1 TITLE PAGE

CLINICAL TRIAL PROTOCOL

A RANDOMISED, EVALUATOR BLINDED, WITHIN SUBJECT, SINGLE-CENTRE EVALUATION OF THE VASOCONSTRICTION PROPERTIES OF MC2-01 CREAM, COMPARED TO 5 OTHER CORTICOSTEROIDS IN HEALTHY SUBJECTS

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2 CLINICAL TRIAL PROTOCOL APPROVAL

The following persons have approved this Clinical Trial Protocol, **on behalf of DDS**, by manually signing in the Table below:

Name & Title	Date & Signature
Johan SELMER, MD VP Medical Affairs	

It is the responsibility of the Investigator to approve the Clinical Trial Protocol comprising any subsequent amendment(s).

The **Principal Investigator** has approved this Clinical Trial Protocol by manually signing in the Table below:

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Catherine QUEILLE-ROUSSEL, MD Investigator	

3 TRIAL SYNOPSIS

Clinical Trial Title: A Randomized, Evaluator Blinded, Within Subject, Single-Centre evaluation of the Vasoconstriction Properties of MC2-01 cream, compared to 5 Other Corticosteroids in Healthy Subjects.

Short Title :
A vasoconstriction test trial with a MC2-01 cream (ranking trial).

Sponsor Trial Number:	MC2-01-C4
Clinical Trial Phase:	Phase 1
Investigator:	Dr Catherine QUEILLE-ROUSSEL
Co-Investigator:	Dr Bernard WAVRANT
Clinical Trial Population:	Healthy subjects, males and females, aged 18 to 50 years old.
Clinical Trial Objectives:	The objective of this trial is to compare the vasoconstriction potential (skin blanching effect) of MC2-01 cream with Clobex 0.05% (clobetasol propionate) lotion, Betamethasone Dipropionate (Augmented) 0.05% (betamethasone dipropionate) cream, Triamcinolone Acetonide 0.1% (triamcinolone acetonide) cream, Locoid® 0.1% (hydrocortisone butyrate) cream, Desowen® 0.05% (desonide) cream and MC2-01 vehicle using the human skin blanching test (McKenzie-Stoughton's test).
Background:	Topically applied corticosteroids elicit a pharmacologic activity (blanching) viewed by many as being "vasoconstrictive" in nature. The skin blanching effect was first described by Mc Kenzie and Stoughton (1) in 1962. This pharmacodynamic response has been correlated with the clinical efficacy of the product in psoriasis (2) and used for years to determine the clinical potency of topical corticosteroid formulations and to classify them within the US topical steroid potency classification. MC2 Therapeutics has developed an innovative dermal pharmaceutical formulation containing calcipotriol (CAL) 0.005 % w/w (50 µg/g) and betamethasone dipropionate (BDP) 0.064 % w/w (0.5 mg/g as betamethasone), MC2-01 cream to ease local application of pharmaceuticals and to significantly enhance local cutaneous penetration of the active ingredients. Currently marketed products are restricted to non- oil-based formulations as calcipotriol and betamethasone are characterized by having a potential incompatibility to exist together in an environment, since calcipotriol requires basic conditions to maintain stability while betamethasone requires acidic conditions.

	MC2-01 cream has been formulated using the PAD™ Technology allowing sufficient protection of the drug substances from degradation during storage.
Clinical Hypothesis:	The blanching effect of the MC2-01 cream is expected to be lower than Clobex, not significantly different from Betamethasone Dipropionate (Augmented) cream and higher than the other references.
Clinical Trial Design:	A single center, single application, randomized, investigator blinded, active and vehicle controlled, intra-individual comparison in healthy volunteers. The subjects will be screened within 2 weeks prior to the Day 1 and then receive a single application of investigational and reference products. All applications will be done on site by a qualified person. The Investigational products will be tested under non-occlusive condition for 16 hours. Clobex lotion (Galderma Labs LP), Betamethasone Dipropionate (Augmented) cream (Taro Pharmaceuticals), Locoid® cream (Precision dermatology), Desowen® cream (Galderma Labs LP) and Triamcinolone Acetonide (Ascend Laboratories LLC) will be used as positive controls. The MC2-01 matching vehicle will be used as negative control. Hence, the seven treatments will be randomly allocated to seven test sites of 2.2 cm diameter on the anterior surface of the forearms (from the antecubital fossa to the wrist). The skin blanching will be assessed by visual scoring.
Methodology:	The trial will consist of a screening phase, a test phase of 2 days, and, if applicable, a follow-up phase. <u>Screening Phase (Day-15 to Day-1):</u> Within 15 days before treatment a screening visit for trial eligibility of the subjects will take place: Medical history and concomitants therapies Physical examination, record of vital signs Urine pregnancy test for female subjects of child-bearing potential Check of inclusion/exclusion criteria Pre-test of blanching response <u>Test Phase (Day 1 to Day 2):</u> Subjects will receive investigational and reference products (matching vehicle and positive references) on Day 1.

	At Day 1: Will be performed: - Re-check of inclusion/exclusion criteria - Urine pregnancy test for female subjects of child-bearing potential - Selection of seven tests sites - Application of the products under non-occluded conditions for 16 hours. **At Day 2:** - Removal of the products - Visual assessments of the skin blanching by 2 trained observers 2 hours after the removal. - Assessment of the local tolerability. During the treatment phase local and systemic adverse events will be reported on an ongoing basis. <u>Follow-up:</u> If an adverse event (serious or non-serious), classified as reasonable_possible related to the trial medication is ongoing at the subject's last visit, a follow-up visit/contact will take place 14 (±2) days after that visit.
Total number of subjects (Planned):	60 subjects will be screened in order to have 36 subjects randomized and at least 30 subjects completed.
Number of clinical trial centers (Planned):	Single center
Region / country involved (Planned):	France
Clinical trial duration:	2 months
Duration of subject participation:	Two days (plus the screening period and the follow-up phase).

Inclusion criteria:

1. Male or female subjects, aged 18 years to 50 years old, having signed and dated an informed consent,
2. Non-smoker subjects,
3. Subjects demonstrating adequate vasoconstriction to Betamethasone Dipropionate (Augmented) cream within 15 days prior to dosing (unoccluded application of Betamethasone Dipropionate (Augmented) cream for 4-6 hours must show a visual score of skin blanching of at least one unit (visual scale (0-4)),
4. Subjects without any signs of skin irritation/disease/disorders/symptoms or blemishes on test sites (e.g. erythema, dryness, roughness, scaling, scars, moles, sunburn),
5. Female subject of non-child bearing potential, defined as surgically sterile or post-menopausal (at least one year post cessation of menses),
6. Female of childbearing potential who has been, in the opinion of the Investigator, using an approved method of birth control (e.g. oral contraception pill or patch, intra-uterine devices, contraceptive implants or vaginal rings, condoms, bilateral tubal ligation) at trial entry and agree to continue until the end of last trial visit.
7. Female subjects of childbearing potential must have a negative urine pregnancy test at screening visit and at Day 1 to continue,
8. Subjects willing and able to follow all the trial procedures and complete the whole trial,
9. Subjects affiliated to a social security system

Exclusion criteria:

1. Female subjects who are breastfeeding,
2. Use of topical corticosteroids on the test areas (forearms) within 4 weeks prior to the screening phase,
3. Use of systemic drugs which may interfere with the blanching reaction including, but not limited to, corticosteroids and other vasoactive drugs (nitrates derivatives, antihypertensive, phenylpropanolamine, diphenhydramine, pseudo-ephedrine, antihistamines, non-steroidal anti-inflammatory drug and aspirin/acetylsalicylic acid), within two weeks prior to screening visit,
4. Use of any other medication would interfere with the trial results, in particular topical drugs applied on the test area within two weeks prior to screening visit,
5. Subject's caffeine (i.e. coffee, cola, soft-drinks containing caffeine) intake greater than 500mg per day (1 cup of coffee contains

approximately 85mg of caffeine) within one day prior to screening visit and until the end of the last visit of the test phase,

6. Subject with a history of drug or alcohol abuse/addiction.
7. Subject with a history of calcium metabolism disorders,
8. Abnormal pigmentation of the skin or skin type, that could, in any way, confound interpretation of the trail results (skin type V to VI on the Fitzpatrick scale),
9. Subjects with obvious difference in skin color between arms,
10. Subjects with any of the following conditions present on the test areas: viral (e.g. herpes or varicella) lesions of the skin, fungal and bacterial skin infections, parasitic infections, atrophic skin, and *striae atrophicae*, fragility of skin veins, ichthyosis and ulcers,
11. Any current systemic or cutaneous disease that could in any way confound interpretation of the trial results (e.g. atopic dermatitis, contact eczema, or psoriasis),
12. Known or suspected hypersensitivity to any component(s) of IMP,
13. Subjects with current participation in any other interventional clinical, based on interview of the subject,
14. Subjects who have received treatment with any non-marketed drug substance (i.e. an agent which has not yet been made available for clinical use following registration) within the last 4 weeks prior to screening phase,
15. Previously enrolled in this clinical trial,
16. Subject who do not accept to avoid strenuous physical activity nor alcohol intake during the study.
17. In the opinion of the (sub)investigator, subjects who are unlikely to comply with the Clinical Trial Protocol (e.g. alcoholism, drug dependency or psychotic state),
18. Subjects in close affiliation with the trial personnel (e.g. immediate family member or subordinate), subjects being a member of the clinical trial personnel, or being an employee of the sponsor or a CRO involved in the trial,
19. Subjects impossible to contact in case of emergency,
20. Subjects who are in an exclusion period in the National Biomedical Research Register of the French Ministry of Health at randomization,
21. Subject under guardianship or hospitalized in a public or private institution, for a reason other than the research or subject deprived of freedom or under the protection of justice.

Investigational Product 1:	
Name / Internal code:	**MC2-01**
Pharmaceutical form:	Cream
Strength/Concentration:	Calcipotriol 0.005 % w/w (50 µg/g) and betamethasone dipropionate 0.064 % w/w (0.5 mg/g as betamethasone)
Route of administration:	Topical
Dosage:	Twenty (20) µL / 2.2-cm diameter site
Investigational Product 2:	
Name / Internal code:	**MC2-01 Vehicle**
Pharmaceutical form:	Cream
Strength/Concentration:	NA
Route of administration:	Topical
Dosage:	Twenty (20) µL / 2.2-cm diameter site
Reference Product 1:	
Name / Internal code:	**Clobex®**
Pharmaceutical form:	lotion
Strength/Concentration:	Clobetasol propionate 0.05%
Route of administration:	Topical.
Dosage:	Twenty (20) µL / 2.2-cm diameter site
Reference Product 2:	
Name:	**Betamethasone Dipropionate (Augmented)**
Pharmaceutical form:	Cream
Strength/Concentration:	Betamethasone dipropionate 0.064% (equivalent to 0.05% betamethasone)
Route of administration:	Route of administration and dosage: Topical.
Dosage:	Twenty (20) µL / 2.2-cm diameter site
Reference Product 3:	
Name:	**Locoid®**
Pharmaceutical form:	Cream
Strength/Concentration:	Hydrocortisone butyrate 0.1%
Route of administration:	Topical.
Dosage:	Twenty (20) µL / 2.2-cm diameter site
Reference Product 4:	
Name:	**Triamcinolone Acetonide**
Pharmaceutical form:	Cream
Strength/Concentration:	Triamcinolone acetonide 0.1%
Route of administration:	Topical
Dosage:	Twenty (20) µL / 2.2-cm diameter site
Reference Product 5:	
Name:	**Desowen®**
Pharmaceutical form:	Cream
Strength/Concentration:	Desonide 0.05%
Route of administration:	Topical
Dosage:	Twenty (20) µL / 2.2-cm diameter site

Evaluation criteria:

The following evaluations will be performed during the trial:

- Visual assessment of skin blanching:

The visual assessment will be performed by two trained readers on Day 2 (2 hours after removal of products).

- Local tolerance / Systemic safety:
  - Local tolerability will be assessed by the Investigator at Day 2.
  - Daily record of AE.

Principal statistical methods:

MC2-01 cream will be compared with Clobex lotion, Betamethasone Dipropionate (Augmented) cream, Locoid® cream, Triamcinolone Acetonide cream, Desowen cream and MC2-01 cream vehicle in terms of visual score of skin blanching 2 hours after a 16-hour application, using an ANOVA having subjects and treatments as factors. Estimates of treatment effect and 95% confidence interval of differences between MC2-01 cream and the reference products will be calculated from the model without correction for multiplicity in the primary analysis. Correction for multiplicity using Dunnett's test will be used as secondary analysis.

Subject Number Calculation:

In total 36 subjects will be randomized in the trial in order to have 30 completed evaluable subjects. Each subject will receive the MC2-01 cream, the 5 steroid-containing treatments and the MC2-01 cream vehicle on 7 different test sites. For details of calculation see section 12.5.

Trial dates:

First Subject In: Late August - Early September 2018

Last Subject Out: October 2018

Table 1 - Schedule of Assessments

Trial Phases:	Screening	Test		Follow-up(2)
Trial Days :	Day-15 to Day-1	Day1	Day2	Day15 (±2days)
Informed Consent Form	☑			
Demographics/Medical history	☑			
Previous treatments/procedures	☑			
Inclusion/exclusion criteria	☑	☑		
Selection of test sites		☑		
Physical exam, vital signs	☑			
Urine pregnancy test(1)	☑	☑		
Screening test for blanching response	☑			
Randomization		☑		
Local tolerance(2)			☑	☑
Application of IMPs		☑		
Product excess removal(3)			☑	
Measurement of skin blanching by 2 trained evaluators(4)			☑	
Concomitant treatments	☑	☑	☑	☑
Adverse events	☑	☑	☑	☑
End of treatment			☑	
End of study				☑

1: For female subject of childbearing potential. Result must be negative to continue the trial.
2: For subjects with a local tolerability scores >0 at Day 2 or if a non-serious adverse event classified as reasonably possibly related to the investigational products or an SAE is ongoing once a subject has completed the test phase (Day 2), a follow-up visit/contact (telephone contact or visit according to the investigator's discretion) will take place up to 14 (±2) days after the end of test phase (D2). AEs and SAEs assessed reasonably possibly related to the trial medication must be follow until it is resolved or until the medical condition of the subject is stable.
3: 16 hours +/- 30 min after IMP application
4: 2 hours +/- 30 min after IMP removal

TABLE OF CONTENTS

Tables Index

Figure Index

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADR	Adverse Drug Reaction
AE	Adverse Event
BDP	Betamethasone Dipropionate
CAL	Calcipotriol
CPCAD	Centre de Pharmacologie Clinique Appliquée à la Dermatologie = name of the trial site [for Clinical Pharmacologie Center Applied to Dermatology]
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Safety Responsible
DDS	Drug Delivery Solutions Aps
EU	European Union
FDA	Food and Drug Administration
FSI	First Subject In
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
LSO	Last Subject Out
RDC	Remote Data Capture
SAE	Serious Adverse Event
SD	Standard Deviation
SOP	Standard Operating Procedure

5 BACKGROUND AND RATIONALE

5.1 Background

Psoriasis is a common, immune-mediated, inflammatory skin disease that is found world-wide. There is no cure for psoriasis. The goal of treatment is to reduce or eliminate its signs and symptoms. Mild to moderate disease is often treated with topical therapies. Among topical therapies, a combination treatment of a Vitamin D analog and a topical glucocorticosteroid has become especially popular. Several studies show that the combination of calcipotriol (CAL) and betamethasone dipropionate (BDP) is superior to each of the single agent (3) (4) (5). There is strong scientific rationale for the combination of vitamin D and glucocorticosteroids both with respect to efficacy and safety (6) (7) (8), and combination treatment with a Vitamin D analog and a topical corticosteroid is recommended in both American and European guidelines (9) (10) (11) (12).

Calcipotriol and betamethasone are incompatible in an environment, since CAL requires basic conditions to maintain stability while betamethasone requires acidic conditions. Currently marketed products are therefore restricted to non-, 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 PADTM 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.

The investigational products (IMP) in the present trial are:

- MC2-01 cream (0.005% w/w CAL, 0.064% w/w BDP),
- MC2-01 cream vehicle.

The dosage of the active agents of the presently tested formulation are 0.005% w/w for calcipotriol and 0.064% w/w for betamethasone (as dipropionate). These concentrations are similar to the ones of the commercially available formulations of calcipotriol and betamethasone dipropionate or the combination of both.

5.2 Rationale for the trial

5.2.1 Rational for the trial design

The human skin blanching assay (vasoconstriction test) described by R. Stoughton and A.W. McKenzie in 1962 (1) has been used for many years by pharmaceutical companies and was accepted by the FDA as a mean to assess the clinical potency of topical corticosteroid formulations. The assay is typically performed with healthy volunteers and with intraindividual comparisons and is based on the ability of corticosteroids to produce skin blanching i.e., vasoconstriction in the dermal microvasculature. The

degree of skin blanching is a measure of inherent potency of the drug and its capacity to diffuse through the stratum corneum.

The original human skin blanching assay (1) used a 16-hour application and visual assessments of the degree of vasoconstriction. Since then, numerous attempts to refine this assay have been done, e.g., by changing the application time and by including colorimetric assessments of the skin color.

The most comprehensive comparison of the vasoconstrictor assay with clinical potency was in the trial by Cornell and Stoughton (2) of over twenty glucocorticoid formulations which involved the comparison of 2 formulations in both the vasoconstrictor assay and double-blind clinical studies in psoriasis. Thirty subjects in each vasoconstrictor and 30 or more subjects in each clinical trial/group (psoriasis) paired comparison was used. In all but two, the comparisons directly agreed with the clinical potency as determined by the bilateral, paired, double-blind studies in psoriasis. All these correlations were done with the single reading (at least 2h after the product removal procedure) after 16h of exposure under a guard (13).

Ranking of the clinical potencies of USA glucocorticoid topical formulations has been based on the Stoughton's skin blanching assay.

5.2.2 Rational for the reference products

In the US potency ranking of commonly used corticosteroids, Group I is the super-potent category. Potency descends with each group to group VII, which is the least potent.

In a ranking assay, the active reference products must be selected to ensure an adequate bracketing to determine the topical corticosteroid potency class of the MC2-01 cream (CA/BDP). It should also demonstrate that the IMP is not different from the target class representative.

The active reference products are listed below including their steroid potency description and Group and Class according to the 7-point US classification system. Several US classification charts (13) (14) (15) (16) and the WHO classification (17) have been used for reference and selection.

Generic name	Group /Class	Potency	Brand name	Rational
Clobetasol propionate 0.05%	I	Ultra High/Super potent	Clobex® lotion	Highest potent
Betamethasone dipropionate 0.05 %	II	High/Potent	Betamethasone Dipropionate (Augmented) cream	Representative of the target potency group and matching steroid for the IMP
Triamcinolone acetonide 0.1%	IV	Medium	Triamcinolone Acetonide cream	Representative of a medium group
Hydrocortisone-17-butyrate 0.1%	V	Medium	Locoid® cream	Representative of a lower medium group
Desonide 0.05%	VI	Low	Desowen® cream	Lowest potency used in psoriasis (face or folds)

Group: From Stoughton (13), the American Academy of Family Physicians (16) and World Health Organization Classification of Topical Corticosteroids (17).

Class: Potency of Topical Corticosteroids (USA classification) (14).

5.3 Risk/benefit ratio assessment

The MC2-01 cream contains two well-known active compounds (CAL/BDP) in a novel topical formulation. The efficacy and safety profile of the combination is well established and have proven to be safe and efficacious, and available data for MC2-01 cream suggest a very benign safety profile resembling that known from the approved CAL/BDP products.

The subject population in MC2-01-C4 will be healthy adult subjects. The products to be tested will be applied to circular test sites (2.2 cm diameter) on the flexor surface of each forearm between the wrist and elbow and removed after 16 hours in order to visually assess, vasoconstriction.

Based on the extensive clinical experience available for the CAL/BDP combination, and in light of the fact that the healthy subjects in the vasoconstriction trial will be exposed to a very limited dose of MC2-01 cream, it is considered that the benefit of obtaining clinical data to evaluate the potency of MC2-01 cream relative to marketed corticosteroids outweighs any potential risks.

6 CLINICAL TRIAL OBJECTIVES AND CLINICAL HYPOTHESIS

6.1 Clinical trial objectives

Primary objective:

The objective of this trial is to compare the vasoconstriction potential (skin blanching effect) of MC2-01 cream with Clobex 0.05% (clobetasol propionate) lotion, Betamethasone Dipropionate (Augmented) 0.05% (betamethasone dipropionate) cream, triamcinolone Acetonide 0.1% (triamcinolone Acetonide) cream, Locoid® 0.1% (hydrocortisone butyrate) cream, Desowen® 0.05% (desonide) cream and MC2-01 vehicle using the human skin blanching test (McKenzie-Stoughton's test).

Secondary objectives:

To assess the local tolerability of MC2-01 cream and the matching vehicle.

7 OVERALL CLINICAL TRIAL DESCRIPTION

7.1 Overall trial design

This is a single center, investigator blinded, active - and vehicle-controlled, single application, intra-individual comparisons on mini-test sites (n=7), involving 36 healthy subjects meeting specific inclusion/exclusion criteria.

Eligible subjects will receive a single application of each of the followings:

- MC2-01 cream containing calcipotriol and betamethasone dipropionate, w/w 0.005% / 0.064%.
- Clobex lotion containing clobetasol propionate 0.05%
- Betamethasone Dipropionate (Augmented) cream containing betamethasone dipropionate 0.05%
- Triamcinolone Acetonide containing triamcinolone acetonide 0.1%
- Locoid® cream containing hydrocortisone-17-butyrate 0.1%
- Desowen® cream containing desonide 0.05%
- MC2-01 cream vehicle

The trial will employ an unoccluded McKenzie-Stoughton trial design based on topical application of a corticosteroid-containing formulation for a period of 16 hours in healthy human volunteers followed by visual estimation of the degree of blanching on a multiple unit scale (0 to 4) by two independent trained observers 2 hours after the end of the application period.

The trial will be conducted with three successive individual phases:

- Screening phase with a screening blanching test.
- Test phase
- Follow-up phase. For subjects with a local tolerability scores >0 at Day 2 or if a non-serious adverse event classified as reasonably possibly related to the investigational products or an Serious Adverse Event (SAE) is ongoing once a subject has completed the test phase (Day 2), a follow-up visit/contact will take place up to 14 (±2) days after the end of test phase (D2). SAEs will be monitored until the Investigator and Sponsor agree that the event is satisfactorily resolved; Telephone contact or visit according to the investigator's discretion.

7.1.1 Screening Phase

A medical screening-examination will be performed at screening which will take place 1 to 15 days before the start of Day 1.

Before any trial related procedure, the subjects will receive the necessary written and verbal information and instructions including informed consent form (written informed consent) and the written subject information sheet. Each subject will receive a unique Subject Identification Number and eligibility will be determined by clinical examination and confirmation of in/exclusion criteria.

During screening procedure general data such as demographics, vital signs (blood pressure and heart rate sitting after 5 minutes at rest), concomitant medication, concurrent diagnoses, sex and skin type will be recorded. Female subjects of childbearing potential will undergo a urine pregnancy test that also must be negative.

A screening test for blanching response will be performed and the subject should have a visual score (single reading) of skin blanching of at least one unit (visual scale (0-4)) after an unoccluded application of Betamethasone Dipropionate (Augmented) cream (20 µL for 4-6 hours), on a forearm test site of 2.2 cm in diameter which will not be used during the test phase.

7.1.2 Test Phase (Day 1 to Day 2)

The start of the treatment phase is defined as Day 1 (Visit 2, baseline). A re-check of all in/exclusion criteria will be performed in subjects who were suitable based on previous examinations. Concomitant medication will be reviewed. Female subjects of childbearing potential will undergo a urine pregnancy test that must be negative.

If all inclusion and exclusion criteria are met, the subject will continue the trial and receive a unique randomization number which determines the application scheme of investigational and reference products for the individual subject (see Section 10.1.4).

Location of test sites

Seven circular sites (2.2 cm diameter) will be outlined on the anterior surface of the forearms (4 sites on one arm and 3 sites on the other). A number will identify them: 1 to 4 on one arm and 5 to 7 on the other arm (from the antecubital fossa to the wrist). The test sites will be delimited using a disposable circular device and a marker pen.

The distal part of the wrist, the veins, and hair covered areas should be avoided. Test sites should be no closer than 3 cm to the antecubital fossa or to the wrist. The distance between two test sites must be at least 2.5 cm center to center (i.e. at least 0.3 cm between site perimeters) and might be in straight line or staggered pattern, depending on the surface suitability (e.g., vascularity, nevi, etc.) and arm length.

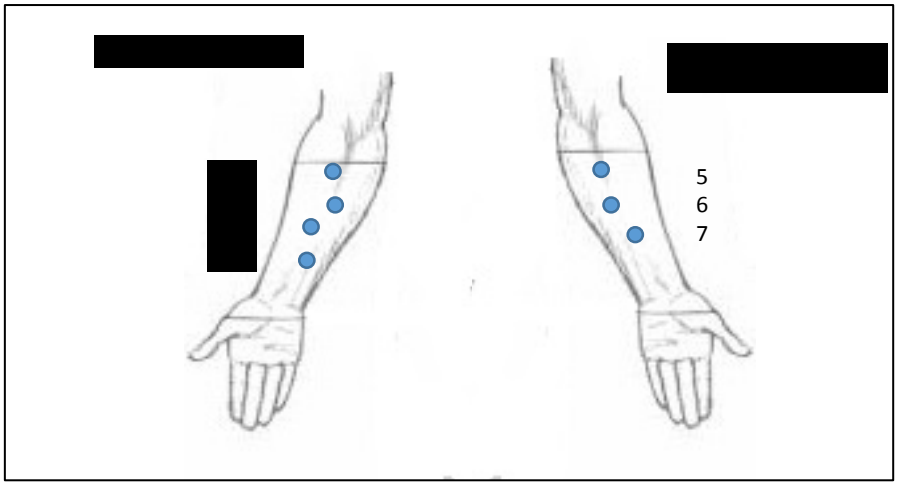

Figure 1- Example of test sites location

Product application

The products will be allocated to each test site according to a pre-determined randomization scheme. The specified dose of each product will be applied to the delimited area and gently massaged into the skin using a gloved finger. Each product will be applied using a different gloved finger.

The test sites will be protected by a plastic ring and covered with a non-occlusive gauze dressing to avoid any lateral spreading of the product from the application site.

At the end of the application period (16 hours after application), any remaining topical product will be gently removed from the skin by 3 consecutive swabbings with dry paper tissue swabs (no washing).

During the application phase, the temperature of the room will be kept constant at 22-24 °C.

Visual assessment of skin blanching

Visual assessments of the skin blanching will be made independently by 2 trained observers 2 hours after the removal of the products, according to a grading scale (0 to 4). During the assessments, the temperature of the room will be kept constant at 22-24°C.

Assessment of local tolerability

At Day 2, the (sub)investigator will assess each test site for local tolerability according to a graded scale.

Local and systemic adverse events (AE) will be assessed at each visit.

7.1.3 Follow-up Phase

A follow-up visit/contact (telephone contact or visit according to the investigator's discretion) will take place up to 14 (±2) days after Day 2 if any of the below conditions apply when the subject has completed the trial:

- The subject has a local tolerability score >0,

- The subject has an ongoing non-serious adverse event classified as reasonably possibly related to the investigational products,

- The subject has an ongoing SAE.

7.2 Discussion of the trial design

Please see 5.2.1. Rational for the trial design.

8 CLINICAL TRIAL DURATION AND TERMINATION

The planned clinical trial duration (from FSI to LSO) is approximately 2 months. The date of end of the clinical trial is defined as the date of the last visit of the last subject who participates in the clinical trial.

The planned duration of recruitment (i.e. From FSI to LSI) is approximately 1 month.

Clinical trial participation for each subject is of 2 days plus the screening phase and a possible follow-up phase.

The sponsor may decide to prematurely terminate or suspend the trial (for example, for non-inclusion or non-compliance with clinical trial protocol, regulation, or GCP) or prematurely suspend the clinical trial (for example, for safety, trial drug(s) quality, regulatory, efficacy, or logistical reason(s) at any time with appropriate notification.

The date of end of the trial will be the date of the last visit of the last Subject undergoing the trial.

9 SELECTION AND DISPOSITION OF CLINICAL TRIAL POPULATION

The volunteers will be recruited via the CPCAD Volunteer Database or from those who spontaneously come to the CPCAD or if needed, via press advertising after approval by the Ethics Committee.

9.1 Number of subjects

Approximately 60 subjects will be pretested in order to get 36 subjects randomized and 30 subjects completed.

9.2 Clinical trial population characteristics

In order to be eligible for the clinical trial, subjects must fulfil all of the following criteria. Some criteria are to be checked during the Screening Phase and/or at Baseline, as specified.

9.2.1 Inclusion criteria

1. Male or female subjects aged 18 years to 50 years old having signed and dated an informed consent,
2. Non-smoker subjects,
3. Subjects demonstrating adequate vasoconstriction to Betamethasone Dipropionate (Augmented) cream within 15 days prior to dosing (unoccluded application of Betamethasone Dipropionate (Augmented) cream for 4-6 hours must show a visual score of skin blanching of at least one unit (visual scale (0-4)),
4. Subjects without signs of skin irritation/disease/disorders/symptoms or blemishes on test sites (e.g. erythema, dryness, roughness, scaling, scars, moles, sunburn),
5. Female subject of non-child bearing potential defined as surgically sterile or post-menopausal (at least one year post cessation of menses),
6. Female of childbearing potential who has been, in the opinion of the Investigator, using an approved method of birth control (e.g. oral contraception pill or patch, intra-uterine devices, contraceptive implants or vaginal rings, condoms, bilateral tubal ligation) at trial entry and agree to continue until the end of the last trial visit,
7. Female subjects of childbearing potential must have a negative urine pregnancy test at screening visit and at Day 1 to continue,
8. Subjects willing and able to follow all the trial procedures and complete the whole trial,
9. Subjects affiliated to a social security system.

9.2.2 Exclusion criteria

1. Female subjects who are breastfeeding,
2. Use of topical corticosteroids on the test areas (forearms) within 4 weeks prior to the screening phase,
3. Use of systemic drugs which may interfere with the blanching reaction including, but not limited to, corticosteroids and other vasoactive drugs (nitrates derivatives, antihypertensive, phenylpropanolamine, diphenhydramine, pseudo-ephedrine, antihistamines, non-steroidal anti-inflammatory drug and aspirin/acetylsalicylic acid), within two weeks prior to screening visit,
4. Use of any other medication would interfere with the trial results, in particular topical drugs applied on the test area within two weeks prior to screening visit,
5. Subject's caffeine (i.e. coffee, cola, soft-drinks containing caffeine) intake greater than 500mg per day (1 cup of coffee contains approximately 85mg of caffeine) within one day prior to screening visit and until the end of the last visit of the test phase,
6. Subject with a history of drug or alcohol abuse/addiction,

7. Subject with a history of calcium metabolism disorders,
8. Abnormal pigmentation of the skin or skin type, that could, in any way, confound interpretation of the trail results (skin type V to VI on the Fitzpatrick scale),
9. Subjects with obvious difference in skin color between arms,
10. Subjects with any of the following conditions present on the test areas: viral (e.g. herpes or varicella) lesions of the skin, fungal and bacterial skin infections, parasitic infections, atrophic skin, and *striae atrophicae*, fragility of skin veins, ichthyosis and ulcers,
11. Any current systemic or cutaneous disease that could in any way confound interpretation of the trial results (e.g. atopic dermatitis, contact eczema, or psoriasis),
12. Known or suspected hypersensitivity to any component(s) of IMP,
13. Subjects with current participation in any other interventional clinical, based on interview of the subject,
14. Subjects who have received treatment with any non-marketed drug substance (i.e. an agent which has not yet been made available for clinical use following registration) within the last 4 weeks prior to screening phase,
15. Previously enrolled in this clinical trial,
16. Subject who do not accept to avoid strenuous physical activity nor alcohol intake during the study.
17. In the opinion of the (sub)investigator, subjects who are unlikely to comply with the Clinical Trial Protocol (e.g. alcoholism, drug dependency or psychotic state),
18. Subjects in close affiliation with the trial personnel (e.g. immediate family member or subordinate), subjects being a member of the clinical trial personnel, or being an employee of the sponsor or a CRO involved in the trial,
19. Subjects impossible to contact in case of emergency,
20. Subjects who are in an exclusion period in the National Biomedical Research Register of the French Ministry of Health at randomization,
21. Subject under guardianship or hospitalized in a public or private institution for a reason other than the research, subject deprived of freedom or under the protection of justice.

9.2.3 Previous and concomitant therapies

Definition

Previous therapies are defined as therapies that have been stopped within the six (6) months preceding the screening visit.

Concomitant therapies are defined as follows:

- any existing therapies ongoing at the time of the screening visit,
- any changes to existing therapies (such as changes in dose or formulation) during the course of the clinical trial, or
- any new therapies received by the subject since the screening visit.

Categories

The following two categories are to be considered for previous and concomitant therapies:

- Drugs/therapies including but not limited to, prescription, over-the-counter (OTC), birth control pills/patches/hormonal devices, vitamins, moisturizers, sunscreens, herbal medicines/supplements, and homeopathic preparations.
- Medical and surgical procedures including, but not limited to, laser/radiation procedures, dermal fillers, X-rays, etc.

Recording

Previous and concomitant therapies are to be recorded on the Drugs/Therapies form (for drugs/therapies) and/or on the Medical and Surgical Procedures form (for medical/surgical procedures) in the CRF.

Concomitant therapies are to be recorded, reviewed, and updated at each visit.

Any new concomitant therapy or modification of an existing therapy may be linked to an adverse event (AE). A corresponding Adverse Event Form must be completed to account for the change in therapy, except in some cases such as therapy used for prophylaxis, dose modification for a chronic condition, etc.

9.2.4 Authorized concomitant therapies

Unless listed under the exclusion criteria (Section 9.2.2, items 2 and 3) or in prohibited concomitant therapies (see Section 9.2.5), all therapies are authorized.

9.2.5 Prohibited concomitant therapies

The following therapies are prohibited because they may interfere with the efficacy and/or safety (for example interaction with the trial drug(s) metabolism) assessment of the trial drug(s):

Listed in Section 9.2.2 items 2 and 3.

If prohibited therapies become a necessary treatment for the safety or best interest of the subject, the sponsor should be notified to discuss possible alternatives prior to administration of a prohibited therapy.

If a subject receives prohibited therapy during the clinical trial, sponsor should be notified to discuss the pertinence and the modalities for the subject to continue in the clinical trial.

9.3 Withdrawal Criteria

Subjects may withdraw for any of the following reasons:

1. Unacceptable treatment efficacy: the investigator is free to withdraw the subject at any time for medical reasons.
2. Unacceptable adverse events: any adverse event that the investigator or the subject considers unacceptable.
3. Exclusion criteria: any exclusion criteria which emerge/become apparent during the subject's participation in the clinical trial.
4. Voluntary withdrawal: subjects will be free to withdraw from the clinical trial at any time and for any reason.
5. Other reasons: other reasons than stated above which requires the subject to (be) withdraw(n) should be specified.

Subjects who are discovered, after enrolment/randomization, not to have fulfilled all in/exclusion criteria at time of enrolment, should be withdrawn from treatment unless the investigator, based on clinical and ethical evaluation, finds withdrawal inappropriate. Such deviation(s) from the Clinical Trial Protocol must be reported to (and IEC/IRB, as appropriate) and recorded in the Clinical Trial Report.

The assessments at the early withdrawal visit should be attempted to be completed for all subjects who withdraw from the treatment for any reasons. The ultrasound measurement should be performed at this early withdrawal visit.

In case of early withdrawal from the trial, a follow-up visit/contact should be planned 14 (+/- 2) days after the last visit for those subjects having an adverse event classified as reasonably possibly related to the trial medication, unless final outcome of the event has been determined in the meantime.

Reason(s) for withdrawal will be recorded in the CRF. Subjects withdrawn will not be substituted.

9.4 Stopping rules

The "Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products" (EMEA/CHMP/SWP/28367/07 Rev. 1) indicates that the protocol should define unambiguous stopping rules which result in an immediate stop to dosing. It should further be specified in the rule if the stop is a final end of dosing or a temporary halt. Restart is possible without a substantial amendment if review leads to a conclusion which is fully within predefined conditions for the relevant stopping criterion.

Any submitted substantial amendment should include a rationale for the proposed dosing and for the continuation of the trial and details of any adjustments to the protocol including additional safety monitoring, if applicable.

Stopping rules should be defined for each of the following:

- final stop to dosing and termination of the trial;

- stopping for an individual subject, at any time in the trial;
- stopping within a cohort
  - when subjects in a cohort are dosed staggered;
  - during multiple dosing;
- progression to the next part of the trial;
- any dose escalation parts of the trial.

Separate rules can be in place for each of the bullet points above, or it may be appropriate to use the same criteria for several areas of the protocol. For example, stopping rules for dose escalation could be the same as those for within a cohort or those for individual subjects. Integrated protocols should clearly outline decision points and criteria for the situation where stopping rules are met.

Stopping rules for healthy volunteer trials should include, but not be limited to:

- a 'serious' adverse reaction (i.e. a serious adverse event considered at least possibly related to the IMP administration) in one subject;
- 'severe' non-serious adverse reactions (i.e. severe non-serious adverse events considered as, at least, possibly related to the IMP administration) in two subjects in the same cohort, independent of within or not within the same system-organ-class.

Consideration should be given to stopping criteria based on a rolling review of the data that takes account of 'moderate' non-serious adverse reactions (i.e. moderate adverse events at least possibly related to the IMP administration) in blinded or unblinded fashion and their relation to PD effects, the number of subjects in which they occur, concurrency of more than one within the same subject and potential safety signals identified for other IMPs in the same class (mechanistic and/or chemical). Changes from baseline measurements should also be considered, and not just absolute cut-offs based on upper or lower limits of normal that might apply for healthy volunteers.

A dose stopping criterion comprising a maximum clinical exposure (Cmax or AUC) should generally be included. When reviewing emerging data in relation to this criterion, the maximum exposure observed in individual subjects within a cohort rather than the mean exposure should be taken into account.

10 CLINICAL SUPPLIES

10.1 Clinical supply identification and use

10.1.1 Trial drug(s) description

Table 2 - Description and usage of the investigational and reference products

	Investigational product 1	**Investigational product 2**	**Reference product 1**	**Reference product 2**
Trade Name or Equivalent	MC2-01	MC2-01 vehicle	Clobex (Galderma Labs LP)	Betamethasone Dipropionate (Augmented) (Taro Pharmaceuticals)
Name of Drug Substance	Calcipotriol + Betamethasone dipropionate	NA	Clobetasol propionate	Betamethasone dipropionate
Pharmaceutical Form	cream	cream	lotion	cream
Concentration	0.005% + 0.064%	NA	0.05%	0.064% w/w (equivalent to 0.05% betamethasone)
Package	60 g aluminum tubes	60 g aluminum tubes	Bottle 59ml	15 g aluminum tubes
Storage conditions	Store between 2-8°C between treatment days – May be store at room temperature below 25°C at the day of treatment application		Store below 30°C	Do not store above 25°C
Dosage (per site)	20 µL	20 µL	20 µL	20 µL
Route	Topical (Cutaneous to the skin)			
Dose Regimen	A single application of each IMP			
Duration of administration	Contact duration of 16 hours (+/- 30 min)			
Location of Treated Area	Area of 2.2 cm diameter			

Table **2** (continued) Description and usage of the investigational and reference products

	Reference product 3	**Reference product 4**	**Reference product 5**
Trade Name or Equivalent	Triamcinolone Acetonide (Ascend Laboratories LLC)	Locoid® (Precision Dermatology)	Desowen® (Galderma Labs LP)
Name of Drug Substance	Triamcinolone acetonide	Hydrocortisone butyrate	Desonide
Pharmaceutical Form	cream	cream	cream
Concentration	0.1%	0.1%	0.05%
Package	30 g tube	30 g aluminum tube	60 g tube
Storage conditions	Store at 20- 25°C	Do not store above 25°C. Do not refrigerate or freeze	Store between 2° and 30°C
Dosage (per site)	20 µL	20 µL	20 µL
Route	Topical (Cutaneous to the skin)		
Dose Regimen	A single application of each IMP		
Duration of administration	Contact duration of 16 hours (+/- 30 min)		
Location of Treated Area	Area of 2.2 diameter		

10.1.2 Subject Identification Number

Upon signature of the ICF, each subject will be assigned a Subject Identification Number.

This Subject Identification Number will be allocated in ascending sequential order to each subject. For the duration of the entire clinical trial, the subject will be identified using the Subject Identification Number for all documentation and discussion.

10.1.3 Method of treatment assignment

Prior to the start of the trial, a randomization list will be generated by a statistician from CPCAD and will be transmitted to the person in charge of the products application.

The list will indicate the assignment of the seven products to the seven different test sites (1-7) of each Subject, according to a Latin squares design. The order of applications will be 1 to 7 for all Subjects.

10.1.4 Randomization number

At Day 1, each Subject who fulfils all inclusion/non-inclusion criteria will be assigned a Randomization Number. This three-digit Randomization Number will be dispensed in the chronological order of his/her inclusion in the trial and no number should be omitted or skipped. The date and time of randomization define this number, independently of the Subject Identification Number that was initially assigned at the Screening visit.

10.1.5 Instructions for use and administration

All applications will be performed at the trial center by a person from the investigational team other than the two independent trained readers. Application will be supervised by a second person also other than the two independent trained readers.

All trial drugs will be accounted for and in no case used in any unauthorized situation. All used and unused trial drugs will be appropriately inventoried and disposed of by the trial center.

10.1.6 Location of test sites

Seven circular sites (2.2 cm diameter) will be outlined on the anterior surface of the forearms. A number will identify them: 1 to 4 on one arm and 5 to 7 on the other arm (from the antecubital fossa to the wrist). The test sites will be delimited using a disposable circular device.

The distal part of the wrist, the veins, and hair covered areas should be avoided. Test sites should be no closer than 3 cm to the antecubital fossa or to the wrist. The distance between two test sites must be at least 2.5 cm center to center (i.e. at least 0.3 cm between site perimeters) and might be in straight line or staggered pattern, depending on the surface suitability (e.g., vascularity, nevi, etc.) and arm length.

As assessment will be visual no untreated control site is required.

10.1.7 Application procedure

The seven tested products will be randomly allocated to 7 sites. The 7 test sites will be numbered from 1 to 7. The treatments will be applied at the investigational site center by a qualified person, using a marker pen to define the areas of products application. A transparent sheet will be used to landmark the test sites location on each forearm.

The person in charge of applications will use a calibrated Eppendorf system with appropriate combitips to dose 20µL of the tested product. One system will be dedicated to one tested product. Before the study start, every system will be checked according to CPCAD SOP PT 013 06 2018 01 18 - Eppendorf multipette. The check form will be retained in the study file. The combitip is filled by removing the plunger, filling the combitip and putting the plunger in place before connecting the combitip to the Eppendorf multipette.

The 20µL of products will be applied to each test site and gently massaged into the skin using a gloved finger. Each product will be applied using a different gloved finger.

After application and rubbing in, the test sites will be protected by a non-occlusive device. At the end of the application period (16 hours after application), remaining topical product will be gently removed from the skin by 3 consecutive swabbings with dry paper tissue swabs (no washing).

10.1.8 Subject Treatment Instructions

At screening phase (visit 1) and Day 1 (visit 2), an instruction sheet will be handed out to the subject. The instructions will apply throughout the trial.

According to this the subject will be instructed that:

- No occlusive dressing is permitted
- The devices should remain in place during the treatment period (16 hours)
- Bathing (bathtub, lake/sea), swimming and sauna is not permitted during Day 1 and Day 2 before the clinical evaluation
- Washing and direct showers on the test sites (forearms) are not allowed during Day 1 and Day 2 before the clinical evaluation
- No excessive sun exposure, as well as any kind of sun exposure of test sites is allowed.
- No sun cream or oil application on the test sites during Days 1 and 2.
- Subjects will abstain from strenuous physical activity and alcohol intake during Day 1 and Day 2 before the clinical evaluation.

10.1.9 Trial drug(s) packaging and labelling

MC2-01 / MC2-01 vehicle will be dispensed in 60 g aluminum tubes. The labels will be printed in French. The text of the labels will detail the information requested by Good Manufacturing Practice and local regulations.

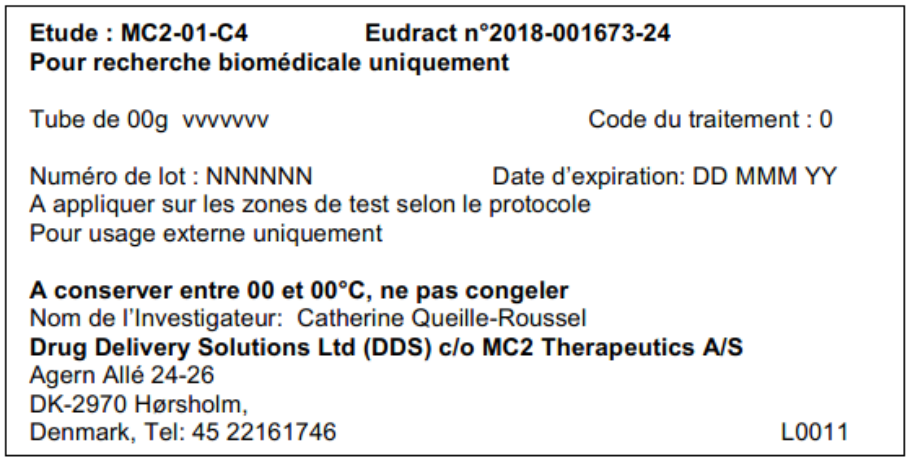

Figure 2- Model of label (in French)

Commercially available reference products will be used from their commercial packaging and packed in a uniform outer package, in order to blind the product.

The products will be coded A, B, C, D, E, F and G.

10.2 Supplies management

10.2.1 Accountability

Upon receipt of the trial drug(s), the designee product manager will maintain accurate records of the trial drug(s) delivery to the clinical trial center, the inventory at the clinical trial center, the reconciliation of all trial drug(s) received from the Sponsor, and the return to the Sponsor or alternative disposal of used and unused trial drug(s).

The designee product manager is required to sign and return the original "Receipt of Clinical Supplies" Form (or any acknowledgment of receipt) upon receipt and inspection of the supplies, fax the signed copy to sponsor and retain a copy within the clinical trial file.

All used and unused clinical trial drug(s) will be appropriately inventoried by the monitor and returned to the Sponsor for destruction as instructed by the sponsor.

All clinical trial drug(s) sent to the Investigator/Institution will be accounted for and no unauthorized use is permitted.

10.2.2 Storage of clinical trial drug(s)

Trial drug(s) must be stored in a safe and secure area with restricted access, under the storage conditions specified by sponsor (see Table 2 - Description and usage of the investigational and reference products).

10.2.3 Dispensing and return

No drug will be dispensed directly to the subject. Trial drugs will be applied at the clinical center on Day 1. The person in charge of product applications will not be the Investigator/evaluator.

In the event of early termination/suspension of the clinical trial, a rapid recall of trial drug(s) will be initiated.

10.2.4 Treatment compliance management and record

Since product applications will be performed by a qualified person and verified by a second individual, who will not be the investigator/evaluator, treatment compliance will be ensured and documented appropriately by trial staff.

10.2.5 Dose modification

Not applicable

10.3 Blinding

10.3.1 Verification of blinding

The trial will be performed as an investigator-blinded trial since the following procedures will be followed in order to prevent the Investigator and/or other Evaluator(s) from coming into contact with the trial materials thereby compromising the blinding of the trial.

All applications will be performed by designated trial personnel at the trial site. The trained observers performing the clinical assessments must not perform the application of the investigational products. Likewise, the site personnel performing the applications will be the only persons at the site having access to the randomization schedule.

The packaging and labelling of the investigational products will allow to distinguish their identity.

The subjects may be able to distinguish between the various applied formulations. They will therefore be instructed not to reveal any information about the trial medications to the (sub)investigator and/or trained observers performing the clinical assessments.

The tubes will be labeled with a letter A, B, C, D, E, F or G by IMP Pharmaceutical Services. IMP Pharmaceutical Services will furthermore create a document, listing which reference product is A, B etc. CPCAD will receive a copy of this document, sealed in an envelope, to be used in case of emergency. Access to the identification of treatment codes will be limited to the designated personnel.

10.3.2 Unblinding during the clinical trial

Emergency unblinding during the clinical trial may be required for therapeutic or for regulatory reasons (for expedited safety reporting).

A blind break system will be available for the investigator. At the clinical center, a sealed document, containing the identification of tubes of trial medication, may be revealed in emergency situation only. This list will be compared with the sequence of applications done for the subject in question by the person in charge of the applications or a designated person different from the investigator/readers. The information will be transmitted to the investigator only for the subject involved and documented.

The Investigator must notify the Sponsor's Clinical Safety Responsible immediately in the event of such an emergency (see contact details in Section 11.2.2.2. The Investigator should notify the Sponsor before breaking the blind in order to discuss this decision with the Sponsor. The Investigator is required to document each case of emergency unblinding on the randomization disclosure form (provided by the Sponsor) and fax the completed form to the CSR immediately.

11 CLINICAL TRIAL ASSESSMENT

11.1 Pharmacodynamic (Skin blanching) assessments

Throughout the trial, the assessment of the blanching response for each individual test site (mini test site) will be performed to the extent possible by the same 2 trained evaluators. In the event there is a change in the assigned readers for a given Subject, the reason for change must be documented. If it is not possible to use the same reader to follow a given Subject, the Sponsor recommends that evaluations between the primary and subsequent evaluator overlap (both evaluators should examine the Subject together and discuss findings) for at least one visit.

11.1.1 Visual Assessment of Skin Blanching

Visual assessment of blanching will be made independently by two trained readers on Day 2 (2 hours after removal of products, following 16 hours application time) according to the following scale:

Table 3 - Skin blanching visual scale

Score*	Description
0	No change in color skin
1	Slight (barely visible) blanching
2	Obvious blanching
3	Intense blanching
4	Blanching judged to be maximal

*Intermediate scores (half units) may be used when needed (e.g. 0.5 for a doubtful blanching).

Two visual score values (one per trained evaluator) will be recorded for each test site.

11.1.2 Assessment of Local Tolerability

At Day 2, the (sub)investigator will assess each test site for local tolerability according to the scale in Table 4.

Table 4 - Local tolerability scale

Score*	Description
0	No reaction
0.5	Only slight erythema
1	Only erythema
2	Erythema with papules or oedema
3	Erythema, oedema with papules, oedema with vesicle
4	Blisters
IR	Irritant reaction including: miliaria (sweet rash), follicular pustules, burn-like reactions, dry scales

Subjects with a local tolerability score >0 will be re-assessed at a follow-up visit.

Cutaneous reactions scored as local tolerability will be reported as local AEs.

11.2 Safety assessment

A safety assessment will be conducted for all subjects at the screening visit (from the Informed consent signature) and every subsequent visit. The safety parameters are AEs, to be recorded as specified in Section 11.2.2.1, global cutaneous tolerance assessments, physical examination and vital signs assessments (Screening visit only).

Adverse events will be reported individually on an ongoing basis.

All clinical medical events, whether observed by the Investigator or reported by the Subject will be considered adverse events and recorded on the appropriate Adverse Event form. Assessment of severity and causality will be based on specific definitions.

11.2.1 Systemic safety assessment

11.2.1.1 General Physical examination

The following body systems should be evaluated as "normal" or "abnormal" by the Investigator, at the screening visit: Skin, Lungs, Abdomen, Eyes/ears/nose/throat, Musculoskeletal system, Lymph nodes, Cardiovascular system.

The Investigator may choose to further investigate any other sign that he/she observes during the physical examination.

All abnormal findings at the screening visit identified as clinically significant by the Investigator, will be recorded in the Medical History form.

For any clinically significant changes from the screening visit, an AE is to be recorded.

11.2.1.2 Vital signs

Evaluation of vital signs will be performed after 5 minutes rest in the sitting position at the screening visit. It will include measurement of systolic and diastolic blood pressure and pulse rate in the supine position.

All abnormal values at the screening visit identified as clinically significant by the Investigator, will be recorded in the Medical History form.

For any clinically significant changes from the screening visit, an AE is to be recorded.

For AEs, whenever possible, the Investigator is to provide a diagnosis rather than to report individual laboratory abnormalities.

11.2.2 Adverse Events

Adverse events (AEs) are to be monitored throughout the course of the clinical trial. All AEs are to be reported on the Adverse Event Form of the CRF with complete information as required. If AEs occur, the main concern will be the safety of the subjects. At the time of the ICF signature, each subject must be provided with the name and phone number of clinical trial center personnel for reporting AEs and medical emergencies.

11.2.2.1 Definitions

Adverse events (AE)

According to ICH E2A, an AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign,

symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Thus, any new sign or symptom or disease, or any clinically significant worsening of an existing sign, symptom or disease compared to the condition at the first visit (including disease treated), should be considered as an AE. Lack of efficacy is not considered as an AE.

Each new episode of a chronic disease (e.g., hay fever, allergy, etc...) should be reported as a new AE.

Any new sign or symptom reported by the subject that appears after accidental or intentional overdose or misuse should also be reported as an AE.

There should be an attempt to report a diagnosis rather than the signs, symptoms associated with the report of an AE. However, a diagnosis should be reported only if, in the Investigator's judgment, it is relatively certain. Otherwise, symptoms or signs should be used to describe the AE.

Serious Adverse events (SAE)

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

- Results in death,
- Is life threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the safety of the subject, and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasia, or convulsions that do not result in hospitalization.

Note: The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe.

Inpatient hospitalization is considered to have occurred if the subject has had to stay for a night at the hospital. The criterion for prolongation of hospitalization is also defined as an extra night at the hospital. Hospitalization may not constitute sufficient grounds to be considered as an SAE if it is solely for the purpose of a diagnostic tests (even if related to an AE), elective hospitalization for an intervention that was already planned before subject enrolment in the clinical trial, admission to a day care facility, social admission (e.g., if the subject has no place to sleep), or administrative admission (e.g., for a yearly examination).

Unexpected adverse drug reaction

According to ICH E6, an unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable trial drug information (e.g., Investigator's

Brochure for an unapproved investigational product or the package insert/summary of product characteristics for an approved product).

Adverse event reporting period

The clinical trial period during which AEs must be reported is the period from when the subject signed the Informed Consent Form to the end of the subject's participation.

The Sponsor should be informed if the Investigator becomes aware of any unusual safety information or any safety information that appears to be drug related involving a subject who has participated in a clinical trial, even after a subject has completed the clinical trial. The Investigator should be diligent in looking for possible latent safety effects that may not appear until a medication has been discontinued.

Severity

Severity is a clinical determination of the intensity of an AE and not of a disease.

The Investigator is to classify the intensity of AEs using the following definitions as a guideline for all AEs occurring during the conducted clinical trial. For this classification, the Investigator will take into account the possible range of the intensity of the event and report the grade of intensity which is the most appropriate according his medical judgment.

- Mild Awareness of signs or symptom, but easily tolerated.
- Moderate Discomfort, enough to cause interference with usual activity
- Severe Incapacitating with inability to work or perform usual activity

Relationship to the trial drug(s)

The Investigator is to determine whether there is a reasonable causal relationship between the trial drug(s) and the AE. Medical judgment should be used to determine the relationship, considering all relevant factors including the pattern of reaction, temporal relationships, positive challenge or re-challenge, relevant medical history, and confounding factors such as co medication or concurrent diseases.

The expression "reasonable causal relationship" is meant to convey in general that there are facts or arguments to suggest a causal relationship (ICH E2A, Section IIIA 1).

The relationship assessment for an AE is to be completed using the following definitions as a guideline for all AEs occurring during clinical trials:

- Reasonable Possibility:

According to the reporting Investigator, there is a reasonable possibility (i.e., suggestive evidence or arguments) that there is a causal relationship irrespective of the dose administered between:

The trial drug (investigational product, active reference, or vehicle, etc.) and the AE,

The clinical trial protocol procedure (e.g. product application, etc.) and the AE.

- No Reasonable Possibility:

No suggestive evidence or arguments can be identified regarding a causal relationship between the trial drug or the clinical trial protocol procedure and the AE.

11.2.2.2 Reporting procedures

Procedures for reporting Adverse Events

The collection of AEs is from the time that subjects signs the ICF to their final visit.

At each post enrolment visit, the Investigator (or sub-Investigator) will question the subject about AEs using an open non-persuasive question to elicit reporting of AEs, for example "Have you noticed any change in your health since the last visit?" Directed questioning and examination will then be performed as appropriate.

Any AE occurring during the AE reporting period, whether it is related to the trial drug(s) or not, will be recorded immediately in the source document, and described on the Adverse Event Form of the [CRF along with the date of onset, severity, relationship to the trial drug(s), and outcome, without omitting any requested and known information. Additional information may be requested under certain circumstances. Adverse Events (AEs) assessed as related to the treatment will be monitored until they are completely or satisfactorily resolved. Other AEs will be monitored until the last visit if they are not resolved or satisfactorily resolved.

The Investigator will obtain and maintain in the subject's files all pertinent medical records, information and medical judgment from colleagues who assisted in the treatment and follow up of the subject. If necessary, the Investigator will contact the subject's personal physician or hospital staff to obtain further details.

Procedure for reporting a Serious Adverse Event

For an SAE occurring during the period of the clinical trial, regardless of whether it is related to the treatment or not, and of whether it is expected or not, the Investigator must do the following:

- Take prompt and appropriate medical action, if necessary. The safety of the subject is the first priority.
- Immediately inform the Clinical Safety Responsible (from the UBC Company) designated by Drug Delivery Solutions Aps (DDS) c/o MC2 Therapeutics A/S of the event by email or Fax and discuss further actions to be taken.

  Email: EUSafety@ubc.com

  Fax number: +41 225 964 446

Additional contact details are provided in the Investigator's site file.

- Complete the Adverse Event Form provided in the e*CRF* as fully as possible.
- Ensure that the event is classified as an SAE.
- Complete the standard Serious Adverse Event Form. Fax or scan and send by e-mail the completed form accompanied by demographics, medical history, previous and concomitant

therapies and adverse event pages of the CRF, and any other relevant information or medical records (e.g., laboratory test results) within 24 hours to UBC.

- Monitor and record the progress of the event until it resolves or reaches a clinically stable outcome, with or without sequelae. For all additional follow-up evaluations, first inform the CSR of the outcome by telephone, then fax or scan and send by e-mail all additional follow-up information to the UBC within 24 hours. Serious Adverse Events (SAEs) will be monitored until the Investigator and Sponsor agree that the event is satisfactorily resolved.
- Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject. If necessary, contact the subject's personal physician or hospital staff to obtain further details.
- Inform the CSR of the final outcome of the event. Send a revised or updated Serious Adverse Event Form and Adverse Event Form, if appropriate.
- Comply with the applicable regulatory requirement(s) related to the reporting of SAEs to the Institutional Review Board (IRB) / Independent Ethics Committee (IEC).

Responsibilities of the Sponsor:

For Suspected Unexpected Serious Adverse Events (SUSAR):

For the researches mentioned in n°1 of the article L. 1121-1 of the Public Health Book concerning drugs and cells therapies, the Sponsor has to declare to the competent authority any suspicion of unexpected Serious Adverse Events (SUSAR) occurring in France and outside the national territory within the following deadlines:

1. In the case of suspected unexpected Serious Adverse Events having caused death or having endangered life, without delay starting from when the Sponsor has been informed;

2. In the case of the others unexpected Serious Adverse Events, at the latest within fifteen days starting from when the Sponsor has been informed.

The Sponsor declares in the form of a follow-up report to the ANSM the relevant further information concerning the unexpected Serious Adverse Events. In the case of suspicion of unexpected Serious Adverse Events having caused death or having endangered life, these further information are notified within eight days starting from the declaration mentioned in 1 °. In the other cases of suspicion of unexpected Serious Adverse Events and in case of new fact mentioned in the article L. 1123-10, the relevant further information are transmitted within a new deadline of eight days starting from the deadline mentioned in 2 °.

> Each SUSAR must be reported in an individual email message and should be sent to: declarationsusars@ansm.sante.fr. A declaration should be also sent to the Eudravigilance: (clinical trials module) https://eudravigilance.ema.europa.eu.

The subject line should be written as follows: *SUSAR_yyyymmdd_name of substance (or trial code no.)_Worldwide unique case identification number_CT*,

Ex: SUSAR_20140115_SUBSTANCE_123456789_CT.

Particular case: SUSARs regarding a clinical trial on medicinal products involving healthy volunteers (whatever the clinical trial phase): the subject line should be written as follows: ***EC-VS-SUSAR*** *_yyyymmdd_name of substance (or trial code no.)_Worldwide unique case identification number_CT.*

The following document should be attached to the message: - CIOMS form (PDF format) / File name labelled as follows: *yyyymmdd_name of substance (or trial code no.)_Worldwide unique case identification number_CT_C*.

Ex: 20140115_SUBSTANCE_123456789_CT_C.

An acknowledgement of receipt will be automatically sent by return email.

For Expected serious adverse reaction or other serious adverse event (clinical trials on a medicinal product involving healthy volunteers):

The Sponsor has to declare without delay to the competent authority the expected Serious Adverse Events and all other Serious Adverse Events occurring in France and outside the national territory.

> Each notification must be reported in an individual email message and should be sent to: declarationsusars@ansm.sante.fr

The subject line should be written as follows: ***EC-VS-EIGA*** *yyyymmdd_name of substance (or trial code no.)_Worldwide unique case identification number_CT.*

The following document should be attached to the message: - CIOMS form (PDF format) / File name labelled as follows: *yyyymmdd_name of substance (or trial code no.)_Worldwide unique case identification number_CT_C*.

An acknowledgement of receipt will be automatically sent by return email.

For other serious adverse event which occurred in France: The only difference compared to other SAEs is that the subject line should be written as follows: ***EC-VS-EVIG*** *yyyymmdd_name of substance (or trial code no.)_Worldwide unique case identification number_CT.*

11.2.3 Pregnancy

Any pregnancy occurring from the date of the informed consent signature and until trial completion must be reported immediately of UBC as soon as it becomes known to the investigator and no longer than 24 hours after first knowledge of the occurrence of the pregnancy (11.2.2.2).

11.3 Other assessments

NA

11.4 Appropriateness of measurements

Visual assessment of the skin blanching used for US ranking trial (13).

Safety is documented by the recording of adverse events, the global cutaneous tolerance, the physical examination and the vital signs assessments.

12 CLINICAL TRIAL VISITS DESCRIPTIONS AND PROCEDURES

12.1 Description of Clinical Trial Visits

A written, signed Informed Consent Form (ICF) must be obtained prior to performing any trial related evaluations and/or procedures for this protocol. The Investigator representative will review and explain the nature of the trial to the Subject and particularly the prohibited activities and the constraints of the trial. A copy of the signed and dated ICF will be provided to the Subject, another copy will be filed in the Investigator site file.

Visual assessments must be conducted by two trained readers for skin blanching response.

Schedule of Assessments is described in Table 1.

12.1.1 Screening Phase

The Screening period takes place within 15 days to 1 day prior to Day 1 visit.

The Investigator or the designed trial person will:

- Review and explain the nature of the trial in detail to the Subject, particularly the prohibited activities and the constraints of the trial.
- Insure that the Subject read and sign the Informed Consent Form. Give a copy to the Subject.
- Perform a urinary pregnancy test for female subject of childbearing potential.
- Assign to the Subject a Subject identification number and give his/her a Subject card.
- Collect information regarding demographics, relevant medical history, previous medications/procedures use and concomitant therapies/procedures use.
- Check inclusion/exclusion criteria.
- Perform a physical examination of the Subject, check vital signs (blood pressure, pulse rate).
- Test for assessment of the blanching response with the reference product on healthy skin
- Complete the Subject Screening & Enrolment log.
- Give the Subject an appointment for the Day 1 visit.

12.1.2 Test Phase

12.1.2.1 Baseline visit (Day 1)

The Investigator or the designated trial person will:

- Re-check inclusion/exclusion criteria including concomitant therapies.
- Ask the Subject about AEs by asking an open-ended question taking care not to influence the Subject's answer, such as "Have you noticed any change in your health since the last visit?" Record all events, as appropriate on the corresponding CRF pages.
- Ask the Subject whether there have been any changes to his/her concomitant therapies/procedures (added, removed, or changed) since the previous visit. Document all changes on the Concomitant Therapy form of the CRF.
- Perform a urinary pregnancy test for female subject of childbearing potential. The test must be negative to continue the trial.
- Preselect seven test sites, 2.2 cm in diameter on the anterior surface of the forearms (4 sites on one forearm and 3 on the other). Mark the selected sites with a cutaneous marker.
- Number the selected test sites from 1 to 7 (Z1-Z7).
- Assign a randomization number to the Subject (this number will be assigned to enrolled Subjects in a sequential order and no numbers will be omitted).
- Complete the Subject Screening and enrolment log and the Subject Identification Code List form indicating the last name, first name and date of inclusion.

- A member of staff other than the Investigator will:
- Apply 20µL of the tested products on the Subject's selected areas using gloves and a multi-pipette Eppendorf.
- Protect the test sites with a non-occlusive gaze dressing (for 16 hours).
- Instruct the Subject to avoid wetting areas (showers, swimming, bath, sauna, Hamman are not allowed).
- Schedule an appointment for the next Visit.

12.1.2.2 Day 2

At this visit, the Investigator or the designated trial person will:

- Ask the Subject about AEs by asking an open-ended question taking care not to influence the Subject's answer, such as "Have you noticed any change in your health since the last visit?" Record all events, as appropriate on the corresponding CRF pages.

- Ask the Subject whether there have been any changes to his/her concomitant therapies/procedures (added, removed, or changed) since the previous visit. Document all changes on the Concomitant Therapy form of the CRF.

A member of staff other than the Investigator/trained readers will:

- Remove the dressings and the product excess on each test site.

Two distinct trained readers will:

- Assess the skin blanching response (2 trained readers) on each test site 2 hours after removal of the products,
- Assess local tolerance by test site using a 4 point-scale for each site.

12.1.3 Follow-up Phase

If an adverse event (serious or non-serious), classified as possible or probably related to the trial medication or not assessable in relation to the trial medication, is ongoing at the subject's last visit, a follow-up visit/contact will take place 14 (±2) days after that visit.

12.1.4 Subject instructions

During the trial, the Subject will be allowed to use, if needed, all types of therapies excluding those listed in the exclusion criteria (section 9.2.2).

If a Subject need to take a concomitant treatment (topical or systemic), he/she should inform the Investigator of it as quickly as possible (at the latest, at the next visit).

The Subject will be instructed to keep the treated areas as dry as possible. Showers and baths are not allowed after the applications. In addition, the Subject will be instructed to avoid excessive sun exposure during the trial. During the trial, the Subject should avoid practicing strenuous exercises during the entire trial period.

Participation in any other clinical trial is prohibited during the course of the trial and for the following month.

13 Statistical Analysis

13.1 Trial population

All subjects recruited for the trial (i.e. signed informed consent obtained and a CRF Book started) will be accounted for in the trial report.

All randomized subjects who receive any trial medication and who contribute any efficacy data in the trial will comprise the full analysis set and will be analyzed for efficacy.

A per protocol analysis set will be defined by exclusion of subjects from the full analysis set, who do not fulfil all of the inclusion criteria or who meet any of the exclusion criteria.

Further subjects and/or subject data may be excluded from the per protocol analysis when agreed upon on the basis of the actual data obtained as evaluated before breaking the randomization code.

All subjects who receive any treatment with trial medication and for whom the presence or confirmed absence of adverse events is available will be included in the safety analysis set and analyzed for safety.

The decisions regarding inclusion/exclusion of subjects and/or subject data from the trial analysis sets will be documented in the Statistical Analysis Plan Update before breaking the randomization code.

13.1.1 Baseline characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for all randomized subjects.

Summary statistics of demographics (age and sex) and of baseline characteristics (height, weight, skin type, heart rate, systolic and diastolic blood pressure, concurrent diagnoses and concomitant medication at baseline) will be tabulated for all randomized subjects.

13.2 Analysis of pharmacodynamic effect (blanching)

The statistical analysis of efficacy will be based on the defined response criteria.

13.2.1 Primary pharmacodynamic criterion

The analysed variable will be the mean between the two readers at each evaluation time.

The results will be expressed by the mean values obtained at each assessment time by product/site.

MC2-01 cream will be compared with Clobex lotion, Betamethasone Dipropionate (Augmented) cream, Triamcinolone Acetonide cream, Locoid® cream, DesOwen cream and MC2-01 cream vehicle in terms of visual score of skin blanching 2 hours after a 16 hours application, using an ANOVA with subjects and treatments as factors. The mean of visual assessments obtained at the same time points from 2 independent trained readers will be used. In case of a significant treatment effect, estimates of treatment effect and 95% confidence interval of differences between reference products and MC2-01 cream will be calculated from the model without correction for multiplicity in the primary analysis. Correction for multiplicity using Dunnett's test will be used as secondary analysis. In case of significant deviation to the normal assumption, a non-parametric approach with Kruskall-Wallis test for the overall product effect and Wilcoxon's Sign Rank Test for the pairwise comparisons will be used.

13.2.2 Secondary pharmacodynamic criterion

Not Applicable

13.3 Analysis of Safety

13.3.1 Local safety

The local tolerance score will be summarized using frequency and percentage by visit and trial product. The worst score will also be summarized.

13.3.2 Adverse events

Adverse events will be coded during the course of the trial and will be in accordance with the current version of the MedDRA dictionary. The adverse events will be tabulated by Preferred Terms and System Organ Class.

The number of subjects experiencing each type of adverse event (according to MedDRA Preferred Terms and System Organ Class) will be tabulated regardless of the number of times each adverse event is reported by each subject.

Adverse events where the investigator has not excluded a causal relationship to trial medication (i.e. not described relationship as “no reasonable possibility”, adverse drug reactions) will be evaluated separately. A table or a description of these ADRs will be produced depending on the number of ADRs. As with adverse events, the number of subjects affected, not the number of events, will be considered.

The causal relationship of adverse events to trial medication and the intensity of adverse drug reactions will be tabulated or described. Where there are several recordings of causal relationship and intensity for the same event, causal relationship will be taken from the last report of the event (since that is when the investigator will be in possession of most information and so best able to judge causal relationship) and intensity will be taken as the worst ever recording. Adverse events observed on the application areas will be tabulated or described by treatment.

13.4 General principles

All significance tests will be two-sided and all confidence intervals will be presented with 95% degree of confidence.

Categorical data will be summarized using the number and percentage of subjects in each category. Continuous data will be summarized using the mean, median, SD, minimum and maximum values.

Very few missing values from primary response criterion are expected. Usually less than 10% of randomized subjects do not attend the last visit in this kind of studies. Drop-outs and missing values will be accounted for by the analysis of end of treatment values using a last observation carried forward approach and by the definition of the trial analysis sets prior to unblinding. All the pre-specified analyses will be reviewed in relation to the blinded data actually obtained and the Statistical Analysis Plan Update will be finalized before breaking the randomization code.

13.5 Number of subjects calculation

The null hypothesis for each pairwise comparison will be no difference in the human skin blanching test :

H0: Δ = 0,

where Δ is the mean difference in visual score between test sites with the compared treatments. The standard assumptions of normality and independence will be used.

According to previous vasoconstriction trial performed by CPCAD, a maximal standard deviation for the difference of 0.65 is assumed.

Using a paired t-test, a two-sided significance level of 5%, with 30 complete subjects, the probability of detecting a difference of 0.5 units assuming a standard deviation for the difference of 0.65 is 98%.

MC2-01 cream will be compared to the five steroid-containing reference products giving at least 92% (0.98) power to obtain 5 significant differences if the true difference with each reference product is at least 0.5 int. MC2-01 cream will also be compared to the matching MC2-01 cream vehicle, but that will have negligible impact on the overall power assuming a difference of at least 1 point between both products.

A total of 36 subjects will be randomized in this trial in order to obtain at least 30 completed evaluable subjects.

14 TRAINING / MONITORING / DATA MANAGEMENT / QUALITY ASSURANCE

14.1 Personnel training

A trial initiation visit will be conducted by the Sponsor with the Investigator and the trial team. During this meeting, an extensive review and discussion of the protocol, procedures, CRF and any other trial material will be conducted. Sponsor's monitoring visits will be performed.

Clinical Research Associates (CRAs) and other applicable personnel will be trained prior to trial initiation to familiarize CRAs with the disease, the Standard Operating Procedures (SOP), the protocol and other trial specific items. Team organization, communication and operational issues will also be discussed.

14.2 Clinical monitoring

The conduct of the clinical trial will be closely monitored by the sponsor's designee (Adhoc Clinical, Te Warde 45,89 Ieper, Belgium) to verify adherence to the clinical trial protocol, ICH GCP guidelines, and applicable SOPs.

The Investigator will allow the CRO/Sponsor's representatives, to have direct access to all clinical trial records, CRFs, corresponding subject medical records, trial drug(s) dispensing records, trial drug(s) storage area, clinical trial facilities, and any other documents considered source documentation.

The Investigator also agrees to assist the representative if required.

14.3 Data management

All data management procedures will be detailed in a Data Management Plan (DMP).

The DMP will describe the Clinical Data Management System (CDMS) that will be used to collect data. The study data will be collected on an electronic data capture (EDC) set up by the CRO. Computerized edit checks and review processes will be performed on an ongoing basis until all data clarifications are resolved. The data will be exported from MySQL database to be stored in appropriate format. After all data clarifications are resolved, coding is approved, and subject's evaluability is determined, the database will be locked.

14.4 Quality assurance / audit / inspection

The clinical trial is conducted under the sponsorship of DDS Ltd in compliance with the applicable international and local regulatory requirements as well as applicable ICH guidelines and in accordance with the SOPs for clinical trial conduct and monitoring from the assigned Contract Research Organization (CRO), Adhoc Clinical.

Audits of the clinical trial center may be conducted by the Sponsor/CRO representatives, and inspection may be performed by Regulatory Authority inspectorates or IECs before, during, or after the clinical trial.

The Investigator will allow and assist the CRO/Sponsor's representatives, IECs and any regulatory agency to have direct access to all requested clinical trial-related records.

For the audits performed by, or on behalf of, sponsors auditors, audit certificate(s) will be provided by Quality Assurance.

14.5 Changes in clinical trial conduct / amendments

14.5.1 Clinical trial conduct

With the exception of eliminating an immediate hazard to a subject, the Investigator should not deviate from the clinical trial protocol or implement any changes without written approval from the Sponsor and prior review and documented approval/favourable opinion from the IEC of a protocol amendment.

Changes that involve only logistical or administrative changes to the clinical trial protocol are authorized. The Investigator should document and explain any deviation from the clinical trial protocol.

14.5.2 Amendments

The Sponsor may modify the clinical trial protocol at any time for ethical, medical, or scientific reasons.

Protocol change to be submitted (Changes as per Substantial amendment in EU):

No amendment can be implemented at clinical trial center, unless to eliminate an immediate hazard to the subjects, without having obtained a favorable opinion from the appropriate Regulatory Authority and/or the IEC in compliance with applicable regulation(s).

Protocol change not to be submitted (Non-substantial amendment for EU):

An amendment will not be issued for modification(s) due to change in logistical or administrative aspects of the clinical trial (e.g., change in contact details for the Sponsor or Sponsor representative) or for non-substantial amendments for the clinical trial center within the European Union. In such cases, these changes will be documented and communicated to clinical trial center in the most appropriate way depending on the nature of the change.

15 ETHICS AND GENERAL CLINICAL TRIAL CONDUCT CONSIDERATIONS

15.1 Independent Ethics Committee (IEC)

This clinical trial protocol and all amendments will be reviewed and approved by the appropriate IECs.

15.2 Ethical conduct of the clinical trial

This clinical trial will be conducted in accordance with the protocol, the HELSINKI declaration (1964) and subsequent amendments, and the ICH GCP, and in compliance with applicable regulatory requirements.

15.3 Subject information and consent

All subjects who participate in this clinical trial are required to be fully informed about the clinical trial in accordance with GCPs guidelines and in accordance with local requirements.

All subjects recruited for this clinical trial will be registered in the National File of Persons Participating in Research involving the Human Person.

The ICF, approved by an IEC, will be fully explained to the subject.

Prior to enrolment into the clinical trial, the subject will sign and date the consent form(s). The Investigator is responsible for maintaining each subject's consent form(s) in the Investigator's site file and providing each subject, with a copy of the signed and dated consent form(s).

15.4 Protection of Personal Data

CPCAD is registered by the French Commission Nationale de l'Informatique et des Libertés (CNIL) as complying with the MR-001 Reference Methodology for processing clinical trial data (Declaration

number 1246487). CPCAD also complies with the local French GDPR (General Data Protection Regulation) law that entered into force on 25 May 2018. The GDPR allows the subject to exercise his/her rights of rectification, opposition, deletion, portability and limitation of the procession of his/her personal data. To assert this right, the volunteer can contact the Investigator.

15.5 Regulatory Authority

The written authorization of the clinical trial by the regulatory authorities (ANSM) will be required prior to the trial implementation.

15.6 Contractual requirements

A contractual agreement will be signed between the CRO/Sponsor and each Investigator/Institution. This document will contain supplementary information, including financial terms, confidentiality, the clinical trial schedule, third party responsibility, and publication rights.

15.7 Data collection and archiving

15.7.1 Data collection

The Investigator must maintain all required records for all subjects. Data for this clinical trial will be recorded in the subject's source documents and on the CRFs provided by the Sponsor. All data should be recorded on the CRFs completely and promptly, and legibly using black ink. A complete set of copies will remain at the clinical trial center with the related data clarification forms.

15.7.2 Source documentation

The Investigator must keep accurate separate records (other than the CRFs) of all subject visits, being sure to include all pertinent clinical trial-related information. A statement should be made indicating that the subjects have been included in this clinical trial and have provided signed written Informed Consent. All AEs must be thoroughly documented.

Results of any diagnostic tests conducted during the clinical trial should also be included in the source documentation.

15.7.3 Archives

All pertinent data, correspondence, and reports, the original or amended clinical trial protocol, and all other material relating to the clinical trial will be maintained securely in Sponsor/CRO/Investigator/ Institution archives for the legally required duration for archiving (15 years after the end of the research or after its premature termination).

The Investigator/Institution should maintain the essential clinical trial documents as specified in Section 8 of ICH GCP, and according to the applicable regulatory requirements.

The Investigator/Institution should take measures to prevent accidental or premature destruction of these documents.

If the Principal Investigator retires, relocates, or withdraws from the responsibility of keeping the clinical trial records for any other reasons, custody must be transferred to a person who will accept the responsibility. The Sponsor/CRO must be notified in writing of the name and address of the new custodian.

15.8 Insurance

A certificate attesting Third Party coverage of CRO/Sponsor will be provided upon request.

15.9 Investigator and Administrative Structure

Not applicable

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17 APPENDICES

Appendix 1: Summary of Product Characteristics (SmPC)/ Product Monographs for Investigational Products – Clobex® lotion

Appendix 2: Summary of Product Characteristics (SmPC)/ Product Monographs for Investigational Products – Betamethasone Dipropionate (Augmented)

Appendix 3: Summary of Product Characteristics (SmPC)/ Product Monographs for Investigational Products – Triamcinolone Acetonide cream

Appendix 4: Summary of Product Characteristics (SmPC)/ Product Monographs for Investigational Products – Locoid® cream

Appendix 5: Summary of Product Characteristics (SmPC)/ Product Monographs for Investigational Products – DesOwen® cream