# CLINICAL STUDY PROTOCOL

Galderma S.A.

Galderma Research & Development, LLC

Protocol Title: A Randomized, Single-Dose, Open-Label, Parallel-Group Study in Healthy Volunteers to Assess the Relative Bioavailability of a Subcutaneous Dose of Nemolizumab When Administered with Auto-Injector Compared to Dual-Chamber Syringe

Protocol Number: RD.06.SPR.201590

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| **IND Number:** | 117122 |
| **EudraCT Number:** | N/A |
| **Name of Investigational Product:** | Nemolizumab (CD14152) |
| **Phase of Development:** | 1 |
| **Indication:** | N/A |
| **Sponsor:** | Galderma S.A.<br>Zählerweg 10<br>CH-6300 Zug<br>Switzerland<br><br>Galderma Research & Development, LLC<br>14501 North Freeway<br>Fort Worth, TX 76177<br>United States |
| **Protocol Version:** | 1.0 |
| **Protocol Date:** | 17MAY2022 |

# 1 PROTOCOL APPROVAL SIGNATURES

**Protocol Title:** A Randomized, Single-Dose, Open-Label, Parallel-Group Study in Healthy Volunteers to Assess the Relative Bioavailability of a Subcutaneous Dose of Nemolizumab When Administered with Auto-Injector Compared to Dual-Chamber Syringe

**Protocol Number:** RD.06.SPR.201590

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation (ICH) guidelines for current GoodClinical Practice (GCP), and applicable regulatory requirements.

**Sponsor Signatory**

PPD

Senior Medical Expert
R&D Medical Advisory

Galderma S.A.
Avenue d'Ouchy 4
1006 Lausanne
Switzerland

PPD

Signature

PPD

Date (DD-Mmm-YYYY)

## 2 STUDY PERSONNEL

***Galderma S.A.***

PPD

***Coordinating Investigator***

PPD

***Lead Medical Director***

PPD

## 3 INVESTIGATOR SIGNATURE PAGE

**Protocol Title:** A Randomized, Single-Dose, Open-Label, Parallel-Group Study in Healthy Volunteers to Assess the Relative Bioavailability of a Subcutaneous Dose of Nemolizumab When Administered with Auto-Injector Compared to Dual-Chamber Syringe

**Protocol Number:** RD.06.SPR.201590

**Confidentiality and Current Good Clinical Practice (GCP)/E6(R2) Compliance Statement**

- I, the undersigned, have reviewed this protocol, including appendixes, and I will conduct the study as described in compliance with this protocol (and amendments), GCP, and relevant International Council for Harmonisation (ICH) guidelines.
- I am familiar with appropriately using the study drug, as described in this protocol and any other information provided by Galderma S.A. including, but not limited to, the current Investigator's Brochure.
- Once the protocol has been approved by the independent ethics committee (IEC)/institutional review board (IRB), I will not modify this protocol without obtaining prior approval of Galderma S.A. and of the IEC/IRB. I will submit the protocol amendments and/or any informed consent form modifications to Galderma S.A. and the IEC/IRB, and approval will be obtained before any amendments are implemented.
- I ensure that all persons or party assisting me with the study are adequately qualified and informed about the Galderma S.A. study drug and of their delegated study-related duties and functions as described in the protocol.
- I ensure that source documents and study records that include all observations on each of the site's study subjects will be attributable, legible, contemporaneous, original, accurate, and complete.
- All information obtained during the conduct of the study regarding the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all case report forms, laboratory samples, or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.
- Information developed in this clinical study may be disclosed by Galderma S.A. to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

| | |
|---|---|
| Name, Title | Investigator Signature |
| Institution | Date (DD-Mmm-YYYY) |

# 4 SYNOPSIS

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|---|---|
| **Title of Study:** | A Randomized, Single-Dose, Open-Label, Parallel-Group Study in Healthy Volunteers to Assess the Relative Bioavailability of a Subcutaneous Dose of Nemolizumab When Administered with Auto-Injector Compared to Dual-Chamber Syringe |
| **Protocol Number:** | RD.06.SPR.201590 |
| **Investigators/Study Sites:** | Approximately 3 study sites are planned in the United States |
| **Phase of Development:** | Phase 1 |
| **Objectives:** | The primary objective is to compare the rate and extent of absorption a single dose of nemolizumab administered with auto-injectors (AI; test) versus dual-chamber syringes (DCS; reference) under controlled conditions in healthy adult subjects.<br><br>The secondary objectives are to assess the safety and immunogenicity of nemolizumab following administration with AI or DCS in healthy adult subjects. |
| **Study Endpoints:** | Primary Endpoints:<br><br>▪ Change of primary pharmacokinetic (PK) parameters: $C_{max}$ (rate of absorption) and $AUC_{0\text{-}inf}$ (extent of absorption) of nemolizumab administered with AI or DCS<br><br>Secondary Endpoints:<br><br>▪ Change of secondary PK parameters ($AUC_{0\text{-}4\ weeks}$ $AUC_{0\text{-}last}$, $T_{max}$, and $t_{1/2}$) of nemolizumab administered with AI or DCS<br><br>▪ Assessment of the immunogenicity (anti-drug antibodies, ADA) of nemolizumab administered with AI or DCS<br><br>▪ CCI [redacted] |
| **Study Design:** | This is a randomized, multicenter, open-label, single-dose, parallel-group study in healthy adult subjects aged 18 to 65 years to assess the relative bioavailability of a 60-mg subcutaneous dose of nemolizumab administered with AI compared to DCS, stratified by injection site. The 60-mg dose will be administered as 2 successive subcutaneous injections of 30 mg (AI or DCS).<br><br>The study duration will be up to 16 weeks and consists of an up to 28-day screening period and a 12-week PK evaluation period.<br><br>The screening period will evaluate subject eligibility. At baseline, approximately 192 subjects will be randomized 1:1 to receive 60 mg nemolizumab delivered with either AI or DCS. Subjects will be further randomized 1:1:1 to receive injection in 1 of 3 injection sites, i.e., abdomen, front upper thigh, or outer upper arm. Approximately 32 subjects in each delivery group will be assigned to each injection site.<br><br>Subjects will receive a 60-mg dose of nemolizumab via 2 subcutaneous injections of 30 mg nemolizumab. Injections should be administered at the same location (i.e., abdomen, front upper thigh, or outer upper arm) on the same side with injection sites at least 1 inch (2.5 cm) apart. Blood samples will be collected before and after nemolizumab administration for up to 12 weeks post-dose for determining the complete serum PK profile of nemolizumab. |

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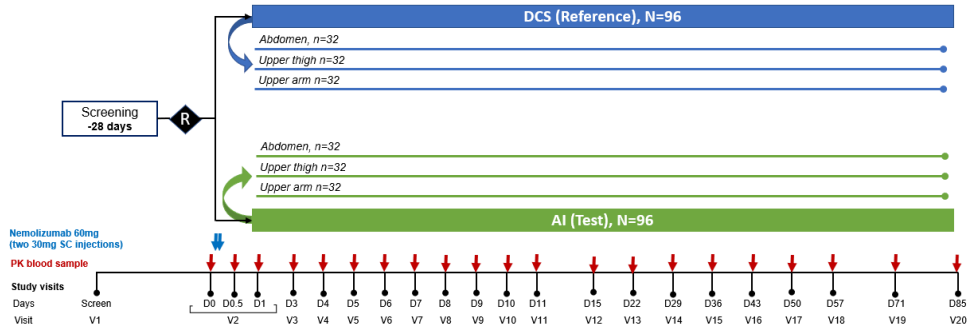
| | A total of 21 blood samples will be collected, i.e., 1 before and 20 after nemolizumab administration (i.e., pre-dose, 12 hours, 24 hours, 3, 4, 5, 6, 7, 8, 9, 10, 11, 15, 22, 29, 36, 43, 50, 57, 71, and 85 days post-dose). Subjects will be confined to the study center for 1 night, from nemolizumab dosing (Day 0) to the morning after nemolizumab dosing (Day 1).<br><br>Clinical assessments will occur according to the Schedule of Assessments. **Figure 1** presents an overview of the study design.<br><br>**Figure 1 Study Design**<br><br>  <br><br>R : randomization<br>D0 : injection day, the pre-dose PK sample will be collected before nemolizumab administration. |
| **Selection of Subjects:** | <u>Inclusion Criteria</u><br><br>Individuals must meet all of the following criteria to be included in the study:<br><br>1. Male and female subjects aged 18 to 65 years at the screening visit.<br><br>2. Body weight ≥ 45 kg and body mass index between ≥ 18.0 and < 30.0 kg/m$^2$ at both screening and baseline visits.<br><br>3. Medically healthy with normal clinical status as judged by the investigator based on medical history, physical examination, and clinical laboratory tests.<br><br>4. Willing to abstain from all prescription medications during the study, (defined hereafter as after signing of informed consent form), except to treat AEs and contraception and as permitted under Exclusion 2. Limited use of non-prescription medications/supplements that are not believed to affect subject's safety or the overall results of the study may be permitted at the discretion of the investigator.<br><br>5. Female subjects of childbearing potential (i.e., fertile, after menarche and, until becoming postmenopausal unless permanently sterile) must agree either to be strictly abstinent throughout the study and for 12 weeks after the study drug injection, or to use an adequate and approved method of contraception throughout the study and for 12 weeks after the study drug injection. Males are not required to use contraception, and there is no restriction on sperm donation.<br><br>Adequate and approved methods of contraception applicable for the subject and/or her partner are:<br><br>▪ Progestogen-only oral hormonal contraception.<br><br>▪ Combination of male condom with cervical cap, vaginal diaphragm, or vaginal sponge with spermicide (double barrier methods). |

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| | ▪ Note: "Double barrier methods" refer to simultaneous use of a physical barrier by each partner. Use of a single barrier method (e.g., condom) with a spermicide is not acceptable.<br>▪ Combined (estrogen- and progestogen-containing) oral, intravaginal, or transdermal hormonal contraception.<br>▪ Injectable or implanted hormonal contraception.<br>▪ Intrauterine devices or intrauterine hormone-releasing system.<br>▪ Bilateral tubal ligation or tube insert (such as the Essure system) at least 3 months before the study.<br>▪ Bilateral vasectomy of partner at least 3 months before the study.<br>6. Female subjects of non-childbearing potential must meet one of these criteria:<br>▪ Absence of menstrual bleeding for 1 year before the screening visit with no other medical reason, confirmed with follicle-stimulating hormone (FSH) level in the postmenopausal range.<br>▪ Documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy at least 3 months before the study.<br>▪ Note: Bilateral tubal ligation is not accepted as reason for non-childbearing potential.<br>7. Willing and able to comply with all of the time commitments and procedural requirements of the clinical study protocol.<br>8. Understand and sign an informed consent form before any investigational procedure(s) are performed.<br><u>Exclusion Criteria</u><br>Individuals meeting any of the following criteria at the screening or baseline visit are ineligible to participate in this study:<br>1. History of hypersensitivity (including anaphylaxis) to an immunoglobulin product (plasma-derived or recombinant, e.g., monoclonal antibody) or to any of the study drug excipients.<br>2. Cutaneous infection within 1 week before the baseline visit or any infection requiring treatment with oral, parenteral antibiotics, antivirals, antiparasitics, or antifungals within 2 weeks before the baseline visit. Note: Subjects with chronic, stable use of prophylactic treatment for recurrent herpes viral infection can be included in this clinical study.<br>3. Any confirmed or suspected coronavirus disease (COVID-19) infection within 2 weeks before the screening or baseline visit. Subjects may be rescreened once the infection has resolved. Resolution of COVID-19 infection can be confirmed by recovery assessment methods, as described in the protocol.<br>4. Positive serology results (hepatitis B surface antigen [HBsAg] or hepatitis B core antibody [HBcAb], hepatitis C [HCV] antibody with positive HCV RNA, or human immunodeficiency virus [HIV] antibody) at the screening visit.<br><u>Note</u>: Subjects with a positive HBcAb and a negative HBsAg can be included if the hepatitis B surface antibody is positive (considered immune after a natural infection). Subjects who are positive for HCV antibody and negative for HCV RNA can be included. |

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| | In the event of rescreening, the serology tests results (e.g., HBV, HCV, HIV) from the first screening can be used by the investigator to assess the eligibility of rescreened subjects if those tests were performed within 6 weeks before the baseline visit.<br>5. Known active or untreated latent tuberculosis (TB) infection.<br>Note: Subjects who have a documented history of completion of an appropriate TB treatment regimen for active or latent TB with no history of re-exposure to TB since their treatment was completed are eligible to participate in the study.<br>6. Known or suspected immunosuppression or unusually frequent, recurrent, severe, or prolonged infections as per investigator judgment.<br>7. History of lymphoproliferative disease or history of malignancy of any organ system within the last 5 years, except for (1) basal cell carcinoma, squamous cell carcinoma in situ (Bowen's disease), or carcinomas in situ of the cervix that have been treated and have no evidence of recurrence in the last 12 weeks before the baseline visit, or (2) actinic keratoses that have been treated.<br>8. Any condition that may interfere with study assessments (e.g., poor venous access or needle phobia).<br>9. Having received a live-attenuated or non-live vaccine within 4 weeks before the baseline visit or are expected to be vaccinated during the study or during the 12 weeks after the study drug injection, except for non-live seasonal vaccinations (e.g., influenza), COVID-19 and/or emergency vaccinations (e.g., rabies, tetanus), which are permitted during the study.<br>10. Previous treatment with nemolizumab.<br>11. History of alcohol or substance abuse within 6 months of the screening visit.<br>12. Planned or expected major surgical procedure during the clinical study.<br>13. Pregnant women (positive serum pregnancy test result at the screening visit or positive urine pregnancy test at the baseline visit), breastfeeding women, or women planning a pregnancy during the study or 12 weeks after the study drug injection.<br>14. Subjects who have donated ≥ 500 mL of blood in the 3 months before dosing.<br>15. Participating or participated in any other study with an investigational drug or device within the past 8 weeks (or 5 half-lives of the investigational drug, whichever is longer) before the screening visit, or is in an exclusion period (if verifiable) from a previous study. |
| **Planned Sample Size:** | From previous studies conducted with nemolizumab, inter-subject standard deviation is expected to be approximately 38.5%, which provides an inter-subject variability coefficient of variation (CV) for the primary PK parameters of 40%. A sample size of 96 subjects per arm (AI or DCS) should provide a 90% power of claiming the bioequivalence between AI and DCS administrations within the range 80.00 to 125.00% for the primary PK parameters with the expected geometric mean ratio of 0.95.<br>Approximately 192 healthy subjects are planned to be randomized in this study. |
| **Investigational Drug:** | Nemolizumab (CD14152) 30 mg will be provided CCI [redacted] for injection for subcutaneous use only after reconstitution in a single-use, prefilled DCS or in a single-use, prefilled AI. Subjects will receive a 60-mg dose of nemolizumab via 2 subcutaneous injections of 30 mg each at the baseline/Day 0 visit |
| **Study Duration:** | The expected duration of each subject's participation in the study is up to 16 weeks, including an up to 28-day screening period and a 12-week evaluation period. |

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| **Pharmacokinetics/ Immunogenicity:** | CCI [redacted] |
| **Safety:** | CCI [redacted] |
| **Statistical Methods and Planned Analyses:** | Analysis Populations<br><br>The safety population (SAF) will consist of all randomized subjects who received the single dose of study drug and will be the primary population for all safety data.<br><br>The PK population will include all randomized subjects who received the dose of study drug and provided suitable PK samples that can be used for the PK analyses. The PK population will be the primary population for PK analyses.<br><br>Primary PK Endpoints<br><br>PK parameters will be calculated with a non-compartmental analysis (NCA) using actual sampling times.<br><br>For the primary PK endpoint analyses, a linear mixed-effect model will assess the log-transformed PK parameters ($AUC_{0\text{-inf}}$ and $C_{max}$) of nemolizumab, with treatment (administration with AI or DCS) and injection site as fixed effects and subject as a random effect. Some clinically important baseline characteristics may also be included in the model. The geometric mean ratio (GMR) between treatments (nemolizumab administered with AI [test] or DCS [reference]) after back-transformation and the corresponding 90% confidence interval (CI) will be provided overall.<br><br>Acceptance criterion for bioequivalence is a 90% CI for the test/reference ratio of the geometric means of the parameters under consideration within the 80.00 to 125.00% range.<br><br>In addition, the GMR and 90% CI will be provided by injection site for information only.<br><br>Secondary PK Endpoints<br><br>$T_{max}$ will be analyzed using the non-parametric Wilcoxon signed-rank test.<br><br>$AUC_{0\text{-4 weeks}}$, $AUC_{0\text{-last}}$, and $t_{1/2}$ will be analyzed using the methods applied for the primary PK parameters.<br><br>CCI [redacted] |

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| | CCI [redacted] |

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# 6 LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AD | atopic dermatitis |
| ADA | anti-drug antibody |
| AE | adverse event |
| AESI | adverse event of special interest |
| AI | auto-injector |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| CI | confidence interval |
| COVID-19 | coronavirus disease 2019 |
| CPK | creatine phosphokinase |
| CRO | contract research organization |
| DCS | dual-chamber, single-use syringe |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| ELISA | enzyme-linked immunosorbent assay |
| ET | early termination |
| FSH | follicle-stimulating hormone |
| GMR | Geometric Mean Ratio |
| GCP | Good Clinical Practice |
| HBcAb | hepatitis B core antibody |
| HBsAg | hepatitis B surface antigen |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| ICF | informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements forPharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| IL | interleukin |
| IRB | Institutional Review Board |
| MAR | missing at random |
| PK | pharmacokinetic |
| PP NRS | peak pruritus numeric rating scale |
| PTC | product technical complaint |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| SAF | safety population |
| SUSAR | suspected unexpected serious adverse reaction |
| TB | tuberculosis |
| TEAE | treatment-emergent adverse event |

| Abbreviation | Definition |
|---|---|
| ULN | upper limit of normal |
| UPT | urine pregnancy test |
| WOCBP | women of childbearing potential |

# 7 INTRODUCTION

## 7.1 Background

Nemolizumab, a humanized anti-human interleukin (IL)-31 receptor A (RA) monoclonal antibody, inhibits the binding of IL-31 to IL-31 RA and subsequent signal transduction. Transgenic mice overexpressing IL-31 exhibited skin lesions resembling those of atopic dermatitis (AD) and scratching behavior, which could be suppressed by treatment with an anti-mouse IL-31 antibody (Dillon 2004) (Grimstad 2009). In cynomolgus monkeys, nemolizumab suppressed IL-31-induced scratching (Oyama 2018).

Nemolizumab administered subcutaneously is in clinical development stage for the treatment of AD and prurigo nodularis (PN). AD is a chronic inflammatory skin disease estimated to occur in 10% to 20% of the population (Weidinger 2016) and up to 25% of children (Eichenfield 2014). The disease is characterized by pruritus (itching), xerosis (skin dryness), and eczematous lesions whose features include erythema, infiltration/papulation, oozing with crusting, excoriations, and lichenification. PN is characterized by symmetrically distributed, multiple, highly pruritic, hyperkeratotic, erosive or crusted nodules and papules (Hyde 1909). This leads to an impaired quality of life and high burden due to severe itching, chronic skin lesions, and lack of treatment options (Warlich 2015).

The nemolizumab standard presentation used in ongoing clinical studies is single-dose, single-use dual-chamber syringe (DCS) CCI for injection (WFI) in 2 separate chambers with assembled finger rest. The DCS is intended for subcutaneous injection after reconstitution. The lyophilized nemolizumab powder is in Chamber 1 and WFI as a reconstitution liquid is in Chamber 2 of the DCS (see Section 11.1). After reconstitution, each syringe contains 61.5 mg/mL of nemolizumab to deliver a dose of 30 mg with nominal injection volume of 0.49 mL (for the 60-mg dose, 2 injections using 2 DCSs are needed).

The nemolizumab pharmacokinetic (PK) profile as well as the safety and tolerability of nemolizumab were generated in previous studies using the DCS.

The nemolizumab PK profile was extensively assessed in subjects with AD in Phase 1, 2, and 2b studies (CIM001JP, CIM003JG, and RD.03.SPR.114322) after repeated doses and in subjects with PN (Phase 2 study, RD.03.SPR.115828). Similar nemolizumab systemic exposure was observed in subjects with AD and subjects with PN when treated with the same dose (0.5 mg/kg).

Overall, PK assessments after subcutaneous injections of weight-based (0.1 to 3 mg/kg) or flat (10 to 90 mg) doses showed a dose-proportional increase of nemolizumab serum concentrations after a single (mg/kg) injection and a less than proportional increase after repeated (mg/kg and flat) administrations. The terminal elimination half-life of nemolizumab was around 2 weeks after single and repeated administrations. The Investigator's Brochure contains additional detailed information on nemolizumab PK.

The safety and efficacy data generated in the Phase 2b dose-finding study supported the selection of the 30-mg dose as the treatment dose for the Phase 3 studies in AD.

Two Phase 3 studies (SPR.118161 and SPR.118169) are randomized, double- blind, placebo-controlled, parallel-group studies in adult and adolescent subjects with moderate-to-severe AD to evaluate the safety and efficacy of nemolizumab administered concomitantly with background topical therapy. Subjects who complete these studies may be eligible to enter the planned Phase 3 long-term extension study.

The Investigator's Brochure contains additional detailed information on nemolizumab safety and tolerability.

The efficacy, safety, tolerability, PK, pharmacodynamics, and immunogenicity of nemolizumab are being fully characterized in the ongoing clinical program.

## 7.2 Study Rationale

During the course of development, nemolizumab in an auto-injector (AI) has been introduced. The AI is a fully disposable, single-use and single-dose injection system intended for subcutaneous injections (see Section 11.1). The AI facilitates subcutaneous injections by patients or caregivers and is the intended presentation for commercial use.

The AI is assembled around a dual-chamber cartridge, containing the same nemolizumab formulation as the DCS. To use information gathered from the DCS development program for support of a marketing authorization application with an AI, a gap analysis was performed in accordance with the Food and Drug Administration (FDA) draft guidance "Bridging for Drug-Device and Biologic-Device-Combination Products". Further chemistry, manufacturing and control data will be generated based on the information identified in the gap analysis. In addition, the current PK study will address the impact of changes in in the drug delivery parameters between AI and DCS (i.e. injection depth, injection angle and injection time)

The bridging strategy includes this PK study to assess the relative bioavailability of a subcutaneous dose of nemolizumab when administered with an AI in comparison to a DCS. The primary objective of this study is to compare the rate ($C_{max}$) and extent (AUC) of absorption of a single 60-mg dose of nemolizumab administered with AI (test) versus DCS (reference) under controlled conditions in healthy adult subjects. The secondary objectives are to assess the safety and immunogenicity of nemolizumab following administration with AI or DCS in healthy adult subjects.

## 7.3 Clinical Studies

The Investigator's Brochure (IB) contains detailed information on clinical and nonclinical studies.

## 7.4 Risk/Benefit Assessment

Results of previous clinical studies in adults demonstrated that treatment with nemolizumab had a marked effect on AD and PN.

Based on the available information on nemolizumab and the risks associated with biologic agents, the potential risks of one 60-mg dose of nemolizumab administered to healthy adult subjects include local or systemic injection-related reactions and skin or non-skin infections. The following specific risk-minimization and safety follow-up measures have been planned in this clinical study:

- The exclusion criteria of this study (i.e., restricting entry of subjects with recent/current infections or known/suspected immunosuppression or unusually frequent, recurrent, severe, or prolonged infections) will prevent non-eligible subjects from receiving nemolizumab. As no data are available in pregnant or breastfeeding women, these subjects are not eligible for this study.
- Subjects who have recently received live-attenuated or non-live vaccines may be considered for enrollment after an appropriate time of 4 weeks has elapsed before the baseline visit. Vaccinations during the study and follow-up period are not permitted, except for use of non-live seasonal vaccinations (e.g., influenza), COVID-19 and/or emergency vaccinations (e.g., rabies, tetanus).

When considering the available data of nemolizumab and the risk-minimization approaches to be implemented, the benefit/risk ratio of nemolizumab is considered favorable in this study.

### 7.5 Dose Selection Rationale

In this study, subjects will receive a 60-mg dose of nemolizumab via 2 subcutaneous injections of 30 mg nemolizumab. The proposed dose corresponds to the loading dose for both DCS and AI presentations and represents the highest strength used in Phase 3 clinical studies with nemolizumab. The extrapolation of the 60-mg dose to the 30-mg dose will be supported by the population PK model built with data collected in previous clinical studies with nemolizumab.

# 8 STUDY OBJECTIVES AND ENDPOINTS

## 8.1 Study Objectives

### 8.1.1 Primary Objective

The primary objective is to compare the rate and extent of absorption of a single dose of nemolizumab administered with AI (test) versus DCS (reference) under controlled conditions in healthy adult subjects.

### 8.1.2 Secondary Objectives

The secondary objectives are to assess the safety and immunogenicity of nemolizumab following administration with AI or DCS in healthy adult subjects.

## 8.2 Study Endpoints

### 8.2.1 Primary Endpoint

- Change of primary pharmacokinetic (PK) parameters: $C_{max}$ (rate of absorption) and $AUC_{0\text{-}inf}$ (extent of absorption) of nemolizumab administered with AI or DCS

### 8.2.2 Secondary Endpoints

- Change of secondary PK parameters ($AUC_{0\text{-}4\ weeks}$, $AUC_{0\text{-}last}$, $T_{max}$, and $t_{1/2}$) of nemolizumab administered with AI or DCS
- Assessment of the immunogenicity (anti-drug antibodies, ADA) of nemolizumab administered with AI or DCS
- CCI [redacted]

# 9 INVESTIGATIONAL PLAN

## 9.1 Description of Overall Study Design and Plan

This is a randomized, multicenter, open-label, single-dose, parallel-group study in healthy adult subjects aged 18 to 65 years to assess the relative bioavailability of a 60-mg subcutaneous dose of nemolizumab administered with AI compared to DCS, stratified by injection site. The 60-mg dose will be administered as 2 successive subcutaneous injections of 30 mg (AI or DCS).

The study duration will be up to 16 weeks and consists of an up to 28-day screening period and a 12-week PK evaluation period.

The screening period will evaluate subject eligibility. At baseline, approximately 192 subjects will be randomized 1:1 to receive 60 mg nemolizumab delivered with either AI or DCS. Subjects will be further randomized 1:1:1 to receive injection in 1 of 3 injection sites, i.e., abdomen, front upper thigh, or outer upper arm. Approximately 32 subjects in each delivery group will be assigned to each injection site.

Subjects will receive a 60-mg dose of nemolizumab via 2 subcutaneous injections of 30 mg nemolizumab. Injections should be administered at the same location (i.e., abdomen, front upper thigh, or outer upper arm) and the same side with injection sites at least 1 inch (2.5 cm) apart. Blood samples will be collected before and after nemolizumab administration for up to 12 weeks post-dose for determining the complete serum PK profile of nemolizumab.

A total of 21 blood samples will be collected, i.e., 1 before and 20 after nemolizumab administration (i.e., pre-dose, 12 hours, 24 hours, 3, 4, 5, 6, 7, 8, 9, 10, 11, 15, 22, 29, 36, 43, 50, 57, 71, and 85 days post-dose). Subjects will be confined to the study center for 1 night, from nemolizumab dosing (Day 0) to the morning after nemolizumab dosing (Day 1).

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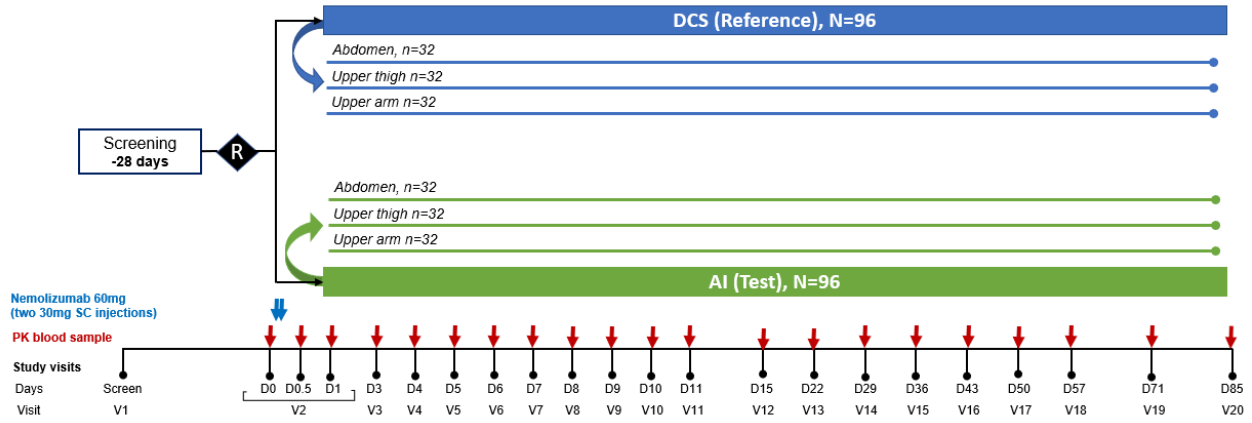
Refer to **Figure 2** for an overview of the study design.

### 9.1.1 Study Visit Scheme

**Figure 2** presents the study design.

**Figure 2 Study Design**




R: randomization
D0; injection day, the pre-dose PK sample will be collected before nemolizumab administration.

## 9.2 Discussion of Study Design

This study will assess the relative bioavailability of a 60-mg subcutaneous dose of nemolizumab administered with AI compared to DCS, stratified by injection site, including abdomen, front upper thigh, or outer upper arm. Overall, a single-dose, open-label, parallel-group PK study in healthy adult subjects is deemed appropriate for this purpose.

The parallel-group design of this study is considered necessary due to the long terminal half-life of nemolizumab ranging from 12.6 to 16.5 days and is in line with the FDA guidance "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product" (Guideline 2016) and the corresponding European guideline (Guideline 2014).

In accordance with the same FDA guidance, the study plans a single-dose administration, since single-dose PK studies are generally more sensitive than steady-state studies in assessing any difference in rate and extent of release of the drug substance from the drug product into the systemic circulation. Furthermore, in the case of nemolizumab, repeated-dose studies demonstrated a limited systemic accumulation over time, with median accumulation below 2, and steady-state concentrations reached after the loading dose. This confirms that the PK profile of nemolizumab is not affected by the number of administrations and can be predicted from single-dose PK parameters.

The choice of heathy adult subjects is supported by the results of the Phase 1 study CIM001JP. Study CIM001JP showed that nemolizumab concentration-time profiles in AD patients and healthy subjects shared the same shape, being described in both groups by a one-compartment distribution model with linear elimination and first-order absorption. Overall, nemolizumab systemic exposure

increased in a dose-dependent manner in the dose range of 0.03 to 3 mg/kg. The only observed difference was a 23 to 26% reduced exposure in AD patients compared with healthy subjects. Owing to its low immunogenicity potential, there are no safety concerns associated with nemolizumab that will preclude investigation in healthy subjects. In addition, the type of disease does not have any effect on nemolizumab PK, as similar systemic exposure and similar PK profiles were observed in subjects with AD (Phase 2 study CIM003JG) and in subjects with PN (Phase 2 study SPR.115828) when treated with the same dose of 0.5 mg/kg.

Only adult subjects will be enrolled in this study as no significant impact of age was evidenced for the nemolizumab PK profile.

A total of 21 blood samples will be collected, i.e., 1 before and 20 after nemolizumab administration (i.e., pre-dose, 12 hours, 24 hours, 3, 4, 5, 6, 7, 8, 9, 10, 11, 15, 22, 29, 36, 43, 50, 57, 71, and 85 days post-dose). PK blood sampling will be performed over a 12-week period after nemolizumab administration to enable a reliable estimation of nemolizumab total systemic exposure for both the AI and DCS. The sampling schedule includes frequent sampling around the expected time to maximum concentration ($T_{max}$ [5–9 days]).

A sample size of 192 subjects, i.e., 96 subjects per arm (AI or DCS), should provide a 90% power of claiming the bioequivalence between AI and DCS administration within the range of 80.00 to 125.00% for the primary PK parameters with the expected GMR of 0.95. This study adopts a conservative approach by requiring the standard bioequivalence range of 80.00 to 125.00% to be met for the primary PK parameters ($AUC_{0\text{-}inf}$, , and $C_{max}$) of nemolizumab.

### 9.3 End of Study

A subject will have fulfilled the requirements for study completion if/when the subject has completed all study procedures as stated in the Schedule of Assessments (**Table 2**).

The end of the study will be the last subject's last visit as stated in the Schedule of Assessments (**Table 2**).

# 10 SELECTION OF STUDY POPULATION

Section 9.1 provides information regarding the number of subjects planned to be randomized.

Refer to Section 17.1 for the statistical considerations on which the sample size is based.

## 10.1 Inclusion Criteria

Individuals must meet all of the following criteria to be included in the study:

1. Male and female subjects aged 18 to 65 years at the screening visit.

2. Body weight ≥ 45 kg and body mass index between ≥ 18.0 and < 30.0 kg/m$^2$ at both screening and baseline visits.

3. Medically healthy with normal clinical status as judged by the investigator based on medical history, physical examination, and clinical laboratory tests.

4. Willing to abstain from all prescription medications during the study, (defined hereafter as after signing of informed consent form), except to treat AEs and contraception, and as permitted under Exclusion 2. Limited use of non-prescription medications/supplements that are not believed to affect subject's safety or the overall results of the study may be permitted at the discretion of the investigator.

5. Female subjects of childbearing potential (i.e., fertile, after menarche and, until becoming postmenopausal unless permanently sterile) must agree either to be strictly abstinent throughout the study and for 12 weeks after the study drug injection, or to use an adequate and approved method of contraception throughout the study and for 12 weeks after the study drug injection. Males are not required to use contraception, and there is no restriction on sperm donation.

   Adequate and approved methods of contraception applicable for the subject and/or her partner are:

   - Progestogen-only oral hormonal contraception.
   - Combination of male condom with cervical cap, vaginal diaphragm, or vaginal sponge with spermicide (double barrier methods).
   - Note: "Double barrier methods" refer to simultaneous use of a physical barrier by each partner. Use of a single barrier method (e.g., condom) with a spermicide is not acceptable.
   - Combined (estrogen- and progestogen-containing) oral, intravaginal, or transdermal hormonal contraception.
   - Injectable or implanted hormonal contraception.
   - Intrauterine devices or intrauterine hormone-releasing system.
   - Bilateral tubal ligation or tube insert (such as the Essure system) at least 3 months before the study.

- Bilateral vasectomy of partner at least 3 months before the study.

6. Female subjects of non-childbearing potential must meet one of these criteria:

   - Absence of menstrual bleeding for 1 year before the screening visit with no other medical reason, confirmed with follicle-stimulating hormone (FSH) level in the postmenopausal range.
   - Documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy at least 3 months before the study.

   Note: Bilateral tubal ligation is not accepted as reason for non-childbearing potential.

7. Willing and able to comply with all of the time commitments and procedural requirements of the clinical study protocol.

8. Understand and sign an informed consent form before any investigational procedure(s) are performed.

### 10.2 Exclusion Criteria

Individuals meeting any of the following criteria at the screening or baseline visit are ineligible to participate in this study:

1. History of hypersensitivity (including anaphylaxis) to an immunoglobulin product (plasma-derived or recombinant, e.g., monoclonal antibody) or to any of the study drug excipients.

2. Cutaneous infection within 1 week before the baseline visit or any infection requiring treatment with oral, parenteral antibiotics, antivirals, antiparasitics, or antifungals within 2 weeks before the baseline visit. Note: Subjects with chronic, stable use of prophylactic treatment for recurrent herpes viral infection can be included in this clinical study.

3. Any confirmed or suspected coronavirus disease (COVID-19) infection within 2 weeks before the screening or baseline visit. Subjects may be rescreened once the infection has resolved. Resolution of COVID-19 infection can be confirmed by recovery assessment methods, as described in the protocol.

4. Positive serology results (hepatitis B surface antigen [HBsAg] or hepatitis B core antibody [HBcAb], hepatitis C [HCV] antibody with positive HCV RNA, or human immunodeficiency virus [HIV] antibody) at the screening visit.

   Note: Subjects with a positive HBcAb and a negative HBsAg can be included if the hepatitis B surface antibody is positive (considered immune after a natural infection). Subjects who are positive for HCV antibody and negative for HCV RNA can be included.

In the event of rescreening, the serology tests results (e.g., HBV, HCV, HIV) from the first screening can be used by the investigator to assess the eligibility of rescreened subjects if those tests were performed within 6 weeks before the baseline visit.

5. Known active or untreated latent tuberculosis (TB) infection.

   Note: Subjects who have a documented history of completion of an appropriate TB treatment regimen for active or latent TB with no history of re-exposure to TB since their treatment was completed are eligible to participate in the study.

6. Known or suspected immunosuppression or unusually frequent, recurrent, severe, or prolonged infections as per investigator judgment.

7. History of lymphoproliferative disease or history of malignancy of any organ system within the last 5 years, except for (1) basal cell carcinoma, squamous cell carcinoma in situ (Bowen's disease), or carcinomas in situ of the cervix that have been treated and have no evidence of recurrence in the last 12 weeks before the baseline visit, or (2) actinic keratoses that have been treated.

8. Any condition that may interfere with study assessments (e.g., poor venous access or needle phobia).
9. Having received a live-attenuated or non-live vaccine within 4 weeks before the baseline visit or are expected to be vaccinated during the study or during the 12 weeks after the last study drug injection, except for non-live seasonal vaccinations (e.g., influenza), COVID-19 and/or emergency vaccinations (e.g., rabies, tetanus), which are permitted during the study.

10. Previous treatment with nemolizumab.

11. History of alcohol or substance abuse within 6 months of the screening visit.

12. Planned or expected major surgical procedure during the clinical study.

13. Pregnant women (positive serum pregnancy test result at the screening visit or positive urine pregnancy test at the baseline visit), breastfeeding women, or women planning a pregnancy during the study or 12 weeks after the study drug injection.

14. Subjects who have donated ≥ 500 mL of blood in the 3 months before dosing.

15. Participating or participated in any other study with an investigational drug or device within the past 8 weeks (or 5 half-lives of the investigational drug, whichever is longer) before the screening visit, or is in an exclusion period (if verifiable) from a previous study.

### 10.3 Rescreening

Screening failures may be rescreened once.

Subjects who are rescreened must sign a new informed consent form (ICF) and be assigned a new subject identification number.

In the event of rescreening, the serology and tuberculosis (TB) tests results from the first screening can be used by the investigator to assess the eligibility of rescreened subjects if those tests were performed within 6 weeks before the baseline visit.

## 10.4 Study Withdrawal, Removal, and Replacement of Subjects

Although the importance of completing the entire study will be explained to the subjects, any subject may discontinue his/her participation in the study at any time and for whatever reason, specified or unspecified, and with no prejudice. No constraints are to be imposed on the subject, and when appropriate, a subject may be treated with other conventional therapy when clinically indicated. Investigators or the Sponsor can also withdraw subjects from the study if deemed necessary.

Reasons for discontinuing the study include:

- Withdrawal by subject
- Protocol violation

  Examples

  - Non-compliance with the study schedule
  - Use of prescription medications, except to treat AEs and contraception.
- Lost to follow-up
- AEs
  - Occurrence of AEs, including laboratory abnormalities, not compatible with the continuation of subject participation in the study, in the investigator's opinion, or unacceptable to the subject to continue, including but not limited to:
    - Serious immediate-type allergic manifestations, including anaphylactic reaction
    - Diagnosis of a malignancy (except curatively treated in situ cervical carcinoma, squamous cell carcinoma [Bowen's disease] or basal cell carcinoma)
    - Opportunistic infections such as but not limited to active TB and other infections whose nature or course suggest an immune-compromised or immune-suppressed status
    - Any serious infection or any severe infection requiring treatment with parenteral antibiotics or oral antibiotics/antivirals/antifungals for > 2 weeks considered related to study drug administration
    - Confirmed or suspected COVID-19 (temporarily, see Section 10.4.2)
- Pregnancy (see Section 10.4.1)
- Physician decision

- Sponsor request
- Study terminated by Sponsor
- Other

The reason(s) for withdrawal will be documented in the electronic case report form (eCRF). Subjects who have been enrolled and treated will not be replaced by another subject.

When a subject discontinues the study, he/she will be assessed and followed according to the guidelines in Section 12.2.1 (Early Termination Visit).

Reasonable efforts will be made to contact subjects who are lost to follow-up. These efforts must be documented in the subject's file.

The Sponsor may terminate the study if SAEs occur or if special circumstances about the investigational product or the company itself occur, making further treatment of subjects impossible. The investigator(s) will be informed of the reason for study termination.

### 10.4.1 Pregnancy

The safety of nemolizumab in pregnant or lactating women has not been established.

Subjects will be instructed that known or suspected pregnancy during the study should be confirmed and reported to the investigator. **If a subject becomes pregnant, the investigator must withdraw the subject from the study without delay.**

The investigator must:

- Follow the procedures for reporting/follow-up of a pregnancy within 24 hours (see Section 14.10.5) of receipt of the information.
- Complete as fully as possible the Pregnancy Surveillance Form(s) (see Section 14.10.5).
- Monitor and record the progress of the pregnancy until its outcome. Contact the subject's regular physician (general practitioner or gynecologist) or hospital staff to obtain further details and ask for regular follow-up information.
- Provide tri-monthly updates until the final outcome of the pregnancy. If the subject can no longer be reached (lost to follow-up), documentation of the non-response/contact with 2 phone calls and a letter (certified with return receipt) is required.
- If the pregnancy leads to an abortion (i.e., voluntary abortion, spontaneous abortion, or therapeutic abortion), in utero death, or congenital anomaly, follow the procedure for declaration of/reporting an SAE (see Section 14.10.3).

The investigator should also be notified of pregnancy during the study (and within 12 weeks after the study drug administration) but confirmed after completion of the study. In the event that a subject is pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the Sponsor after delivery.

Full details will be recorded on the withdrawal page (exit form), or an SAE report will be completed if the subject has completed the study. Pregnancy is not to be considered an AE; however, it must be monitored and reported as described in Section 14.10.5.

### 10.4.2 Coronavirus Disease 2019

If subjects experience confirmed or suspected COVID-19 infection within 2 weeks before the screening or baseline visits, they are not eligible for this study. Subjects may be rescreened once the infection has resolved.

Resolution of COVID-19 infection can be confirmed by recovery assessment methods, as described below:

- For symptomatic subjects: At least 14 days have passed since recovery, defined as resolution of fever without the use of fever-reducing medications and improvement in respiratory symptoms (e.g., cough, shortness of breath)
- For asymptomatic subjects: At least 21 days have passed since the first positive PCR test and no symptoms

Note: The above should be considered minimum criteria. Where the local guidelines are more stringent for infection resolution criteria, those must be applied.

Subjects in whom COVID-19 is confirmed or suspected during the study, should follow the local regulations, and come back to the study center after appropriate quarantine time and once the infection has resolved. COVID-19 must be specified as the reason for missed visits.

See Appendix 1 for additional guidance for management of subjects and study conduct during the COVID-19 pandemic.

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### 11.3 Measures to Minimize Bias: Study Treatment Assignment and Blinding

#### 11.3.1 Method of Study Treatment Assignment

Upon confirmation of eligibility for a subject to participate in the study, a unique randomization number will be assigned to that subject manually at the baseline visit.

Approximately 192 subjects will be randomized 1:1 to receive 60 mg nemolizumab delivered with either AI or DCS. Subjects will be further randomized 1:1:1 to receive injection in 1 of 3 injection sites, i.e., abdomen, front upper thigh, or outer upper arm. Approximately 32 subjects in each delivery group will be assigned to each injection site.

### 11.3.2 Blinding

Not applicable because this is an open-label study.

## 11.4 Dosage Modifications

Dosage modification of the study drug will not be permitted during the study. Any inadvertent dose modification(s) should be reported to the Sponsor/CRO.

The rationale for the nemolizumab dose/dose regimen is provided in Section 7.5.

## 11.5 Treatment Accountability and Compliance

Study drug will be provided to the investigational site, and site personnel will acknowledge receipt of the study drug as defined in the current version of the pharmacy manual to confirm the shipment condition and content. If a damaged shipment is received and/or a temperature excursion has been experienced, he/she will notify the Sponsor/CRO and follow the guidelines according to the current version of the pharmacy manual.

The designated personnel will also maintain accurate records of the study drug throughout the clinical study, including the inventory delivered to the study center, the use by each subject, the reconciliation of all delivered and received DCS units, and the return/destruction of unused study drug as specified in the current version of the pharmacy manual. No unauthorized use is permitted. Used AI and DCS units will be properly documented in drug accountability records. Unless a product technical complaint (PTC) is detected or an event occurs before, during, or just after the injection, the used AI and DCS can be disposed in an appropriate sharps container and according to waste regulation(s) in the country. An AI or DCS involved in a malfunction or an investigator or subject complaint must be retained on site and designated personnel must proceed as defined in the current version of the pharmacy manual. Refer to Section 11.7 for product technical complaints.

The study monitor will check the study supplies at each study center at any time during the study. The study monitor will ensure that the investigator (or designee) has correctly documented the study drug received, dispensed, and returned/destroyed on the dispensing log provided. A full drug accountability log will be maintained at the study center. The study monitor will arrange collection of any unused study drug not destroyed by the site. The study monitor will also perform an inventory of study drug at the close-out visit to the study center. All discrepancies must be accounted for and documented.

### 11.5.1 Dispensing and Return of Study Drug

All drug preparation must be appropriately performed and documented by the designated personnel. Any error to prepare dosing solution must be reported to the study monitor promptly and be properly documented. At the end of the study, the reconciliation/return/destruction process for all unused study drug will be conducted according to the sites' standard operating procedures, local regulations, and best practices, as described in the current version of the pharmacy manual. If the site cannot destroy drug, then the unused study drug will be returned to the CRO/drug depot for destruction.

### 11.5.2 Compliance

Treatment compliance will be assessed through the treatment records and drug dispensation logs.

As study drug is administered in the clinic, treatment compliance will be overseen and documented by the investigator and study staff (using the treatment records and drug accountability records). At a minimum, date, time, dose, injector (site staff), and site of injection should be accurately recorded to confirm that the single 60-mg dose of study drug was properly administered.

## 11.6 Prior and Concomitant Therapy

Prior therapies are defined as therapies stopped within the 3 months before the screening visit, unless relevant to the inclusion/exclusion criteria.

Concomitant therapies/medications are defined:

- Any existing therapies ongoing at the time of the screening visit,
- Any changes to existing therapies (such as change in dose, formulation, or application frequency) during the study, or
- Any new therapies received by the subject since the screening visit.

These 2 categories are to be considered for prior and concomitant therapies:

- Drugs/therapies include but are not limited to prescription, over-the-counter, birth control pills/patches/hormonal devices, vitamins, moisturizers, sunscreens, herbal medicines/supplements, and homeopathic preparations.
- Medical and surgical procedures (e.g., phototherapy, exodontia). Procedures whose sole purpose is diagnosis (non-therapeutic) are not included.

Prior and concomitant therapies for drugs/therapies or for medical/surgical procedures are to be recorded in the appropriate eCRF.

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

At each visit, investigators should also confirm concomitant therapies for contraception. Contraceptive counseling should occur at screening.

Any new concomitant therapy or modification of an existing therapy may be linked to an AE. In such cases, a corresponding AE Form should be completed to account for the new therapy or change in therapy (see Section 11.4).

### 11.6.1 Permitted Concomitant Therapy

Subjects will be included into this study if they will abstain from all prescription medications during the study, except to treat AEs and contraception. Limited use of non-prescription medications/supplements that are not believed to affect subject's safety or the overall results of the study may be permitted at the discretion of the investigator in consultation with the Sponsor, if required.

### 11.6.2 Prohibited Medication/Therapy

Please refer to Section 11.6.1.

Vaccinations during the study are not permitted, except for the following non-live vaccines:

- Seasonal vaccinations (e.g., influenza),
- Emergency vaccinations (e.g., rabies or tetanus),
- COVID-19 vaccinations.

Wherever possible, it is recommended to avoid administration of seasonal and COVID-19 vaccinations within 1 week of the baseline visit.

## 11.7 Product Technical Complaints

All AI and DCS units must be inspected before preparation/injection by the persons performing the preparation/injection to ensure absence of visual defects that could lead to an AI or DCS PTC. This also includes the needle and plunger rod. If doubt occurs, the AI or DCS should not be used, and the deficiency must be reported as defined in the pharmacy manual.

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## 12 STUDY PROCEDURES

A written, signed ICF, is required before any study-related procedures are performed.

Upon provision of the signed ICF, each subject will be assigned a unique subject identification number. During the entire clinical study, the subject will be identified using the subject identification number in all documentations and discussion.

The planned study assessments are in Section 12.1. At each visit, assessments/procedures should be performed in the following order:

1. Patient-reported safety measurements
2. Assessments including safety; electrocardiogram (ECG) should be done before vital signs measurements (and blood draws). See Section 14.5.
3. Sample collections for PK and laboratory assessments, including ADA
4. Administration of study drug injections at the baseline visit (Day 1)

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## 12.2 Duration of Subject Participation

The expected duration of each subject's participation in the study is up to 16 weeks, including an up to 28-day screening period and a 12-week evaluation period.

### 12.2.1 Early Termination Visit

Subjects who prematurely discontinue from the study should complete an ET visit at the time of discontinuation. A final visit is required 12 weeks after study drug administration.

### 12.2.2 Unscheduled Visit

The subject should be reminded to adhere to the study schedule. Unscheduled visits are defined as visits to repeat testing for abnormal laboratory results or follow-up of AEs. Visits outside of the visit window are not considered unscheduled visits.

Assessments to be conducted at the unscheduled visit will depend on the reason for the visit: the procedures/assessments in Section 12.1 may be conducted, but not all are required. Blood sample collection for ADA analyses is only required during unscheduled visits conducted for safety reasons, when safety labs are collected for the management/monitoring of an AE. When unscheduled visits are needed for the monitoring of the same AE, ADA collection is not required if already done at the first unscheduled visit of the series. Additional collection of samples for ADA analysis should be performed per investigator's judgment.

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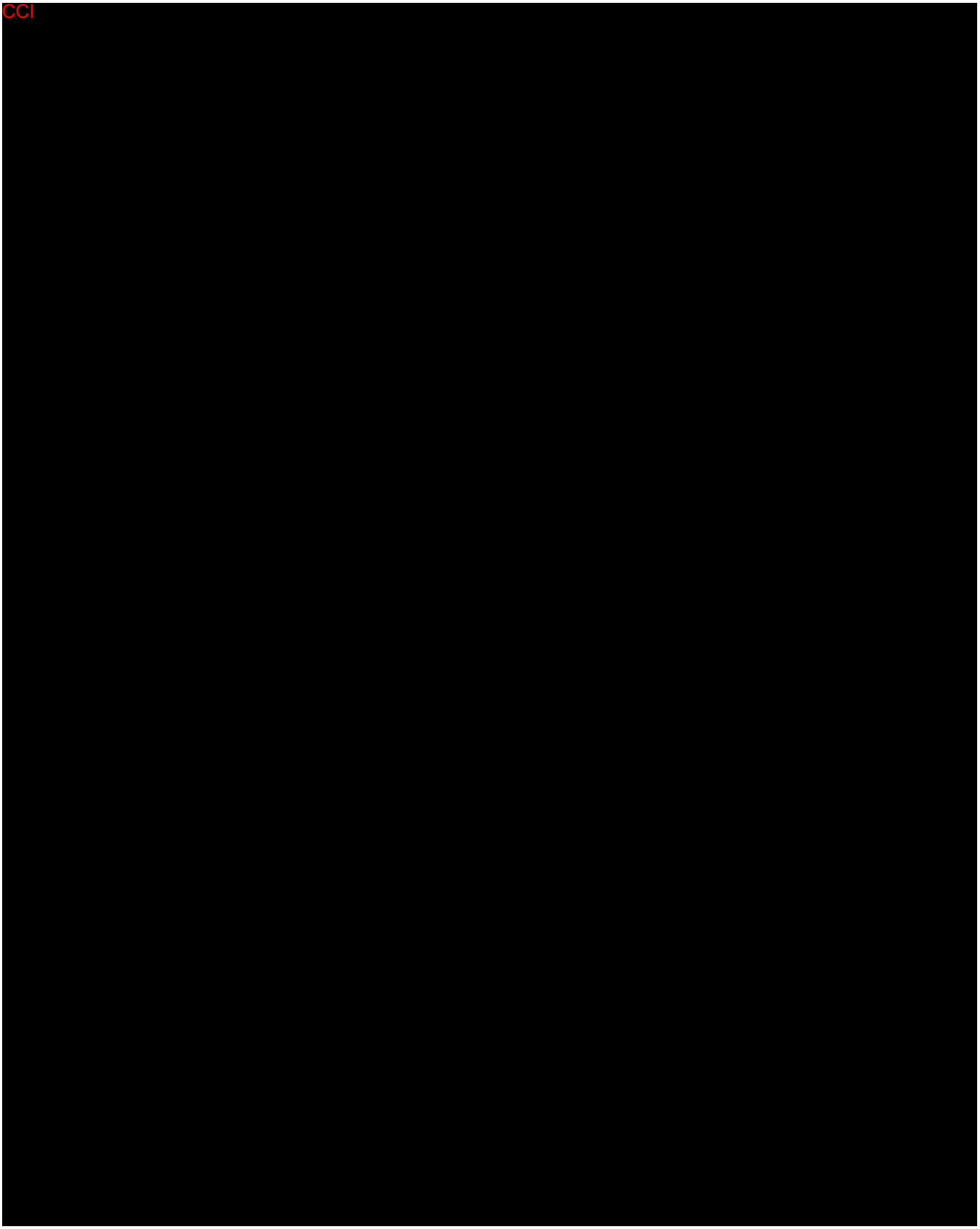

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# 14 SAFETY ASSESSMENTS

Safety assessments will be conducted for all subjects at the screening visit (upon signing of the ICF) and at every subsequent visit.

## 14.1 Medical History

Medical history will be recorded at screening. Investigators should document the subject's pre-existing conditions, including all prior relevant (e.g., atopic/allergic conditions such as asthma) and significant illnesses, before the screening visit. Medical history will include alcohol consumption and smoking history, if applicable. Medical history will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA).

Additionally, demographic data will be collected for all subjects and include but are not limited to age, sex, race, etc., according to applicable regulations.

## 14.2 Vital Signs

Vital signs will be evaluated at the screening, baseline, and certain subsequent scheduled visits according to Section 12.1. Vital signs will include pulse rate, systolic and diastolic blood pressure (after the subject has been sitting for at least 5 minutes), and body temperature. All abnormal values at the screening visit identified as clinically significant by the investigator will be recorded in the medical history form. Any clinically significant changes from the screening visit will be recorded as an AE.

## 14.3 Physical Examination

Complete physical examination should be performed at the screening, baseline, and certain subsequent scheduled visits, according to Section 12.1. A complete physical examination will include assessments of the head, ears, eyes, nose, throat, neck (including thyroid), skin/integumentary system, cardiovascular system, respiratory system, gastrointestinal system, musculoskeletal system, lymph nodes, nervous system, and extremities.

The investigator should assess all abnormal findings for clinical significance. All clinically significant abnormal findings at the screening visit will be recorded in the medical history form. Any clinically significant changes from the screening visit will be recorded as an AE.

## 14.4 Height and Weight

Height and weight will be measured, according to Section 12.1.

Subjects must weigh at least 45 kg and have a body mass index between $\geq 18.0$ and $< 30.0$ kg/m$^2$ at both screening and baseline visits to be enrolled into this study.

### 14.5 Electrocardiogram

A 12-lead ECG will be performed and read locally according to visits specified in Section 12.1 using the ECG machine provided. ECGs will be performed in the supine position at the time points described in the Schedule of Assessments and before any scheduled vital sign measurements and blood draws. Subjects should be monitored for potentially clinically significant ECG results. Tests with abnormal results deemed clinically significant should be repeated to ensure reproducibility of the abnormality. ECG abnormalities present at screening should be recorded in the medical history form. Any abnormalities considered by the investigator clinically significant after the screening visit are to be recorded as AEs and discussed with the medical monitor, as needed.

### 14.6 Clinical Laboratory Evaluation

The hematology laboratory analyses, clinical chemistry laboratory analyses, and urinalyses will be performed at the clinical site. Reference ranges will be supplied by the local laboratory and used by the investigator to assess the laboratory data for clinical significance and pathological changes.

The investigator or medically qualified sub-investigator must review and evaluate laboratory values for each subject promptly. For each out-of-range laboratory result, the investigator or designee will evaluate whether he/she considers it clinically significant, defined as meeting at least 1 of these conditions:

- The abnormality suggests a disease and/or organ toxicity, or
- The abnormality is of a degree that requires additional active management, e.g., discontinuation of the drug, close observation, more frequent follow-up assessments, or further diagnostic investigation.

If the investigator observes a clinically significant laboratory result, the test will be repeated soon, and the subject will be monitored until the value returns to normal and/or an adequate explanation for the abnormality is found.

Investigators also may repeat specific laboratory test(s) or procedure(s) where the investigator suspects an inaccuracy or false result and that may affect the safety of the subject or interpreting the study results, only after discussion with medical monitor.

All clinically significant out-of-range laboratory values at the screening visit will be recorded in the medical history form (report a diagnosis rather than the laboratory value). All clinically significant out-of-range laboratory values after the screening visit are to be reported as an AE if this abnormality was not present at the screening visit or is assessed as having worsened since the screening visit (i.e., changed significantly from the screening visit). The investigator should diagnose an AE when reporting the abnormal laboratory value.

Subjects should be reminded to be well hydrated before all visits for phlebotomy. Subjects should fast for at least 8 hours before the visits when blood chemistry testing is planned, except for the screening visit. The screening visit laboratory values must be available before the baseline visit. Laboratory testing conducted in a non-fasting state will not be a protocol deviation.

The total blood volume to be drawn will remain below the limits defined in the (Guideline 2009).

Additional samples may be required if medically indicated (e.g., when an abnormal laboratory value is observed and requires a re-test).

See Section 14.7, Section 14.8, and Section 14.9 for details regarding pregnancy testing, virology, and TB testing samples, respectively.

The following laboratory safety tests will be performed as specified in Section 12.1.

### 14.6.1 Hematology

Hemoglobin, hematocrit, white blood cell count (with differential including eosinophils), red blood cell count, platelet count, and mean cell volume.

### 14.6.2 Clinical Chemistry

Creatinine, AST, ALT, gamma glutamyl transferase, alkaline phosphatase, lactate dehydrogenase, total bilirubin, direct bilirubin, albumin, total protein, uric acid, sodium, potassium, calcium, chloride, glucose, urea, total cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein, creatine phosphokinase (CPK). CPK isoenzyme test will be performed only if CPK is elevated to > 2.5 × upper limit of normal (ULN). The investigator should also contact the medical monitor in such situations.

For postmenopausal subjects (i.e., absence of menstrual bleeding for 1 year before the screening visit), postmenopausal status will be confirmed with a high FSH level in the postmenopausal range.

### 14.6.3 Urinalysis

pH, glucose, ketones, blood, protein, leukocytes, nitrites, bilirubin, urobilinogen, and specific gravity.

## 14.7 Pregnancy Testing

All women of childbearing potential (WOCBP) will have a serum pregnancy test at the screening visit and urine pregnancy tests (UPTs) at subsequent visits according to Section 12.1. Pregnancy test results must be available before the administration of the study drug.

Subjects with a positive serum pregnancy test result at screening must not be enrolled.

UPTs with a sensitivity < 25 IU/L will be provided to the study centers for the study.

UPTs will be performed at the study centers, and all other samples will be sent to local laboratory for analysis.

If the result of a UPT is positive, it must be confirmed with a serum pregnancy test. Subjects with a positive serum pregnancy test result during the study must be withdrawn from the study.

### 14.8 Virology

Virology including HBsAg, HBcAb, HCV, HIV-1 and HIV-2 antibodies will be assessed at the screening visit. Subjects with a positive HBcAb and a negative HBsAg can be included if the hepatitis B surface antibody is positive (considered immune after a natural infection). Subjects who are positive for HCV antibody and negative for HCV RNA can be included.

### 14.9 Tuberculosis Testing

Immunosuppressant biologic treatments have been shown to increase the risk of TB infection or to cause conversion from latent to active TB sometimes. Because of this, subjects will be screened for active or latent TB before entry into this study.

#### 14.9.1 Definitions

Active TB is a disease caused by Mycobacterium tuberculosis in any part of the body and that is in an active state as determined by either a smear or culture taken from any source in the person's body which tests positive for TB or by radiographic evidence. Individuals with active TB are symptomatic, depending upon the location of the disease (most commonly in the lungs but also possibly in the brain, kidneys, spine, or elsewhere), and can spread the infection to others.

Latent TB is said to exist when an individual is infected with Mycobacterium tuberculosis, as evidenced by a positive Interferon Gamma Release Assay (Mazurek 2010), such as QuantiFERON-TB Gold, but is asymptomatic and has no evidence of active infection on screening pathology or radiographic tests. Such individuals do not pass the disease to others and should commence a course of prophylactic antimycobacterial treatment to eliminate the infection and commit to completing the course of treatment.

#### 14.9.2 Tuberculosis Screening

Ideally, as part of the medical history, the subject should be asked if they have presented with active or latent TB in the past and whether they have received a bacillus Calmette-Guérin vaccination. They should also be asked if they have been in contact with any individuals known to have active TB or been placed in any circumstances that may have exposed them to an increased risk of TB infection, such as travel to TB endemic regions, close contact with persons with active TB, or workplace risk (e.g., prison, hospitals).

A subject who tests positive for latent TB (with a positive QuantiFERON-TB Gold test) should be referred to the subject's treating physician for follow-up unless the subject has a documented history of completion of an appropriate TB treatment regimen with no history of re-exposure to TB since her/his treatment was completed. If the result is indeterminate, the test may be repeated once.

If confirmed indeterminate, the subject should then be managed as though he/she has a positive test result.

### 14.10 Adverse Events

**Adverse Event Definition:** An AE is defined as any untoward medical occurrence in a clinical study subject administered a medicinal product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with using a medicinal (investigational) product, whether or not it is related to the medicinal (investigational) product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction, or the significant worsening of the indication under investigation not recorded elsewhere in the eCRF under specific efficacy assessments.

Note(s):

- Any new sign or symptom reported by the subject that appears after accidental or intentional overdose or misuse of study drug should be reported as an AE.
- A diagnosis should be reported on the AE Form, instead of signs, symptoms, or abnormal laboratory values.
- Pregnancy is not to be considered an AE; however, it must be monitored and reported as described in Section 14.10.5.
- Each worsening of a chronic disease from the screening visit should be reported as a new AE.

The investigator or designee will report all AEs that occur from the time the ICF is signed until the end of the study. The Sponsor/CRO should be informed if the investigator learns of any safety information that appears to be drug-related, even after the subject has completed the clinical study.

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

Any AE during the AE reporting period, whether it is related to the study drug(s) or not, will be recorded immediately in the source document and described on the AE Form along with the date of onset, severity, relationship to the study drug(s), and outcome, omitting no requested and known information. Additional information will be requested under certain circumstances.

AEs assessed as related to the treatment or study procedure will be monitored until they have resolved or reached a stable condition. Other AEs will be monitored until the last visit if they have not resolved or reached a stable condition.

The investigator will obtain and maintain in the subject’s files all pertinent medical records, information and medical judgment from colleagues who assisted in the treatment and follow-up of

the subject. If necessary, the investigator will contact the subject's personal physician or hospital staff to obtain further details.

**Assessment of Severity:** Each AE will be assigned a category by the investigator:

- **Mild:** An AE easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities.
- **Moderate:** An AE sufficiently discomforting to interfere with normal everyday activities; intervention may be needed.
- **Severe:** An AE that prevents normal everyday activities; treatment or other intervention usually needed.

If there is a change in severity of an AE, it must be recorded as a separate event.

**Assessment of Causality:** The investigator is to determine whether there is a reasonable causal relationship between the AE and exposure to the study drug (i.e., nemolizumab or placebo) and/or study procedure (e.g., injection, topical background therapy, blood sample collection). Medical judgment should determine the relationship, considering all relevant factors including the pattern of the reaction, temporal relationships, relevant medical history, and confounding factors such as co-medication or concurrent diseases.

The expression “reasonable causal relationship” conveys in general there are facts or arguments to suggest a causal relationship (ICH E2A, Section IIIA 1).

The relationship assessment for an AE is to be completed using these definitions as a guideline for all AEs during this clinical study:

**Reasonable Possibility:** According to the reporting investigator, there is a reasonable possibility (i.e., suggestive evidence or arguments) there is a causal relationship despite the dose administered:

- Between the study drug and the AE, and/or
- Between the clinical study protocol procedure (e.g., injection, topical background therapy, blood sample collection) and the AE

**No Reasonable Possibility:** No suggestive evidence or arguments can be identified regarding a causal relationship between the study drug or the clinical study protocol procedure and the AE.

**Action Taken:** The investigator will describe the action taken in the appropriate section of the eCRF:

- None
- Study drug stopped
- Study drug temporarily interrupted
- Concomitant medication (any additions or discontinuations)

- Other, specify

**Follow-up of Adverse Events:** All investigators should follow-up with subjects with AEs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Details of AE resolution must be documented in the eCRF.

CCI [redacted]

**Documentation and Reporting of Adverse Events:** AEs should be reported and documented under the procedures outlined below. All AEs during the study must be documented on the relevant eCRF pages. The following data should be documented for each AE:

- Description of the symptom event
- Classification of "serious" or "not serious"
- Severity
- Date of first occurrence and date of resolution (if applicable)
- Action taken
- Causal relationship
- Outcome of event (unknown, recovered, not yet recovered, recovered with sequelae, death [with date and cause reported])

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CCI [redacted]



### 14.10.2 Serious Adverse Events

An SAE is any untoward medical occurrence or effect that, at any dose,

- Results in death.
- Is life-threatening (an AE is life-threatening if the subject was at immediate risk of death from the event as it occurred, i.e., it does not include a reaction that might have caused death had it occurred in a more serious form).
- Requires or prolongs inpatient hospitalization. (Complications during hospitalization are AEs and SAEs if they prolong the hospitalization. Inpatient hospitalization is considered to have occurred if the subject has had to stay for a night at the hospital. The criterion for prolongation of hospitalization is also defined as an extra night at the hospital. Hospitalization may not constitute sufficient grounds to be an SAE if it is solely for diagnostic tests [even if related to an AE], elective hospitalization for an intervention already planned before subject enrollment in the clinical study, admission to a day care facility, social admission [e.g., if the subject has no place to sleep], or administrative admission [e.g., for a yearly examination]. The details of such hospitalizations must be recorded on the medical history or physical examination eCRF.)
- Results in persistent or significant disability/incapacity. (An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the ability to carry out normal life functions.)
- Results in a congenital anomaly/birth defect.
- An important medical event that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon medical judgment, the event may jeopardize the safety of the subject, and may require medical or surgical intervention to prevent 1 of the outcomes listed above in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasia, or convulsions that do not result in hospitalization.

### 14.10.3 Serious Adverse Event Reporting

For any SAE during the clinical study, whether or not related to the study drug and/or procedure, the investigator must:

1. Take prompt medical action, if necessary. The safety of the subject is the first priority.
2. Ensure that the event is evaluated as an SAE. Immediately notify (**within 24 hours of receipt of the event**) the CCI [redacted] of an SAE report, by email or fax number on the SAE form,

CCI [redacted]

The demographics, medical history, drugs/therapies, and medical and surgical procedures forms must also be available for review in the eCRF.

4. Send any relevant information or anonymized medical records (e.g., laboratory test results) to the CCI [redacted], within 24 hours of receipt of this relevant information.

5. Monitor and record the progress of the event until it resolves or reaches a stable condition, with or without sequelae. For all additional follow-up evaluations, complete an updated SAE report within 24 hours of receipt of the updated information.

6. Obtain and maintain in the subject files all pertinent medical records, information, and medical judgments from colleagues who participate in the treatment and follow- up of the subject. If necessary, contact the subject's personal physician or hospital staff to obtain further details.

7. When the outcome of the event is known, complete an updated SAE report, if appropriate.

8. Prompt notification of SAEs by the investigator is essential so legal obligations and ethical responsibilities toward the safety of subjects are met. The Sponsor must notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. The Sponsor or its delegate (i.e., the CRO) will comply with country-specific regulatory requirements relating to safety reporting to regulatory authorities, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators. Investigator safety reports are prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and are forwarded to investigators as necessary.

   An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor or its delegate (i.e., the CRO) will file it (i.e., within the Trial Master File), and will notify the IRB/IEC, if appropriate according to local requirements.

9. Comply with the applicable regulatory requirement(s) related to the reporting of SAEs to the IRB/IEC.

### 14.10.4 Procedure for Reporting an Adverse Event of Special Interest

For any AESI during the clinical study, whether or not related to the treatment, the investigator must:

1. Take prompt medical action, if necessary. The safety of subjects is the first priority.

2. Ensure that the event is evaluated as an AESI. Notify (within 3 days of receipt of the event) CCI [redacted] of an AESI report, by email or fax. Refer to Section 14.10.1.

CCI [redacted]

   The demographics, medical history, drugs/therapies, and medical and surgical procedures forms must also be available for review in eCRF.

3. Send any relevant information or medical records (e.g., laboratory test results) to CCI [redacted] within 3 days of receipt of this relevant information.

4. Monitor and record the progress of the event until it resolves or reaches a stable condition, with or without sequelae. For all additional follow-up evaluations, update the AESI form within 3 days of receipt of the updated information.

5. Obtain and maintain in the files all pertinent medical records, information, and medical judgments from colleagues who participate in the treatment and follow-up of the subject. If necessary, contact the subject's personal physician or hospital staff to obtain further details.

6. When the outcome of the event is known, update the AESI form, if appropriate.

### 14.10.5 Procedure for Reporting Pregnancies

Any pregnancy during clinical studies where the fetus could have been exposed to the study drug must be monitored until its outcome to ensure the complete collection of safety data. If a subject becomes pregnant, the investigator must:

1. Withdraw the subject from the clinical study. The subject must receive no further injection of the study drug.

2. Complete fully the Pregnancy Surveillance Form - Part I: History and Start of Pregnancy. Send by email or fax along with the exit form within 24 hours of receipt of the information, to CCI [redacted] Refer to Section 14.10.5.

   Note: Immediate pregnancy reporting is required by the investigator if it occurs during the clinical study or within 12 weeks (± 5 days) of receiving the last dose of study drug, whether or not the event is considered related to the investigational product.

3. Monitor and record the progress of the pregnancy until its outcome. Contact the subject's regular physician (general practitioner or gynecologist) or hospital staff to obtain further details and ask for regular follow-up information.

4. Provide tri-monthly updates until the final outcome of the pregnancy, by completing the Pregnancy Surveillance Form - Part II: Course and Outcome of Pregnancy. For all additional

follow-up evaluations, send the form by email or fax CCI [redacted] CCI [redacted] within 24 hours of receipt of the information. If the subject can no longer be reached (i.e., lost to follow-up), documentation of the non-response/contact with 2 phone calls and a letter (certified with return receipt) is required.

5. At the outcome of the pregnancy, complete fully the Pregnancy Surveillance Form - Part II: Course and Outcome of Pregnancy. Print and send the form by email or fax to CCI [redacted] within 24 hours of receipt of the information.

6. If the pregnancy leads to an abortion (i.e., voluntary abortion, spontaneous abortion, or therapeutic abortion), in utero death or congenital anomaly, follow the procedure for declaration of/reporting an SAE (see Section 14.10.3).

### 14.10.6 Suspected Unexpected Serious Adverse Reactions

AEs that meet these criteria will be classified as SUSARs and reported to the appropriate regulatory authorities under applicable regulatory requirements for expedited reporting:

- Serious
- Unexpected (i.e., the event contradicts the Reference Safety Information in the IB for nemolizumab)
- There is at least a reasonable possibility there is a causal relationship between the event and the study treatment

The Sponsor or its delegate will comply with country-specific regulatory requirements relating to safety reporting to regulatory authorities, IRB/IEC and investigators. Investigator safety reports are prepared for SUSARs according to local regulatory requirements and Sponsor policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SUSAR or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor or its delegate will file it (i.e., within the Trial Master File), and will notify the IRB/IEC, if appropriate according to local requirements.

### 14.10.7 Overdose

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. The investigator must immediately notify the Sponsor of any occurrence of overdose with study drug (see Section 14.10).

# 15 PHARMACOKINETIC ANALYSIS

# 16 PHARMACOKINETIC PARAMETERS

PK parameters will be calculated by a dedicated CRO with a non-compartmental analysis (NCA) using actual sampling times. For PK calculations, the program package Phoenix WinNonlin (Version 8.1 or above) will be used. Phoenix WinNonlin will also be used to generate concentration-time plots. Details related to the calculation of PK parameters will be described in a PK plan, which will be finalized before the beginning of PK analysis.

The following PK parameters will be calculated:

Primary PK parameters

| | |
|---|---|
| $C_{max}$ | Observed maximum serum concentration |
| $AUC_{0\text{-}inf}$ | Area under the concentration-time curve extrapolated to infinity, calculated, if feasible, as $AUC_{0\text{-}last} + C_{last}/\lambda_z$, where $C_{last}$ is the last measurable drug concentration |

Secondary PK parameters

| | |
|---|---|
| $AUC_{0\text{-}4\ weeks}$ | Area under the concentration-time curve over the specified interval, calculated with the linear trapezoidal method |
| $AUC_{0\text{-}last}$ | Area under the concentration-time curve from administration to the last observed concentration time t, calculated with the linear trapezoidal method |
| $T_{max}$ | Time to achieve $C_{max}$ |
| $t_{1/2}$ | Half-life, calculated, if feasible, as $\ln 2/\lambda_z$ |
| Cl/F | Total body clearance for extravascular administration, calculated, if feasible, as $dose/AUC_{0\text{-}inf}$ |
| $V_d/F$ | Apparent volume of distribution for extravascular administration, calculated, if feasible, as $dose/AUC_{0\text{-}inf} \bullet \lambda_z$ |

For parameters requiring the terminal elimination rate constant $\lambda_z$ to be estimated, it will be calculated, if feasible, by log-linear regression using at least 3 concentration-time points excluding $C_{max}$.

All individual concentration data and PK parameters will be listed for AI and DCS together with summary statistics of geometric mean, median, arithmetic mean, standard deviation, CV, and minimum and maximum. Plots will be provided in original scale and semi-logarithmic scale for each subject in addition to mean data plots.

## 16.1 Exposure-Response Analysis

If the confidence intervals (CIs) for the primary PK parameters are outside the 80.00 to 125.00% acceptance range, acceptance of greater differences in PK parameters might be supported based on a clinical justification that these differences are clinically irrelevant PK/pharmacodynamic (PD) models may support lack of clinically meaningful impact on AD (peak pruritus numeric rating scale [PP NRS], Eczema Area and Severity Index, and Investigator's Global Assessment) or PN (PP NRS) clinical endpoints. This approach is based on the observation that, within the considered magnitude of dose changes, relationship between dose and average exposure is linear. Details related to exposure-response analysis will be described in a PK plan, which will be finalized before the beginning of PK analysis.

# 17 STATISTICAL ANALYSIS

A statistical analysis plan will be prepared after the protocol is approved. This document will explain the definition of analysis variables and analysis methodology to address all study objectives. The statistical analysis plan will serve as a compliment to the protocol and supersedes it if differences occur.

The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed. All primary and secondary efficacy endpoints, and safety endpoints will be summarized. Summary statistics will be presented by treatment group. For continuous variables, data will be summarized with the number of subjects (N), mean, standard deviation, median, minimum, and maximum by treatment group. For categorical variables, data will be tabulated with the number and proportion of subjects for each category by treatment group.

## 17.1 Determination of Sample Size

From previous studies conducted with nemolizumab, inter-subject standard deviation is expected to be approximately 38.5%, which provides an inter-subject variability CV for the primary PK parameters of 40%. A sample size of 96 subjects per arm (AI or DCS) should provide a 90% power of claiming the bioequivalence between AI and DCS administration within the range 80.00 to 125.00% for the primary PK parameters with the expected GMR of 0.95.

Approximately 192 healthy subjects are planned to be randomized in this study.

## 17.2 Analysis Populations

**Safety Population:** The safety population (SAF) will consist of all randomized subjects who received the single dose of study drug and will be the primary population for all safety data.

**Pharmacokinetic Population:** The PK population will include all randomized subjects who received the dose of study drug and provided evaluable data that can be used for the PK analyses. The PK population will be the primary population for PK analyses.

## 17.3 Statistical Analysis of Pharmacokinetic Parameters

### 17.3.1 Primary Pharmacokinetic Endpoints

For the primary PK endpoint analyses, a linear mixed-effect model will assess the log transformed PK parameters ($AUC_{0\text{-}inf}$ and $C_{max}$) of nemolizumab, with treatment (administration with AI or DCS) and injection site as fixed effects and subject as a random effect. Some clinically important baseline characteristics may also be included in the model. The AUC and $C_{max}$ GMR between treatments (nemolizumab administered with AI [test] or DCS [reference]) after back-transformation and the corresponding 90% CI will be provided overall.

Acceptance criterion for bioequivalence is a 90% CI for the test/reference ratio of the geometric means of the parameters under consideration within the 80.00 to 125.00% range.

In addition, the GMR and 90% CI will be provided by injection site for information only.

### 17.3.2 Secondary Pharmacokinetic Endpoints

$T_{max}$ will be analyzed using the non-parametric Wilcoxon signed-rank test.

$AUC_{0\text{-last}}$, $AUC_{0\text{-4 weeks}}$, and $t_{1/2}$ will be analyzed using the methods applied for the primary PK parameters.

## 17.4 Safety Analysis

**Adverse Events:** All reported AEs will be coded using the most recent version of MedDRA. TEAEs, defined as those AEs after the first administration of study treatment until last study visit, will be tabulated in frequency tables by System Organ Class and Preferred Term. Additional summary tables will be provided for SAEs, AEs related to the study drug(s) (reasonable possibility, no reasonable possibility), AEs related to the study procedure, AESIs, and AEs leading to treatment discontinuation and study withdrawal. For an AE, a subject will be counted once even if he/she has experienced multiple episodes of that AE.

Pretreatment AEs will be listed separately.

**Clinical Laboratory:** Laboratory data (absolute values and change from baseline) will be summarized by visit and treatment group. In addition, the number and percentage of subjects below, within, and above the laboratory reference ranges and the number and percentage of subjects who met criteria of potential clinically significant value will be summarized by treatment group. Shift tables will be generated using the reference ranges. Reference ranges will be provided in the laboratory manual.

**Vital Signs:** All vital signs and weight data (absolute values and change from baseline) will be summarized by visit and treatment group. In addition, the number and percent of subjects with clinically significant abnormal values (of clinical concern as identified by the investigator) will be summarized by treatment group.

**12-Lead Electrocardiogram:** The number and percentage of subjects with ECGs that are abnormal/clinically significant and abnormal/not clinically significant will be displayed by treatment at each visit.

**Concomitant Medications:** Prior and concomitant medications will be coded according to the most recent version of the World Health Organization Drug Dictionary Enhanced for Concomitant Medication and summarized.

### 17.5 Anti-Drug Antibody Analysis

The incidence of positive ADA results will be summarized and plotted (absolute occurrence, percent of subjects, and treatment-emergent ADA) in the SAF.

### 17.6 Handling of Missing Data

The statistical procedure will be conducted without imputing values to the missing observations.

# 18 STUDY MANAGEMENT

## 18.1 Approval and Consent

### 18.1.1 Regulatory Guidelines

This study will be conducted under the accepted version of the Declaration of Helsinki and/or all relevant regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the US Code of Federal Regulations (CFR), in compliance with International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines, and according to the appropriate regulatory requirements in the countries where the study was conducted.

### 18.1.2 Institutional Review Board/Independent Ethics Committee Regulatory Guidelines

Conduct of the study must be approved by an appropriately constituted IEC/IRB. Approval is required for the study protocol, protocol amendments (if applicable), IB, ICFs, recruitment material and subject information sheets and other subject-facing material.

### 18.1.3 Informed Consent

For each study subject, written informed consent will be obtained before any protocol- related activities. As part of this procedure, the principal investigator or designee must explain orally and in writing the nature of the study, its purpose, procedures, expected duration, alternative therapy available, and the benefits and risks involved in study participation. The subject should be informed that he/she may withdraw from the study at any time, and the subject will receive all information required by local regulations and guidelines for ICH. The principal investigator will provide the Sponsor or its representative with a copy of the IEC-/IRB-approved ICF before the start of the study.

## 18.2 Data Management

The designated CRO will be responsible for activities associated with the data management of this study. This will include, but is not limited to, setting up a relevant database and data transfer mechanisms, along with validation of data and resolution of queries. All data management activities will be detailed in the data management plan.

Study centers will enter data directly into an electronic data capture (EDC) system by completing the eCRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study center. Data to be recorded directly on the eCRF will be identified and the eCRF will be considered the source document. Any changes to the data entered into the EDC system will be recorded in the audit trail.

### 18.3 Source Documents

Source documents are considered all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. The investigator will provide direct access to source documents and/or source data in the facilitation of study-related monitoring, audits, review by IECs/IRBs, and regulatory inspections.

The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's study subjects.

Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, not obscure the original entry, and be explained if necessary.

Sponsor monitors, auditors, and regulatory inspectors should have direct access to source data.


### 18.5 Monitoring

The study will be monitored according to the monitoring plan to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

Monitoring visits and contacts will be made at appropriate times during the study. The principal investigator will assure he/she and adequate site personnel are available throughout the study to collaborate with clinical monitors. Clinical monitors must have direct access to source documentation to check the completeness, clarity, and consistency of the data recorded in the eCRFs for each subject.

The investigator will provide to the clinical monitor all source documents and medical records necessary to review protocol adherence and eCRFs. In addition, the investigator will work closely with the clinical monitor and, as needed, provide them appropriate evidence that the study is being conducted under the protocol, applicable regulations, and GCP guidelines.

### 18.6 Quality Control and Quality Assurance

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, security, and reliability of the study data presented to the Sponsor lies with the investigator generating the data.

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## 18.7 Protocol Amendment and Protocol Deviation

### 18.7.1 Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that do not affect the safety of subjects or the conduct of the study will be classed as administrative amendments and will be submitted to the IEC/IRB for information only. The Sponsor will ensure that acknowledgment is received and filed. Amendments classed as substantial amendments must be submitted to the appropriate regulatory authorities and the IECs/IRBs for approval and will not be implemented at sites until such approvals are received other than with an urgent safety measure.

### 18.7.2 Protocol Deviation

Should a protocol deviation occur, the Sponsor must be informed soon. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. Protocol deviations will be reported to the IRB/IEC and under applicable regulatory authority mandates.

Changes that involve only logistical or administrative changes to the clinical study protocol are authorized. The investigator should document and explain any deviation from the clinical study protocol. Major deviations are categorized into these categories:

- Eligibility deviations (inclusion/exclusion criteria)
- Improper reconstitution and administration of study medication
- Non-compliance with study medication per the investigator's discretion
- Non-compliance with study procedures if the consequence of non-compliance would compromise either the subject's safety and/or the study integrity, primary endpoint, and/or is not in line with GCP/ICH guidelines
- Use of prohibited concomitant therapies

All protocol deviations will be identified, evaluated, and closed before the respective database lock (final analysis) and will be described in the clinical study report. Protocol deviations incurred because of the COVID-19 pandemic should be specifically recorded as a COVID-19 deviation. Further details of protocol deviations will be provided in the Protocol Deviation and Non-Compliance Management Plan.

### 18.8 Ethical Considerations

This study will be conducted under this protocol, the accepted version of the Declaration of Helsinki and/or all federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the CFR; EU 536/2014, Annex 1, D, 17 (a); and in compliance with GCP guidelines.

IECs/IRBs will review and approve this protocol and the ICF. All subjects must give written informed consent before participation in the study.

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[redacted]

### 18.10 Publication Policy/Disclosure of Data

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the investigator and others performing the clinical study will be subject to the terms of a clinical study agreement agreed between the institution and the Sponsor or their designee.

Regarding such rights, the Sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. To facilitate such ownership, investigators must assign all such inventions either to their institution or directly to the Sponsor or its designee, as set forth in the clinical study agreement.

### 18.11 Subject Confidentiality

Monitors, auditors, and other authorized agents of the Sponsor and/or its designee, the IEC(s) approving this research, and that of any other applicable agency(ies), will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results or in publications, the subjects' identities will remain confidential.

All personal data collected and processed for this study should be managed by the investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and under the national and/or local laws and regulations on personal data protection.

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## Appendix 1 Specific Guidance for Study Conduct and Subject Safety during the Coronavirus Disease 2019 (COVID-19) Pandemic

This guidance applies during the COVID-19 pandemic, as defined by regional and/or local authorities. The updates summarized below relate to the referenced sections of the protocol.

**Section 7.4 Risk/Benefit Assessment**

During the COVID-19 pandemic, additional risks to participants may exist, including general environmental risks (e.g., being outside the home, possible contact with unsanitized surfaces) and study-related activities (e.g., interaction with study staff).

Potential new subjects with known or suspected COVID-19 are ineligible for study enrollment until the infection has resolved. Potential new subjects in a high-risk population for COVID-19 (e.g., 60 years and older), should be temporarily deferred until the COVID-19 risk has subsided at the location of the enrolling site, according to investigator judgment. Risk mitigation measures to be implemented for enrolled subjects and for new subjects during the COVID-19 pandemic are detailed in **Additional Measures for Subjects Amidst COVID-19 Pandemic** below. Subjects with known or suspected COVID-19 during the study should follow the local regulations and come back to the study center after appropriate quarantine time and once the infection has resolved. Known or suspected COVID-19 will also be followed as an AESI.

**New Subsection to Section 9.1, Description of Overall Study Design and Plan: Additional Measures for Subjects Amidst COVID-19 Pandemic**

All investigational sites should act according to site regulations, to guidelines and restrictions implemented by local authorities, and to best practices for conducting clinical research during the COVID-19 pandemic.

*Guidance for New Subjects:*

Best practices in place must be followed when evaluating eligibility of subjects to participate in the study during the COVID-19 pandemic.

For potential subjects in a high-risk population for COVID-19 (e.g., 60 years and older), deferring participation in the study should be considered. Deferment of enrollment is based on the potential risk posed by generic environmental risks (e.g., being outside home, possible contact with unsanitized surfaces) and study-related activities (e.g., interaction with study staff).

For potential subjects in the low-risk population for COVID-19 (e.g., less than 60 years of age and without comorbidities), the risks and benefits of participation in the study should be assessed case by case.

If at the time of screening, in the opinion of the Investigator, the subject will not be willing and able to reach the investigational site and comply with the time commitments and requirements of the clinical study protocol, the subject should not be considered for enrollment. The subject may be rescreened at a later time.

Pre-screening phone calls should be conducted to exclude potential candidates/subjects who display possible symptoms of COVID-19 or are at high risk of having been exposed to COVID-19.

*Guidance for Enrolled Subjects*:

If the local situation allows for subjects to reach the clinical investigational site and complete all study procedures, these measures should be taken:

- Implement and document in the subject's records regular communication with the subject to ensure early detection of potential signs/symptoms of COVID-19, and provide adequate advice, as per local medical practice and public health guidelines for suspected COVID-19. Please refer to the Centers for Disease Control (CDC): https://www.cdc.gov/coronavirus/2019-ncov/index.html
- Report COVID-19 (confirmed or suspected) as an AE:
  - if any seriousness criterion is met, also report as an SAE (see Section 14.10.3).
  - if it occurs during the clinical study following the study drug administration, also report as an AESI (see Section 14.10.4).
- Implement preventive infection control measures against COVID-19 following local guidelines (e.g., good hygiene practice, clean techniques, and use of personal protective equipment such as gloves, goggles, and masks).

If the local situation allows for subjects to reach the investigational site and complete only some study procedures where visit duration needs to be limited, the above measures also apply.

Subjects can be dosed at baseline visit only if, considering the local situation and risk of exposure to COVID-19, the site considers that:

- The study drug subcutaneous injection can be performed at the investigational site according to the instructions in the protocol, pharmacy manual and instruction for use, including preparation of study drug by the pharmacist or other qualified personnel.

If the local situation does not allow for subjects to reach the investigational site during the study:

- Remote collection of data by Investigator or delegate is still to be done for these assessments at the regularly scheduled visit time, by phone or video call:
  - AE collection
  - Concomitant therapies used
  - UPT results (for WOCBP)
- All laboratory samples should be collected at the site and analyzed at the local lab. Only when subject safety cannot be assured otherwise and subject cannot reach the site, a local laboratory test (i.e., hematology, blood chemistry, urinalysis) can be performed and reported, based on investigator judgment.

All missing assessments should be appropriately documented with COVID-19 recorded as the reason, where applicable.

*Monitoring:* On-site interim monitoring visits may not be feasible during COVID-19 restrictions; therefore, remote monitoring will be completed until on-site monitoring can be conducted again. Site monitoring activity will comply with the processes documented within the COVID-19 Site Management Risk Assessment Form.