MOR106
CLINICAL STUDY PROTOCOL

Project number:	MOR106	CSP Version:	4.0
Study Number:	MOR106-CL-204	Date:	25-Jun-2019
Study Title	**A randomized, double-blind, placebo-controlled, multicenter Phase 2 study to evaluate the safety and tolerability of subcutaneous MOR106 administered concomitantly with topical corticosteroids for eight weeks, in adult subjects with moderate to severe atopic dermatitis.**		
Status	Final	Development Phase:	2
EudraCT No:	Not applicable	CT.gov No:	NCT03864627
IND No:	[redacted]		
Sponsor:	Galapagos NV, Generaal De Wittelaan L11 A3, 2800 Mechelen, Belgium		
Study Physician:	[redacted]		
General Protocol / Applicable Country(ies)	General Protocol		

EMERGENCY CONTACT INFORMATION

In case of a **serious adverse event (SAE)** or a **special situation** (see Section 9.1.6) during the clinical study, or in case of pregnancy within 24 weeks after after last dose of study medication, the investigator must report this immediately, and under no circumstances later than **24 hours** following the knowledge of the SAE, special situation, or pregnancy, as follows:

<[redacted] SAE Fax #: [redacted]>
<or>
<E-mail: [redacted]

In case of medical **questions** during the course of the study, the investigator must contact the contract research organization (CRO) Medical Monitor or, if unavailable, his/her back up.

CRO Medical Monitor:
[redacted]
Mobile Phone: [redacted]
Office Phone: [redacted]
Email address: [redacted]

Sponsor Back-up contact:
[redacted]

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CLINICAL STUDY PROTOCOL (CSP) HISTORY

CSP / Amendment #	Date	General / Country Specific
CSP Version 1.0	15 August 2018	General, initial protocol. Not submitted.
CSP Version 2.0	22 August 2018	General, minor updates of the protocol. Not submitted.
CSP Version 3.0	15 October 2018	General, update of protocol before submission.
CSP Version 4.0 (amendment 1)	25 June 2019	General, update of exclusion criteria

SUMMARY OF CHANGES

CSP version 4.0, amendment 1 (25-Jun-2019)

The overall reason for the amendment:

The protocol was updated to refine the wording regarding the use of biologics for AD (exclusion criterion 4) and related to wording of history of Hepatitis A and B (exclusion criterion 5).

The changes made to the clinical study protocol MOR106-CL-204 Version 3.0, dated 15-Oct-2018, are listed below, reflecting a brief rationale of each change and the applicable sections.

Rationale: The wording regarding the prior use of biologics for AD has been updated to exclude only prior use of dupilumab. There is only one biologic currently approved for AD which is dupilumab. To avoid incurring any potential bias by including patients who have failed dupilumab treatment and are potentially treatment resistant, dupilumab will continue to be excluded. All other prior biologics will be considered as for prior non AD biologics, with a washout period of 5 half lives or 12 weeks.

Applicable Section: 4.5.2. Exclusion Criterion 4 (i and v)

Rationale: The wording has been updated in line with sponsors updated template text to allow subjects with a history of Hepatitis A and Hepatitis B to be included.

Applicable Section: 4.5.2. Exclusion Criterion 5

LIST OF TABLES

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

[redacted]	[redacted]
AD	atopic dermatitis
ADA	anti-drug antibody
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
AUC_{τ}	area under the serum concentration-time curve for the dosing interval
AST	aspartate aminotransferase
BSA	body surface area
CD1	cluster of differentiation 1
C_{max}	maximum observed serum concentration
CSP	clinical study protocol
CSR	clinical study report
CRO	contract research organization
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
DNA	deoxyribonucleic acid
EASI	Eczema Area and Severity Index
EC_{50}	50% effective concentration
ECG	electrocardiogram
ED	early discontinuation
ETD	early treatment discontinuation
EU	European Union
FIH	first-in-human
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice

GGT	gamma glutamyl transferase
HBc	hepatitis B core
HBs	hepatitis B surface
HOME	Harmonising Outcome Measures in Eczema
HIV	human immunodeficiency virus
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethical Committee
IGA	Investigators' Global Assessment
IgE	immunoglobulin E
IgG1	immunoglobulin G1
IL-17C	interleukin 17C
IL-17RE	interleukin 17 receptor E
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
ISR	injection site reaction
iSRC	independent Safety Review Committee
IWRS	interactive web response system
LD	loading dose
LFT	liver function test
MAD	multiple ascending dose
NOAEL	no observed adverse effect level
[redacted]	[redacted]
NYHA	New York Heart Association
PD	pharmacodynamics
PK	pharmacokinetic
[redacted]	[redacted]
PUVA	psoralen and ultraviolet A
Q2W	once every 2 weeks
Q4W	once every 4 weeks

QTcB	QT interval corrected for the heart rate using Bazett's formula
QTcF	QT interval corrected for the heart rate using Fridericia's formula
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
[redacted]	[redacted]
SOC	System Organ Class
[redacted]	[redacted]
SUSAR	suspected unexpected serious adverse reaction
TARC	thymus and activation regulated chemokine
TBL	total bilirubin level
TCS	topical corticosteroid
TCI	topical calcineurin inhibitor
TEAE	treatment-emergent adverse event
Th2	type 2 T helper cell
TNF-α	tumor necrosis factor-alpha
ULN	upper limit of normal
UVB	ultraviolet B
VAS	visual analogue scale
WOCBP	women of childbearing potential

Definition of Terms

BMI	weight (kg) / (height [m])^2
QTcB	$QTcB = QT / \sqrt{RR}$
QTcF	$QTcF = QT \times (1000/RR)^{1/3}$

1. SUMMARY

Objectives:

Primary Objective

– To investigate the safety and tolerability of repeated subcutaneous (s.c.) doses of MOR106 administered concomitantly with topical corticosteroids (TCS) in subjects with moderate to severe atopic dermatitis (AD) who are candidates for systemic therapy.

Secondary Objectives

– To evaluate the pharmacokinetics (PK) of repeated s.c. doses of MOR106 administered concomitantly with TCS.
– To monitor the occurrence of anti-drug antibodies (ADA) as a measure of immunogenicity after repeated s.c. doses of MOR106 administered concomitantly with TCS.

Other Objectives

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Design:

This is a randomized, double-blind, placebo-controlled, multicenter Phase 2 study of repeated s.c. doses of 320 mg MOR106 or placebo, administered concomitantly with TCS. On Day 1 a loading dose (LD) will be administered (i.e. 2 x 320 mg MOR106, or placebo).

Adult subjects with moderate to severe AD who are candidates for systemic therapy will be randomized 2:1 to receive MOR106 or placebo every other week via s.c. injections (on Days 1, 15, 29, and 43). The 8-week treatment period, finishing on Day 57, is followed by a 16-week follow-up period, finishing on Day 169. A total of 60 subjects (n=40 on MOR106, and n=20 on placebo) will be enrolled in this study.

Rationale:

This study is being conducted to obtain safety and preliminary efficacy information on the s.c. administration of MOR106 with concomitant TCS in subjects with moderate to severe AD who are candidates for systemic therapy in comparison to placebo with TCS.

TCS have been the primary treatment option for AD patients for many years and are commonly used as the first line of pharmacologic treatment in patients whose symptoms cannot be controlled with general measures such as allergen and irritant avoidance, skin hydration, and skin moisturization. TCS are also used to treat AD exacerbations. Therefore, many patients may use MOR106 in combination with TCS. For this reason, it is judicious to assess if MOR106 can be safely co-administered with TCS and to assess the added benefit. In order to standardize treatment conditions, the concomitant application of TCS and MOR106 or placebo starts on Day 1 for all subjects after a washout period for TCS of at least 7 days prior to the baseline visit (i.e. Day 1).

Endpoints:

Primary Endpoint

– The incidence and severity of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events of special interest (AESIs) through Day 169/ early discontinuation (ED) visit.

Secondary Endpoints

– MOR106 serum concentrations after repeated s.c. administrations from baseline through Day 169/ED visit.
– Occurrence of ADA from baseline through Day 169/ED visit.

Other Endpoints

[redacted]

– [redacted]
– [redacted]
– [redacted]
– [redacted]
– [redacted]

2. INTRODUCTION

Atopic Dermatitis (AD) is a chronic pruritic inflammatory skin disease that occurs most frequently in children, but also affects adults (Garmhausen, Hagemann, & Bieber, 2013). The main features of AD are the impairment of the skin barrier and dysfunction of the immune system accompanied with dry skin and severe pruritus that is associated with cutaneous hyperactivity to various environmental stimuli.

In AD the main goals of treatment are improving the appearance of the skin and relieving symptoms. Topical corticosteroids (TCS) are the most frequently prescribed class of drugs but long-term therapy is hampered by risks of skin atrophy, dyspigmentation, acneiform eruptions and risks associated with systemic absorption (growth retardation, hypo-thalamic-pituitary axis effects etc.). Topical calcineurin inhibitors (TCI) are safe and effective short-term treatments but are not suitable for use on severely affected skin. Repeated application of topical therapies over a long period is both time consuming and inconvenient to patients and their families and leads to poor patient adherence with treatment. Patients with moderate to severe AD that is not controlled with optimal topical therapy may require phototherapy or systemic immunosuppressant treatment to achieve adequate disease control. Oral immunosuppressants and glucocorticoids are also effective as short-term or intermittent therapies. However, long-term use is again restricted by concerns over toxicity and side effects. Dupilumab, a monoclonal antibody directed against IL-4 receptor alpha has been recently approved for the treatment of moderate to severe AD in adults by the Food and Drug Administration (Dupixent, 2016), by the European Medicines Agency and Health Canada (Dupixent Product Monograph, 2017/2018).

In inflammatory skin disorders, evidence has accumulated implicating interleukin 17C (IL-17C) as a potential important pro-inflammatory agent. IL-17C expression is induced in cultured keratinocytes by pro-inflammatory cytokines (tumor necrosis factor-alpha [TNF-α] and IL-1β) or bacteria (Ramirez-Carrozzi, Sambandam, & Luis, 2011) (Johansen, Riis, & Gedebjerg, 2011). IL-17C itself induces the expression of cytokines, pro-inflammatory mediators, and antimicrobial peptides in epidermal keratinocytes. Increased IL-17C levels were observed in AD subjects leading to an approximately 3-fold upregulation in a one week production rate compared to healthy subjects (Timmis, 2015). In skin biopsies, IL-17C was mainly expressed by the keratinocytes and to some extent in endothelial cells and infiltrating immune cells (Johansen, Riis, & Gedebjerg, 2011) (Johnston, Fritz, & Dawes, 2013). In animal models, intradermal injections of IL-17C, or keratinocytes overexpressing IL-17C, induced skin inflammation or spontaneous psoriatic-like lesions (Ramirez-Carrozzi, Sambandam, & Luis, 2011) (Johnston, Fritz, & Dawes, 2013). In IL-17C or IL-17RE (i.e. IL17C receptor subunit) knock-out mice, the psoriasiform skin inflammation induced by imiquimod, a well-established model, was significantly reduced (Ramirez-Carrozzi, Sambandam, & Luis, 2011).

MOR106 is a purified human recombinant Immunoglobulin G_1 (IgG_1) monoclonal antibody that binds with a high affinity to human IL-17C, thereby neutralizing its biological activity. It is produced in Chinese Hamster Ovarian cells by recombinant expression technology. MOR106 has significant effects in different rodent inflammatory skin models of AD and psoriasis. Nonclinical safety studies have demonstrated the absence of any adverse effects up to the highest dose tested (see Section 2.1.3) offering beneficial safety margins for

testing the proposed clinical doses and schedules of this study (see Section 4.2.1). The results of the first-in-human (FIH) Phase 1 study have shown that MOR106 is generally well tolerated in healthy male subjects and subjects with moderate to severe AD, with supportive data from exploratory efficacy assessments in this AD subject group (Timmis, 2015). To date, MOR106 is the first known IL-17C antagonist being evaluated in clinical studies.

This study is being conducted to obtain preliminary safety information on the s.c. administration of MOR106 with concomitant TCS in subjects with moderate to severe AD who are candidates for systemic therapy. Many patients may use MOR106 in combination with TCS. For this reason, it is prudent to assess if MOR106 can be safely co-administered with TCS.

The following paragraphs summarize the results of prior nonclinical (see Section 2.1) and clinical (see Section 2.2) studies for MOR106, more details can be found in the latest investigator's brochure (IB; Edition 3, 29 May 2018).

This clinical study will be conducted in accordance with the current International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice (ICH-GCP) Guideline E6 (see also Section 10).

2.1. Background - Nonclinical Studies

2.1.1. Nonclinical Pharmacology

2.1.1.1. Primary and Secondary Pharmacology

MOR106 binds with a high apparent affinity to human IL-17C (50% effective concentration [EC_{50}] of 19 ± 6.9 pM). Binding of MOR106 to human IL-17C is approximately 14- to 20-fold stronger compared to binding to cynomolgus monkeys and mice IL-17C, respectively. Binding of MOR106 is specific for IL-17C.

In vitro, MOR106 potently inhibits the binding of human IL-17C to its specific receptor IL-17RE and inhibits the biological activity of IL-17C. MOR106 inhibits the activity of cynomolgus monkeys and mice IL-17C with similar potencies as human IL-17C in contrast to the biochemical binding assay.

MOR106 prevented the occurrence of an AD-like skin inflammation in two different mouse models of AD. MOR106 reduced symptoms of the AD-like syndrome in the MC903 (calcipotriol) mouse model, with a significant impact on epidermal and dermal thickening, inflammation and type 2 T helper cell (Th2)-like gene expression. MOR106 also reduced the development of atopy and overt dermatitis in the skin barrier defective flaky tail model, with effects on gross clinical appearance, acanthosis, mast cell infiltration and serum levels of IgE and Th2-related cytokines IL-4 and thymus and activation regulated chemokine (TARC).

2.1.1.2. Safety Pharmacology

[redacted]

2.1.2. Nonclinical Pharmacokinetics

[redacted]

2.1.3. Toxicology

[redacted]

[redacted]

2.2. Background - Clinical Studies

To date, MOR106 has been administered during the single (SAD) and multiple ascending dose (MAD) parts of the FIH Phase 1 study MOR106-CL-101 (Timmis, 2015), as well as in an ongoing Phase 2 study (MOR106-CL-201, 2017) and an ongoing Phase 1 (MOR106-CL-102, 2018).

[redacted]

2.2.1. Clinical Pharmacokinetics and Immunogenicity

[redacted]

[redacted]

2.2.2. Clinical Safety

[redacted]

2.2.3. Clinical Efficacy

[redacted]

3. CLINICAL STUDY OBJECTIVES

3.1. Primary Objective

– To investigate the safety and tolerability of repeated subcutaneous (s.c.) doses of MOR106 administered concomitantly with topical corticosteroids (TCS) in subjects with moderate to severe atopic dermatitis (AD) who are candidates for systemic therapy.

3.2. Secondary Objectives

– To evaluate the PK of repeated s.c. doses of MOR106 administered concomitantly with TCS.
– To monitor the occurrence of anti-drug antibodies (ADA) as a measure of immunogenicity after repeated s.c. doses of MOR106 administered concomitantly with TCS.

3.3. Other Objectives

– [redacted]
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4. INVESTIGATIONAL PLAN

4.1. Clinical Study Design

This is a randomized, double-blind, placebo-controlled, multicenter Phase 2 study of repeated s.c. doses of 320 mg MOR106 or placebo, administered concomitantly with TCS. On Day 1 a loading dose (LD) will be administered (2 x 320mg MOR106, or placebo).

Adult subjects with moderate to severe AD who are candidates for systemic therapy will be randomized 2:1 to receive MOR106 or placebo every other week via s.c. injections (on Days 1, 15, 29, and 43). The 8-week treatment period, finishing on Day 57, is followed by a 16-week follow-up period, finishing on Day 169. A total of 60 subjects (n=40 on MOR106 and n=20 on placebo) will be enrolled in this study.

The screening visit will take place 7 to 28 days before baseline visit on Day 1. From screening onwards, subjects will apply a bland emollient at least twice daily, for at least 7 days prior to the baseline visit (i.e. Day 1). Emollient use must continue at least twice daily throughout the study (once daily in areas of TCS application).

TCS will not be permitted within 7 days prior to the baseline (Day 1) visit.

From Day 1 onwards, all subjects will apply concomitant open-label, once daily treatment with a medium potency TCS product. Other topical medications, such as a lower potency TCS or topical calcineurin inhibitors (TCI), may be used in addition to treat AD lesions located on the face, flexural, and genital areas. Once control has been achieved (i.e. lesions have cleared or almost cleared), TCS or TCI application to areas from which lesions have cleared will be limited to 2 days every week, in an interval of 3 or 4 days, until the end of the treatment period. TCS or TCI use will be reviewed at every visit by the investigator.

During the 16-week follow-up period, topical treatment of residual active AD lesions may continue as needed at the investigator's discretion.

Eligible subjects will undergo baseline evaluations and randomization, receiving first investigational medicinal product (IMP) dosing on Day 1. Following the completion of the first IMP administration, subjects will remain on site for a minimum of 2 hours after the injections. After the second (i.e. Day 15) and subsequent administrations subjects will remain on site for a minimum of 1 hour after each injection.

An interim analysis (after approximately 50% of the subjects having reached the end of treatment period) and a primary analysis (after the end of the treatment period for all subjects) are planned (please refer to Section 7.3.2). At the end of the study the final analysis will be conducted.

For the in- and exclusion criteria please refer to Section 4.5.1, "Inclusion Criteria" and Section 4.5.2, "Exclusion Criteria". A schematic diagram of clinical study design is provided in **Figure 1**.

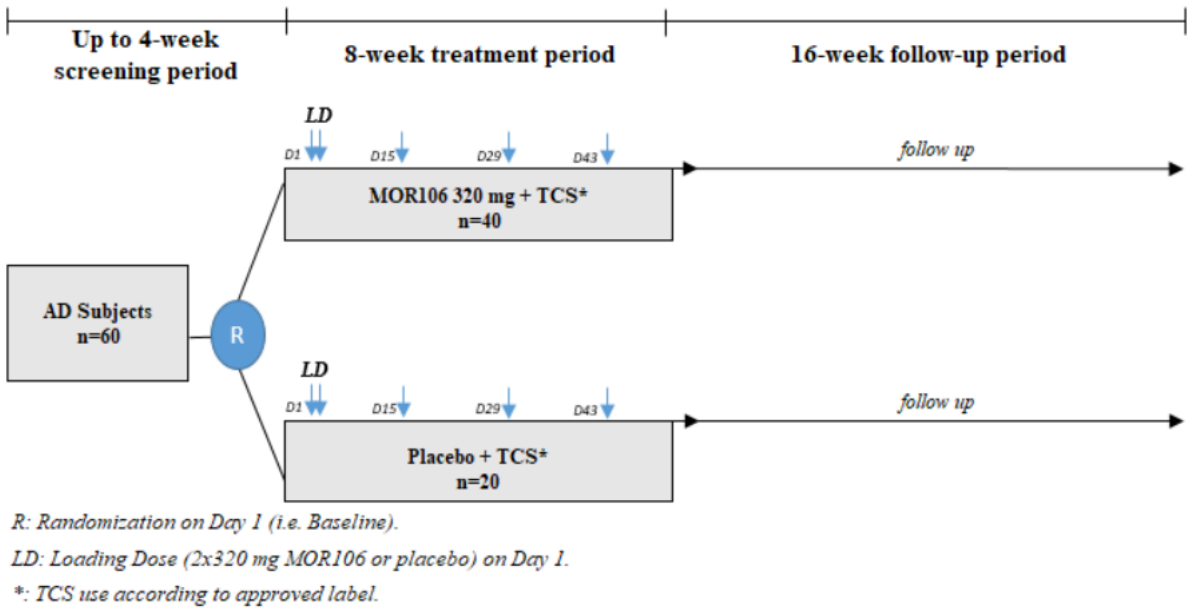


Figure 1: Schematic overview of the study design.

For detailed info regarding dosage form, packaging and labeling of the IMP please refer to Section 5.2, "Dosage and Administration" and Section 5.3, "Packaging, Labeling and Distribution".

The end of the study is reached when the last follow-up visit or contact as planned according the Schedule of Activities (see Section 6.10) of the last subject is performed.

4.2. Clinical Study Rationale

This study is being conducted to obtain safety and preliminary efficacy information on the s.c. administration of MOR106 with concomitant TCS in subjects with moderate to severe AD who are candidates for systemic therapy in comparison to placebo with TCS.

TCS have been the primary treatment option for AD patients for many years and are commonly used as the first line of pharmacologic treatment in patients whose symptoms cannot be controlled with general measures such as allergen and irritant avoidance, skin hydration, and skin moisturization. TCS are also used to treat AD exacerbations. Therefore, many patients may use MOR106 in combination with TCS. For this reason, it is prudent to assess if MOR106 can be safely co-administered with TCS and what added benefit this may have. In order to standardize treatment conditions, the concomitant application of TCS and MOR106 or placebo starts on Day 1 for all subjects after a washout period for TCS of at least 7 days prior to the baseline visit (i.e. Day 1).

4.2.1. Dosing Rationale

For this study a MOR106 dose of 320 mg s.c. is selected. This dose is the anticipated highest targeted dose for Phase 3 and is supported by safety data obtained in the FIH with i.v. dosing. It provides safety information that would cover potential lower doses as well.

Based on the PK results of the FIH study MOR106-CL-101 in AD subjects (Timmis, 2015), MOR106 serum levels were simulated for the s.c. dose planned for the current study (i.e. 320 mg Q2W including a LD at Day 1 over a 8-week treatment period). The following conservative assumptions were taken into consideration:

- Bioavailability following s.c. dosing in AD subjects was assumed at a maximum of 100%.
- C_{max} will be identical between s.c. and i.v. dosing.
- The proposed fixed LD of 640 mg s.c. on Day 1 (i.e. 2 x 320 mg) would translate into for example a 16 mg/kg dose in a 40 kg person (i.e. reflecting a body weight at the low end of the possible range considering study inclusion and exclusion criteria). The fixed dose of 320 mg administered every two weeks would translate into 8 mg/kg in a 40 kg person.

Following these simulations, the expected C_{max} and exposure (AUC) values for MOR106 in this study are covered by the results of the FIH MOR106-CL-101 (Timmis, 2015). In addition, AD subjects in study MOR106-CL-101 were dosed once weekly with i.v. doses of 1, 4 and 10 mg/kg. [redacted]

The addition of a loading dose on Day 1 (i.e. doubling the initial dose on Day 1) leads to steady-state-like trough or average drug levels directly after start of treatment. With regard to drug exposure vs. clinical efficacy, it is expected that clinical effects following MOR106 treatment/dosing are most likely linked to such stable drug levels as commonly reported for this compound class. (BLA761061, 2017).

Preclinically, the proposed dosing design is supported by the results of the 13-week i.v. repeat-dose toxicity study in mice (Perron, 2017) as well as the 4-week s.c. repeat-dose toxicity study in cynomolgus monkeys (Grote-Wessels, 2018). Further details are available in the IB.

The total treatment duration of a maximum of 8 weeks in this study is covered by the duration and results of the 13-week i.v. toxicity study in mice. In this preclinical study, systemic toxicity was evaluated by administering MOR106 i.v. once weekly (5-min bolus) for 13 weeks, followed by a 13-week recovery period. MOR106 was well tolerated up to the highest dose studied at 200 mg/kg (NOAEL). A safety margin of approximately 18-fold in C_{max} and 8-fold in exposure (i.e. AUC) is expected based on the observed NOAEL (i.e. observed animal values exceeding expected human values). In addition, results of the 4-week s.c. toxicity study in cynomolgus monkeys demonstrated that MOR106 was well tolerated not only systemically but also locally at the injection site after repeated s.c. dosing once weekly up to the highest dose tested at 300 mg/kg (NOAEL).

In summary, the available nonclinical and clinical safety package are considered sufficient to support the s.c. administration of MOR106 at a loading dose of 640 mg (i.e. 2 x 320 mg on Day 1) followed by 320 mg Q2W for 8 weeks in adult subjects with moderate to severe AD in study MOR106 CL-204.

4.2.2. Clinical Study Design Rationale

A placebo-controlled design is used to account for the high placebo effect that can be observed in the given population. The overall treatment period of 8 weeks is proposed to allow for a thorough investigation of the safety profile over a time period where already significant clinical treatment effects of both antibodies can be expected. A follow-up period of 16 weeks is selected to further monitor any MOR106 induced clinical effects and to observe any potential ADA development after treatment stop.

The clinician and subject-rated scales selected for this study are based on recommendations made by the Harmonising Outcome Measures for Eczema (HOME) trials group (Spuls, Gerbens, & Simpson, 2017) (Schmitt, Spuls, & Thomas, 2014). They are established scales recognized in this field.

[redacted]

4.3. Endpoints

4.3.1. Primary Endpoint

– The incidence and severity of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events of special interest (AESIs) through Day 169/ED visit.

4.3.2. Secondary Endpoints

– MOR106 serum concentrations after repeated s.c. administrations from baseline through Day 169/ED visit.
– Occurrence of ADA from baseline through Day 169/ED visit.

4.3.3. Other Endpoints

[redacted]

4.4. Potential Risks and Benefits

No risk factors for clinical use of MOR106 were identified based on the mode of action of the antibody (i.e. IL-17C antagonism). Two relevant nonclinical species were identified (mouse and cynomolgus monkey). Toxicity studies in these species applied a multiple of the doses anticipated for human use whereas no systemic drug-related AEs were observed (i.e. NOAEL in each nonclinical safety study defined at the highest dose studied) (Manciaux, 2016a), (Manciaux, 2016b), (Perron, 2017), and (Grote-Wessels, 2018). S.c. administration of MOR106 in cynomolgus monkeys did also not reveal any relevant observations of local intolerance during a 4-week period of time, up to 300 mg/kg. No sign for treatment-related immunotoxicity and no risk for a cytokine release syndrome became apparent during the study. Nevertheless, potential reactions will be monitored in this clinical study.

Data on the biology of the target IL-17C (a member of the IL-17 cytokine family) indicates a role of IL-17C as a regulatory cytokine for innate immune function in epithelial cells.

By neutralizing the biological activity of human IL-17C, MOR106 may have the potential of providing benefit as an effective and safe long-term treatment. This is in comparison to current oral immunosuppressants and glucocorticoids that are only approved as short-term or intermittent therapies, because their long-term use is restricted by concerns over toxicity and side effects.

The FIH study, MOR106-CL-101, has not identified any safety risks for i.v. administered MOR106 up to 20 mg/kg single doses. One healthy subject exhibited transient ADA development without any effect on PK and without impact on clinical safety findings.

In the FIH study MAD part i.v. administered MOR106 was well tolerated with no identified safety risks at doses up to four weekly doses of 10 mg/kg. One subject with moderate to severe AD developed a positive ADA titer during the follow-up period exhibiting clearing effects on the PK. There was no impact of the ADA formation on safety of this subject. The results from the exploratory objectives in the FIH study in terms of efficacy support the potential of MOR106 in the treatment of moderate to severe AD. The risk of immunogenicity will be thoroughly monitored throughout the trial.

Overall, it is considered that MOR106 does not pose a significant safety risk for the study subjects. In addition a beneficial effect of MOR106 on top of topical steroids may be experienced by the subjects with AD.

4.5. Clinical Study Population

4.5.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study.

1. Able and willing to comply with the protocol requirements, and signing the informed consent form (ICF) as approved by the IEC/IRB, prior to any screening evaluations.
2. Male or female between 18-65 years of age (extremes included), on the day of signing the ICF.
3. A BMI between 18-40 kg/m², inclusive.
4. Diagnosis of AD for at least one year since first diagnosis as per the Hanifin and Rajka Criteria.
5. EASI ≥16 at the screening and ≥16 at the baseline visit (Day 1 predose).
6. IGA score ≥3 (on the 0 to 4 IGA scale, in which 3 is moderate and 4 is severe) at the screening and baseline visits.
7. Greater than or equal to 10% body surface area (BSA) of AD involvement at the screening and baseline visits.
8. Willingness to use a non-medicated, simple bland emollient twice daily for at least 7 days before the baseline visit and throughout the study.
9. Subject is a candidate for systemic therapy and has a history of inadequate response to TCS or TCI before screening visit, as per investigator's opinion.
10. Subject has at least one AD lesion for which treatment with medium potency TCS is indicated.
11. Female subjects must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline. The exception are women who are surgically sterile (hysterectomy, bilateral salpingectomy and bilateral oophorectomy), or postmenopausal (i.e. at least 12 consecutive months without menstruation, without an alternative medical cause [including hormone replacement therapy]). A determination of follicle stimulating hormone (FSH) can be performed with FSH >35 mIU/mL confirming postmenopausal status without menstruation for ≥24 months.

12. Female subjects of childbearing potential must use a highly effective method of contraception from 28 days prior to the first dose of IMP, throughout the study, and for at least 24 weeks after the last dose of IMP.
13. Non-vasectomized male subjects with a female partner of childbearing potential must agree to use a condom, in addition to another highly effective form of contraception used by the female partner, from prior to the first dose, throughout the study, and for at least 24 weeks after the last dose of IMP.

4.5.2. Exclusion Criteria

Subjects meeting any of the following exclusion criteria are not eligible for participation in this study:

1. Prior treatment with MOR106.
2. Known hypersensitivity to any IMP ingredients as determined by the investigator (such as, but not limited to, anaphylaxis requiring hospitalization).
3. AD lesions located predominantly (≥50% of the cumulative lesional area) on face and genital areas.
4. Having used any of the following treatments:
   - i. *Original criterion (CSP Version 3.0, dated 15-Oct-2018):*

     Prior exposure to a biologic therapy for AD.
   - i.1 *Change of the original criterion (CSP Version 4.0, dated 25-Jun-2019):*

     Prior exposure to Dupilumab.
   - ii. Immunosuppressive/immunomodulating drugs (e.g. systemic corticosteroids, cyclosporine, mycophenolate-mofetil, IFN-γ, azathioprine, methotrexate) within 4 weeks of baseline (Day 1) visit.
   - iii. Phototherapy (ultraviolet B [UVB] or Psoralen Ultraviolet A [PUVA]) for AD within four weeks of baseline (Day 1) visit.
   - iv. Treatment with TCS or TCI within 7 days before the baseline (Day 1) visit.
   - v. *Original criterion (CSP Version 3.0, dated 15-Oct-2018):*

     Treatment with biologics (for non-AD indications) within five half-lives (if known) or 12 weeks prior to baseline visit, whichever is longer.
   - v.1 *Change of the original criterion (CSP Version 4.0, dated 25-Jun-2019):*

     Treatment with biologics within five half-lives (if known) or 12 weeks prior to baseline visit, whichever is longer.
   - vi. Regular use (more than two visits per week) of a tanning booth/parlor within 4 weeks of the baseline visit.
5. *Original criterion (CSP Version 3.0, dated 15-Oct-2018):*

   Positive serology for hepatitis B (positive hepatitis B surface [HBs] antigen and/or positive hepatitis core antibody [HBc]) or hepatitis C (anti-HCV) or any history of

hepatitis from any cause with the exception of hepatitis A. Subjects who are immune to hepatitis B because of vaccination can be included.

5.1 *Change of the original criterion (CSP Version 4.0, dated 25-Jun-2019):*

Positive serology for hepatitis B (positive hepatitis B surface [HBs] antigen and/or positive hepatitis core antibody [HBc]) or hepatitis C (anti-HCV) or any history of hepatitis from any cause with the exception of hepatitis A and B. Subjects who are immune to hepatitis B because of vaccination can be included.

6. History of or a current immunosuppressive condition (e.g. human immunodeficiency virus [HIV] infection, as determined by a positive HIV test at screening).
7. Subjects with a history of varicella zoster virus who experienced any episode or recurrence of herpes zoster infection within 1 year of screening must be excluded. (A history of herpes simplex types 1 or 2 or vaginal candidiasis is permitted.)
8. Any concurrent illness, condition, disability, or clinically significant abnormality (including laboratory tests, a New York Heart Association Classification (NYHA) greater than or equal to III/IV) or clinically significant illness in the 3 months prior to initial IMP administration that, in the investigator's opinion, represents a safety risk for the subject's participation in the study, may affect the interpretation of clinical safety or efficacy data, or may prevent the subject from safely completing the assessments required by the protocol.
9. Any of the following laboratory abnormalities:
    i. Hemoglobin (Hb) <12 g/dL (male) or <10 g/dL (female)
    ii. White blood cell count $<3.0 \times 10^9$ cells/L
    iii. Neutrophil count $<1.5 \times 10^9$ cells/L
    iv. Platelet count $<100 \times 10^9$ cells/L
    v. Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2x upper limit of normal (ULN)
    vi. Total bilirubin level >1.5 x ULN
10. History of malignancy within the past 5 years prior to screening with the exception of excised and curatively treated non-metastatic basal cell carcinoma or squamous cell carcinoma of the skin.
11. Clinically significant abnormalities at the discretion of the investigator detected on vital signs or physical examination (other than AD) at screening or baseline (Day 1 predose).
12. Active drug or alcohol abuse.
13. Subjects who have had or will have an attenuated live vaccination within 4 weeks of the first dosing.
14. Participation in another experimental therapy study within 90 days or five times the half-life of the experimental therapy, whichever is longer, prior to dosing for this study.
15. Investigator or any sub-investigator, research assistant, pharmacist, study coordinator, or other staff who is directly involved in the conduct of the study, or relative thereof.

16. Active chronic or acute skin infection requiring treatment with systemic (i.e. oral, s.c., i.v.) antibiotics, antivirals or antifungals within 4 weeks of baseline, or clinical signs of infective eczema within 7 days before baseline (Day 1 predose) (Note: subjects may be rescreened after infection resolves). Oral fluconazole for vaginal yeast infection and oral antiviral medication for herpes labialis and herpes genitalis is permitted.
17. Pregnant or breast feeding female subject (or subject is planning to become pregnant).
18. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (e.g. tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution or unusually frequent, recurrent, or prolonged infections, per investigator judgment.
19. Not able to manage the electronic diary (e-diary) as per assessment of the investigator.
20. Any condition or circumstances that in the opinion of the investigator may make a subject unlikely or unable to complete the study or comply with study procedures and requirements.

4.5.3. Prohibition and Restrictions

4.5.3.1. Precautions for Sexual Intercourse

Highly effective contraceptive measures for both males and females of childbearing potential must be documented in the source documents.

4.5.3.1.1. Female Subjects

In line with the Heads of Medicines Agencies (HMA)'s Clinical Trial Facilitation Group (CTFG) recommendation, female subjects are considered of non-childbearing potential if they meet one of the following criteria:

- No menses for 12 or more months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Permanently surgically sterile (bilateral oophorectomy, i.e. surgical removal of ovaries, bilateral salpingectomy or hysterectomy, i.e. surgical removal of uterus).

All other female subjects are considered to be of childbearing potential (WOCBP) and must use one of the following highly effective methods of birth control prior to the first dose of IMP, during the clinical study and for at least 24 weeks after the last dose of IMP:

- Combined (estrogen and progesterone containing) (oral, intravaginal, transdermal) hormonal contraception associated with inhibition of ovulation plus a barrier method[1].

[1] As there is no current data available regarding potential interactions between IMP and hormonal contraceptives, female subjects who use hormonal contraception should supplement this with a barrier method (preferably male condom).

- Progesterone-only hormonal (oral, injectable, implantable) contraception associated with inhibition of ovulation plus a barrier method[1].
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject.

Periodic abstinence (e.g. calendar, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a clinical study, withdrawal, spermicides only and lactational amenorrhea method are not acceptable as methods of contraception.
In case a WOCBP has a vasectomized partner, provided that partner is the sole sexual partner of the WOCBP clinical study participant and that the vasectomized partner has received medical assessment of the surgical success, then she is not required to use an additional form of contraception.

Within these limits, the specific forms of contraception employed are left to the discretion of the subject, the investigator, and/or the subject's physician.

The safety of MOR106 during breastfeeding is unknown. Women who are nursing are not allowed to take part in this clinical study.

No ova donation is allowed from first dose of IMP during the clinical study until 24 weeks after the last dose of IMP.

4.5.3.1.2. Male Subjects

Non-vasectomized male subjects with female partners of childbearing potential must be willing to use a condom from the time of the first dose of IMP, during the clinical study, and for at least 24 weeks after the last dose of IMP, in addition to having their female partner use one of the following forms of contraception:

- Combined (estrogen and progesterone containing) (oral, intravaginal, transdermal) hormonal contraception associated with inhibition of ovulation.
- Progesterone-only hormonal (oral, injectable, implantable) contraception associated with inhibition of ovulation.
- Intrauterine device.
- Intrauterine hormone-releasing system.

Sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments is considered a highly effective contraceptive measure. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Periodic abstinence (e.g. calendar, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a clinical study, withdrawal, spermicides only and lactational amenorrhea method are not acceptable methods of contraception.

In a case where the female partner of a male subject has undergone documented surgical sterilization that was performed more than 1 year before screening, then the subject is not required to use an additional form of contraception.

Vasectomized male subjects with female partners of childbearing potential are not required to use an additional form of contraception providing that surgical sterilization has been successful (documented azoospermia by semen analysis).

No sperm donation is allowed from first dose of IMP during the clinical study until 24 weeks after the last dose of IMP.

4.5.3.2. Prior and Concomitant Medications

All medications in relation to the treatment of AD that are not allowed in accordance with the inclusion and exclusion criteria should not be used during the study. All allowed standard treatment should remain on a stable dose until completion of the Day 169 (or ED) visit, if possible.

Prior medications (with the exception of medications used for treatment of AD) used in the 3 months prior to Day 1 will be recorded in the electronic case report form (CRF). Medications used for the treatment of AD received during the last 12 months before Day 1 will be recorded in the CRF. These include any systemic therapy, biologics, or phototherapy ever used for the treatment of AD.

4.5.3.2.1. Topical Corticosteroids (TCS)

Subjects will not use any TCS for at least 7 days prior to the baseline (Day 1) visit.

From Day 1 onwards, all subjects will apply concomitant open-label, once daily treatment with TCS as follows:

- Medium potency TCS (e.g. Triamcinolone 0.1% cream or Mometasone furoate 0.1% cream or another sponsor approved TCS) to be used as per approved label.
- Other topical medications, such as a lower potency TCS or TCI, may be used to treat AD lesions located on the face, flexural, and genital areas as per approved label.
- Once control has been achieved (lesions have cleared or almost cleared), TCS or TCI application to areas from which lesions have (almost) cleared, will, under the supervision of the investigator, be limited to twice weekly in intervals of 3-4 days until the end of the treatment period (D57).
- During the follow-up period (D57 to D169), topical treatment of residual active AD lesions may continue as needed at the investigator's discretion. This treatment can be stepped up or stepped down as clinically indicated per investigator's discretion.
- During the follow-up period (D57 to D169), in the event of an AD flare, initiation or escalation of TCS therapy will be recorded as rescue therapy in the follow-up period.

– All TCS (and TCI if used) use will be recorded daily by the subject in a diary from screening visit onwards and throughout the study and will be reviewed at each onsite visit by the investigator.

Detailed instructions on TCS management will be described in a separate study reference manual.

4.5.3.2.2. Emollients

Subjects should apply emollient (moisturizers) at least twice daily for at least 7 consecutive days prior to baseline and continue the treatment throughout the study (including follow-up period). Emollient use should continue at least twice daily (once daily in areas of TCS application) throughout the study, even in the event of eczematous areas improving or resolving. Emollient use must be recorded in the CRF as concomitant medication and use will be recorded daily by the subject in a diary from screening onwards and will be reviewed at each onsite visit by the investigator.

Subjects should not apply their emollient within 6 hours prior to skin assessments. The emollient can be applied after completion of skin assessments.

There must be no active ingredients which could potentially affect AD in the emollient. This includes urea, ceramides, and antimicrobials.

If subjects at screening are using a non-medicated emollient, and are eligible for the study they must continue the use of this throughout the study. If subjects at screening are not using a non-medicated emollient and are eligible for the study, they must start using one once all screening assessments are completed.

4.5.3.2.3. Permitted Medications

Apart from the prohibited medications listed in Section 4.5.3.3 treatment with concomitant medications is permitted throughout the study. This includes oral contraceptives, nasal and inhaled corticosteroids, and oral antihistamines. All concomitant medicines must be locally approved and administered at a dose that is considered standard-of-care for the treated indication. It is required that these medications are given at a stable dose prior to study entry and preferably continued without variation of dose or regimen during the study.

In a case where additional concomitant medication need to be administered or dose adjustments for pre-existing conditions (except for AD) need to be performed during the study, the risk/benefit ratio to the subject must be carefully assessed and consideration given to the timing of any necessary introduction of new medications. Continuation of the subject should be reviewed and can be discussed with the medical monitor if needed.

Oral antibiotics to treat atopic dermatitis-associated superficial skin infections are also permitted for up to two weeks duration.

4.5.3.3. Prohibited Concomitant Medications and Procedures

The following medications are prohibited throughout the study participation:

- Topical corticosteroids, except as described in Section 4.5.3.2.1
- Systemic corticosteroids
- Topical tacrolimus and pimecrolimus
- Leukotriene inhibitors
- Allergen immunotherapy
- Systemic treatment for AD with an immunosuppressive / immunomodulating substance (including but not limited to, cyclosporine, mycophenolate-mofetil, azathioprine, methotrexate, biologics or interferon gamma or investigational drugs other than MOR106)
- Treatment with a live (attenuated) vaccine
- Photopheresis, immunoapharesis/-adsorption

The following concomitant procedures are prohibited throughout study participation:

- Elective major surgical procedures
- Concomitant ultraviolet (UV) procedures (phototherapy [narrow band UVB, UVB, UVA1 or PUVA1])
- Tanning in a bed/ booth

4.5.3.4. Rescreening

Subjects may only be rescreened with the approval of the medical monitor. If a subject is rescreened, all screening assessments will be repeated and a new screening number will be applied. If a subject is rescreened, the screening window will begin once the first rescreening assessment has been initiated.

4.5.3.5. Food and Beverage Restrictions

Subjects are not allowed to take alcohol 24 hours before screening and each IMP administration and should abstain from alcohol for 24 hours after dosing. Subjects must limit their alcohol intake during the study to no more than three glasses of wine or beer or equivalent per day.

4.5.4. Treatment Discontinuation (Temporarily and Permanently), Subject Withdrawal and Study Termination

A subject may be withdrawn from the clinical study at any time without the subject's consent if the investigator or sponsor determines that it is not in the best interest of the subject to continue participation. In such case, the reason for withdrawal will be documented in the source documents, and the subject will complete the early discontinuation (ED) visit and /or follow-up visits for safety assessments.

Treatment with IMP should be discontinued by the investigator (preferably after discussion with the CRO medical monitor, who may consult and must inform the sponsor's study physician) for any of the following conditions:

- Life-threatening AE or a SAE that places the subject at immediate risk.
- Serious infections deemed related to study treatment by the investigator, and requiring parenteral antimicrobial therapy and/or hospitalization.

- Confirmed pregnancy in a female subject or female partner of a male subject (due to likely unblinding of the subject).
- Arrhythmia or conduction abnormality, including but not limited to prolonged QT interval corrected for the heart rate using Fridericia's formula (QTcF), where the severity is categorized as Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher (QTc >500 ms on at least two separate ECGs).
- Increase in liver function tests (LFTs):
  - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) elevations >8x ULN: IMP treatment should be withheld and the LFTs should be repeated. IMP should be discontinued permanently if the results are confirmed.
  - AST and/or ALT elevations >3x ULN and <8x ULN: IMP treatment should be withheld.
    - If LFTs do not return to normal within 2 weeks then the IMP should be discontinued permanently.
    - If LFTs return to normal within 2 weeks then IMP could be restarted with close monitoring (e.g. repeat testing twice per week for the first 2 weeks then weekly for the following month). In the event LFTs become abnormal at any subsequent point during the trial (i.e. after rechallenge) then the IMP should be permanently discontinued.
  - AST and/or ALT elevations >3x ULN **and** total bilirubin level (TBL) >2x ULN or international normalized ratio (INR) >1.5: IMP treatment should be withheld and the LFTs should be repeated. IMP should be discontinued permanently if the results were confirmed.
  - AST and/or ALT elevations >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%): IMP treatment should be withheld, LFT repeated and IMP discontinued if LFT confirmed **or** if symptoms and signs persist.

When test results need to be confirmed, the subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. In addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma glutamyl transferase (GGT), INR, and alkaline phosphatase. A detailed history, including relevant information (e.g. review of ethanol, recreational drug and supplement consumption, family history, sexual history, travel history, history of contact with a jaundiced subject, surgery, blood transfusion, history of liver or allergic disease, and work exposure) should be collected. Further testing for acute hepatitis A, B or C infection and liver imaging (e.g. biliary tract) may be warranted. All cases confirmed on repeat testing with no other cause for LFT abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

Every effort should be made to keep subjects in the study and on treatment. However, the investigator can consider stopping the treatment with IMP, preferably after consultation with the sponsor's study physician, in case of concerns about the subject's safety, major protocol noncompliance, serious or severe AEs or worsening of the disease condition,

which in the investigator's opinion needs an alternative treatment approach not being covered in the clinical study (e.g. rescue medication).

When study treatment is discontinued, the subject will be requested to return for Early Treatment Discontinuation (ETD) visit and will be asked to continue the follow-up period until end of study.

Subjects will be informed prior to clinical study entry that they are allowed to withdraw from the clinical study. At any time and for any reason, a subject's participation in the clinical study may terminate at his/her request without prejudice to his/her future medical care. The subject will be encouraged to share the reason(s) for withdrawal so this can be documented in the source documents, and to complete the ED/ETD visit and follow-up visits for safety assessments, but will not be obliged to do so.

Subjects who withdraw from the clinical study without contact with the site (lost-to-follow-up) should be contacted by the site so that their health status can be assessed and documented in the source documents. The site should make every effort to understand whether the subject is alive, including checking the medical records and contacting general practitioner or relatives, if necessary. All attempts must be documented in the source documents.

The sponsor has the right to terminate the clinical study at any time in case of safety concerns or if special circumstances concerning the IMP or the company itself occur, making further treatment of subjects impossible. In this event, the investigator(s) and relevant authorities will be informed of the reason for clinical study termination.

4.6. Measures to Minimize Bias

4.6.1. Randomization

At screening, subjects will be assigned a subject screening number in ascending order (per site level), which should not be skipped. When subjects are confirmed to be eligible for the clinical study, they will be assigned a subject randomization number in ascending order. Allocation of each subject to a given treatment will be done using a centralized electronic system (interactive web response system [IWRS]), according to a pre-specified randomization scheme prepared by an independent statistician at the CRO. Subjects will be randomized in a 2:1 ratio to MOR106 or placebo.

4.6.2. Blinding and Unblinding

This is a randomized, double-blind clinical study. The subject and the entire clinical study team, including the investigator, clinical study coordinator, and sponsor personnel are blinded to treatment assignment. Details on unblinding procedures for the interim and primary analysis are in Section 7.3.2).

The site pharmacist(s) or appropriately qualified member of the clinical study staff, are unblinded to treatment and assigned by the investigator to prepare and administer the IMP that corresponds to the assigned subject identification number. All staff members not involved in IMP preparation and/or administration are blinded to treatment assignment.

The blind can be broken via IWRS only if the investigator deems it necessary for the safety of a subject. The investigator is encouraged to discuss considerations to break the blind with the CRO medical monitor, whenever possible, and where the situation allows. However, the responsibility to break the treatment code in emergency situations resides solely with the investigator. The investigator is not required to discuss unblinding beforehand if he or she feels rapid emergency unblinding is necessary, but is required to inform the sponsor in a timely fashion after unblinding has occurred.

If the blind is broken for any reason during the course of the clinical study, the moment on which the blind was broken and all other relevant information will be documented by the investigational site. The reason for breaking the blind will be indicated and justified in the source documentation, together with the confirmation that the subject discontinued the study treatment with unblinding as the reason for discontinuation.

If an AE leads to unblinding, the AE will be given as the reason for unblinding. All subjects who are unblinded should, where possible, complete the ETD visit. Any AEs should be followed until resolution.

Code-break information (via IWRS vendor) will be provided to the bioanalytical laboratory responsible for serum drug determination sample analysis, the laboratory responsible for biomarker analysis, and to the sponsor pharmacovigilance lead for SAE reporting purposes.

4.6.3. Independent Safety Review Committee

To safeguard the safety of the subjects, an independent Safety Review Committee consisting of independent dermatology and statistical experts will be implemented to review accumulating unblinded safety data for the clinical study, specifically the review of any skin related AEs and serious adverse reactions. The specific responsibilities, composition, meeting formats and details of output provided for the meetings of the independent Safety Review Committee will be outlined in detail in an Independent Safety Committee Charter. Members of the independent Safety Review Committee will not be involved in the day-to-day conduct of the study.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Identity of the Investigational Medicinal Products

MOR106
The active pharmaceutical ingredient (API) of MOR106 is a human IgG1 monoclonal antibody that binds with a high apparent affinity to human IL-17C.

For s.c. injection the API of MOR106 is formulated as a sterile, stable and highly concentrated liquid formulation of 160 mg/mL filled in a 2R clear glass vial with a rubber stopper and blue crimp cap with an extractable volume of 1 mL. The formulation buffer for s.c. injection consists of L-histidine, L-Arginine, and 0.02% Polysorbate 20, pH 6.0.

Placebo
For s.c injections of placebo sterile formulation buffer of MOR106 in 2R clear glass vial with a rubber stopper and blue crimp cap with an extractable volume of 1 mL is available.

5.2. Dosage and Administration

The IMP will be prepared by an unblinded and adequately trained member of the clinical center pharmacy staff as designated by the principal investigator.

S.c. injections of MOR106 or placebo will be performed by an unblinded administrator who is not performing or involved in any of the study assessments.

Appropriate measures will be taken to keep the subjects blinded from the administered IMP. Details will be provided in the study reference manual.

For the single dose s.c. injection, the following components will be supplied to the clinical centers:
- Vials containing 160 mg/mL MOR106 injectable solution, buffered at a pH 6.0.
- Vials containing formulation buffer of MOR106, pH 6.0 (Placebo).

The following doses will be used:
- MOR106 320 mg (2 mL at 160 mg/mL) every 2 weeks (Q2W) s.c. injection, including a LD of 2 x 320 mg in total (2 x 2 mL) on Day 1.
- Corresponding placebo s.c. injection (2 mL formulation buffer) plus an additional s.c. injection (2 mL) on Day 1.

S.c. injection sites should be alternated among the different quadrants of the abdomen (avoiding the navel and waist areas) so that the same site is not injected for two consecutive visits. The quadrant injected should be documented in the CRF. Full details on the s.c. administration will be provided in the pharmacy manual. To allow for adequate assessment of the ISRs study treatment should be administered into an area of normal looking skin (where possible). Instructions for assessing and recording ISRs will be provided in the study reference manual.
The dose-corresponding-volume of MOR106 drug product for s.c. injection will be collected in a syringe and injected with a suitable hypodermic needle for s.c. injection. As placebo, the same volume of placebo solution as the dose-corresponding-volume of MOR106 drug product, will be collected in a syringe and injected with a suitable hypodermic needle for s.c. injection.

Detailed instructions on IMP management will be provided in the pharmacy manual.

5.3. Packaging, Labeling and Distribution

IMP packages will be labeled with clinical study-specific details, including storage conditions.

All manufacturing, packaging, and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements.

The distribution of the IMP to the clinical site will only occur after the required local documentation is obtained including clinical study approval by Competent Authorities and

the IECs/IRBs, documentation on which the assessment of the investigator's qualifications was based (e.g. curriculum vitae) and the signed and dated study agreement and financial agreement.

5.4. Storage

Sites are to store the IMP supplies in a secure area at 2-8°C (i.e. 36-46 °F) until dispensed. Sites will be required to monitor the storage temperature by using a suitable temperature-recording device in order to establish a record of compliance with these storage conditions.

Details for the appropriate monitoring of the storage temperature and handling of temperature excursions will be provided in the pharmacy manual.

5.5. Treatment Compliance and Drug Accountability

The pharmacist or other designated clinical site personnel should maintain a log of the total amount of IMP received at site, date/time of IMP preparation, and administration to the subjects. IMP supplies for each subject will be inventoried and accounted for throughout the clinical study. At the end of the treatment period these records will be checked against the inventory by the study monitor. All IMP supplies will be stored in locked facilities.

Upon sponsor approval all unused IMP and empty IMP packages will be destroyed at the site. If destruction by the site is not possible or the destruction process is found unacceptable by the sponsor, the IMP should be returned to the drug supplier/drug depot as appropriate.

Detailed instructions on IMP handling will be provided in the pharmacy manual.

6. CLINICAL STUDY ASSESSMENTS

Every effort should be made to ensure that CSP-required tests and procedures are completed as described in the Schedule of Activities (see Section 6.10). To avoid inter-observer variability, every effort should be made to ensure that all safety and efficacy evaluations are completed by the same individual who made the initial baseline determinations.

6.1. Timing of Assessments

ICF needs to be signed before any study procedure, including screening procedure, is carried out.

The study assessments will be undertaken at time points as specified in the Schedule of Activities in Section 6.10. A window of ±1 day is allowed for Visit 4 and a window of ±2 days is allowed for all visits from Visit Day 15 onwards (Day 15 included).

Visit dates are always calculated from Day 1 (unless subject discontinues early and attends ETD visit). If a subject has an ETD visit, the follow-up visits are performed 14, 28, 42, 56, 70, 84, 98 and 112 days after the ETD visit.

Subjects who are discontinued from treatment during the dosing period will perform Day 57/ETD visit (14 days after the last dose) as the last visit in the dosing period before entering the follow-up period.

Subjects reported outcomes ([redacted] are to be completed on site by the subject preferably before any other study-related procedures is performed.

[redacted]

12-Lead ECGs, vital signs, and physical examinations are to be recorded before invasive procedures are performed.

Blood samples should be taken after all noninvasive procedures (including completion of questionnaires) have been finished.

During the treatment period, procedures and assessments are to be performed prior to administration of IMP, except where indicated. For predose assessments, those should be done within 3 hours predose.

The following collection time windows apply:

- 12-Lead ECGs: A window of ±15 minutes is allowed for the Day 1 and Day 43 postdose assessments.
- Blood sampling: For samples < 24h: +/- 10 min; 24h samples: +/- 1 hour; 48, 72 and 96h samples: +/- 2 hours.
- Urine sampling: predose (within 2 hours before IMP dosing).

Safety assessments should be repeated at other time points and additional assessments made if clinically indicated.

6.2. Unscheduled Visits

Additional visits can be performed at other time points for any safety assessments, if clinically indicated. These unscheduled visits and outcomes of additional assessments need to be recorded in the source and if performed before the subject's last visit per CSP, also in the CRF.

In case of an unscheduled visits, the following procedures and assessments should be performed:

- Record the reason for the unscheduled visit.
- Perform the assessments and procedures related to the reason for the unscheduled visit as deemed to be indicated by the investigator.
- Record AEs.
- Record concomitant medication and therapies.

6.3. Initial Subject and Disease Characteristics

Subjects will be asked to attend the clinical center for a screening assessment. After giving written informed consent, demographic data (age, sex and ethnicity) and a medical history

will be taken, including questions regarding medication intake. A physical examination will be performed, including measurement of body weight and height.

Vital signs (systolic and diastolic blood pressure, heart rate, body temperature) will be measured and a 12-lead ECG will be recorded. Subjects should rest for at least 5 minutes in the supine position before the ECG recording, blood pressure, and heart rate measurement.

Fasting blood and urine samples will be collected for clinical laboratory safety tests.

The inclusion and exclusion criteria will be checked to assess eligibility for the study. All screening tests will be reviewed to confirm eligibility before randomization and dosing.

6.4. Efficacy Assessments

Clinician-reported outcomes will be assessed throughout the study [redacted]. Where possible, these assessments should be performed by the same investigator, or adequately qualified and trained designee, at each visit.

Subject-reported outcomes will be assessed [redacted].

Samples of these different clinician- and subject-reported outcomes are provided in the study reference manual. Subject-reported outcomes will be available in the subject's local language.

6.4.1. [redacted]

[redacted]

6.4.2. [redacted]

[redacted]

6.4.3. [redacted]

[redacted]

[redacted]

6.4.4. [redacted]

[redacted]

6.4.5. [redacted]

[redacted]

6.4.6. [redacted]

[redacted]

6.4.7. [redacted]

[redacted]

[redacted]

[redacted]

6.4.8. [redacted]

[redacted]

6.4.9. [redacted]

[redacted]

6.5. Safety Assessments

This section describes methods and timing for all safety assessments and recording. Additional assessments (e.g. unscheduled clinical laboratory tests or extra vital signs recordings) are allowed to ensure appropriate collection of safety data and to assess any perceived safety concerns.

6.5.1. Adverse Events

The AE reporting period for safety surveillance begins when the subject signs the ICF and ends at their last follow-up visit.

Detailed definitions, ratings, and reporting requirements for AEs, SAEs, and AESIs are found in Section 9.

6.5.2. Clinical Laboratory Evaluations

The following clinical laboratory safety tests will be performed:

– Hematology: hematocrit, hemoglobin, red blood cell count, white blood cell count, white blood cell differential count (absolute and relative), and platelets.

- Clinical chemistry: glucose, urea, creatinine, uric acid, sodium, potassium, calcium, chloride, phosphorus, AST, ALT, GGT, total bilirubin, alkaline phosphatase, albumin, total proteins, triglycerides, cholesterol, high density lipoprotein, low density lipoprotein, C-reactive protein, and total IgE.
- Urinalysis: proteins (semi-quantitative) and ketones can be tested via standard test strip; microscopic examination of the sediment (cylinders, erythrocytes, leukocytes) if indicated (when the test strip was positive for blood and/or proteins).
- Serology (only at screening): HBs antigen, HBc antibody, and hepatitis C antibody, and HIV 1 and 2. Positive hepatitis, and HIV results should be reported by the investigator as required by local law.
- Pregnancy test for females of childbearing potential: serum beta human chorionic gonadotropin at screening, urine dipstick before dosing on Day 1 and at all time points thereafter. In case of doubt, determination of FSH can be done at the central laboratory to confirm menopause.

The clinical laboratory evaluations will be performed at visits specified in the Schedule of Activities in Section 6.10 (see also Section 6.1, "Timing of Assessments"). On dosing days, blood and urine samples will be collected prior to dosing. Blood sampling for clinical lab should be done in fasting conditions (for at least 8 hours). Results from the screening visit will be used for the inclusion/exclusion criteria on the baseline visit (Day 1).

Reference ranges will be supplied by the central laboratory. Clinical laboratory values outside the normal range will be flagged and clinical relevance will be assessed by the investigator. Only laboratory test abnormalities judged as clinically significant by the principal investigator should be recorded as AEs.

Retesting of clinical laboratory screening tests is allowed once only for technical reasons (e.g. sample hemolyzed, out of stability or late arrival at central laboratory). Retesting of laboratory tests for safety or if medically indicated in the opinion of the investigator is always allowed.

The total amount of blood to be taken during the clinical study will not exceed 330 mL. This includes all scheduled samples and sampling for PK and/or PD assessments. Additional samples for subject safety would be allowed when needed, if relevant. For more details, see Section 6.9.

The details of blood and urine sample handling and shipment instructions will be provided in a separate laboratory manual.

6.5.3. Physical Examination

Physical examinations or targeted physical examination will be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation and as delegated by the principal investigator; at visits specified in the Schedule of Activities in Section 6.10 (see also Section 6.1). The person conducting the physical examination will document this in the subject's medical records. Clinically significant abnormal findings should be recorded as AEs.

The physical examination will include an assessment of the following systems: general, cardiovascular, respiratory, gastrointestinal, musculoskeletal, neurological, head and neck, skin (other than AD), thyroid and endocrine and other.

The targeted physical examination will include an assessment of the cardiovascular, respiratory, gastrointestinal systems, and the skin.

6.5.4. Vital Signs

Vital signs (systolic and diastolic blood pressure, heart rate, and body temperature) will be recorded in a standardized manner (i.e. after the subject has rested in a supine position for 5 minutes) at visits specified in the Schedule of Activities in Section 6.10 (see also Section 6.1, "Timing of Assessments"). Vital sign parameter normal ranges are presented in Appendix 1. Clinically significant abnormal values should be recorded as AEs.

Height will only be assessed at screening. Weight will be assessed at screening, and on a monthly basis as per Schedule of Activities (See Section 6.10).

6.5.5. 12-lead Electrocardiogram

At the time points specified in the Schedule of Activities (see Section 6.10 and also Section 6.1, "Timing of Assessments"), a 12-lead ECG will be recorded. ECG recordings will be performed before blood sampling and after subjects rested for 5 minutes in supine position. In case an indwelling catheter is used, ECGs may be recorded after blood sampling, provided that there is at least 30 minutes between catheter insertion and the ECG recording. When catheter insertion would fail, the 12-lead ECG needs to be taken before the venipuncture and at least 30 minutes after the failed attempt.

Triplicate ECGs will be performed before dosing at baseline only within a time span of approximately 6 minutes, with an approximate 3-minute interval between ECGs. Parameters to be recorded include the following: heart rate, PR interval, QRS interval, uncorrected QT interval, morphology, and rhythm analysis. Central reading will be performed for all ECGs at the time points specified in the Schedule of Activities. Central reading will be performed on blinded basis by a cardiologist. Details regarding central ECG reading will be provided in the study reference manual.

QT interval corrected for the heart rate using Fridericia's formula (QTcF) and QT interval corrected for the heart rate using Bazett's formula (QTcB) will be derived during the statistical analysis. ECG parameter normal ranges are presented in Appendix 1. QTc will be considered as normal if ≤450 ms (male) and ≤460 ms (female), while a prolongation of QTc to ≥500 ms or an increase from baseline >60 ms will be considered a threshold of concern. Immediately after recording, the ECG will be reviewed by the investigator on clinical significant abnormalities. This immediate review during the visit needs to be documented in the subject's source. Clinically significant abnormal values should be recorded as AEs.

6.5.6. Other Safety Assessments

6.5.6.1. Injection Site Reactions (ISRs)

The incidence, extent, and/or severity of ISRs (erythema, edema, induration, tenderness, and itching) will be assessed by the investigator on dosing days (before injection and one hour after completion of the injection). Information on ISRs will be collected for all subjects. Tenderness (pain/discomfort on palpation) and itching will be assessed by subjects using a 0-100 mm visual analogue scale (VAS). The extent (largest diameter in mm) of erythema, edema, and induration will be assessed. If present, the diameter of induration should be recorded. In addition, erythema and edema will be qualitatively assessed one hour post completion of the injection, and at follow-up visits through the end of study or until the injection site appears normalized at two consecutive assessments, based on all parameters evaluated.

The following scales will be used to qualitatively describe the grade of erythema and edema:

Erythema:
0 = no erythema
1 = very slight erythema (barely perceptible)
2 = well-defined erythema
3 = moderate to severe erythema
4 = severe erythema (beet redness) to slight eschar formation (injuries in depth)

Edema:
0 = no edema
1 = very slight edema (barely perceptible)
2 = slight edema (edges well-defined)
3 = moderate edema (raised >1 mm)
4 = severe edema (raised >1 mm and beyond area of exposure)

ISRs should be recorded as AEs in line with the Adverse Event Reporting requirements detailed in Section 9.3.1 and graded using the CTCAE grading scale (v5.0) (CTCAE, 2017):

1. Grade 1: Tenderness with or without associated symptoms (e.g. warmth, erythema, itching).
2. Grade 2: Pain; lipodystrophy; edema; phlebitis.
3. Grade 3: Ulceration or necrosis; severe tissue damage; operative intervention indicated.
4. Grade 4: Life-threatening consequences; urgent intervention indicated.
5. Grade 5: Death.

In case of severe ISRs (CTCAE Grade 3 or higher) subjects should be evaluated by the investigator as soon as possible and subsequent dosing should be discussed with the CRO medical monitor and sponsor to review whether the subject remains eligible to proceed. Subjects withdrawn due to ISRs will not be replaced.

Investigator site staff should photograph any severe ISR, if possible. Instructions for the photography are provided in the study reference manual.

6.5.6.2. Management of ISRs

Injections site reactions should be treated by the investigator following local standard operating procedures/policies.

In case of severe ISRs (CTCAE Grade 3 or higher) subjects should be evaluated by the investigator as soon as possible and subsequent dosing should be discussed with the CRO medical monitor and sponsor to review whether the subject remains eligible to proceed.

6.6. Pharmacokinetic and Immunogenicity Assessments

Blood samples for PK and Immunogenicity (ADA) assessment will be collected on the visits specified in the Schedule of Activities in Section 6.10 (see also Timing of Assessments, Section 6.1). In total 17 blood samples will be collected at various time points for analysis of MOR106 and 8 blood sample for the assessment of ADA in serum.

Samples will be obtained by venipuncture (or indwelling cannula), preferably in the forearm.

The details of blood sample collection, handling, storage, and shipment instructions will be provided in a separate laboratory manual.

6.7. Pharmacodynamic Assessments

Blood samples [redacted], will be collected on the visits specified in the Schedule of Activities in Section 6.10 (see also Section 6.1). Samples will be collected by venipuncture (or indwelling cannula) preferably in the forearm into tubes.

The details of blood sample handling and shipment instructions will be provided in a separate laboratory manual.

[redacted]

6.8. Other Assessments

6.8.1. [redacted]

[redacted]

[redacted]

6.8.2. Skin Swabs

Skin culture samples for assessment of the presence of bacteria, yeast and fungi will be collected by cotton swab from the lesional surface of the area of worst eczema involvement and another swab from a non-lesional area of skin (within 5 cm of the lesional site) will be collected. Samples will be collected from the same lesional and non-lesional areas at baseline (Day 1 predose), and Days 57/ETD and 169 (end of study) or ED.

The detailed procedure for collecting skin culture samples is provided in the laboratory manual.

6.8.3. [redacted]

[redacted]

6.9. Sample Management

6.9.1. Blood and Urine Samples for Routine Safety Tests, Serology, FSH and Pregnancy Tests

All blood and urine samples for routine safety tests, serology, FSH and pregnancy tests will be analyzed in a central laboratory and will be destroyed after analysis.

6.9.2. Blood Samples for PK, ADA, and PD

After the end of the study (e.g. last subject last visit), all PK, ADA and PD samples obtained during the clinical study may be stored for a period of maximum 5 years, after which the samples will be destroyed. The sample storage period will be in accordance with the IRB/IEC-approved ICF and applicable laws (e.g. health authority requirements).

The stored samples shall only be used by the sponsor, sponsor partners, and/or other companies contracted by the sponsor, for research related to this clinical study or based on regulatory requirements. Any research outside the context described in this CSP may only

be conducted after approval by the IRB/IEC and Regulatory Authority and after obtaining informed consent from the subject.

No characterization of human genetic material (genes, DNA, RNA) will be undertaken on these samples. If research is performed on genetic material of the samples then this can only be performed in context of the described CSP (example: biomarker analysis) and the data obtained may in no case be used for the purpose of identification or re-identification of subjects.

6.9.3. [redacted]

[redacted]

6.10. Schedule of Activities

For detailed instructions on the clinical study procedures, please see referred Sections below and Timing of Assessments (Section 6.1).

EVENT	SCREENING PERIOD	TREATMENT PERIOD						FOLLOW-UP PERIOD							
Study Day (D)[1]	**D-28 to D-7**	**D1**	**D4 ±1**	**D15 ±2**	**D29 ±2**	**D43 ±2**	**D57 ±2/ ETD[2]**	**D71 ±2**	**D85 ±2/**	**D99 ±2**	**D113 ±2**	**D127 ±2**	**D141 ±2**	**D155 ±2**	**D169 ±2/ ED**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Informed consent (Section 10.4.2)	✓														
Inclusion/exclusion criteria (Section 4.5)	✓	✓													
Demographics (Section 6.3)	✓														
Medical history (Section 6.3)	✓														
(Targeted) Physical examination (Section 6.5.3)	✓	✓		✓[3]	✓	✓[3]	✓	✓[3]	✓	✓[3]	✓[3]	✓[3]	✓[3]	✓[3]	✓[3]
Vital signs (Section 6.5.4)	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Height (only at screening) and /or weight (Section 6.3)	✓				✓		✓								
12-lead ECG (Section 6.5.5)	✓	✓[4]				✓[4]	✓		✓		✓				✓
Pregnancy test[5] (Section 6.5.2)	✓	✓			✓		✓				✓				✓

[1] Visit dates are always calculated from Day 1 (unless subject discontinues early and attends an Early Treatment Discontinuation visit (ETD). If a subject has an ETD visit, the follow-up visits are performed 14, 28, 42, 56, 70, 84, 98 and 112 days after the ETD visit.
[2] Subject who are discontinued from treatment during the treatment period will perform Day 57/ETD visit (14 days after the last dose) as the last visit in the treatment period before entering the follow-up period.
[3] During these study visits, a targeted physical examination, consisting of cardiovascular, respiratory, gastrointestinal, and skin examination will be performed.
[4] At Day 1, ECG to be taken before dosing (triplicate ECGs) and approximately 1 hour after dosing. At Day 43, single ECG before dosing and approximately 1h after dosing.
[5] Females of childbearing potential only. Serum pregnancy test at screening, urine test before dosing on Day 1 and at all indicated time points thereafter.

EVENT	SCREENING PERIOD	TREATMENT PERIOD						FOLLOW-UP PERIOD							
Study Day (D)[1]	**D-28 to D-7**	**D1**	**D4 ±1**	**D15 ±2**	**D29 ±2**	**D43 ±2**	**D57 ±2/ ETD[2]**	**D71 ±2**	**D85 ±2/**	**D99 ±2**	**D113 ±2**	**D127 ±2**	**D141 ±2**	**D155 ±2**	**D169 ±2/ ED**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Clinical laboratory safety tests (incl. hematology, biochemistry and urinalysis), prior to injection on dosing days (Section 6.5.2)	✓	✓		✓	✓	✓	✓		✓			✓		✓	✓
Serology (Section 6.5.2)	✓														
[redacted]	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
[redacted]		✓		✓	✓	✓	✓	✓		✓		✓		✓	✓
Train and check compliance of e-diary use	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
[redacted]	Recording twice daily throughout study														
e-diary: TCS use	Recording daily throughout study														
e-diary: emollient use	Recording twice daily throughout study														
Provide Subject Participation Card (Section 10.2.4)	✓														
Skin swab (lesional and non-lesional) (Section 6.8.2)		✓					✓								✓
[redacted]		✓[6]					✓[6]								

[redacted]

EVENT	SCREENING PERIOD	TREATMENT PERIOD						FOLLOW-UP PERIOD							
Study Day (D)[1]	**D-28 to D-7**	**D1**	**D4 ±1**	**D15 ±2**	**D29 ±2**	**D43 ±2**	**D57 ±2/ ETD[2]**	**D71 ±2**	**D85 ±2/**	**D99 ±2**	**D113 ±2**	**D127 ±2**	**D141 ±2**	**D155 ±2**	**D169 ±2/ ED**
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
[redacted]		✓					✓								✓
Immunogenicity assessment (ADAs; prior to injection on dosing days) (Section 6.6)		✓			✓		✓		✓		✓		✓		✓
PK blood samples (Section 6.5.6.1)		✓[7]	✓	✓[7]	✓[7]	✓[7]	✓	✓	✓	✓	✓	✓	✓	✓	✓
PD and biomarker blood samples, (prior to injection on dosing days) (Section 6.7)		✓			✓		✓		✓		✓		✓		✓
Randomization (Section 4.6.1)		✓													
IMP dosing (Section 5.2)[8]		✓		✓	✓	✓									
Injection site reactions (Section 6.5.6.1)		✓	✓	✓	✓	✓	✓								
(S)AE assessment (Sections 6.5.1, 9.2)	Throughout the study														
Prior/Concomitant medications (Section 4.5.3.2)	Throughout the study														

[7] PK samples have to be taken before injection and 1 hour after the injection (+/- 10 minutes) on Day 1. Samples have to be taken before injection on Days 15, 29, and 43.
[8] A loading dose, consisting of two consecutive injections will be performed on Day 1.

7. STATISTICAL METHODS

All statistical methods will be detailed in a statistical analysis plan (SAP). All relevant data collected in this clinical study will be documented using summary tables, figures, and subject data listings.

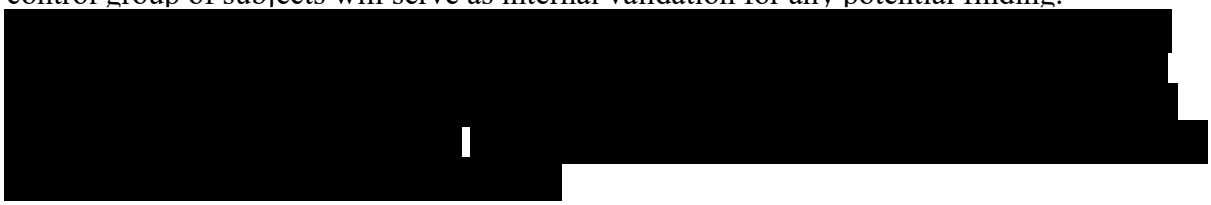
An interim analysis may be performed when approximately 50% of subjects have reached the end of treatment period. The primary analysis includes all subjects that have completed their Day 57 visit or discontinued earlier. The final clinical study report (CSR) will be written at the end of the trial.

The SAP will be prepared before the first interim analysis starts. Any deviations from the protocol are to be justified in the SAP.

7.1. Determination of Sample Size

Strict statistical criteria were not used to determine the sample size. A total of 60 subjects (40 subjects on MOR106 treatment and 20 subjects on placebo) will be enrolled in this study, resulting in an estimated 51 evaluable subjects, which should give reasonable precision around the estimates derived for safety, PK, PD, and efficacy evaluation.

With a sample size of 40 subjects on MOR106, there is a 87% probability to observe at least one occurrence of an adverse event if the natural incidence of this adverse event is 5%. The control group of subjects will serve as internal validation for any potential finding.



7.2. Population for Analyses

7.2.1. All Screened Subjects

All subjects who signed and dated an ICF and underwent screening assessments to check whether or not they are eligible to participate in the clinical study.

7.2.2. All Randomized Subjects

All enrolled subjects who underwent all screening assessments and were found to be eligible for the clinical study and who were randomized into the clinical study.

7.2.3. Full Analysis Set

All randomized subjects who have received/used at least one dose of IMP and have at least one post-baseline assessment.

7.2.4. Per-Protocol Set

All Full Analysis Set subjects who did not have a major protocol deviation that impacts the efficacy results (as defined in a protocol deviation plan). The determination of the per-protocol population will be finalized and documented prior to database lock and unblinding.

7.2.5. Safety and Immunogenicity Analysis Set

All randomized subjects who used at least one dose of IMP.

7.2.6. Pharmacokinetic Analysis Set

Subset of the safety set, selecting all subjects who have available and evaluable serum concentration data (e.g. excluding all protocol deviations or AEs that may have an impact on the PK analysis).

7.2.7. Pharmacodynamic Analysis Set

Subset of the safety set, selecting all subjects who have a baseline and at least one post-baseline evaluable PD value (e.g. excluding all protocol deviations that may have an impact on the PD analysis).

7.3. Statistical Analyses

7.3.1. General Statistical Considerations

Summary tabulations will be presented and will display the number of observations, mean, standard deviations and/or standard error, as appropriate, median, minimum, and maximum for continuous variables, and the number and percentage per category for categorical data. In addition to tabulated descriptive statistics, graphical data displays may be used to summarize the data. Unless otherwise noted, inferential statistics will be interpreted at the 2-sided 5% significance level. Data may be pooled across centers.

7.3.2. Interim Analysis

An interim analysis may be performed when approximately 50% of the randomized subjects have completed the treatment period. The interim analysis may be conducted in order to obtain early information for planning of further studies and regulatory interactions.

The results of the interim analysis will not be used to amend the current study. Sponsor personnel not involved in the day-to-day conduct of the study will be unblinded to perform analyses of the data and interpretation of the results. No study subjects or blinded study personnel involved in the day-to-day conduct (such the site staff, investigators and the operational team) will have access to the unblinded data before the database is locked for the final analysis. Details will be provided in the SAP.

7.3.3. Primary analysis

The primary analysis will be performed when all subjects have completed their Day 57 visit or discontinued earlier.

The results of this analysis will not be used to modify or terminate the current study. The team performing or interpreting the analyses will be unblinded, but every effort will be made to keep the subject and investigator and those close to data entry/cleaning blinded until the database will be locked for the final analysis. At the time point of primary endpoint analysis, demographics, reason for early discontinuation from the study, all selected efficacy assessments, and safety (i.e. AEs, SAEs, AESIs, and laboratory tests) will be summarized. Analyses and populations to be used for the primary analysis will be similar to those for the final analysis and details wil be described in the SAP.

7.3.4. Final analysis

The final analysis will be performed when all subjects have completed their last study visit (i.e. Day 169), or discontinued earlier. Details will be provided in the SAP.

7.3.5. Analyses of Demographics and Baseline Characteristics

Subject disposition (including reasons for early discontinuation), protocol deviations, demographics, baseline characteristics, medical history, and concomitant therapies, will be analyzed descriptively based on the safety analysis set, and the full analysis set if the latter is different from the former.

7.3.6. Analyses of Efficacy Parameters

Efficacy endpoint analyses will be performed using the Full Analysis Set. Efficacy data will be summarized using descriptive statistics of actual values, changes from baseline, and percent changes from baseline, with 95% confidence intervals. Binary and categorical endpoints will be presented by number (percent) of subjects per treatment group and visit.

Changes and percent changes from baseline for continuous endpoints [redacted] will be analyzed using an mixed-effects model for repeated measures. The model will include terms for treatment and visit as fixed effects, country and baseline value (continuous) as covariates, and treatment-visit as interaction term.

Binary parameters [redacted]) will be analyzed using a generalized estimating equation model. The model will include treatment and visit as fixed effects, country and baseline value (continuous) as covariates, and treatment-visit as an interaction term.

Time to event endpoints will be presented using the Kaplan-Meier estimates and the two treatment groups will be compared using a log-rank test.

More details will be provided in the SAP.

The primary approach will be the observed case approach without imputation of missing data. In case of unexpected high attrition rates, sensitivity analyses including the use of multiple imputation methods may be considered. If more than 10% of subjects included in the full analysis set population are excluded from the per protocol analysis, a per protocol analysis will be performed.

Additional exploratory analyses and graphical presentations may be performed when deemed useful to better understand the data and will be detailed in the SAP.

7.3.7. Analysis of Immunogenicity Data

ADA status (positive/negative), titer (when ADA status was positive), and potential drug interference in the assay when ADA negative (yes/no) will be summarized descriptively for each part of the study, by treatment group, and time point.

7.3.8. Analyses of Safety Data

All safety analyses will be performed using the Safety Analysis Set (Section 7.2.5). Subjects will be analyzed according to the treatment they actually received. All safety data collected on or after the first dose of IMP administration up to the last follow-up visit after the last dose of IMP, unless specified otherwise, will be summarized by treatment group according to the IMP received. Clinical safety will be addressed by assessing AEs, laboratory assessments, physical examinations, vital signs, and 12-lead ECGs. Special attention will be paid to ISRs.

7.3.8.1. Extent of Exposure

A subject's extent of exposure to IMP will be generated from the IMP administration page of the CRF. Extent of exposure data will be summarized by treatment group. Extent of exposure to IMP will be expressed as the number of days between the first and last dose of IMP, inclusive, regardless of temporary interruptions in IMP administration and summarized by treatment group.

In addition, the number (percentage) of subjects who received all six doses, only five doses, four doses, etc. will also be summarized.

7.3.8.2. Adverse Events

Clinical and laboratory AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities. System Organ Class (SOC), High Level Group Term, High Level Term, Preferred Term, and Lower-Level Term will be attached to the clinical database.

Treatment-emergent adverse events (TEAEs) are defined as those with an onset date/time on or after the start date/time of the first IMP administration (including the follow-up period). Additionally, analyses will also be created, restricted to events with an onset date on or after the IMP start and up to 30 days after last dose of IMP.

Summaries (number and percentage of subjects) of TEAEs per subject by SOC and Preferred Term will be provided by treatment group. TEAEs will also be summarized by causal relationship to IMP and severity. In addition, TEAEs leading to premature discontinuation of IMP will be summarized and listed. Also, all SAEs, including the non-treatment-emergent SAEs, will be listed.

Counts tables will also be provided for the ISRs and skin events of special interest. Details will be provided in the SAP.

7.3.8.3. Clinical Laboratory Evaluations

Laboratory assessments will be analyzed descriptively. Changes from baseline (Day 1 predose) and shifts according to normal ranges will be presented as well. Analyses will be done per treatment group.

7.3.8.4. Physical Examinations

Only abnormal post-baseline physical examination results will be listed.

7.3.8.5. Vital Signs

Vital signs will be analyzed descriptively. Changes from baseline (Day 1 predose) and shifts according to normal ranges will be presented as well. Analyses will be done per treatment group.

7.3.8.6. 12-Lead Electrocardiogram

A descriptive analysis will be done for the 12- lead ECG. Changes from baseline (Day 1 predose) and shifts according to normal ranges (Appendix 1) will be presented as well. Frequency analyses of subjects with a QTc prolongation of more than >60 ms change from baseline; ≥501 ms will be presented as well. Analyses will be done per treatment group.

7.3.8.7. Other Safety Assessments

Counts tables will be provided for the ISRs.

7.3.9. Pharmacokinetic Analyses

For subjects in the PK analysis set, individual serum concentrations of MOR106 will be listed. Descriptive statistics will be calculated by day for the serum concentrations and on the listed PK parameter. Mean (± standard error) serum concentrations of MOR106 versus time will be plotted using both linear and semi-logarithmic scales.

Only terminal elimination half-life ($t_{1/2}$ expressed in h) will be determined for MOR106 serum concentrations by non-compartmental analysis using individual concentration-time profiles.

Time to reach steady-state will be assessed by visual inspection of the trough serum concentrations as well as by means of a mixed effect analysis of variance on ln-transformed trough serum concentrations, with subject as random effect and day as fixed effect. Comparison between days will be performed.

MOR106 serum levels will be analyzed using population PK analyses, which will be reported separately.

7.3.10. Pharmacodynamic Analyses

PD data will be summarized using descriptive statistics of actual values, changes from baseline, and percent changes from baseline. Details will be provided in the SAP.

7.3.11. Analysis of Other Assessments

Exploratory efficacy, safety/PK or PK/PD analyses may be added when deemed useful to better understand the collected data. Individual and/or mean ± standard error efficacy, safety, PD, and/or MOR106 serum concentrations may be plotted against one another. Details will be provided in the SAP and/or in a separate analysis plan, as appropriate.

7.3.12. Additional Statistical Considerations

Not applicable.

8. DATA MONITORING

8.1. Independent Medical Review

To safeguard the safety of the subjects, an independent Safety Review Committee (iSRC) consisting of independent dermatology and statistical experts will be implemented to review any accumulating unblinded safety data for the clinical study, specifically the review of any skin related AEs and serious adverse reactions. The specific responsibilities, composition, meeting formats and details of output provided for the meetings of the iSRC will be outlined in detail in an independent Safety Review Committee Charter.

9. SAFETY REPORTING

9.1. Definitions of Adverse Events, Serious Adverse Events, and Special Situations

9.1.1. Adverse Events

An AE is any untoward medical occurrence, new or worsening of any pre-existing condition, in a clinical study subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related. AEs may also include pre- or post-treatment complications that occur as a result of CSP-specified procedures, worsening of the targeted disease, overdose, drug abuse/misuse reports, or occupational exposure. Pre-existing conditions that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

9.1.2. Serious Adverse Events

An SAE is defined as an AE that:

- Results in death,
- Is life-threatening (Note: The term ‘life-threatening’ in the definition of ‘serious’ 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 were more severe.),
- Requires in-patient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect,
- Is medically significant (medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed in the definition above).

9.1.3. Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or intensity is not consistent with the applicable product reference safety information. For MOR106, the expectedness of an AE will be determined by whether or not it is listed in the reference safety information part of the IB MOR106.

9.1.4. Adverse Events of Special Interest

Categories of AESIs are defined as follows:

- ISRs (Grade 3 or higher).
- Skin related AEs (except exacerbations and infective exacerbations of AD).

9.1.4.1. Injection Site Reactions (ISRs)

ISRs will be assessed as described in Section 6.5.6.1. The physician in attendance will do whatever is medically needed for the safety and well-being of the subject. The subject will remain under observation as long as medically indicated.

All ISRs should be recorded as AEs in line with the Adverse Event Reporting requirements detailed in section 9.3.1 and graded using the CTCAE grading scale (v5.0) (CTCAE, 2017).

Severe ISRs (CTCAE Grade 3 or higher) should be reported as SAEs in accordance with the expedited reporting requirements detailed in Section 9.3.2.

9.1.4.2. Skin Related Adverse Events

Subjects experiencing a skin related AE (except exacerbations and infective exacerbations of AD and ISRs) occurring after the first administration with study drug, should be examined by a dermatologist as soon as possible. The dermatologist will do whatever is necessary for the safety and well-being of the subject. A full narrative description of the skin related AE must be provided and the medical monitor and sponsor medical lead should be informed as soon as possible. Skin related AEs meeting seriousness criteria will be reported on an SAE report form within 24 hours. The sponsor will be supported by an independent dermatologist in the medical review of skin related AEs.

For all skin related AESI, photography of the lesion(s) should be taken and where medically relevant, additional testing as required is permitted and may include the following recommended assessments:

- Skin swab of the lesion.
- Biopsy of the lesion.
- Additional blood sample for cytokine analysis.

9.1.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance based on the investigator's judgment are not considered AEs or SAEs. However, laboratory abnormalities (e.g. clinical chemistry, hematology, and urinalysis) or other abnormal (clinical study-specific) assessments (e.g.

ECG, radiography, vital signs) that require medical or surgical intervention, are associated with signs and/or symptoms, and/or lead to IMP interruption, modification or discontinuation must be recorded as an AE or SAE if they meet the definition as described in Sections 9.1. If the laboratory abnormality is part of a syndrome, the syndrome or diagnosis is to be reported (e.g. anemia instead of decreased hemoglobin).

9.1.6. Special Situations

Special situations are situations that have a possible impact on the safe use of the IMP. These situations might be or might not be associated with AEs.

- Pregnancy
- Abuse or misuse of IMP
  - Abuse of IMP is defined as the persistent or sporadic, intentional excessive use of the IMP, which is accompanied by harmful physical or psychological effects.
  - Misuse of IMP is defined as a situation where the IMP is intentionally and inappropriately used not in accordance with the product information.
- Drug interaction or food interaction with IMP
  - A drug interaction with IMP is defined as a situation in which there is evidence or a suspicion that the IMP interacts with another drug when both are administered together.
  - A food interaction with IMP is defined as a situation in which there is evidence or a suspicion that the IMP interacts with a food when taken together.
- Medication error with IMP
  - A medication error with IMP is defined as an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the subject.
- Occupational exposure to IMP
  - Occupational exposure to IMP is defined as an exposure to the IMP as a result of one's professional or non-professional occupation.
- Overdose with IMP
  - An overdose of IMP is defined as the administration of a quantity of the IMP given per administration or cumulatively, which is any dose higher than the prescribed treatment.
- Product complaint or quality defect of IMP
  - Product complaint or quality defect of IMP is defined as complaints or defects of the IMP arising from potential deviations in the manufacture, packaging or distribution of the IMP.

9.2. Assessment of Adverse Events and Serious Adverse Events

The investigator is responsible for assessing AEs and SAEs for causality and severity. This is the basis for the sponsor's final review and confirmation of accuracy and completeness of event information and causality assessments.

9.2.1. Assessment of Causality

The investigator is responsible for assessing the causal relationship to IMP(s) administration or study procedures (e.g. invasive procedures such as venipuncture) based on her/his clinical

judgment. The following decision choice will be used by the investigator to describe the causality assessment between the reported event or laboratory test abnormality and the IMP. When the causality assessment is ‘possible, probable or certain’, the IMP will be considered suspected and a ‘unrelated or unlikely’ causality will be considered as not suspected.

- **Unrelated:**
  Time relationship to IMP intake is improbable. Related to other etiologies such as concomitant medications or subject's clinical state.
- **Unlikely:**
  Time relationship to IMP intake is improbable (but not impossible). Concomitant disease or other drugs provide plausible explanations.
- **Possible:**
  Time relationship to IMP intake is reasonable. Event or laboratory test abnormality, could also be explained by disease or other drugs. Information on IMP withdrawal may be lacking or unclear.
- **Probable:**
  Time relationship to IMP intake is reasonable. Unlikely to be attributed to concurrent disease or other drugs. Response to withdrawal is clinically reasonable and rechallenge not required.
- **Certain:**
  Time relationship to IMP intake is plausible. Cannot be explained by concomitant disease or other drugs. Response to withdrawal is plausible (pharmacologically, pathologically). Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon). Rechallenge satisfactory, if ethical and necessary.

It should be emphasized that ineffective treatment (worsening of the disease) should not be considered as causally related in the context of AE reporting.

9.2.2. Assessment of Severity

The severity of AEs should be graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (CTCAE, 2017). If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening) or Grade 5 (fatal) to describe the maximum intensity of the AE. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 1.

Table 1: Grading of AE Severity

Grade	Adjective	Description
Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate	Local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4	Life-threatening	Urgent intervention indicated.
Grade 5	Death	Death-related AE.

* Instrumental activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality. This is upon the investigator's assessment.

If there is a change in intensity (worsening or improvement) of an AE, it must be recorded.

9.2.3. Outcome

Each AE must be rated by choosing among:

- Recovered/resolved;
- Recovered/resolved with sequelae;
- Recovering/resolving;
- Not recovered/ not resolved;
- Fatal;
- Unknown.

9.3. Investigator Requirements and Instructions for Reporting Adverse Events / Serious Adverse Events /Pregnancies, and Other Special Situations to the Sponsor

9.3.1. Adverse Events

The AE reporting period for safety surveillance begins when the subject signs the ICF and ends at the subject's last follow-up visit (the last follow-up visit after the last dose of IMP). In this period, all new AEs, regardless of cause or relationship, derived by spontaneous, unsolicited reports of subjects, by observation and by routine open questioning (such as "How do you feel?") need to be recorded in the source and in the CRF.

In case an AE is ongoing at the time of the last follow-up visit, the investigator needs to follow-up on the subject until AE resolution or reasonable stabilization and to document in the subject's source documentation. No related updates or additional data on the AE should be reported in the CRF.

If a subject is documented as lost-to-follow-up, ongoing/unknown outcome AEs will not be followed-up.

If the AE meets the criteria for seriousness, the SAE form must be completed and sent to the sponsor within 24 hours (see Section 9.3.2).

9.3.1.1. Adverse Events of Special Interest (AESI)

AESIs need to be reported immediately, and AESIs meeting seriousness criteria need to be reported immediately as an SAE, and under no circumstances should this exceed 24 hours following the knowledge of the SAE.

Details on events of special interest can be retrieved under Section 9.1.4. Additional information as detailed in Section 9.1.4 will be captured in the CRF.

9.3.2. Serious Adverse Events

Subjects experiencing an SAE or an emergency situation will be examined by a physician as soon as possible. The subject will remain under observation as long as medically indicated. Appropriate laboratory tests will be performed until all parameters return to normal or are otherwise explained or stable.

All SAEs, whether or not deemed IMP-related, must be recorded in the CRF and on the SAE form. The investigator must report each SAE immediately, and under no circumstances should this exceed 24 hours following the knowledge of the SAE, as is indicated on Page 2 under "Emergency Contact Information".

The SAE form should at least contain identifiers of the subject and the reporter, SAE term and statement of relatedness to the IMP, and at a later stage if not yet available within 24 hours, the form needs to be completed with a clearly written narrative describing signs, symptoms, and treatment of the event, diagnostic procedures, as well as any relevant laboratory data and any sequelae (preferably by the investigator).

Follow-up and outcomes should be reported and documented in the source documents for all subjects that experience an SAE. It is important that the information provided on the SAE form matches the information recorded on the CRF for the same event.

Copies of additional laboratory tests, consultation reports, post-mortem reports, hospital case reports, autopsy reports, and other documents should be sent when requested and available. Only subject number should appear on the copies, and all names and initials should be blackened and rendered illegible. Follow-up reports relative to the subject's subsequent course must be submitted until the event has subsided or, in case of permanent impairment, until the condition stabilizes.

Any SAE that occurs after the post-treatment follow-up visit but within 30 days of the last dose of IMP(s), regardless of causality, should also be reported (Emergency Contact

Information on Page 2). Investigators are not obligated to actively seek SAEs after the CSP-defined follow-up period. However, if the investigator is informed about an SAE that occurs at any time after the subjects' post-treatment follow-up visit and the event is deemed relevant to the use of IMP, he/she should promptly document and report the event to the sponsor by using the SAE form.

9.3.3. Pregnancy

All initial reports of pregnancy in female subjects and pregnancies in partners of male subjects included in the clinical study must be recorded and documented in the source documents and on the pregnancy form. The investigator must report each pregnancy immediately, and under no circumstances should this exceed 24 hours following the knowledge of the pregnancy, as is indicated on Page 2 under "Emergency Contact Information".

All pregnancies should be followed-up until delivery or pregnancy interruption. The investigator will contact the subject or partner of the subject after giving consent, at the expected time of delivery for follow-up and for information regarding the outcome of the newborn. Abnormal pregnancy and/or abnormal newborn outcomes are considered SAEs and must be reported using the SAE form.

9.3.4. Reporting of Special Situations (Other Than Pregnancy) and Associated Adverse Events

In case a special situation is not associated with an AE, the special situation should be reported within 24 hours by using the special situations form as is indicated on Page 2 under "Emergency Contact Information"

In case a special situation is associated with an AE, the special situation should be reported within 24 hours by using the special situations form and the associated AE should be reported as specified in Section 9.3.1.

In case a special situation is associated with an SAE, the special situation should be reported within 24 hours by using the SAE form (and not the special situations form) and the associated SAE should be reported as specified in Section 9.3.2.

9.4. Sponsor Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable United States Federal Drug Administration Code of Federal Regulations, the European Union (EU) Clinical Trials Directive (2001/20/EC) and relevant updates, and other country specific legislation or regulations, the sponsor may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions, or suspected unexpected serious adverse reactions (SUSARs). The sponsor or a specified designee will notify worldwide regulatory agencies and the relevant IEC/IRB in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined using reference safety information section in the IB or relevant local label as applicable.

All concerned investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any IMP(s). The investigator should notify the IEC/IRB of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This clinical study is conducted in accordance with the current applicable regulations, ICH-GCP Guideline E6, and local regulations.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of clinical study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

The name and address of each third-party vendor (e.g. CRO) used in this study and the sponsor's study team members will be maintained in the investigator's and sponsor's files as appropriate.

10.1. Sponsor's Responsibilities

10.1.1. Regulatory Approval / Notification

Prior to clinical study start, this CSP together with all relevant documentation will be submitted to the local regulatory authorities for review and approval and/or notification in compliance with local requirements.

10.1.2. Clinical Study Closure Considerations

The sponsor reserves the right to close the investigational site or end the clinical study at any time for any reason. In case of an early termination of the clinical study or temporary halt by the sponsor, the IEC/IRB should be notified within 15 calendar days unless otherwise specified by the IEC/IRB, including a detailed written explanation of the reasons for the termination/halt.

The end of clinical study declaration will be submitted to the regulatory authorities and IEC/IRB after the complete clinical study has ended in all participating centers, in all countries. This notification will also be submitted within 90 days of the end of the clinical study in a given country/member state or within the timelines required by the local regulations.

Reasons for the closure of an investigational site include but are not limited to:

- Successful completion of the clinical study at the center.
- The overall required number of subjects for the clinical study has been recruited.
- Failure of the investigator to comply with the CSP, ICH-GCP Guidelines or local regulations.
- Inadequate recruitment of subjects by the investigator.

Reasons for early termination of a clinical study by the sponsor may include but are not limited to:

- Safety concerns.
- Sufficient data suggesting lack of efficacy.

10.1.3. Indemnification

Under the conditions of a contract concluded between investigator, site, and sponsor or designee, which shall prevail, sponsor shall, except in case of gross negligence or willful misconduct, indemnify and hold harmless the investigator and his/her medical staff from any claim arising from the clinical study activities carried out in compliance with the CSP, sponsor's instructions, and applicable local regulations.

The investigator must notify the sponsor immediately upon notice of any claims or lawsuits.

10.1.4. Insurance

Sponsor shall maintain insurance coverage that is sufficient to cover its obligations and that is consistent with human clinical study local regulations. Save in case of gross negligence or willful misconduct of the investigator, and provided that the subject has been treated according to the CSP and sponsor's instructions, any injury caused to a subject which is the direct result of his/her participation to the clinical study shall be covered by sponsor's insurance.

10.1.5. Reporting

Where required by IEC/IRB per local requirements, at least once a year the investigator will provide the IEC/IRB with a progress report to allow review of the clinical study (see Section 10.4.1). At the end of the clinical study, the results of the clinical study will be reported in a single CSR. A summary or full report, depending on the requirements, will be provided to the investigators, to the applicable regulatory authorities and IECs/IRBs if required by the applicable regulatory requirements.

10.1.6. Publication

It is understood by the investigator that the sponsor shall be free to use the compound-related information which is generated during the clinical study and may disclose it to other clinical investigators and to regulatory agencies. As a consequence, the investigator agrees to provide all clinical study results and data generated during this clinical study to sponsor.

The investigator shall not be authorized to submit the results of this clinical study and any data for publication or presentation without the prior written approval of the sponsor which shall not be unreasonably withheld.

However, it is understood and agreed by the investigators that their results and/or findings shall not be authorized for publication prior to sponsor's publication of the overall clinical study results. The investigator agrees that prior to the publication of any results, he/she shall provide sponsor with a draft copy of the intended publication. Sponsor shall have the right to review it and to make any comments. In accordance with generally accepted scientific collaboration principles, co-authorship with any staff member sponsor involved in the clinical

study, will be discussed and mutually agreed upon before submission of any manuscript to a publisher.

10.2. Investigator's Responsibilities

10.2.1. Financial Disclosure

The disclosed financial interest of the investigators must be collected before screening of the first subject, following clinical study completion at the investigator site, and 1 year following overall clinical study completion. The investigators should promptly update this information if any relevant changes occur during this period. Disclosable financial interests will be recorded on the Investigator Financial Disclosure Form.

Any investigator(s) added as investigational staff directly involved in the treatment or evaluation of the subject with direct and significant contribution to the study data must complete the Investigator Financial Disclosure Form at the beginning of their participation in the clinical study. For any investigator(s) leaving the site prior to clinical study completion, an Investigator Financial Disclosure Form should be obtained at the end of their contribution to the clinical study.

10.2.2. Source Data and Data Capture

The nature and location of all source documents need to be identified and documented to ensure that all sources of original data required to complete the CRF are known and are accessible for verification by the monitor.

Source data may be directly captured from devices transferred from third partners (e.g. laboratory data) or entered manually into the CRF. The CRF completion guidelines will be provided to each investigational site.

It is recommended that the author of an entry in the source documents should be identifiable. Following ICH-GCP Guidelines, direct access to source documents must be granted for the purpose of verifying that the data recorded on the CRF are consistent with the original source data.

10.2.3. Archiving

The investigator shall maintain the clinical study-specific documents as specified in Section 8 "Essential Documents for the Conduct of a Clinical Study" of the ICH-GCP Guidelines (ICH-E6) and as required by the applicable regulatory requirement(s). The investigator should take measures to prevent accidental or premature destruction of these documents.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor.

Under no circumstance shall the investigator relocate or dispose of any clinical study documents before having obtained a written approval of the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this clinical study, the investigator must permit access to such reports. The subject is granting access to his/her source data by signing the informed consent.

Any difficulty in storing original documents must be discussed with the monitor prior to the initiation of the clinical study.

10.2.4. Participation Cards

If the subjects are not under 24-hour supervision of the investigator or his/her staff (out-subjects), they must be provided with a subject participation card indicating the name of the IMP, the clinical study number, the investigator's name and a 24-hour emergency contact number. The subject should be advised to keep the participation card in his/her wallet at all times.

10.3. Confidentiality

The subject will receive all information as required by the EU General Data Protection Regulation, namely the identity and contact details of the controller, the contact details of the data protection officer, the clinical research purposes, the legal basis for the processing, the recipients of the personal data, the transfer of the personal data to third countries and respective safeguards, the retention periods, the fair processing of his data, and all his/her data subject’s rights. All details are listed in the ICF.

All information concerning the product and the sponsor’s operations (such as patent applications, formulae, manufacturing processes, basic scientific data or formulation information supplied to the investigator by the sponsor and not previously published) is considered confidential by the sponsor and should not be disclosed by the investigator to any third party without the sponsor’s prior written approval. The investigator agrees to use this information only in accomplishing the clinical study and will not use it for other purposes.

In order to permit easy identification of the individual subject during and after the clinical study, the investigator is responsible for keeping an updated Subject Identification Code List. The monitor will review this document for completeness. However, the investigator must guarantee the subject’s anonymity will be maintained. Therefore, in order to ensure subject confidentiality, the Subject Identification Code List will remain at the center and no copy will be made.

10.4. Ethical Considerations

10.4.1. Independent Ethics Committee (IEC) / Institutional Review Board (IRB)

This clinical study can only be undertaken after full approval of the CSP, informed consent, any other written information given to subjects, and subject recruitment materials has been obtained from the IEC/IRB. This approval document must be dated and clearly identify the clinical study and the related clinical study documents being approved, including the subject compensation programs, if applicable.

During the course of clinical study at least the following documents will be provided to the IEC/IRB per local requirements:

- Changes to the IB
- Reports of AEs that are serious, unlisted and associated with the investigational drug (in compliance with IEC/IRB, per local requirements)
- CSP amendments
- Informed consent revision(s)

CSP amendments and applicable ICF revisions must promptly be submitted to the IEC/IRB for review and approval prior to implementation of the change(s), except when necessary to eliminate an immediate hazard to the clinical study subjects, or according to local requirements.

The IEC/IRB is responsible for continuous review of the clinical study. Where required by IEC/IRB per local requirements, at least once a year the investigator will provide the IEC/IRB with a progress report to allow review of the clinical study. Additional progress reports should be provided according to local legal requirements. These requests and (re) approvals, if applicable, should be documented in writing.

10.4.2. Informed Consent

The principal investigator or designated personnel must explain the clinical study and the implications of participation (e.g. objectives, methods, anticipated benefits, and possible risks) to potential subjects according to applicable regulations prior to any clinical study-related activity. Subjects will be informed that their participation is voluntary and that they may withdraw from the clinical study at any time. They will be informed that choosing not to participate or to withdraw from the clinical study will not have an impact on the care the subject will receive for the treatment of his/her disease. In case the subject is unable to read and write, an impartial witness must confirm the informed consent.

The subject will be given sufficient time to read the ICF and to ask additional questions. After this explanation and before entry in the clinical study, consent should be appropriately recorded by means of the subject's personally dated signature (or, if applicable, by the signature of an independent witness who certifies the subject's consent in writing) and by the investigator’s signature. After having obtained the consent, a copy of the signed and dated informed consent must be given to the subject.

If new information becomes available that may be relevant to the subject’s willingness to participate in the clinical study, the subject will be informed in a timely manner by means of an updated ICF. This amended ICF will be signed and dated by the subject (or, if applicable, by an independent witness) and the investigator to document the willingness of the subject to continue with the clinical study.

This signed and dated amended version will be filed together with the initial signed and dated ICF.

The skin biopsy sub-study and eczema area photography are optional and separate ICFs need to be obtained from the subjects. Subjects can participate in the main clinical study without having to participate in one of the sub-studies. Subjects will also be informed that their participation for the sub-studies is voluntary and that they may withdraw their consent at any time. If a subject chooses to withdraw consent for a sub-study then the investigator or designated personnel must inform the sponsor.

A pregnant partner who agrees that information will be gathered about her pregnancy and the birth and health of her baby, will sign a specific ICF to participate in the data collection.

10.5. Data Quality Control / Assurance

10.5.1. Monitoring

This clinical study will be monitored by sponsor representatives according to their current Standard Operating Procedure for the monitoring of clinical studies as described in the monitoring plan.

To guarantee adequate protection of the subjects and to guarantee the quality of the data, the sponsor will ensure oversight of any clinical study-related duties and functions carried out on its behalf, including clinical study-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s).

10.5.2. Audit and Inspection

To ensure compliance with relevant regulations, an independent quality assurance representative, regulatory authorities and/or IECs/IRBs may review this clinical study. This implies that auditors/inspectors will have the right to inspect the clinical study center(s) at any time during and/or after completion of the clinical study and will have access to the data generated during the clinical study, source documents, and subject's files. By participating in this clinical study, investigators agree to this requirement.

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12. APPENDICES

Appendix 1: Normal Ranges

NORMAL RANGES FOR VITAL SIGNS

Normal ranges applicable in supine position (after 5 minutes):

Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Heart rate (bpm)
90≤ BSP ≤140	45≤ DBP ≤90	40≤ HR ≤100

NORMAL RANGES FOR ECG PARAMETERS

Normal ranges applicable in supine position (after 5 minutes):

PR (ms)	QRS (ms)	QTc (ms)	Heart rate (bpm)
110≤ PR ≤220	QRS ≤120	QTc ≤450 (male) QTc ≤460 (female)	40≤ HR ≤100

SIGNATURE PAGE – SPONSOR

Study Title: **A randomized, double-blind, placebo-controlled, multicenter Phase 2 study to evaluate the safety and tolerability of subcutaneous MOR106 administered concomitantly with topical corticosteroids for eight weeks, in adult subjects with moderate to severe atopic dermatitis.**

This clinical study protocol has been reviewed and approved by the sponsor to ensure compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practices (GCP) and applicable regulatory requirements.

CSP Version: 4.0 **Date:** 25-Jun-2019

Medical Leader	Signature	Date

SIGNATURE PAGE – INVESTIGATOR

Study Title: **A randomized, double-blind, placebo-controlled, multicenter Phase 2 study to evaluate the safety and tolerability of subcutaneous MOR106 administered concomitantly with topical corticosteroids for eight weeks, in adult subjects with moderate to severe atopic dermatitis.**

I, the undersigned, have read this clinical study protocol and will conduct the study as described in compliance with the clinical study protocol, in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practices (GCP) and applicable regulatory requirements.

CSP Version: 4.0 **Date:** 25-Jun-2019

Investigator	Signature	Date