria:	Adverse event (AE) incidence and severity, laboratory test results (serum biochemistry, urinalysis, pregnancy testing for female subjects of childbearing potential), Electrocardiogram (ECG), vital signs assessments, physical examination.
Statistical Methods:	<p>Primary Endpoint</p> <p>The primary efficacy endpoint is the proportion of subjects in each treatment group with 'treatment success' at Week 8, defined as a minimum 2-point decrease from Baseline to Week 8 in PGA score; i.e., a score of 0 (clear) or 1 (almost clear) disease for subjects with moderate disease at Baseline; or a score of 0 (absent) for subjects with mild disease at Baseline.</p> <p>Non-inferiority Evaluation</p> <p>The PGA response rate for MC2-01 cream and for active comparator at Week 8 will first be compared with that for MC2-01 cream vehicle at Week 8 for a superiority evaluation, based on the Intent to Treat (ITT) Population, using a LOGISTIC model with treatment, baseline value of PGA and study site as independent variables. Missing data will be imputed using multiple imputations (MI).</p> <p>If and only if superiority to vehicle for both MC2-01 cream and for active comparator can be claimed at the 5% significance level, the non-inferiority (NI) analysis of the primary endpoint will then be conducted based on the PP Population. The PGA success rate of MC2-01 cream at Week 8 will be compared with that of active comparator at Week 8, using a non-inferiority margin of 10% points.</p> <p>The percentage of subjects in each group with treatment response will be calculated along with its 95% confidence interval (CI) using normal approximation. A 95%, 2-sided CI on the difference between MC2-01 cream and active comparator will be computed using normal approximation. MC2-01 will be considered non-inferior to Active Comparator if the lower bound of the 2-sided 95% CI is $\geq -10\%$ points.</p> <p>Sensitivity Analyses</p> <p>As sensitivity analyses, the analyses of superiority will also be made based on the ITT population using other imputation methods than MI (last observation carried forward (LOCF), baseline observation carried forward (BOCF), non-</p>

	<p>responder imputation (NRI)). Further an analysis based on the Per Protocol (PP) population and using complete case analysis with no imputation of missing data will be made.</p> <p>The non-inferiority analysis of the primary endpoint will also be performed based on the ITT population using a variety of imputation methods as sensitivity analyses (MI, LOCF, BOCF, NRI)</p> <p>For the sensitivity non-inferiority analysis using MI, the treatment difference will be evaluated for each of the multiple imputed datasets using PROC FREQ with RISKDIFF option. The estimates and standard errors of the response rate difference based on the imputed datasets will be combined by applying Rubin's rules in PROC MIANALYZE and the 95% CI of the difference will be computed.</p> <p>Secondary Endpoints</p> <p>Secondary endpoints are the following</p> <ul style="list-style-type: none">• Percentage change from Baseline in the mPASI score at Week 8;<ul style="list-style-type: none">○ Superiority evaluation: The percentage change will be compared between MC2-01 cream vs. vehicle and active comparator vs. vehicle for superiority using an analysis of covariance (ANCOVA) model with treatment, baseline PGA severity (mild/moderate), baseline mPASI and study site as independent variables. The analysis will be based on the ITT population using multiple imputation.○ Non-inferiority evaluation: The percentage change will be compared between MC2-01 cream and active comparator using a similar model as for the evaluation of superiority. Non-inferiority will be claimed if the lower limit of the relevant two-sided CI (see derivation of alpha level below), derived from the difference in LSMEANS, will be $\geq -10\%$. The analysis will be based on the PP population with no imputation of missing data.• Subject assessment of treatment convenience at Week 8 using a Psoriasis Treatment Convenience Scale (PCTS)<ul style="list-style-type: none">○ Superiority evaluation: PCTS will be compared for superiority between MC2-01 cream and active comparator using an ANOVA model with treatment and trial site as independent variables; superiority will be claimed if the lower limit of the relevant two-sided CI (see derivation of alpha level below), derived from the difference in LSMEANS, will be ≥ 0. The analysis will be based on the ITT population. Missing and invalid PCTS scores will be imputed using the last valid measure prior to the visit.
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	<ul style="list-style-type: none"> • Change in itch intensity assessed on a numerical rating scale (Itch by NRS) from baseline to Week 4: <ul style="list-style-type: none"> ○ Superiority evaluation. (MC2-01 cream vs MC2-01 cream vehicle). Superiority between MC2-01 cream and vehicle will be assessed by using an ANCOVA model with treatment, baseline PGA severity (mild/moderate), baseline Itch by NRS value and analysis site as independent variables. The primary analysis will be based on the ITT population, using multiple imputations • Percentage of subjects with four-point improvement on the numerical rating scale (Itch by NRS) from baseline to Week 4 <ul style="list-style-type: none"> ○ Superiority evaluation (MC2-01 cream vs MC2-01 cream vehicle). The analysis is made on the subgroup of subjects from the ITT populations with Itch (assessed by NRS) ≥ 4 at baseline. Superiority between MC2-01 cream and vehicle will be assessed by using a logistic model with treatment, baseline PGA severity (mild/moderate), baseline Itch by NRS value and analysis site as independent variables. Missing data will be imputed using multiple imputations. <p>The global Type-I error will be controlled by the following testing procedure:</p> <ol style="list-style-type: none"> 1. Secondary endpoints will be tested only if the primary endpoint will reject the Null-hypothesis; 2. The two secondary endpoints ‘Percentage reduction from Baseline in the mPASI score at Week 8, and Subject assessment of treatment convenience at Week 8 using a Psoriasis Treatment Convenience Scale will be tested in with a loopback procedure with initial error probability weights 2/3 for H1 (mPASI) and 1/3 for H2 (subject assessment of treatment convenience), resulting in $\alpha_1=0.0333$ and $\alpha_2=0.0167$. If any of the Null-hypotheses can be rejected, the respective error probability will be shuffled to the other hypothesis 3. If and only if both non-inferiority of MC2-01 to active comparator with respect to Percentage reduction from Baseline in mPASI as well as superiority of MC2-01 vs. active comparator with respect to Psoriasis treatment convenience scale has been demonstrated, superiority of MC2-01 vs vehicle with respect to the below endpoints will be tested in a hierarchical manner: <ul style="list-style-type: none"> • Change in itch intensity assessed on a numerical rating scale (Itch by NRS) from baseline to Week 4
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	<ul style="list-style-type: none"> • Percentage of subjects with four-point improvement on the numerical rating scale (Itch by NRS) from baseline to Week 4 (In the subgroup of subjects with an NRS score ≥ 4 at baseline) <p>All secondary endpoints will be described using summary statistics. For mPASI and NRS, absolute values, absolute reduction, and percentage reduction from baseline will be summarized using mean, median, SD, quartiles and ranges for each treatment group by visit. Frequency counts and percentages of NRS 4-point improvement responders will be provided for each treatment group by visit. For PTCS score, absolute values will be summarized using descriptive statistics for each treatment group by visit.</p> <p>Other Endpoints</p> <p><u>Efficacy</u></p> <ul style="list-style-type: none"> • PGA success rate at Week 4; • Percentage change from Baseline in the mPASI score at Week 4; • Number of subjects with PASI 50 (at least 50% reduction in mPASI from Baseline) at Week 4 and Week 8; • Number of subjects with PASI 75 (at least 75% reduction in mPASI from Baseline) at Week 4 and Week 8; • Change from Baseline in SGA at Week 4 and Week 8. <p><u>Patient reported outcomes (PRO)</u></p> <ul style="list-style-type: none"> • Change in DLQI score at Week 4 and Week 8; The DLQI will be scored according to the developer instructions. Missing values, if any, will be incorporated based on the developers scoring instructions. The DLQI will also be summarised by the following domains: symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. • Change in EQ-5D score at Week 4 and Week 8. The EQ-5D will be scored according to the developer instructions. • Change in itch intensity assessed on a numerical rating scale (Itch by NRS) from baseline to Week 1 as well as Week 8 (MC2-01 cream vs MC2-01 cream vehicle).
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	<p>Other efficacy endpoints (PASI 50 and PASI 75) will be analysed following the same method as described for the primary efficacy analysis, except that no formal non-inferiority test will be conducted.</p> <p>Change from Baseline in SGA at Week 4 and Week 8 will be analysed using an ANCOVA model with treatment, baseline PGA severity (mild/moderate) baseline SGA and study site as independent variable. The subject convenience data will be summarised using summary statistics for each treatment group.</p> <p>The Patient reported outcomes DLQI, EQ-5D, and Itch by NRS will be analysed using an ANCOVA model with treatment, baseline PGA severity (mild/moderate), analysis site and respective baseline patient reported outcome as independent variables.</p> <p>Safety: The assessment of safety will be based mainly on the frequency of AEs and on the number of laboratory values that fall outside of predetermined ranges. AEs will be presented in data listings and summarised by frequency and severity for each treatment group. Laboratory and vital sign data will be presented in data listings. Abnormal laboratory findings will be presented.</p>
Trial Sites:	Approximately 57 trial sites in the US
Planned Dates of Trial:	2 nd quarter, 2017

Table 1-1 Visit Schedule and Assessments

Visit	Screening/ Visit 0 ^{a)}	Visit 1	Visit 2	TC (Visit 3)	Visit 4	Visit 5	Visit 6 /ET ^{b)}	FollowUp, Visit 7 ET ^{c)}
		Week 0	Week 1	Week 2	Week 4	Week 6	Week 8	Week 10
	Up to Day -30	Day 0	Day 7±2	Day 14±2	Day 28±2	Day 42±2	Day 56±2	Day 70±2
Informed Consent ^{d)}	X	X						
Inclusion/Exclusion Criteria	[X]	X						
Demographics, medical history	[X]	X						
Concomitant medication	[X]	X	X		X	X	X	X
Concurrent diagnoses	[X]	X						
Physical Exam	[X]	X			X		X	
Vital signs		X			X		X	
Pregnancy Test ^{e)}	[X]	X			X		X	
Biochemistry/Urinalysis		X ^{f)}			X ^{f)}		X ^{f) g)}	X ^{f) g)}
ECG		X ^{f)}			X ^{f)}		X ^{f)}	
Randomisation		X						
SGA		X	X		X	X	X	
DLQI questionnaire		X	X		X		X	
EQ-5D questionnaire		X			X		X	
Psoriasis Treatment Convenience Scale			X		X		X	
Itch by NRS		X	X		X		X	
PGA scoring	[X]	X	X		X	X	X	
mPASI scoring	[X]	X	X		X	X	X	
Body Surface Area (BSA) involvement	[X]	X			X		X	
Dispensing of IP		X	X		X	X		
Return of IP			X		X	X	X	
Compliance			X	X	X	X	X	
Local skin reactions		X	X		X	X	X	X
AE(s) ^{h)}		X	X	X	X	X	X ⁱ⁾	X ⁱ⁾
Return all trial materials							X	X

TC = telephone call; ET = early termination; ECG = electrocardiogram; PGA = physician's global assessment; mPASI = modified Psoriasis Area and Severity Index; SGA = subject's global assessment; DLQI= Dermatology Life Quality Index; EQ-5D = EuroQOL five dimensions questionnaire, Itch by NRS; Itch by Numerical Rating Scale, IP = investigational product; AE = adverse event.

- a) A washout period of up to 4 weeks must be completed if the subject has been treated with anti-psoriatic treatments or other relevant medication, as defined by exclusion criteria. Items denoted in **[brackets]** must be reviewed at Visit 0/Screening prior to commencing a washout, to assess if the subject is otherwise eligible. Such items must be checked for any change in eligibility status at Visit 1/Baseline after the washout is completed.
- b) Procedures for subjects who withdraw from the study before Visit 6/Week 8.
- c) Procedures for subjects who withdraw from the study after Visit 6/Week 8 but before Visit 7/Week 10
- d) Informed consent must be signed both by subject and investigator or designee before any trial related procedures are carried out. For subjects requiring a washout period, informed consent must be completed prior to washout.
- e) For female subjects of childbearing potential.
- f) If a laboratory or ECG result is abnormal and judged as clinical significant, the investigator or designee must follow-up as clinically appropriate (this may involve requesting repeat samples).
- g) If albumin-corrected serum calcium is above the reference range at the last on-treatment visit, a follow-up test at ET must be performed.
- h) AEs are to be collected from the date of signing informed consent, i.e., during the washout period.
- i) Monitor AEs that are considered related to the trial product until they are resolved or until the medical condition of the subject is stable.

2.0 INTRODUCTION

2.1 Background

Psoriasis is a common, immune-mediated, inflammatory skin disease that is found world-wide. The prevalence of diagnosed psoriasis in the United States (US) is approximately 3%¹ whereas the prevalence in Europe varies anywhere from 0.6 to 6.5%² with an average of approximately 3%³. The clinical course is unpredictable, but in most cases, psoriasis is a chronically remitting and relapsing disease. Chronic stable plaque psoriasis (psoriasis vulgaris) is the most common form of the disease, accounting for 85-90 % of cases⁴. Plaque-type psoriasis or psoriasis vulgaris is the most common form of the disease, and manifests as raised, red, scaly patches with silver scales. The lesions are usually distributed symmetrically, and occur most commonly on the extensor parts of elbows and knees; scalp, lumbosacral region and umbilicus⁵. Patients with psoriasis have reduced quality of life with reduced levels of employment and income⁶, and studies have shown that patients with psoriasis are emotionally and physically impaired by their disease comparable to that seen with cancer, heart disease, rheumatoid arthritis, diabetes or depression^{7,8}.

Individuals with psoriasis appear to be at an elevated risk of developing other chronic and serious health conditions, such as metabolic syndrome/type 2 diabetes, cardiovascular disease, psoriatic arthritis and other chronic inflammatory diseases^{9,10}.

There is no cure for psoriasis. The goal of treatment is to reduce or eliminate its signs and symptoms. Mild to moderate disease is often treated with topical therapies. Among topical therapies, a combination treatment of a Vitamin D analog and a topical glucocorticosteroid has become especially popular. Several studies show that the combination of calcipotriene (CAL) and betamethasone dipropionate (BDP) is superior to each of the single agent¹¹⁻¹³. There is strong scientific rationale for the combination of vitamin D and glucocorticosteroids both with respect to efficacy and safety¹⁴⁻¹⁶, and combination treatment with a Vitamin D analog and a topical corticosteroid is recommended in both American and European guidelines¹⁷⁻²⁰.

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

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

2.2 Rationale of the Trial

In this trial, the MC2-01 cream will be compared with the marketed product CAL/BDP combination gel/topical suspension, which is marketed under the brand name Taclonex[®] Topical Suspension in US and Daivobet[®]Gel or Dovobet[®] Gel in the rest of the world. This product is a liquid oil that contains the active ingredients CAL/BDP (w/w 0.005%/0.064%) in the same concentrations as MC2-01 cream.

The cosmetic qualities of a topical product is of importance for patient adherence to treatment, and currently marketed CAL/BDP products are restricted to non-aqueous oil-based formulations that are sticky and inconvenient to many patients²¹. The MC2-01 cream possesses superior cosmetic properties to most other topical formulations, and the purpose of the trial is to compare the clinical efficacy, safety, and convenience of this cream to the Taclonex[®] Topical Suspension/Daivobet[®] Gel/Dovobet[®] Gel.

The cosmetic qualities of a topical product are of importance for patient adherence to treatment, and the purpose of the trial is to compare this topical with the marketed CAL/BDP combination gel/topical suspension. The results of the Psoriasis Treatment Convenience Scale will be used as secondary endpoint. The scale has been tested for content validity and the trial will be used to finalise the psychometric validation.

2.3 Benefit-risk Assessment

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

The active ingredients in the investigational products (CAL and BDP) are known to be effective for the treatment of psoriasis. The safety and efficacy profiles for marketed products with these ingredients (formulated as ointment, gel/topical suspension and more recently aerosol foam) are well known.

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

The side effects reported with CAL/BDP topical formulations been mild and reversible upon stopping therapy. Systemic exposure of the MC2-01 cream will be tested under maximum use conditions in parallel with this phase 3. For this reason, all patients in the current trial will be monitored closely for both for both systemic and local safety with special focus on signs/symptoms of hypercalcemia or suppression of HPA axis as well as cardiac safety including periodic electrocardiograms (ECGs).

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

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 outcome²².

3.0 TRIAL OBJECTIVES AND PURPOSE

The primary objective is to show therapeutic non-inferiority of MC2-01 cream to active comparator, as well as to characterise the safety profile of MC2-01 cream in subjects with psoriasis vulgaris.

4.0 TRIAL DESIGN

4.1 Overall Trial Design

This is a Phase 3, international, randomised, investigator-blind, multicentre, vehicle and comparator controlled, parallel-group, 3-arm trial designed to show therapeutic non-inferiority of MC2-01 (CAL and BDP) cream to active comparator in subjects with mild-to-moderate psoriasis vulgaris.

Trial subjects will be enrolled at approximately 57 investigative sites in the US. Approximately 791 subjects who meet the trial entry criteria will be randomly assigned in a 3:1:3 ratio to receive either MC2-01 cream, MC2-01 cream vehicle, or active comparator. Subjects will apply trial medication to affected non-scalp areas of the body (trunk and/or limbs) topically once daily for 8 weeks.

The maximum trial duration for each subject will be approximately 14 weeks and includes a screening period of up to 4 weeks (if washout of prohibited medications is required), an 8-week treatment period, and a follow-up period of 2 weeks. After having provided written informed consent, the subject will undergo screening procedures. At the end of the screening period, eligible subjects will be randomly assigned to one of the trial treatment groups on Day 0 (Visit 1/Baseline) of the treatment period.

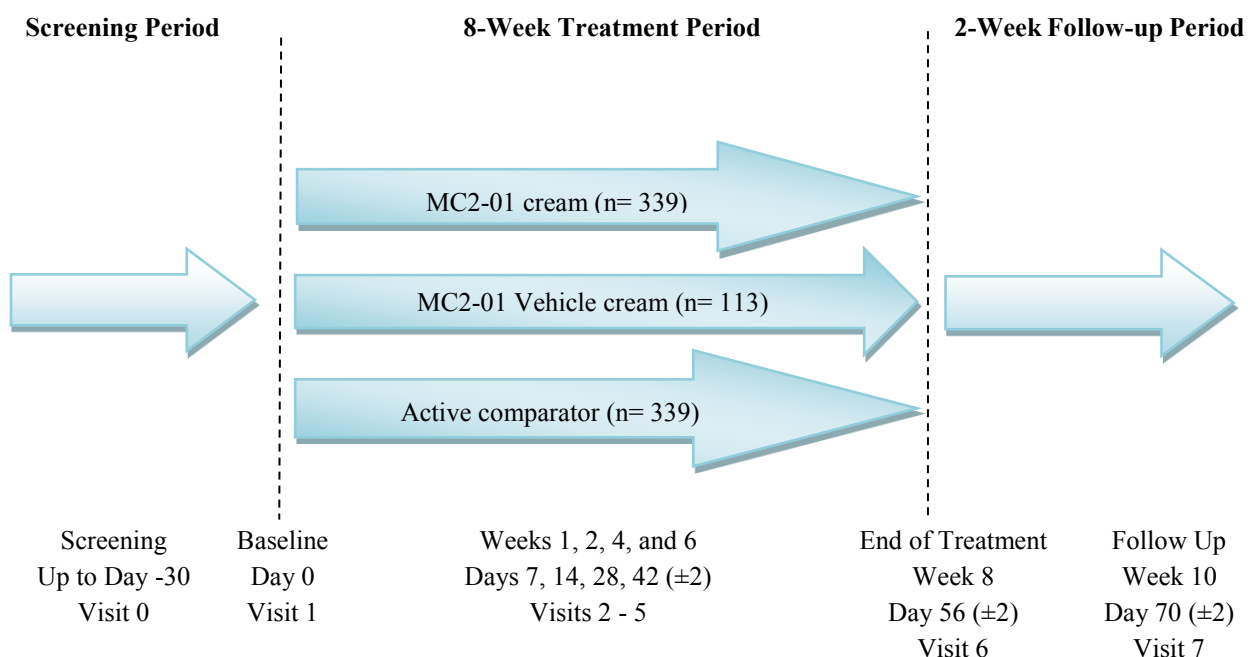
During the treatment period, subjects will return to the trial site according to the trial schedule for interim efficacy assessments, and assessment of compliance with the treatment regimen, concomitant medications, and adverse events (AEs).

During the treatment period, the investigator will score the disease severity of the subject using the physician's global assessment (PGA), modified Psoriasis Area and Severity Index (mPASI)

and body surface area (BSA) involvement; and the subject will perform a disease assessment using subject's global assessment (SGA). The subjects will be asked to complete the Dermatology Life Quality Index (DLQI), EuroQOL five dimensions (EQ-5D), Icthy by NRS and the Psoriasis Treatment Convenience Scale questionnaires. Safety assessments (local skin reaction, AEs, laboratory tests, electrocardiogram (ECG), vital signs and physical examination) will be performed.

The trial design is summarised in [Figure 4-1](#).

Figure 4-1 Trial Design



4.2 Trial Endpoints

4.2.1 Primary Endpoint

The primary efficacy endpoint is the proportion of subjects in each treatment group with 'treatment success' at Week 8, defined as a minimum 2-point decrease from Baseline to Week 8 on the PGA of disease severity on the trunk and limbs; i.e., a score of 0 (clear) or 1 (almost clear) disease for subjects with moderate disease at Baseline; or a score of 0 (clear) for subjects with mild disease at Baseline.

4.2.2 Secondary Endpoints

Secondary endpoints are the following:

- Percentage change from Baseline in the mPASI score at Week 8;
- Subject assessment of treatment convenience at Week 8 using a Psoriasis Treatment Convenience Scale
- Change in itch intensity assessed on a numerical rating scale (Itch by NRS) from baseline to Week 4 (MC2-01 cream vs MC2-01 cream vehicle)
- Proportion of subjects with four-point improvement on the numerical rating scale (Itch by NRS) from baseline to Week 4 (MC2-01 cream vs MC2-01 cream vehicle)

4.2.3 Safety Endpoints

Safety endpoints include the following:

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

4.2.4 Other Endpoints

Efficacy

- PGA success rate at Week 4;
- Percentage change from Baseline in the mPASI score at Week 4;
- Number of subjects with PASI 50 (at least 50% reduction in mPASI from Baseline) at Week 4 and Week 8;
- Number of subjects with PASI 75 (at least 75% reduction in mPASI from Baseline) at Week 4 and Week 8;
- Change from Baseline in SGA at Week 4 and Week 8.

Patient reported outcome

- Change from Baseline in DLQI score at Week 4 and Week 8;
- Change from Baseline in EQ-5D score at Week 4 and Week 8.
- Change in itch intensity assessed on a numerical rating scale (Itch by NRS) from baseline to Week 1 as well as Week 8 (MC2-01 cream vs MC2-01 cream vehicle)

5.0 SELECTION OF TRIAL POPULATION

5.1 Subject Population

Approximately 791 subjects will be enrolled to provide approximately 712 completed subjects evaluable for the primary analysis. An individual subject will be allowed to participate in the trial one time only. A rationale for the choice of sample size is provided in [Section 8.2](#) of this protocol.

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

5.2 Inclusion Criteria

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

1. Have provided written informed consent.
2. Generally healthy males or non-pregnant females, of any race or ethnicity, who are at least 18 years of age at the time of screening;
3. Have a clinical diagnosis of plaque psoriasis (psoriasis vulgaris) of at least 6 months duration that involves the trunk and/or limbs that is amenable to topical treatment with a maximum of 100 g of trial medication per week.
4. Have a PGA of disease severity of mild or moderate on the body (trunk and/or limbs);
5. An mPASI score of at least 2;
6. Have a treatment area involving 2- 30% of the body surface area (BSA);
7. Female subjects must be of either:
 - Non-childbearing potential, i.e., post-menopausal for at least 1 year or have a confirmed clinical history of sterility (e.g., hysterectomy or tubal ligation) or,
 - Childbearing potential with a negative urine pregnancy test prior to initiation of trial treatment, to rule out pregnancy.
8. Female subjects of childbearing potential must be willing to use effective contraception at trial entry and until completion. Effective contraception is defined as follows:
 - oral/implant/injectable/transdermal/ estrogenic vaginal ring contraceptives, intrauterine device, condom with spermicide, diaphragm with spermicide;
 - abstinence or partner's vasectomy are acceptable if the female agrees to implement one of the other acceptable methods of birth control if these conditions do not any longer apply.

5.3 Exclusion Criteria

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

-
1. Current diagnosis of unstable forms of psoriasis, including guttate, erythrodermic or pustular psoriasis;
 2. Other inflammatory skin disease in the treatment area that may confound the evaluation of the psoriasis vulgaris (e.g., atopic dermatitis, contact dermatitis, tinea corporis);
 3. Presence of pigmentation, extensive scarring, pigmented lesions or sunburn in the treatment areas, which could interfere with the rating of efficacy parameters;
 4. Planned excessive or prolonged exposure to either natural or artificial sunlight, including tanning booths, sun lamps, etc;
 5. History of hypersensitivity to any component of the test product or reference product;
 6. Current or past history of hypercalcemia, vitamin D toxicity, severe renal insufficiency, or severe hepatic disorders;
 7. Females who are pregnant, breast feeding, or planning a pregnancy;
 8. Systemic treatment with biological therapies, whether marketed or not, with a possible effect on psoriasis vulgaris within the following time periods prior to Visit 1/Baseline and during the trial:
 - Etanercept – within 4 weeks prior to randomisation,
 - Adalimumab, Alefacept, Infliximab – within 8 weeks prior to randomisation,
 - Ustekinumab – within 16 weeks prior to randomisation,
 - Other products – within 4 weeks/5 half-lives prior to randomisation (whichever was longer).
 9. Use of systemic treatments that suppress the immune system (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 baseline visit and during the trial;
 10. Use of phototherapy (psoralen + ultraviolet A radiation [PUVA] and ultraviolet B radiation [UVB]) within 4 weeks prior to Visit 1/Baseline and during the trial;
 11. Use of topical treatments (e.g., corticosteroids, vitamin D analogs, retinoids, PDE4 inhibitors, salicylic acid, pimecrolimus, tacrolimus, anthralin, tar), except for emollients and non-medicated shampoos, with a possible effect on psoriasis within 2 weeks prior to Visit 1/Baseline;
 12. Have clinical signs of skin infection with bacteria, viruses, or fungi;
 13. Known Human Immunodeficiency Virus (HIV) infection
 14. Have any chronic or acute medical condition that, in the opinion of the investigator, may pose a risk to the safety of the subject, or may interfere with the assessment of safety or efficacy in this trial;

15. Require the use of any concomitant medication that, in the investigator's opinion, has the potential to cause an adverse effect when given with the investigational product (IP) or will interfere with the interpretation of the trial results;
16. Initiation of, or expected changes to, concomitant medication that may affect psoriasis (e.g., beta-blockers, chloroquines, lithium, and angiotensin converting enzyme [ACE] inhibitors);
17. Participation in another clinical trial or received an investigational product or non-marketed drug substances within 30 days prior to screening.
18. In the opinion of the investigator, the subject is unlikely to comply with the clinical trial protocol.

5.4 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 investigator should advise the subject on follow-up safety evaluations.

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

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

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

If a subject withdraws from the trial, all efforts will be made to complete a final evaluation if possible. The withdrawal procedures for subjects who withdraw during the treatment period are the same as those for the End of Treatment visit (Visit 6/Week 8). Subjects who withdraw after Visit 6 (Week 8) are to undergo the Visit 7 (Week 10) procedures.

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

5.5 Replacement Policy

After trial enrolment has been completed, subjects who prematurely discontinue the trial after randomisation will not be replaced.

6.0 TRIAL TREATMENTS

6.1 Investigational Product

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

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

6.2 Active Comparator Product

The active comparator is a marketed CAL/BDP gel/topical suspension, w/w 0.005%/0.064%, approved in the US as Taclonex[®] Topical Suspension and in the rest of the world as Dovobet[®] Gel /Daivobet[®] Gel. For this phase 3 trial, the reference product will be sourced in the US.

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

6.3 Dosing Regimen

Subjects must apply the trial product topically once daily preferable in the evening to affected areas on the trunk (including the neck) and/or limbs, i.e., arms (including the back of the hands) and legs (including the buttocks and the top of the feet) for 8 weeks. The face, scalp, genitals and intertriginous areas should not be treated with the IP.

Subjects are to record the date and time of application in the subject diary. The weekly dose is not to exceed 100 g, and the treated area should not exceed 30% of the BSA. It is preferable that no trial product will be applied within 4 hours of on-treatment trial visits.

Detailed application instructions will be provided in the subject instructions.

6.4 Dose Modification

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

6.5 Packaging, Labeling, and Storage

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

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

The, MC2-01 cream and MC2-01 cream vehicle, will be supplied to the clinical site(s) as tubes containing 60 g of product. The MC2-01 cream and MC2-01 cream vehicle are to be protected from light and 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.

The active comparator will be supplied to the clinical site(s) as bottles containing 60 g of product. The active comparator is to be protected from light and stored below 25°C (below 77°F), however the product must not be refrigerated.

6.6 Assignment to Treatment

6.6.1 Randomisation

Randomisation will be performed using a validated system that automates the random assignment of treatment groups to randomisation numbers. Treatment assignment will be via a central interactive web response (IWR) system in accordance with a pre-planned computer-generated randomisation schedule in a 3:1:3 ratio (MC2-01 cream: MC2-01 cream vehicle: active comparator).

Randomisation will be performed stratified by baseline severity and study site. The central randomisation procedure will limit the number of subjects with mild disease (based on the PGA) to 30% of the total population.

Randomisation data will be kept strictly confidential, accessible only to authorised persons, until the time of un-blinding.

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

6.6.2 Blinding

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

and other trial staff involved in the evaluation of subjects and conduct of the trial. Subjects will be instructed not to reveal the formulation of the IPs to the trial investigator.

For details of the procedure for un-blinding of individual subjects in cases of emergency see [Section 13.1](#).

6.7 Prior, Concomitant, and Prohibited Therapy

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

6.7.1 Washout of Prohibited Medications Prior to Enrollment

A washout period of up to 4 weeks must be completed if the subject has been treated with any medication as specified in the exclusion criteria ([Section 5.3](#)).

6.7.2 Prohibited Medications During the Trial

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

- Use of biological psoriasis therapies;
- Use of oral systemic treatments with a possible effect on psoriasis (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).
- Initiation of dosing or changes in dosage of drugs that are known to have an effect on psoriasis should be avoided. This includes, but is not limited to, beta-blockers, chloroquines, lithium, and ACE inhibitors.
- Emollients on the psoriasis affected areas.

6.7.3 Allowed Treatment on the Face, Scalp, Skin Folds and Genital Skin Only

Subjects may receive laser treatment and use shampoos containing the active ingredients zinc pyrithione, salicylic acid, selenium sulfide, ketoconazole, or tar. Subjects may use an emollient on the face, scalp, skin folds, and genital skin.

6.8 Treatment Compliance

Records of trial product used and dosages administered will be kept during the trial. The trial monitor will note product accountability during site visits and at the completion of the trial.

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

Subjects who are consistently noncompliant will be counseled.

Subjects will be asked to return all used and unused tubes/bottles in the outer box at each visit. All returned tubes/bottles 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

7.1 Trial Procedures

The visit schedule and assessments are summarised in [Table 1-1](#).

7.2 Trial Visits and Assessments

7.2.1 Visit 0/Screening (Day -30 to Day 0)

Screening procedures should be completed no more than 30 days prior to Visit 1/Baseline (Day 0). Visit 0/Screening and Visit 1/Baseline can occur on the same day if no washout of prohibited medications is required. The following screening procedures will be performed at the screening visit:

- Review trial information with subject and obtain written informed consent.
- Review inclusion and exclusion criteria with the subject to determine the subject's eligibility.
- Collect medical history;
 - complete skin disease history including the year the subject was diagnosed with psoriasis
 - other medical/surgical history if the subject received concomitant medication for the condition
 - all other medical/surgical conditions within the last 12 months if the subject did not receive concomitant medication
 - demographic information, including skin phenotype, using the Fitzpatrick classification scale.

-
- Review and record prior medication (used within the previous 30 days) and concomitant medication (medications currently used).
 - Review and record any current medical diagnoses.
 - Perform the following investigator assessments:
 - PGA of disease severity,
 - mPASI scoring,
 - Determination of involved BSA.
 - Perform a urine pregnancy test (UPT) in female subjects of childbearing potential and instruct these female subjects to use approved form(s) of contraception.
 - If a washout period is required, initiate the washout period and schedule the Visit 1/Baseline (Day 0) visit.
 - If the Visit 0/Screening and Visit 1/Baseline (Day 0) procedures are being performed on the same day, perform the procedures specified in [Section 7.2.2](#).

7.2.2 Visit 1/Baseline (Day 0)

If a prior Screening visit did not occur, perform the procedures listed in [Section 7.2.1](#).

The following procedures are to be performed at Visit 1/Baseline:

- Review inclusion and exclusion criteria to ensure that the subject is qualified for trial participation.
- Have the subject perform the following patient-reported outcomes (PROs):
 - SGA of disease severity
 - DLQI questionnaire
 - EQ-5D questionnaire.
 - Itch by NRS
- Perform a physical examination: including height and weight (without shoes) and vital signs (systolic and diastolic blood pressure and heart rate).
- Review and record any medication(s) used in the period since Visit 0/Screening.
- Perform a UPT for females of childbearing potential. Ensure that female subjects of childbearing potential are using approved method(s) of contraception.
- Perform a 12-lead ECG.
- Record any AEs that occurred after the informed consent form was signed.
- Assess treatment area for local skin reactions.
- Collect blood and urine samples for laboratory analyses.

- Perform the following investigator assessments:
 - PGA of disease severity,
 - mPASI scoring,
 - Determination of involved BSA.
- Perform randomisation.
- Dispense the IP and diary. Provide instructions to the subject on IP application.
- Schedule the next visit, at approximately the same time of day as the current visit.

7.2.3 Visit 2/ Week 1 (Day 7 ±2)

- Have the subject perform the following PROs:
 - SGA of disease severity,
 - Psoriasis Treatment Convenience Scale,
 - DLQI questionnaire,
 - Itch by NRS
- Collect the IP from the subject.
- Assess compliance as specified in [Section 6.8](#).
- Review any concomitant medication used since the previous trial visit.
- Perform the following investigator assessments of efficacy:
 - PGA of disease severity,
 - mPASI scoring.
- Assess treatment area for local skin reactions.
- Record any AEs.
- Dispense the IP.
- Schedule the next visit at approximately the same time of day as the current visit.

7.2.4 Telephone Call (TC)/Visit 3/Week 2 (Day 14 ±2)

The subject is contacted by phone for evaluation of safety and adherence to the treatment schedule. Can be an on-site visit if judged necessary by the Investigator.

7.2.5 Visit 4/Week 4 (/Day 28 ±2)

- Have the subject perform the following PROs:
 - SGA of disease severity,
 - DLQI questionnaire,

- EQ-5D questionnaire,
- Psoriasis Treatment Convenience Scale.
- Itch by NRS
- Collect the IP from the subject.
- Assess compliance as specified in [Section 6.8](#).
- Review any concomitant medication used since the previous trial visit.
- Collect blood and urine samples for laboratory analyses.
- Perform a physical examination; including weight without shoes, and measurement of vital signs (systolic and diastolic blood pressure and heart rate).
- Perform a UPT for females of childbearing potential. Ensure that female subjects of childbearing potential are using approved method(s) of contraception.
- Perform a 12-lead ECG.
- Perform the following investigator assessments of efficacy:
 - PGA of the disease severity,
 - mPASI scoring,
 - Determination of involved BSA.
- Assess treatment area for local skin reactions.
- Record any AEs.
- Dispense the IP.
- Schedule the next visit.

7.2.6 Visit 5/Week 6 (Day 42 ±2)

- Have the subject perform the PRO: SGA.
- Collect the IP from the subject.
- Assess compliance as specified in [Section 6.8](#).
- Review any concomitant medication used since the previous trial visit.
- Perform the following investigator assessments of efficacy:
 - PGA of the disease severity,
 - mPASI scoring.
- Assess treatment area for local skin reactions.
- Record any AEs.
- Dispense the IP.

- Schedule the next visit.

7.2.7 Visit 6/Week 8 (End of Treatment) (Day 56 ±2)

- Have the subject perform the following PROs:
 - SGA of disease severity,
 - DLQI questionnaire,
 - EQ-5D questionnaire,
 - Psoriasis Treatment Convenience questionnaire.
 - Itch by NRS
- Collect any unused trial medication, the subject diary, and any other trial materials from the subject.
- Assess compliance as specified in [Section 6.8](#).
- Review any concomitant medication used since the previous trial visit.
- Collect blood and urine samples for laboratory analyses.
- Perform a physical examination; including weight without shoes, and measurement of vital signs (systolic and diastolic blood pressure and heart rate).
- Perform a UPT for females of childbearing potential. Ensure that female subjects of childbearing potential are using approved method(s) of contraception.
- Perform a 12-lead ECG.
- Perform the following investigator assessments of efficacy:
 - PGA of the disease severity,
 - mPASI scoring,
 - Assess involved BSA.
- Assess treatment area for local skin reactions.
- Record any AEs.
- Schedule the next visit.

7.2.8 Visit 7/Week 10 (Follow Up /End of Trial) (Day 70 ±2 days)

- Collect any remaining trial materials from the subject.
- Review any concomitant medication used since the previous trial visit.
- If required (i.e., if albumin-corrected serum calcium is above the reference range at the last on-treatment visit; or if follow-up is required of a previous abnormal and significant laboratory result), collect samples for follow-up laboratory analysis.
- Assess treatment area for local skin reactions.

- Record any AEs.
- Release subject from the trial.

7.2.9 Early Termination

If a subject withdraws from the trial **prior to the Visit 6/Week 8 (End of Treatment) visit**, the subject is to return to the site to return the trial medication. All End of Treatment procedures should be performed.

- Have the subject perform the following PROs:
 - SGA of disease severity,
 - DLQI questionnaire,
 - EQ-5D questionnaire,
 - Psoriasis Treatment Convenience questionnaire.
 - Itch by NRS
- Collect all trial materials from the subject, including unused trial medication and the subject diary.
- Assess compliance as specified in [Section 6.8](#).
- Review any concomitant medication used since the previous trial visit.
- Perform a physical examination; including weight without shoes, and measurement of vital signs (systolic and diastolic blood pressure and heart rate).
- Perform a UPT for females of childbearing potential.
- Perform a 12-lead ECG.
- Collect blood and urine samples for laboratory analyses.
- Perform the following investigator assessments of efficacy:
 - PGA of the disease severity,
 - mPASI scoring,
 - Assess involved BSA.
- Assess treatment area for local skin reactions.
- Record any AEs.

If a subject withdraws from the trial **after the Visit 6/Week 8 (End of Treatment) visit but before the Visit 7/Week 10 (End of Trial) visit**, the subject is to return to the site. The following procedures should be performed:

- Collect all trial materials from the subject, including unused trial medication.

- Review any concomitant medication used since the previous trial visit.
- If required (i.e., if albumin-corrected serum calcium is above the reference range at the last on-treatment visit; or if follow-up is required of a previous abnormal and significant laboratory result), collect samples for follow-up laboratory analysis.
- Record any AEs.
- Assess treatment area for local skin reactions.

7.2.10 Unscheduled Visit and Telephone Calls

An unscheduled visit may be performed at any time during the trial if judged necessary by the Investigator, such as for a severe reaction and clinically significant AE. Details of the event must be recorded in the subject's records.

7.3 Investigator Assessments

The investigator assessments are to be performed by a dermatologist, a physician with at least 1 year of experience in dermatology, or a Physician Assistant with at least 2 year of experience in dermatology. For physicians and Physician Assistants who do not fulfill the requirement regarding dermatological experience and other state licensed professionals who have the ability to diagnose, treat and prescribe medications, the person must be preapproved by the sponsor. The assessments are to be performed as specified in the visit schedule ([Table 1-1](#)).

7.3.1 Physician's Global Assessment

The Physician's Global Assessment (PGA) measures the investigator's or designee's impression of the disease at a single point using a defined, 5-point, static PGA scale (clear, almost clear, mild, moderate, or severe); see [Table 7-1](#). The PGA assessment will represent the *average* lesion severity on the trunk and limbs. 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 7-1 Physician's Global Assessment (PGA)

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

7.3.2 Extent and Severity of Redness, Thickness, and Scaliness

At all visits, the investigator or designee will assess the extent and severity of the subjects' psoriasis using an mPASI scoring system (excluding scalp, face, and flexures).

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

0 = no involvement

1 = < 10%

2 = 10% - 29%

3 = 30% - 49%

4 = 50% - 69%

5 = 70% - 89%

6 = 90% - 100%

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

Redness

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

Thickness

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

Scaliness

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

7.3.3 Body Surface Area Involvement of Psoriasis Vulgaris

The investigator or designee will assess the extent of the subject's psoriatic involvement on the trunk and limbs (excluding scalp, face, and flexures) at the visits specified in [Table 1-1](#).

The total psoriatic involvement on the trunk and limbs (excluding genital and intertriginous areas) will be recorded as a percentage of the total BSA, estimating that the surface of the subject's full, flat palm (including the five digits) correlates to approximately 1% of the total BSA. The purpose of this is to obtain an estimate of the area on the trunk and limbs to be treated with trial medication.

7.3.4 Local Skin Reactions

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

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

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

The intensity of each local skin reaction category is to be graded according to the scale in [Table 7-2](#). 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 7-2](#) and the subject will tell which one to mark.

Signs and symptoms fulfilling the AE definition should be reported as AEs.

Table 7-2 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	Coarse 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 last for up to an hour	Pronounced and last for several hours

7.4 Patient Reported Outcomes (PROs)

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

7.4.1 Subject Global Assessment of disease severity (SGA)

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

- 0 = Clear; no psoriasis symptoms at all.
- 1 = Very mild; very slight psoriasis symptoms that do not interfere with daily life.
- 2 = Mild; slight psoriasis symptoms that interfere with daily life only occasionally.
- 3 = Moderate; definite psoriasis symptoms that interfere with daily life frequently.
- 4 = Severe; intense psoriasis symptoms that interfere or restrict daily life very frequently.

7.4.2 Dermatology Life Quality Index (DLQI)

The DLQI²⁴ is a validated questionnaire consisting of 10 questions relating to the degree to which the subject's skin condition affected their daily activities.

7.4.3 EuroQOL five dimensions questionnaire (EQ-5D)

The EQ-5D is one of the most commonly used generic questionnaires to measure health-related quality of life (QOL)²⁵. It consists of a questionnaire and a visual analog scale (EQ-VAS). The EQ-VAS records the subject's perceptions of their own current overall health and can be used to monitor changes over time. The self-assessment questionnaire is self-reported description of the subject's current health in 5 dimensions i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

7.4.4 The Psoriasis Treatment Convenience Scale

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

7.4.5 Itch by Numerical Rating Scale (Itch by NRS)

To assess the intensity of psoriasis itch, a numerical rating scale is used. The Itch by NRS is a 10-point scale with the ends representing the two extremes of itch intensity, i.e., from 0 (no itch at all) to 10 (worst itch one can imagine). The subject should rate the worst intensity of itch within the previous 24 hours.

7.5 Assessment of Pharmacokinetics (not applicable)

Pharmacokinetics will not be assessed in this trial.

7.6 Assessment of Safety

7.6.1 Adverse Events

7.6.1.1 Adverse Events Assessments

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

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

Any AE that meet the serious criteria must be reported on the eCRF and on a separate SAEs report form. SAEs must be reported to the United BioSource Corporation (UBC) within 24 hours of awareness.

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

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

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

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

7.6.1.2 Timing

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

7.6.1.3 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).

7.6.1.4 Relationship of an Adverse Event to Trial Treatment

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

Not Related	The AE is clearly explained by another cause not related to the trial product administration; the temporal relationship of the AE to IP administration makes a causal relationship unlikely, or, concomitant medication, therapeutics interventions, or underlying condition provide a sufficient explanation for the observed AE
Possibly Related	The AE and administration of trial product are temporally related, but the AE can be explained equally well by causes other than the trial product administration
Probably Related	The AE and use of trial product are temporally related, and the AE is more likely explained by trial product administration than by other causes
Definitely Related	The AE and trial product administration are related in time, and a direct association can be demonstrated. Concomitant medication, therapeutics interventions, or underlying conditions do not provide a sufficient explanation for the observed AE

7.6.1.5 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 Brochure²⁶ (for MC2-01 cream) or Taclonex[®] Topical Suspension prescribing information²³ (for active comparator).

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

7.6.1.6 Trial Medication Overdose

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

The maximum weekly dose should not exceed 100 g, and the treated area should not be >30% of the body surface area.

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

7.6.1.7 Pregnancy

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

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

7.6.2 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 hospitalization may be considered an SAE when, based on appropriate medical judgment, they may jeopardize 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 hospitalizations that are known at the time of signing the ICF will not be recorded as SAEs, however they will be recorded as AEs only.

Any SAE, whether or not deemed drug-related or expected, must be reported immediately to the MC2 or designee as soon as it becomes known to the investigator and not later than within 24 hours of his/her knowledge of the occurrence of an SAE (see [Section 13.2](#)). The investigator will document such events in the best possible detail on the SAE Report Form.

A suspected unexpected serious adverse reaction (SUSAR) is an SAE that is both unexpected (not consistent with the current Investigator's Brochure for MC2-01²⁶ gel or Taclonex[®] Topical Suspension prescribing information²³) and for which there is evidence to suggest a causal relationship between the drug and the SAE. The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be informed of SUSARS according to local requirements. All investigators participating in the trial will also be notified of unexpected SAEs. The sponsor or designee 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](#).

7.6.3 Safety Laboratory Assessments

Blood and urine samples will be collected for routine safety laboratory tests and urinalysis as specified in the visit schedule ([Table 1-1](#)). Clinical laboratory specimens will be analysed by a central licensed and accredited laboratory facility according to the laboratory's standard operating procedures. The following tests will be performed:

- Serum biochemistry: serum calcium (albumin corrected), serum albumin, serum alkaline phosphatase, serum phosphate, plasma parathyroid hormone.
25-OH Vitamin D, only at Visit 1.
- Urinalysis: urinary calcium, urinary phosphate, urinary calcium:creatinine ratio.
- Pregnancy testing: all female subjects of child-bearing potential will undergo serum/urine pregnancy testing at Screening/Baseline visit(s) as specified in [Section 7.6.4](#).

The investigator may collect additional blood or urine samples to repeat any laboratory test that is abnormal post-dosing and is considered clinically significant. Abnormal laboratory results at the last scheduled visit may require additional collection of samples on an “as needed” basis until: a) the values return to the baseline value, b) the values are within normal limits, c) the values are clinically stable, or d) the investigator determines that further follow-up is unnecessary. The investigator will record the date and time of all additional samples collected. If the investigator establishes a clear explanation for the laboratory abnormality, he or she will record this explanation in the eCRF.

If serum calcium is above the reference range at Visit 6/Week 8 visit, a follow-up test must be performed at the next visit (Visit 7/Week 10).

7.6.4 Pregnancy Testing

Female subjects of child-bearing potential will undergo a routine urine pregnancy test (UPT) at the Visit 0/Screening and/or Visit 1/Baseline before any trial-specific procedures are performed. If the UPT is positive, the subject will not be permitted to enroll in the trial.

Routine UPTs will be repeated at Visit 4/Week 4 and Visit 6/Week 8/End of Treatment (or Early Termination). At the investigator’s discretion, additional testing for pregnancy may be performed for verification purposes. If there is a suspicion of pregnancy at any time during the trial, a urine sample will be obtained and tested. Should a subject become pregnant during the trial, treatment must be discontinued.

All pregnancies should be immediately reported to the sponsor or designee and followed through to resolution (i.e., delivery, miscarriage, or abortion). The report should be submitted within the same timelines as an SAE (within 24 hours of knowledge), although a pregnancy per se is not considered an SAE.

7.6.5 Vital Signs

At Visit 1/Baseline, Visit 4/Week 4 and Visit 6/Week 8, the investigator or designee will take measurements of vital signs, including blood pressure and heart rate (pulse) with the subject in the sitting position with approximately 5 minutes rest prior to measurement. The same arm is to be used for all measurements.

7.6.6 Physical Examination

At Visit 1/Baseline, Visit 4/Week 4, and Visit 6/Week 8, the investigator or designee will complete a general physical examination including measurements of height (at Screening only) and weight (with indoor clothing and without shoes).

During the trial, any new clinically significant findings of signs/symptoms that could indicate systemic safety will be reported as AEs. Any signs/symptoms of hypercalcemia or suppression of HPA axis will be carefully monitored and if necessary the subject will be withdrawn from the trial.

The Fitzpatrick skin type will be assessed according to the classification scheme in [Table 7-3](#).

Table 7-3 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

7.6.7 Electrocardiogram

A 12-lead ECG will be recorded at Visit 1 (Day 0/Baseline), Visit 4 (Week 4), and Visit 6 (Week 8) or the Early Termination visit if the subject withdraws prior to Week 8. Recording will take place after 5 min rest in supine position.

All printed ECGs will be evaluated by the investigator or a designee, and will also be sent to a central laboratory for interpretation. Additional (unscheduled) ECGs can be recorded for safety reasons at any time based on the judgment of the investigator.

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

7.7 Appropriateness of Measurements

The assessments to be used in this trial are the standardised and most widely accepted methods for evaluating safety and efficacy in studies of psoriasis.

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 and un-blinded. Any changes to the methods described in the final SAP will be described and justified in the clinical trial report. All statistical analyses will be performed using SAS statistical software (Version 9.2 or higher). Statistical significance will be tested at the 2-sided 5% level unless otherwise specified.

Subjects will be randomised in a 3:1:3 ratio (MC2-01 cream: MC2-01 cream vehicle: active comparator), stratifying by centre and baseline severity. The aim is to randomise 14 subjects or more at each site. 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. Trial sites yielding fewer than 14 subjects overall will be combined in order of geographical proximity. The exact composition of these “analysis sites” will be determined and documented prior to breaking the trial blind. To investigate the homogeneity of the primary efficacy outcome across analysis sites, a Forest plot will be prepared showing the PGA treatment success rate difference of each analysis site. Outliers will be investigated and sensitivity analysis excluding outliers may be performed if deemed necessary.

8.2 Sample Size and Power Considerations

The primary endpoint is the proportion of subjects who achieve a minimum 2-point decrease from Baseline in PGA at Week 8. The primary endpoint will be used for the non-inferiority evaluation.

The sample size calculation is based on the non-inferiority margin for the difference in PGA response.

Non-inferiority margin:

The non-inferiority margin was determined according to the draft Food and Drug Administration (FDA)-Guidance for Industry: Non-inferiority Clinical Trials²⁷ as a fixed margin.

A summary of responders, based on the PGA, at Week 8 from 3 randomised trials of calcipotriene and betamethasone dipropionate gel^{11;28;29} is shown below in order to determine the statistical margin M1 and the clinical margin M2. The clinical margin M2 is used in the determination of sample size.

Trial	Daivobet		Vehicle		Daivobet - Vehicle	
	N	PGA success %	N	PGA success %	%	99% CI
Menter et al, 2013 ²⁸	482	29.0	95	6.3	22.7	(14.4, 31.1)
Langley et al, 2011 ²⁹	183	39.9	91	5.5	34.4	(23.2, 45.6)
Fleming et al, 2010 ¹¹	162	27.2	40	0	27.2	(18.2, 36.2)
Total					26.2	(19.9, 32.6)

CI = confidence interval

The lower 99%-confidence limit of the response difference between calcipotriene/betamethasone dipropionate gel and vehicle was calculated to be 19.9%. Therefore, the prespecified M1 margin was determined to be 19.9%, a conservative choice for the active control effect size. The largest loss of effect that would be clinically acceptable (M2) is set to 10% points.

Assumptions for the non-inferiority comparison:

- The lower non-inferiority boundary for M1 is set to 19.9% for the difference between vehicle and active comparator in response rates according to PGA.
- The lower non-inferiority boundary for M2 is set to 10% points for the difference between MC2-01 cream and active comparator in response rates according to PGA.

Assumptions for sample size calculation:

- The response of active comparator is assumed to be 30%.
- The absolute difference of MC2-01 cream and active comparator is assumed to favor MC2-01 cream by at least 2.5 percentage points. The treatment difference between MC2-01 cream and active comparator was estimated based on preliminary results from a plaque psoriasis trial that showed slightly better efficacy for MC2-01 cream compared with active comparator.
- The power should be at least 90%.
- The error probability is set to 0.05 for a 2-sided test.

Under these assumptions, a sample size of N=305 per active treatment group is calculated. Assuming 90% completion rate of the randomised subjects, a total sample size of N=339 per active treatment group is required to be randomised.

The comparison to vehicle to show superiority of MC2-01 cream and active comparator will need N=103 per treatment group under the assumption of a vehicle responder-rate of 11%, a response rate of at least 30% for the MC2-01 cream and active comparator, and 90% power. Following a 3:1:3 randomisation ratio, 113 subjects will be randomised to receive the MC2-01 vehicle cream (assuming a 90% completion rate).

A total enrolment of approximately 791 subjects is planned to have approximately 712 completed subjects.

8.3 Analysis Populations

The analysis populations are defined as follows:

- Intent to Treat (ITT) population will include all randomised subjects.
- Per Protocol (PP) population will include subjects in the ITT population who complete the trial without any major protocol violations. The composition of the PP population will be determined and documented in blind reviews of the database conducted prior to unblinding the trial database. Subjects may be excluded from PP population if any of the following criteria are met.
 - Failure to meet key Inclusion/Exclusion criteria; I.e. violation of inclusion/exclusion criteria that according to medical judgement may impact the primary endpoint analysis;
 - Usage of restricted medications/treatments; I.e. medications/treatments that according to medical judgement may impact the primary endpoint analysis;
 - Nonadherence to the visit schedule; at Week 8 \pm 7 days
 - Noncompliance with the trial treatment regimen; adherence to the treatment schedule defined as application of IP as specified by the investigator for at least 80% of the days from Week 4 to Week 8
 - Noncompliance with the trial treatment regimen; adherence to the treatment schedule is defined as application of IP as per subject diary for at least 80% of the days from Day 1 to Week 8;
- Safety population will include all subjects who were randomised and dispensed the trial medication at Randomisation/Day 0, excluding subjects who return all the trial medication unused.

The ITT and PP Population will be used for the analyses of the primary efficacy endpoint. The PP population will be considered as the primary population for analyses of therapeutic non-inferiority

of MC2-01 vs active comparator. The ITT analysis will be considered as the primary population for the analysis of superiority of MC2-01 and active comparator vs. vehicle. A similar approach will be used for the secondary efficacy endpoints. The Safety Population will be used for the analyses of safety endpoints.

8.4 Handling of Missing Data

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

For analyses using the ITT population, a variety of methods will be used to impute missing primary efficacy endpoints, including multiple imputation (MI), last-observation-carried forward (LOCF), baseline-observation-carried-forward (BOCF), and non-responder imputation (NRI). MI will be the primary imputation method. Sensitivity analyses utilising LOCF, BOCF, and NRI will also be performed to assess the robustness of imputation assumptions.

Multiple imputation: Post-baseline missing PGA data will be multiply imputed separately for each treatment group using a Markov Chain Monte Carlo (MCMC) method to obtain a monotone missing data pattern after which imputation is done using a monotone regression method. The imputation model will include: duration (days) of psoriasis, prior systemic biologic use for psoriasis (yes/no), baseline PGA score, and PGA scores at weeks 1, 4, 6, and 8. The number of imputations will be set to 100. Similar multiple imputation methods will be used for other efficacy endpoints.

8.5 Analysis of Efficacy

8.5.1 Primary Efficacy Endpoint(s)

The primary efficacy endpoint is the proportion of subjects in each treatment group with ‘treatment success’ at Week 8, defined as a minimum 2-point decrease from Baseline to Week 8 on the Physician’s Global Assessment (PGA) of disease severity on the trunk and limbs; i.e. 0 (clear) or 1 (almost clear) disease for subjects with moderate disease at Baseline; or a score of 0 (clear) for subjects with, a score of mild disease at Baseline.

8.5.1.1 Analysis of the primary endpoint

Superiority Analysis

The primary analysis of superiority will be based on the ITT population using multiple imputation

The PGA response rate for MC2-01 cream and for active comparator at Week 8 will first be compared with that for MC2-01 cream vehicle at Week 8 for a superiority evaluation. The superiority will be tested using a logistic model with treatment, baseline value of PGA and analysis site as independent variables. Superiority will be achieved at the 5% significance level ($p < 0.05$; two-sided). For the superiority analysis using MI, the estimate and standard error of the log odds

ratio will be evaluated for each of the multiple imputed datasets and combined in PROC MIANALYZE.

Non-inferiority (NI) analysis

If and only if superiority to MC2 cream vehicle for both MC2-01 cream and for active comparator can be claimed at the 5% significance level, the non-inferiority (NI) analysis of the primary endpoint will be conducted based on the PP Population. The PGA success rate of MC2-01 cream at Week 8 will be compared with that of active comparator at Week 8, using a therapeutic non-inferiority margin of 10% points.

The percentage of subjects in each group with treatment response will be calculated along with its 95% confidence interval (CI) using normal approximation. A 95%, 2-sided CI on the difference between MC2-01 cream and active comparator will be computed using normal approximation. MC2-01 will be considered non-inferior to Active Comparator if the lower bound of the 2-sided 95% CI is $\geq -10\%$ points.

8.5.1.2 Sensitivity Analyses

As sensitivity analyses, the analyses of superiority will also be made based on the ITT population using other imputation methods than MI (LOCF, BOCF, NRI). Further an analysis based on the PP population and using complete case analysis with no imputation of missing data will be made.

The non-inferiority analysis of the primary endpoint will also be performed based on the ITT population using a variety of imputation methods as sensitivity analyses (MI, LOCF, BOCF, NRI)

For the sensitivity non-inferiority analysis using MI, the treatment difference will be evaluated for each of the multiple imputed datasets using PROC FREQ with RISKDIFF option. The estimates and standard errors of the response rate difference based on the imputed datasets will be combined by applying Rubin's rules in PROC MIANALYZE and the 95% CI of the difference will be computed.

8.5.2 Secondary Efficacy Endpoints

Secondary endpoints are the following:

- Percentage change from Baseline in the mPASI score at Week 8;
 - Superiority evaluation: The percentage change will be compared between MC2-01 cream vs. vehicle and active comparator vs. vehicle for superiority using an analysis of covariance (ANCOVA) model with treatment, baseline PGA severity (mild/moderate), baseline mPASI and study site as independent variables. (See derivation of alpha level below). The analysis will be based on the ITT population using multiple imputation.

- Non-inferiority evaluation: The percentage change will be compared between MC2-01 cream and active comparator using a similar model as for the evaluation of superiority. Non-inferiority will be claimed if the lower limit of the relevant two-sided CI (see derivation of alpha level below), derived from the difference in LSMEANS, will be $\geq -10\%$. The analysis will be based on the PP population with no imputation of missing data.
- Subject assessment of treatment convenience at Week 8 using a Psoriasis Treatment Convenience Scale (PCTS)
 - Superiority evaluation: PCTS will be compared for superiority between MC2-01 cream and active comparator using an ANOVA model with treatment and trial site as independent variables; superiority will be claimed if the lower limit of the relevant two-sided CI (see derivation of alpha level below), derived from the difference in LSMEANS, will be ≥ 0 . The analysis will be based on the ITT population. PCTS score will be calculated as sum of questions 1 to 5. The score is to be calculated if at most two of the questions have missing answers, in which case the missing answers will be imputed from the mean of the answered questions. If more than two questions have missing answers, the PCTS score will be considered as missing. A PCTS score is defined as valid, if subjects have used the study medication at some point within 7 days prior to the day of the assessment. A PCTS score is considered as invalid if subjects have discontinued study medication for more than 7 days prior to the day of assessment. Invalid measurements will not be applied in the analysis of that visit. Missing and invalid PCTS scores will be imputed using the last valid measure prior to the visit. This approach corresponds to a ‘PCTS while on treatment’ estimand. The PCTS will be psychometrically tested in the trial.
- Change in itch intensity assessed on a numerical rating scale (Itch by NRS) from baseline to Week 4:
 - Superiority evaluation. (MC2-01 cream vs MC2-01 cream vehicle). Superiority between MC2-01 cream and vehicle will be assessed by using an ANCOVA model with treatment, baseline PGA severity (mild/moderate), baseline Itch by NRS value and analysis site as independent variables. The primary analysis will be based on the ITT population, using multiple imputation
- Percentage of subjects with four-point improvement on the numerical rating scale (Itch by NRS) from baseline to Week 4
 - Superiority evaluation (MC2-01 cream vs MC2-01 cream vehicle). The analysis is made on the subgroup of subjects from the ITT populations with Itch (assessed by

NRS) ≥ 4 at baseline. Superiority between MC2-01 cream and vehicle will be assessed by using a logistic regression model with treatment, baseline PGA severity (mild/moderate), baseline Itch by NRS value and analysis site as independent variables. Missing data will be imputed using multiple imputations.

The global Type-I error will be controlled by the following testing procedure:

1. Secondary endpoints will be tested only if the primary endpoint will reject the Null-hypothesis;
2. The two secondary endpoints ‘Percentage reduction from Baseline in the mPASI score at Week 8, and Subject assessment of treatment convenience at Week 8 using a Psoriasis Treatment Convenience Scale will be tested with a loopback procedure³⁰ with initial error probability weights 2/3 for H1 (mPASI) and 1/3 for H2 (subject assessment of treatment convenience), resulting in $\alpha_1=0.0333$ and $\alpha_2=0.0167$. If any of the Null-hypotheses can be rejected, the respective error probability will be shuffled to the other hypothesis
3. If and only if both non-inferiority of MC2-01 to active comparator with respect to Percentage reduction from Baseline in mPASI as well as superiority of MC2-01 vs. active comparator with respect to Psoriasis treatment convenience scale has been demonstrated, superiority of MC2-01 vs vehicle with respect to the below endpoints will be tested in a hierarchical manner based on a significance level of 5%:
 - Change in itch intensity assessed on a numerical rating scale (Itch by NRS) from baseline to Week 4
 - Percentage of subjects with four-point improvement on the numerical rating scale (Itch by NRS) from baseline to Week 4 (In the subgroup of subjects with an NRS score ≥ 4 at baseline)

All secondary endpoints will be described using summary statistics. For mPASI and NRS, absolute values, absolute reduction, and percentage reduction from baseline will be summarised using mean, median, SD, quartiles and ranges for each treatment group by visit. Frequency counts and percentages of NRS 4-point improvement responders will be provided for each treatment group by visit. For PTCS score, absolute values will be summarized using descriptive statistics for each treatment group by visit.

8.5.3 Other Endpoints

Other endpoints will be the following:

Efficacy

- PGA success rate at Week 4;
- Percentage change from Baseline in the mPASI score at Week 4;
- Number of subjects with PASI 50 (at least 50% reduction in mPASI from Baseline) at Week 4 and Week 8;
- Number of subjects with PASI 75 (at least 75% reduction in mPASI from Baseline) at Week 4 and Week 8.
- Change from Baseline in SGA at Week 4 and Week 8;

Patient reported outcomes

- Change DLQI score at Week 4 and Week 8; The DLQI will be scored according to the developer instructions. Missing values, if any will be incorporated based on the developers scoring instructions. The DLQI will also be summarised by the following domains: symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment.
- Change in EQ-5D score at Week 4 and Week 8. The EQ-5D will be scored according to the developer instructions
- Change in itch intensity assessed on a numerical rating scale (Itch by NRS) from baseline to week 1 as well as from baseline to Week 8 (MC2-01 cream vs MC2-01 cream vehicle)

Other efficacy endpoints (PASI 50 and PASI 75) will be analysed following the same method as described for the primary efficacy analysis, except that no formal non-inferiority test will be conducted.

Change from Baseline in SGA at Week 4 and Week 8 will be analysed using an ANCOVA model with treatment, baseline PGA severity (mild/moderate) baseline SGA and study site as independent variable. The subject convenience data will be summarised using summary statistics for each treatment group.

The Patient reported outcomes DLQI, EQ-5D, and Itch by NRS will be analysed using an ANCOVA model with treatment, baseline PGA severity (mild/moderate), analysis site and respective baseline patient reported outcome as independent variables.

Statistical analyses for the other endpoints will be exploratory only and not for statistical inference.

8.6 Analysis of Safety

The assessment of safety will be based mainly on the frequency of AEs and on the number of laboratory values that fall outside of predetermined ranges. AEs will be presented in data listings and summarised by frequency and severity for each treatment group. 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.

8.6.1 Adverse Events

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

8.6.2 Local Skin Reaction Assessment

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

The LSR intensities, scored as 0=none, 1=mild, 2=moderate, or 3=severe, will be summarised by trial visit for each of the LSR categories.

For the LSR sum score, the Area Under the Curve (AUC) will be calculated for each subject: 1) from Baseline to Week 1; 2) from beginning of Week 1 to end of Week 4; and 3) from beginning of Week 5 to End of Trial and 4) from Baseline to End of Trial. These parameters will be compared between treatment groups using ANOVA.

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

8.6.3 Other safety variables

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

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

Clinical laboratory data will be summarised by presenting shift tables using extended normal ranges (baseline to most extreme post-baseline value), by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges), and by the flagging of notable values in data listings.

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

9.0 CHANGES IN THE PLANNED TRIAL

9.1 Protocol Amendments

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

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

9.2 Termination or Suspension of the Trial

MC2 reserves the right to terminate or suspend the trial at any time. In case of premature termination or suspension of the trial, the contract research organization (CRO) project manager will promptly inform the investigators, regulatory authorities, and IRBs about the premature termination or suspension, including the reason for it. In terminating the trial, MC2 and the investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

10.0 DATA HANDLING AND RECORD KEEPING

10.1 Recording of Data

10.1.1 Source Documents

Source data are all the information in original records and copies of original records of clinical findings, observations, or other activities in the trial, which are necessary for the reconstruction and evaluation of the trial. The identification of any data to be recorded directly on the eCRFs is to be considered source data.

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

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

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

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

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

10.1.2 Case Report Forms

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

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

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

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

10.2 Retention of Documents

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

11.0 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Direct Access to Source Documents

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

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

11.2 Monitoring Procedures

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

11.3 Audit and Inspection

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

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

12.0 ETHICS

12.1 Ethical Conduct of the Trial

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

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

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

12.3 Subject Information and Consent

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

12.4 Disclosure and Confidentiality

12.5 Confidentiality of Trial Documentation

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

12.6 Privacy of Individual Health Information

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

13.0 EMERGENCY PROCEDURES

13.1 Emergency Un-blinding

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

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

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

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

13.2 Reporting of Serious Adverse Events and Pregnancies

13.2.1 Contact Person(s) and Number(s)

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

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

13.2.2 Reporting Procedures

Serious Adverse Events

For each SAE, the investigator will complete a Serious Adverse Event Report Form and assess the relationship of each SAE to trial treatment. The completed form(s) should be sent electronically to the UBC using the SAE Reporting fax number within 24 hours of first knowledge of the SAE.

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

14.0 INSURANCE

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

15.0 PUBLICATION POLICY

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

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

16.0 REFERENCE LIST

- (1) Kurd SK, Gelfand JM. The prevalence of previously diagnosed and undiagnosed psoriasis in US adults: results from NHANES 2003-2004. *J Am Acad Dermatol* 2009;60:218-224.
- (2) Chandran V, Raychaudhuri SP. Geoepidemiology and environmental factors of psoriasis and psoriatic arthritis. *J Autoimmun* 2010;34:J314-J321.
- (3) Schafer T. Epidemiology of psoriasis. Review and the German perspective. *Dermatology* 2006;212:327-337.
- (4) Nestle FO, Kaplan DH, Barker J. Mechanisms of Disease: Psoriasis. *N Engl J Med* 2009;361:496-509.
- (5) Griffiths CE, Barker J. Pathogenesis and clinical features of psoriasis. *Lancet* 2007;370:263-271.
- (6) Horn EJ, Fox KM, Patel V, Chiou CF, Dann F, Lebwohl M. Association of patient-reported psoriasis severity with income and employment. *J Am Acad Dermatol* 2007;57:963-971.
- (7) Dubertret L, Mrowietz U, Ranki A et al. European patient perspectives on the impact of psoriasis: the EUROPSO patient membership survey. *Br J Dermatol* 2006;155:729-736.
- (8) Rapp SR, Feldman S, Exum ML, Fleischer AB, Jr., Reboussin DM. Psoriasis causes as much disability as other major medical diseases. *J Am Acad Dermatol* 1999;41:401-407.
- (9) Boehncke WH, Boehncke S, Tobin AM, Kirby B. The 'psoriatic march': a concept of how severe psoriasis may drive cardiovascular comorbidity. *Experimental Dermatology* 2011;20:303-307.
- (10) Zanni GR. Psoriasis: issues far more serious than cosmetic. *Consult Pharm* 2012;27:86.
- (11) Fleming C, Ganslandt C, Guenther L et al. Calcipotriol plus betamethasone dipropionate gel compared with its active components in the same vehicle and the vehicle alone in the treatment of psoriasis vulgaris: a randomised, parallel group, double-blind, exploratory study. *Eur J Dermatol* 2010;20:465-471.
- (12) Kaufmann R, Bibby AJ, Bissonnette R et al. A new calcipotriol/betamethasone dipropionate formulation (Daivobet) is an effective once-daily treatment for psoriasis vulgaris. *Dermatology* 2002;205:389-393.

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- (13) Lebwohl M, Tyring S, Bukhalo M et al. Fixed Combination Aerosol Foam Calcipotriene 0.005% (Cal) Plus Betamethasone Dipropionate 0.064% (BD) is More Efficacious than Cal or BD Aerosol Foam Alone for Psoriasis Vulgaris: A Randomized, Double-blind, Multicenter, Three-arm, Phase 2 Study. *J Clin Aesthet Dermatol* 2016;9:34-41.
 - (14) Lovato P, Norsgaard H, Tokura Y, Ropke M. Calcipotriol and betamethasone dipropionate exert additive inhibitory effects on the cytokine expression of inflammatory dendritic cell-Th17 cell axis in psoriasis. *J Dermatol Sci* 2016;81:153-164.
 - (15) Gniadecki R, Gniadecka M, Serup J. Inhibition of glucocorticoid-induced epidermal and dermal atrophy with KH 1060--a potent 20-epi analogue of 1,25-dihydroxyvitamin D3. *Br J Pharmacol* 1994;113:439-444.
 - (16) Norsgaard H, Kurdykowski S, Descargues P et al. Calcipotriol counteracts betamethasone-induced decrease in extracellular matrix components related to skin atrophy. *Arch Dermatol Res* 2014;306:719-729.
 - (17) Menter A, Korman NJ, Elmets CA et al. Guidelines of care for the management of psoriasis and psoriatic arthritis Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. *J Am Acad Dermatol* 2009;60:643-659.
 - (18) Samarasekera E, Sawyer L, Parnham J, Smith CH. Assessment and management of psoriasis: summary of NICE guidance. *BMJ* 2012;345:e6712.
 - (19) Dauden E, Bewley A, Lambert J, Girolomoni G, Cambazard F, Reich K. Expert recommendations: the use of the fixed combination calcipotriol and betamethasone dipropionate gel for the topical treatment of psoriasis. *J Eur Acad Dermatol Venereol* 2014;28 Suppl 2:22-32.
 - (20) Hendriks AG, Keijsers RR, de Jong EM, Seyger MM, van de Kerkhof PC. Efficacy and safety of combinations of first-line topical treatments in chronic plaque psoriasis: a systematic literature review. *J Eur Acad Dermatol Venereol* 2013;27:931-951.
 - (21) Fouere S, Adjadj L, Pawin H. How patients experience psoriasis: results from a European survey. *J Eur Acad Dermatol Venereol* 2005;19 Suppl 3:2-6.
 - (22) Carroll C, Feldman S, Camacho FT, Balkrishnan R. Better medication adherence results in greater improvement in severity of psoriasis. *Br J Dermatol* 2004;151:895-897.
 - (23) FDA. Taclonex Topical Suspension Prescribing Information. 2017. http://www.taclonex.com/pdf/Taclonex_topical_USPI.pdf
 - (24) Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) - simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994;19:210-216.

- (25) Rabin R, de CF. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med* 2001;33:337-343.
- (26) MC2 Therapeutics. Investigational Brochure MC2-01 cream, version 3, 2017 or most current version.
- (27) FDA. Non-Inferiority Clinical Trials to Establish Effectiveness. 2017.
- (28) Menter A, Gold LS, Bukhalo M et al. Calcipotriene plus betamethasone dipropionate topical suspension for the treatment of mild to moderate psoriasis vulgaris on the body: a randomized, double-blind, vehicle-controlled trial. *J Drugs Dermatol* 2013;12:92-98.
- (29) Langley R, Gupta A, Papp K, Wexler D, Osterdal ML, Curcic D. Calcipotriol plus betamethasone dipropionate gel compared with tacalcitol ointment and the gel vehicle alone in patients with psoriasis vulgaris: a randomized, controlled clinical trial. *Dermatology* 2011;222:148-156.
- (30) Wiens BL, Dmitrienko A. The fallback procedure for evaluating a single family of hypotheses. *J Biopharm Stat* 2005;15:929-942.

17.0 APPENDICES

Appendix 1: Contact List of MC2, Protocol Authors, Vendors, and International Coordinating Investigator

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

Sponsor

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

Protocol Author

Linda Stein Gold, MD, International Coordinating Investigator
Barbara Liptak, Medical Writer, Novella
Knud Kragballe, MD, Medical Advisor
Birgitte Vestbjerg, Director Clinical Operation, MC2 Therapeutics
Jin Wei, Manager, Clinical Biostatistics Dermatology Division, Novella

International Coordinating Investigator

Linda Stein Gold, MD
Henry Ford Medical Center – New Center One
Department of Dermatology
3031 West Grand Boulevard, Suite 800
Detroit, MI 48202

Appendix 2: Vendors

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

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

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

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

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

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

CLINICAL TRIAL PROTOCOL APPROVAL FORM

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

Protocol number: MC2-01-C2

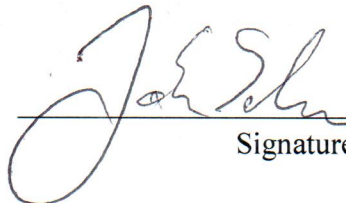
Protocol title: A Randomised, Multicentre, Investigator-Blind, Parallel-Group Trial to Evaluate the Efficacy and Safety of MC2-01 Cream Compared to MC2-01 Cream Vehicle and Active Comparator in Subjects with Mild-to-Moderate Psoriasis Vulgaris

Version: 3.0

Date: 27 February 2018

The following person has approved this clinical trial protocol:

Johan Selmer, MD
VP Medical Affairs
MC2 Therapeutics


28-FEB 2018
Signature and date

CLINICAL TRIAL PROTOCOL APPROVAL FORM

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

Protocol number: MC2-01-C2

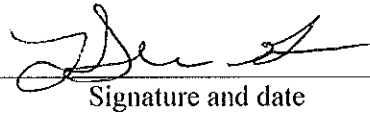
Protocol title: A Randomised, Multicentre, Investigator-Blind, Parallel-Group Trial to Evaluate the Efficacy and Safety of MC2-01 Cream Compared to MC2-01 Cream Vehicle and Active Comparator in Subjects with Mild-to-Moderate Psoriasis Vulgaris

Version: 3.0

Date: 27 February 2018

The following person has approved this clinical trial protocol:

Linda Stein Gold, MD
International Coordinating Investigator
Henry Ford Medical Center



Signature and date

3/1/18

CLINICAL TRIAL PROTOCOL APPROVAL FORM

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

Protocol number: MC2-01-C2

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

Version: 3.0

Date: 27 February 2018

The following person has approved this clinical trial protocol:

Carol Udell
Senior Director, Clinical Data
Management and Biostatistics
Novella

DocuSigned by:
Carol Udell 01-Mar-2018 | 08:07:51

 Signer Name: Carol Udell
Signing Reason: I approve this document
Signing Time: 3/1/2018 5:07:48 AM PST
Signature and date
CE741CD0FE9741ECA29CB39E84B183BB