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1 CLINICAL STUDY PROTOCOL

Galderma S.A.
Galderma Research and Development, LLC

A Randomized, Double-Blind, Placebo-Controlled Study to Assess Immunization Responses in Adult and Adolescent Subjects with Moderate-to-Severe Atopic Dermatitis Treated with Nemolizumab

Protocol Number: RD.06.SPR.118380

IND Number:	117122
EudraCT Number:	Not applicable
Name of Investigational Product:	Nemolizumab (CD14152)
Phase of Development:	2
Indication:	Moderate-to-severe atopic dermatitis
Sponsor:	Galderma S.A. Zählerweg 10 6300 Zug Switzerland Galderma Research and Development, LLC 14501 North Freeway Fort Worth, Texas 76177 United States
Protocol Version:	4.0
Protocol Date:	06JUL22

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PROTOCOL APPROVAL SIGNATURES

Protocol Title: Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Study to Assess Immunization Responses in Adult and Adolescent Subjects with Moderate-to-Severe Atopic Dermatitis Treated with Nemolizumab

Protocol Number: RD.06.SPR.118380

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

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INVESTIGATOR SIGNATURE PAGE

Protocol Title: Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Study to Assess Immunization Responses in Adult and Adolescent Subjects with Moderate-to-Severe Atopic Dermatitis Treated with Nemolizumab

Protocol Number: RD.06.SPR.118380

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

- I, the undersigned, have reviewed this protocol, including appendices, 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 thoroughly familiar with the appropriate use of the study drug, as described in this protocol and any other information provided by Galderma S.A./Galderma R&D, LLC 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./Galderma R&D, LLC and of the IEC/IRB. I will submit the protocol amendments and/or any informed consent form modifications to Galderma S.A./Galderma R&D, LLC 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./Galderma R&D, LLC study drug and of their delegated study-related duties and functions as described in the protocol.
- I ensure that source documents and trial records that include all pertinent observations on each of the site's trial subjects will be attributable, legible, contemporaneous, original, accurate, and complete.

- I understand that all information obtained during the conduct of the study with regard to 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./ Galderma R&D, LLC to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

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2 SYNOPSIS

Title of Study:	A Randomized, Double-Blind, Placebo-Controlled Study to Assess Immunization Responses in Adult and Adolescent Subjects with Moderate-to-Severe Atopic Dermatitis Treated with Nemolizumab
Protocol Number:	RD.06.SPR.118380
Investigators/Study Sites:	Approximately 60 study sites are planned in the United States
Phase of Development:	Phase 2
Objectives:	Primary objective: The primary objective is to assess the effect of nemolizumab (CD14152) on humoral immune responses to tetanus and meningococcal vaccination in adult and adolescent subjects with moderate-to-severe atopic dermatitis (AD). Secondary objective: The secondary objectives are to assess the safety and efficacy of nemolizumab (CD14152) after a 16-week treatment period in adult and adolescent subjects with moderate-to-severe AD.
Study Endpoints:	**Primary endpoint:** Proportion of subjects with a positive serum IgG response to tetanus toxoid at Week 16 (4 weeks post-vaccination) defined as: • ≥ 4-fold increase in anti-tetanus IgG concentrations from baseline in subjects with pre-vaccination anti-tetanus IgG concentrations ≥ 0.1 IU/mL OR • ≥ 0.2 IU/mL anti-tetanus IgG concentrations in subjects with pre-vaccination anti-tetanus IgG concentrations < 0.1 IU/mL **Secondary endpoints:** <u>Vaccine response endpoints:</u> • Proportion of subjects with a positive serum IgG response to tetanus toxoid at Week 16 defined as: o ≥ 2-fold increase in anti-tetanus IgG concentrations from baseline in subjects with pre-vaccination anti-tetanus IgG concentrations ≥ 0.1 IU/mL OR o ≥ 0.2 IU/mL anti-tetanus IgG concentrations in subjects with pre-vaccination anti-tetanus IgG concentrations < 0.1 IU/mL • Proportion of subjects with serum anti-tetanus IgG concentrations of ≥ 0.1 IU/mL at Week 16

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	• Proportion of subjects with serum anti-tetanus IgG concentrations of ≥ 1.0 IU/mL at Week 16 • Proportion of subjects with a positive serum bactericidal antibody response to meningococcal serogroup C polysaccharide at Week 16 (4 weeks post-vaccination) defined as ≥ 4-fold increase in serum bactericidal assay (SBA) reciprocal titer from baseline • Proportion of subjects with a positive serum bactericidal antibody response to meningococcal serogroup C polysaccharide at Week 16 defined as SBA reciprocal titer ≥ 8 CCI [redacted] <u>Safety endpoints:</u> • Incidence and severity of adverse events (AEs), including AEs of special interest (AESI), treatment-emergent AEs (TEAEs), and serious AEs (SAEs)
Study Design:	This is a randomized, double-blind, placebo-controlled, multi-center, parallel-group study in adult and adolescent subjects (≥ 12 to 54 years) with moderate-to-severe AD. Eligible subjects must have a documented history of inadequate response to topical AD medication(s). Approximately 245 subjects will be randomized 1:1 to receive either 30 mg nemolizumab (with a 60 mg loading dose) or placebo, stratified by baseline disease severity (CCI [redacted]

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	The study consists of a 2- to 4-week screening period, a 16-week treatment period, and an 8-week follow-up period (12 weeks after the last study drug injection). The screening period will evaluate subject eligibility. Subjects will apply a moisturizer at least once daily, beginning at screening. Subjects using a stable regimen of low- or medium-potency topical corticosteroid (TCS) with or without topical calcineurin inhibitor (TCI) at the screening visit (ie, ≥ 14 days prior to the baseline visit) should continue their therapy regimen. Subjects not using a stable regimen of TCS with or without TCI at the screening visit should not use these topical therapies during the study unless required as rescue therapy. At the baseline visit, subjects will receive a loading dose of nemolizumab (60 mg) or placebo via 2 subcutaneous injections. Nemolizumab (30 mg) or placebo will then be administered via a single subcutaneous injection every 4 weeks (Q4W) at Week 4, 8, and 12. At the Week 12 visit, subjects will also receive single doses of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis PPD and quadrivalent meningococcal conjugate PPD vaccines. Clinical assessments will occur according to the schedule of assessments. Refer to Figure 1 for an overview of the study design. Subjects will continue to apply a moisturizer at least once daily throughout the study. Subjects using background topical therapy (TCS with or without TCI) from the screening visit will continue use in the treatment period, which should be adjusted according to the disease activity and tolerability, based on investigator clinical judgment. (Subjects not using background topical therapy from the screening visit should not apply background topical therapy in the study.) If deemed to be medically necessary by the investigator (eg, to control intolerable AD signs/symptoms), topical and/or phototherapy rescue therapies can be prescribed to any subject at any time during the study, except during the screening period. Subjects who complete the Week 16 treatment period may be eligible to enroll into a long-term extension (LTE) study (Protocol 118163). The follow-up visit is not required for subjects who participate in the LTE study. Subjects who decline or are not eligible to enter into the LTE study will complete a follow-up visit at Week 24 (12 weeks after their last study drug injection). Subjects who discontinue the study prematurely should complete an early termination visit and a follow-up visit 12 weeks after their last study drug injection. An independent data monitoring committee (IDMC) will review and monitor subject safety throughout the study, and an independent adjudication committee (IAC) will review all asthma-related AEs.
Selection of Subjects:	**Inclusion Criteria:** Individuals must meet all of the following criteria to be included in the study: 1. Male or female subjects aged ≥ 12 years through 54 years at the screening visit. **Note: Enrollment of subjects aged 12 to 17 years will begin after an interim PK and safety analysis of data from the phase 2 study SPR.116912 are conducted by the sponsor and an IDMC to determine whether enrollment of this age group**

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	is safe. Following Independent Ethics Committees/Institutional Review Boards approval, the sponsor will send a written communication to the site confirming that the study is open for enrollment of adolescents. Adolescents must not be enrolled in the study until such communication is received. 2. Chronic AD for at least 2 years before the screening visit, and confirmed according to American Academy of Dermatology Consensus Criteria (Appendix 1)[2] at the time of the screening visit. 3. EASI score ≥ 16 at both the screening and baseline visits. 4. IGA score ≥ 3 (based on the IGA scale ranging from 0 to 4, in which 3 is moderate and 4 is severe) at both the screening and baseline visits. 5. AD involvement ≥ 10% of BSA at both the screening and baseline visits. 6. Peak (maximum) pruritus NRS score of at least 4.0 at the screening and baseline visit. Peak pruritus (PP) NRS score at screening will be determined by a single NRS assessment (score ranging from 0 to 10) for the 24-hour period immediately preceding the screening visit. Baseline PP NRS score will be determined based on the average of daily NRS scores (score ranging from 0 to 10) during the 7 days immediately preceding baseline (rounding is not permitted). A minimum of 4 daily scores out of the 7 days immediately preceding baseline is required for this calculation. CCI [redacted]

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	CCI [redacted]

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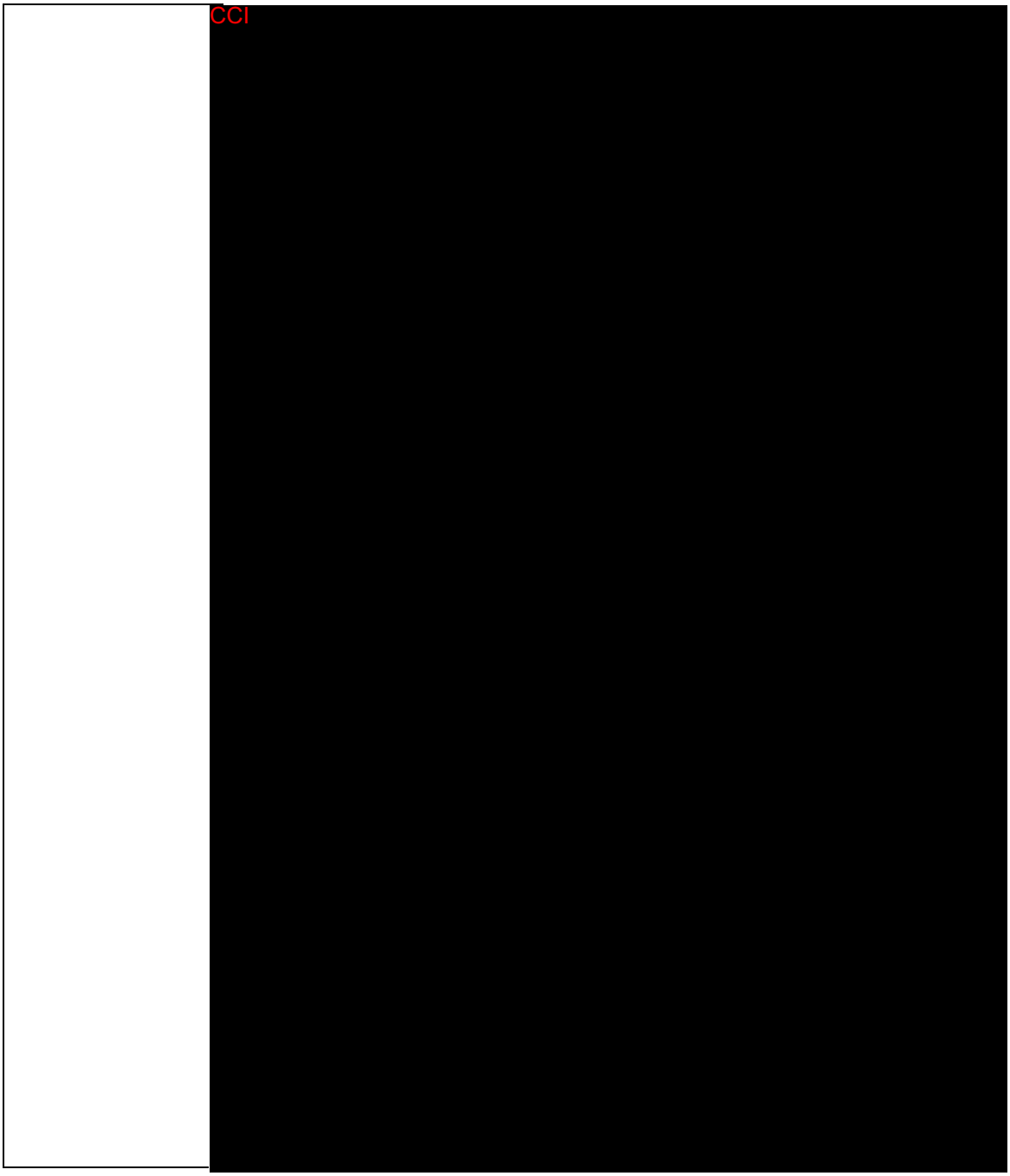
	Exclusion Criteria: Individuals meeting any of the following criteria at screening or baseline are ineligible to participate in this study 1. Body weight < 30 kg. 2. History of hypersensitivity (including anaphylaxis) to an immunoglobulin product (plasma-derived or recombinant, eg, monoclonal antibody) or to any of the study drug excipients. 3. History of severe allergic reaction to either vaccine or to vaccine components, including alum, thimerosal, phenol. 4. Subjects for whom administration of the meningococcal vaccine provided in this study is contraindicated or medically inadvisable, according to prescribing information of the commercially available vaccine. 5. Subjects for whom administration of the tetanus, diphtheria, and pertussis vaccine provided in this study is contraindicated or medically inadvisable, according to prescribing information of the commercially available vaccine, especially a history of seizures or progressive encephalopathy after previous dosing. 6. Receipt of any vaccine (except inactivated influenza vaccine) within 12 weeks prior to screening, any meningococcal vaccine within 1 year prior to screening, or any tetanus-, diphtheria-, or pertussis-containing vaccine within 5 years prior to screening.
	CCI [redacted]



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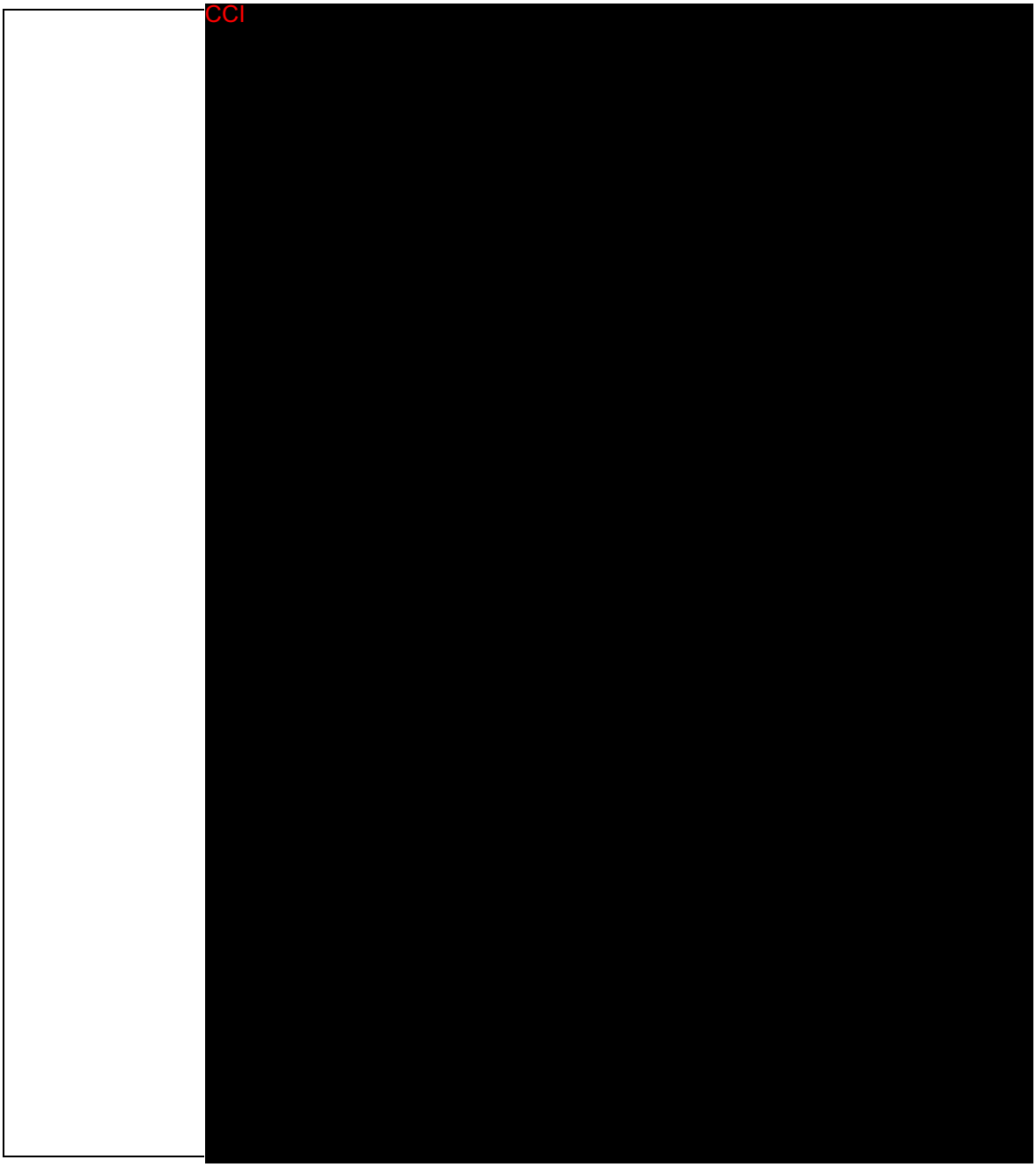

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Planned Sample Size:	Approximately 245 subjects are planned to be randomized in this study.
Therapies:	**Investigational Therapy** Nemolizumab (CD14152) 30 mg and placebo will be provided as lyophilized powder for solution for injection for subcutaneous use only after reconstitution in a single-use pre filled dual-chamber syringe [DCS]. Subjects will receive a loading dose of nemolizumab (eg, 60 mg) or placebo by 2 subcutaneous injections at baseline and a single 30-mg dose at Weeks 4, 8, and 12. **Immunization** At the Week 12 visit, subjects will receive single doses of Tdap and MCV4 vaccines. **Moisturizer** Subjects will apply a moisturizer at least once daily, and liberally as needed, to dry skin and AD lesions beginning at screening, and throughout the study. The subjects' current moisturizer or a moisturizer recommended by the investigator may be used. Use should not occur within 8 hours before each clinic/office visit. Whenever possible, subjects should use the same moisturizer throughout the study. **Topical Background Therapy** At the screening visit (≥14 days prior to baseline), subjects who are using a stable regimen of medium- or low-potency TCS therapy, with or without TCI therapy, should continue their therapy regimen in the study. Background therapy use should be adjusted to the disease activity and tolerability of the subject, including tapering when signs and symptoms improve, discontinuation when lesions clear, and restarting if signs and symptoms recur, at the discretion of the investigator. Subjects who are not using a stable regimen of topical therapy at the screening visit should not use topical background therapy during the study, unless required as rescue therapy. Subjects with a history of intolerance to TCS or for whom TCS is not advisable (eg, hypersensitivity, significant skin atrophy) must not use TCS background therapy. **Rescue Therapy** If deemed to be medically necessary by the investigator (eg, to control intolerable AD signs/symptoms), topical and/or phototherapy rescue treatments can be prescribed to the subjects at any time during the study except during the screening period. Subjects receiving any rescue therapy during the screening period are not eligible to participate in the study. Subjects receiving systemic rescue during the treatment period must discontinue study treatment. As a general guideline and per individual investigator judgment, rescue therapy should not be prescribed within the first 2 weeks after baseline (ie, Week 2) to allow a minimum time for study drug exposure.

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	Permitted rescue therapies during the treatment period include: • TCS (higher potency than used at baseline for subjects using TCS background therapy; any potency for subjects not using TCS background therapy) • TCI (only for subjects not using TCI background therapy at baseline) • Phototherapy Rescue treatments are only approved and/or standard of care treatments that directly treat AD. Antihistamines, sleep aids, topical and systemic antibiotics, and anti-itch creams are not considered to be rescue therapy because they do not directly treat AD. Whenever possible, investigators should first use topical medications as rescue therapy before escalating to systemic. If subjects receive topical treatments or phototherapy as rescue therapy, study drug administration should be continued unless there is a safety concern according to the investigator's judgment. If subjects receive systemic rescue therapy, they should permanently discontinue study treatment.
Reference Therapy:	Matching placebo
Treatment Duration:	The expected duration of each subject's participation in the study is up to 28 weeks, including an up to 4-week screening period, a 16-week treatment period, and an 8-week follow-up period (12 weeks after the last study medication injection). The 12-week follow-up visit is not required for subjects who will continue in the LTE study (Protocol 118163).
Immunogenicity:	The following vaccine response assessments are planned according to the schedule of assessments: • Tetanus toxoid IgG antibody concentration • Meningococcal serogroup C SBA reciprocal titer
Efficacy:	CCI [redacted]
Safety:	The following safety assessments are planned according to the schedule of assessments: • AEs, including TEAE, AESIs, and SAEs • Clinical laboratory tests

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	• Physical examination and vital signs • Respiratory examination and assessments (ie, asthma control test [ACT], peak expiratory flow [PEF]) • Electrocardiogram
CCI [redacted]	[redacted]
Statistical Methods and Planned Analyses:	The Intent-to-Treat population (ITT) will consist of all randomized subjects. The modified Intent-to-Treat population (mITT) will consist of all randomized subjects who received at least one dose of study drug and vaccine injection, have an evaluable vaccine response and did not receive any systemic rescue therapy prior to the post-vaccination vaccine response assessment. The Safety population (SAF) will include all randomized subjects who receive at least 1 dose of study drug. The mITT population will be the primary population for vaccine response analyses. The ITT populationwill be the primary population for all efficacy analyses, and all safety data will be summarized based on the SAF population. **Vaccine Response Endpoints:** For the primary vaccine response endpoint, the estimate of the corresponding proportion of subjects with a positive serum IgG response to tetanus toxoid at Week 16 will be adjusted for the randomization stratum baseline CCI [redacted] (Moderate vs Severe) using the Cochran-Mantel-Haenszel (CMH) estimate of the risk difference and corresponding 2-sided 90% CI. This primary analysis will be conducted on the mITT population. Subjects in receipt of systemic rescue medication will not be vaccinated. As the primary analysis will be conducted on the mITT, no imputation is required. As sensitivity analysis, the same analysis will be conducted on the ITT population, and any subjects without an evaluable vaccine response will be regarded as a Non-Responder. A further analysis will be performed on the ITT with data as observed (ie, no imputation of missing data at Week 16). All secondary vaccine response endpoints will be analyzed on the mITT, analyzed using the same methods as for the primary vaccine response endpoint above. CCI [redacted]

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	CCI [redacted] **Safety Analyses:** The incidence of TEAEs, drug-related TEAEs, SAEs, TEAEs leading to study drug discontinuation and treatment-emergent AESIs will be included in incidence tables, summarized by System Organ Class (SOC) and Preferred Term (PT). Additionally, the incidence of TEAEs by maximum severity will be presented by SOC and PT. Clinical laboratory data and vital signs will be summarized, including observed values and change from baseline values, as well as numbers of subjects with values outside limits of the normal range, including shifts from baseline at each time point. Summary tables will be provided for 12-lead ECG, physical examination (full and symptom-oriented), ACT, PEF, and respiratory exam, by treatment group and visit where appropriate. CCI [redacted] **Sample Size:** Approximately 245 subjects will be randomized (~123 per arm) to show that the 90% confidence interval of the proportion difference between treatment groups will exclude a difference of more than 10%.

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3.1 List of In-text Tables

3.2 List of In-text Figures

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4 LIST OF ABBREVIATIONS

ACT	Asthma Control Test
AD	atopic dermatitis
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AP	Average pruritus
AST	aspartate aminotransferase
CCI [redacted]	
CI	confidence interval
COVID-19	coronavirus disease-19
CPK	creatine phosphokinase
CRO	contract research organization
CYP450	cytochrome P450
DCS	dual-chamber, single-use syringe
CCI [redacted]	
ECG	electrocardiogram
eCRF	electronic case report form
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IAC	Independent Adjudication Committee
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	independent data monitoring committee
IEC	Independent Ethics Committee

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CCI	[redacted]
IgE/G/M	immunoglobulin E/G/M
IL	interleukin
IRB	Institutional Review Board
IRR	injection-related reaction
IRT	interactive response technology
ITT	intent-to-treat
KLH	keyhole limpet hemocyanin
LOCF	last observation carried forward
LTE	long-term extension
MCV4	quadrivalent meningococcal conjugate vaccine
MI	multiple imputation
mITT	modified intent-to-treat
NAb	neutralizing antibody
NCA	non-compartmental analysis
NRS	numeric rating scale
PEF	peak expiratory flow
PK	pharmacokinetics
CCI	[redacted]
PRN	pro re nata (when necessary or as needed)
PRO	patient-reported outcome
PT	preferred term
PTC	product technical complaint
Q4W	every 4 weeks
SAE	serious adverse event
SAF	safety analysis population
SAP	statistical analysis plan
SC	subcutaneous
CCI	[redacted]
SIN	subject identification number
SNRI	serotonin-norepinephrine reuptake inhibitor

SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TCI	topical calcineurin inhibitor
TCS	topical corticosteroid
TEAE	treatment-emergent adverse event
Th2	type 2 helper T [cell]
TMF	Trial Master File
ULN	upper limit of normal
UPT	urine pregnancy test
US	United States
WOCBP	women of childbearing potential

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5 INTRODUCTION

5.1 Background on Moderate-to-Severe Atopic Dermatitis

Atopic dermatitis (AD) is a chronic inflammatory skin disease estimated to occur in 10% to 20% of the population[1] and up to 25% of children.[2] 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.

The cause of AD, although still not completely understood, is probably multifactorial and involves complex interrelation between susceptibility genes, immunological factors, infections, and environmental factors to produce a skin barrier disturbance as well as immunologic dysregulation and inflammation.[3,4,5] There are abundant data indicating cross-talk between the immune and neural system in induction of pruritus through activation of cytokine receptors on peripheral nerves. [6]

Upon stimulation with allergens, dendritic cells in the skin stimulate type 2 helper T cells (Th2) and cause the subsequent release of pro-inflammatory cytokines, including interleukin (IL)-4, IL-5 and IL-13. High levels of Th2 cytokines in AD skin increase serine protease, which leads to further skin barrier dysfunction, and IL-31, which leads to pruritus and further inflammation and barrier dysfunction.[7,8] The AD pathogenesis also involves Th17 and Th22 cells and Th1 cells in the chronic phase of AD. [9]

IL-31 is involved in both primary AD pathophysiology and perpetuation of the itch-scratch cycle. IL-31 is preferentially produced by Th2 cells, following induction by IL-4, and its expression is consistently increased in the skin lesions of AD patients.[7,10,11] Furthermore, the IL-31 receptor A (IL-31 RA) was found to be expressed in several tissues including the dorsal root spinal ganglia, which contain sensory nerve cells,[12] and keratinocytes.[13] Through interaction with its receptor, IL-31 promotes pruritus, Th2-driven inflammation, and interrupts keratinocyte proliferation and differentiation.[7,8,14,15] Together, these findings suggest that IL-31 is involved in the pathogenesis of pruritus and in inflammation in AD.

The scratching behavior associated with pruritus is believed to exacerbate AD lesions by causing mechanical damage to the skin, allowing the penetration of foreign antigens,

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triggering inflammatory responses, and leading to further aggravation of dermatitis and itching. This vicious circle of scratching → exacerbation of dermatitis → aggravation of itching is known as the "itch-scratch cycle".[16]

Topical agents are the mainstay of AD therapy. Despite the demonstrated efficacy of topical treatments, they are not always sufficient to control moderate-to-severe AD in some patients, who therefore require the addition of phototherapy or a systemic treatment to achieve sufficient control of AD.[17] Due to the above described predominant role of IL-31 in mediation of inflammatory itch, targeting and blocking the IL-31 pathway is expected to have a therapeutic effect in patients with AD, as well as those with other inflammatory pruritic conditions such as prurigo nodularis (PN), which are not adequately controlled by existing therapies.

5.2 Background on Nemolizumab

Nemolizumab (CD14152) is a humanized anti-human IL-31 receptor A (RA) monoclonal modified immunoglobulin G (IgG) 2 antibody comprising a structure of 2 H-chains (445 amino acid residues) and 2 L-chains (214 amino acid residues) connected by 16 disulfide bonds. Nemolizumab inhibits the binding of IL-31 to IL-31RA and subsequent transduction of the IL-31 signal into the cell.

5.2.1 Nonclinical Studies

The Investigator's Brochure (IB) contains detailed information on non-clinical studies.

In in vitro pharmacology studies, the characteristics of nemolizumab as an anti-IL-31RA neutralizing antibody were investigated. It was shown that nemolizumab binds to human and monkey IL-31RA, inhibits binding of IL-31 to IL-31RA and inhibits signaling via IL-31A. Nemolizumab did not affect the behavior of IL-6 and oncostatin M that utilize gp130, a cytokine receptor that has homology to IL-31RA. FcγRs and complement C1q are important molecules for eliciting the constant region-mediated effector activity of an antibody. Based on its binding affinity to FcγRs and human complement C1q, the risk of constant region-mediated effector activity was considered to be lower for nemolizumab than for IgG1. Nemolizumab did not show any antibody-dependent cell-mediated

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cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and direct cell death-inducing activities in IL-31RA overexpressing A549 cells.

In non-clinical safety studies, nemolizumab was well tolerated and safe in cynomolgus monkeys at doses of up to 25 mg/kg once every 2 weeks in 3- and 6-month intermittent SC dose toxicity studies. There was no immunotoxic effect after repeat dosing in the monkey. In the 6-month toxicology study, nemolizumab did not affect immunoglobulin (Ig)M or IgG responses to the T-cell dependent antigen keyhole limpet hemocyanin (KLH) compared to controls when KLH was administered after 23 weeks of nemolizumab treatment.[18]

5.2.2 Pharmacokinetic Profile

The pharmacokinetic (PK) profile of nemolizumab was extensively assessed in subjects with AD. PK assessments after subcutaneous (SC) 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 administrations of flat doses between 30 and 90 mg. The terminal elimination half-life of nemolizumab was approximately 2 weeks after single and repeated administrations. No significant systemic accumulation was observed, and steady state concentrations were achieved from 16 weeks of treatment without a loading dose and from 4 weeks of treatment when a loading (flat 2×) dose was administered. The systemic exposure to nemolizumab appeared to be slightly lower in AD subjects compared to healthy volunteers.

The PK profile of nemolizumab was also assessed in the phase 2a study with PN subjects, where a nemolizumab dose of 0.5 mg/kg was administered. Similar nemolizumab PK profiles were observed in subjects with AD and in subjects with PN. The similarity in nemolizumab exposure between the 2 populations was also confirmed using population PK modeling. The IB contains additional detailed information on the nemolizumab PK profile.

CCI [redacted]

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CCI [redacted]

5.2.3 Clinical Studies

The IB contains detailed information on clinical studies.

Studies have been completed in healthy subjects and subjects with AD, PN and uremic pruritus. Results of Phase 2 studies in AD and PN subjects are summarized below.

5.2.3.1 Phase 2b Dose-Ranging Study: Atopic Dermatitis

The phase 2b study was a randomized, placebo-controlled, double-blind, parallel-group, dose-ranging study to evaluate the efficacy, safety, and pharmacokinetics of various doses of nemolizumab in moderate-to-severe AD subjects with severe CCI [redacted]

A total of 226 adult subjects were randomized: 57 subjects were randomized to placebo and 169 subjects were randomized to nemolizumab arms (55 subjects to 10 mg, 57 subjects to 30 mg, and 57 subjects to 90 mg). Overall, all demographic and baseline disease characteristics were similar in all treatment groups.

The primary efficacy endpoint was percent change from baseline in CCI [redacted] to Week 24. At the Week 24 visit, a greater percent change reduction in CCI was observed with the nemolizumab 30-mg dose (least squares mean difference vs placebo = 16.7%) and the difference was statistically significant (95% confidence interval [CI] = -30.2, -3.2; p = 0.016) compared to placebo. The nemolizumab 10-mg dose showed a marginally statistically significant difference vs placebo (least squares mean difference = 13.6%; 95% CI = -27.3, 0.0; p = 0.051). However, the difference between the nemolizumab 90-mg dose and placebo did not achieve statistical significance.

The CCI [redacted] rate was statistically significant ($p < 0.05$) for all nemolizumab doses at all timepoints from Week 2.

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All doses of nemolizumab were associated with a slightly higher incidence of treatment-emergent adverse events (TEAEs) when compared to placebo. There was no increase in the incidence of skin infections in the nemolizumab compared to the placebo groups, although there was a higher incidence of non-skin infections with nemolizumab (mainly rhinopharyngitis and upper respiratory tract infections). There was a dose-dependent increase of asthma flares (1 [1.8%], 2 [3.6%], 7 [12.3%], and 10 [17.5%] in placebo, 10 mg, 30 mg, and 90 mg, respectively) in subjects with pre-existing asthma. Events were mostly mild or moderate (1 severe event with the highest dose), manageable, and reversible under treatment with study drug. Local and systemic injection-related reactions (IRRs) occurred more frequently in the placebo group compared to the active treatment groups. Finally, there was a low incidence of peripheral edema, with no serious cases and no imbalance with the placebo arm. There was a comparable percentage of subjects discontinuing treatment due to TEAE in the placebo and active treatment arms.

There was 1 non-related AE with a fatal outcome (82-year-old subject treated with the 10-mg dose died due to non-study drug-related aspiration pneumonia and cardiopulmonary arrest). Three suspected unexpected serious adverse reactions (SUSARs) were recorded in the study: exacerbation of AD (10-mg dose, withdrawal from study), septic shock (90-mg dose, sepsis, *Staphylococcus aureus*–positive blood culture, recovered/resolved without sequelae), and phlegmon/cellulitis of the right cheek (30-mg dose, recovered/resolved without sequelae). All doses of nemolizumab were associated with a slightly higher incidence of serious TEAEs (1 [1.8%], 3 [5.5%], 2 [3.5%], and 2 [3.5%] in placebo, 10 mg, 30 mg, and 90 mg, respectively) but not severe TEAEs (6 [10.7%], 3 [5.5%], 5 [8.8%], and 2 [3.5%] in placebo, 10 mg, 30 mg, and 90 mg, respectively) when compared to placebo.

CCI [redacted]

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.

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5.2.3.2 Phase 2a Safety and Efficacy Study: Prurigo Nodularis

The phase 2a study was a randomized, placebo-controlled, double-blind, parallel-group, multi-center study to evaluate the safety and efficacy of nemolizumab in subjects suffering from PN over a 12-week treatment period.

A total of 70 subjects were randomized: 36 subjects were randomized to placebo and 34 subjects were randomized to nemolizumab 0.5 mg/kg. Sixty subjects (85.7%) completed the study. Demographic characteristics were similar in both treatment groups. Disease characteristics at baseline were similar in both treatment groups, with the exception of the Prurigo Activity Score (PAS) at baseline, which was slightly higher in the placebo compared with the nemolizumab group, and more subjects in the nemolizumab group had a severe CCI [redacted] compared with the placebo group.

The primary efficacy endpoint was percent change from baseline in CCI [redacted] to Week 4 (weekly average of the peak). Nemolizumab was clinically and statistically significantly superior to placebo in reducing the CCI [redacted] at Week 4 (difference between treatment groups -38.0%; 95% CI -51.0, -25.0; p<0.001).

The proportion of subjects with CCI [redacted], a secondary endpoint, was higher in the nemolizumab group compared with the placebo group at Week 12 and at a follow-up visit at Week 18, and the differences were statistically significant (Week 12: difference 17.2%; p=0.020; Week 18: difference 32.0%; p=0.001).

Secondary endpoints also included CCI [redacted] at other time points, Average Pruritus CCI [redacted] PP and AP Verbal Rating Scale, Dynamic Pruritus Scale, and PAS. Improvements were statistically significantly greater in the nemolizumab group than in the placebo group at all time points for pruritus endpoints and at or before Week 12 for PAS endpoints.

The most frequently reported TEAE was nasopharyngitis, the incidence of which was similar in the nemolizumab group (5 subjects, 14.7%) and the placebo group (4 subjects, 11.1%). The incidence of neurodermatitis was higher in the placebo group (5 subjects, 13.9%) compared with the nemolizumab group (2 subjects, 5.9%). The incidence of AD was higher in the nemolizumab group (3 subjects, 8.8%) compared with the placebo

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group (0 subjects). The percentage of subjects with severe TEAEs was higher in the nemolizumab group (5 subjects, 14.7%) compared with the placebo group (1 subject, 2.8%). The incidence of TEAEs leading to permanent discontinuation of the study drug was similar between the nemolizumab and placebo groups.

The incidence of treatment-emergent SAEs was similar between the nemolizumab group (4 subjects, 11.8%) and the placebo group (3 subjects, 8.3%). Neurodermatitis was the most frequently reported treatment-emergent SAE, for which all subjects were in the placebo group (3 subjects, 8.3%). One subject in the nemolizumab group had a treatment-emergent SAE related to study drug (dermatitis psoriasiform). There were no deaths reported during the study.

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5.3 Clinical Risks/Benefits

5.3.1 Nemolizumab

Results of previous clinical studies in adults demonstrated that treatment with nemolizumab had a marked effect on AD, pruritus, and pruritus-related sleep loss. Overall, nemolizumab was well tolerated when used as monotherapy or concomitantly with a topical corticosteroid (TCS).

Based on the currently available information on nemolizumab and the risks associated with biologic agents in general, the important potential risks of nemolizumab treatment include local and systemic IRRs, newly diagnosed asthma or worsening of asthma, exacerbation of AD, and skin and non-skin infections.

The following specific risk-minimization and safety follow-up measures have been planned in this clinical study:

a. The protocol will exclude subjects with asthma exacerbation requiring hospitalization in the preceding 12 months before screening, subjects whose asthma has not been

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well-controlled (ie, symptoms > 2 days per week, nighttime awakenings 2 or more times per week, or some interference with normal activities) during the last 3 months before the screening visit, Asthma Control Test (ACT) score ≤ 19, and subjects with peak expiratory flow (PEF) below 80% of the predicted value. At all visits, all subjects will be asked about respiratory changes and a respiratory examination will be performed. Peak expiratory flow measurements will be performed for all subjects at screening, baseline, and regular intervals throughout the study. For subjects with a history of asthma, PEF measurements and ACT will be administered at all visits. Subjects diagnosed with de novo asthma will perform PEF and ACT assessments at all visits starting with the visit in which the diagnosis was confirmed. Subjects with a medical history of asthma will be referred to the physician managing their asthma if ACT ≤ 19, PEF < 80% of the predicted value, and/or unexpected worsening of asthma is observed or reported. Subjects without a medical history of asthma will be referred to a respiratory specialist if respiratory changes suggestive of asthma are observed or reported. An independent adjudication committee (IAC) will review all asthma AEs reported during the course of the study.

b. The exclusion criteria of this clinical study (ie, restricting entry of subjects with recent/current infections or known/suspected immunosuppression or unusually frequent, recurrent, severe, or prolonged infections) will prevent non-eligible patients from receiving nemolizumab. As no data are available in pregnant or breastfeeding women, these patients are not eligible for this study.

c. A slight trend of dose-dependent increase of peripheral edema was reported in the nemolizumab phase 2a study CIM003JG. Most events were mild (11 of 21), no case was serious, and none resulted in premature treatment discontinuation; no case was associated with renal or cardiac AEs. There were a few subjects reporting peripheral edema in the phase 2b 114322 study (2 [3.6%], 2 [3.6%], 4 [7%], and 2 [3.5%] in placebo, 10-mg, 30-mg, and 90-mg groups, respectively). Peripheral edema will be followed as an AE of special interest (AESI) in this study.

d. As nemolizumab has not been evaluated in pediatric populations, with studies in adolescents currently ongoing, safety will be evaluated closely throughout the study,

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including a follow-up visit 12 weeks after the last study drug administration for subjects who do not rollover into the nemolizumab long-term extension (LTE) study.

e. An independent data monitoring committee (IDMC) will monitor the safety data regularly throughout the study, including the AESIs listed in Section 13.1.1, which were defined based on the currently available safety information on nemolizumab and the risks associated with biologic agents in general.

In conclusion, when taking into consideration the currently available data of nemolizumab and the risk-minimization approaches to be implemented, the benefit/risk ratio of nemolizumab is considered to be favorable in this study.

5.3.2 Vaccines

During the study, subjects will also receive single doses of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (PPD and meningococcal (Groups A, C, Y, and W-135) polysaccharide dipththeria toxoid conjugate PPD vaccines. Contraindications, risks, warnings, and precautions of vaccination are as outlined in the respective prescribing information (Appendix 2, Appendix 3).[19,20]

Based on known cellular and immunological responses of IL-31RA signaling, putative risks of immune interference by nemolizumab following vaccination have not been previously identified.

5.4 Study Rationale and Dose Selection

The aim of the study is to investigate whether nemolizumab has an effect on the immunological response to vaccination in AD subjects. Although nemolizumab is not expected to impact immunization responses, the mechanism of IL-31 signaling in immunity is not yet fully elucidated, and the effect of blocking Th2 cell signaling via IL-31 on vaccination response has not been tested.

Two different common vaccines (Tdap and MCV4) that result in activation of both T cells and B cells to elicit an effective immune response were selected for use in this study

to evaluate a broad immunological impact of coadministration of vaccines and nemolizumab.

The nemolizumab dose was selected based on the outcome of the Phase 2b dose-ranging study in adults SPR.114322, where the 30-mg dose (with 60-mg loading dose), when administered every 4 weeks (Q4W), provided the best benefit/risk ratio of the 3 doses (10 mg, 30 mg, and 90 mg) evaluated. The 30-mg dose was therefore selected as the dose to be developed for the treatment of AD. Across the full range of subject body weights in the Phase 2b study, the 30-mg dose (with 60-mg loading dose) provided a comparable observed exposure with respect to the body weight-based dose of 0.5 mg/kg tested during the Phase 2a AD and PN studies.

Adolescent subjects will be enrolled after the sponsor confirms the safety of the 30-mg Q4W dose in adolescents in a separate clinical study (SPR.116912).

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6 STUDY OBJECTIVES AND ENDPOINTS

6.1 Study Objectives

6.1.1 Primary Objective

The primary objective is to assess the effect of nemolizumab (CD14152) on humoral immune responses to tetanus and meningococcal vaccination in adult and adolescent subjects with moderate-to-severe AD.

6.1.2 Secondary Objectives

The secondary objectives are to assess the safety and efficacy of nemolizumab (CD14152) after a 16-week treatment period in adult and adolescent subjects with moderate-to-severe AD.

6.2 Study Endpoints

6.2.1 Primary Endpoint

The primary endpoint of this study is the proportion of subjects with a positive serum IgG response to tetanus toxoid at Week 16 (4 weeks post-vaccination) defined as:

- ≥ 4-fold increase in anti-tetanus IgG concentrations from baseline in subjects with pre-vaccination anti-tetanus IgG concentrations ≥ 0.1 IU/mL

  OR

- ≥ 0.2 IU/mL anti-tetanus IgG concentrations in subjects with pre-vaccination anti-tetanus IgG concentrations < 0.1 IU/mL

6.2.2 Secondary Endpoints

6.2.2.1 Vaccine Response Endpoints

The secondary vaccine response endpoints are as follows:

- Proportion of subjects with a positive serum IgG response to tetanus toxoid at Week 16 defined as:

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- ≥ 2-fold increase in anti-tetanus IgG concentrations from baseline in subjects with pre-vaccination anti-tetanus IgG concentrations ≥ 0.1 IU/mL

  OR

- ≥ 0.2 IU/mL anti-tetanus IgG concentrations in subjects with pre-vaccination anti-tetanus IgG concentrations < 0.1 IU/mL

- Proportion of subjects with serum anti-tetanus IgG concentrations of ≥ 0.1 IU/mL at Week 16
- Proportion of subjects with serum anti-tetanus IgG concentrations of ≥ 1.0 IU/mL at Week 16
- Proportion of subjects with a positive serum bactericidal antibody response to meningococcal serogroup C polysaccharide at Week 16 (4 weeks post-vaccination) defined as ≥ 4-fold increase in serum bactericidal assay (SBA) reciprocal titer from baseline
- Proportion of subjects with a positive serum bactericidal antibody response to meningococcal serogroup C polysaccharide at Week 16 defined as SBA reciprocal titer ≥ 8

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6.2.2.3 Safety Endpoint

The safety endpoint of this study is as follows:

- Incidence and severity of adverse events (AEs), including AESI (see Section 13.1.1), treatment-emergent AEs, and serious AEs

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7 INVESTIGATIONAL PLAN

7.1 Description of Overall Study Design and Plan

This is a randomized, double-blind, placebo-controlled, multi-center, parallel-group study in adult and adolescent subjects (≥ 12 to 54 years) with moderate-to-severe AD. Eligible subjects must have a documented history of inadequate response to topical AD medication(s).

Approximately 245 subjects will be randomized 1:1 to receive either 30 mg nemolizumab (with a 60 mg loading dose) or placebo, stratified by baseline disease severity CCI [redacted] 16.9).

The study consists of 3 periods with up to 28 weeks total study duration: a 2- to 4-week screening period, a 16-week treatment period, and an 8-week follow-up period (12 weeks after the last study drug injection).

Screening Period

The screening period will evaluate subject eligibility. Subjects will apply a moisturizer at least once daily, beginning at screening. Subjects using a stable regimen of low- or medium-potency TCS with or without topical calcineurin inhibitor (TCI) at the screening visit (ie, ≥ 14 days prior to the baseline visit) should continue their therapy regimen. Subjects not using a stable regimen of TCS with or without TCI at the screening visit should not use these topical therapies during the study unless required as rescue therapy.

Rescue therapies are not permitted during the screening period.

Treatment Period

At the baseline visit, subjects will receive a loading dose of nemolizumab (60 mg) or placebo via 2 subcutaneous injections. Nemolizumab (30 mg) or placebo will then be administered via a single subcutaneous injection Q4W at Week 4, 8, and 12. At the Week 12 visit, subjects will also receive single doses of PPD [redacted] vaccines. Clinical assessments will occur according to the schedule of assessments in Table 4.

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Subjects will continue to apply a moisturizer at least once daily. Subjects using background topical therapy (TCS with or without TCI) from the screening visit will continue use in the treatment period, which should be adjusted according to the disease activity and tolerability, based on investigator clinical judgment. (Subjects not using background topical therapy from the screening visit should not apply background topical therapy in the study.) If deemed to be medically necessary by the investigator (eg, to control intolerable AD signs/symptoms), topical and/or phototherapy rescue therapies can be prescribed to any subject at any time during the study, except during the screening period.

Subjects who complete the Week 16 treatment period may be eligible to enroll into an LTE study (Protocol 118163).

Follow-Up Period

The follow-up visit is not required for subjects who participate in the LTE study.

Subjects who decline or are not eligible to enter into the LTE study will complete a follow-up visit at Week 24 (12 weeks after their last study drug injection).

Subjects who discontinue the study prematurely should complete an early termination visit and a follow-up visit 12 weeks after their last study drug injection.

The follow-up visit will be conducted 8 weeks after completing the treatment period and/or 12 weeks after the last study drug injection. Twelve weeks corresponds to approximately 5 half-lives when nemolizumab 30 mg is dosed subcutaneously every 4 weeks.

An IDMC will review and monitor subject safety throughout the study, and an IAC will review all asthma-related AEs. Details on the IDMC and IAC, including the plan of analysis for outputs, the composition of the committees, the procedures, roles, responsibilities and their communications are provided in the IDMC and IAC charters, respectively.

An overview of the study design is present in Figure 1.

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Figure 1: Study Design

7.2 Discussion of Study Design

The study population is selected based on the need to understand the effect of nemolizumab on immune responses to vaccination in subjects with AD. Tetanus and meningococcal vaccines were selected for evaluation in subjects ≥ 12 years through 54 years of age based on their standard use, heterogeneous preparation (toxoid and conjugate polysaccharide), and indicated population. A placebo arm is included in the study to ensure any effect on vaccination response by nemolizumab can be detected.

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To evaluate the effect of nemolizumab on humoral immune responses to vaccination, the PK profile of nemolizumab was considered. No accumulation in serum is observed after repeated administration of nemolizumab. Nemolizumab demonstrates a time linear PK profile with steady state concentrations achieved by Week 4 following administration of a loading dose. The PK profile of Nemolizumab is predictable with time and is not affected by the immunogenicity of Nemolizumab; therefore, a treatment duration > 4 weeks is acceptable to evaluate this response.

The 16-week treatment period is considered adequate to measure immune responses to tetanus and meningococcal vaccination administered at Week 12 (immune response measured 4 weeks post-vaccination) as well as to evaluate the safety and efficacy of nemolizumab, with final study dose scheduled for Week 12.

Immunization response to Tdap will be measured as anti-tetanus antibody titers (absolute anti-tetanus IgG concentrations and fold-increase in anti-tetanus IgG concentrations from baseline), taking into account subjects' pre-vaccination anti-tetanus IgG concentrations. Immunization response to MCV4 will be assessed as anti-meningococcal serogroup C functional humoral response (SBA reciprocal titer and fold-increase in SBA reciprocal titer from baseline). These endpoints were selected based on positive response criteria defined by each vaccine [19,20] and by regulatory guidance [21,22,23] to demonstrate antibody quantitative and qualitative effects, respectively.

As the anti-tetanus IgG titer of ≥ 0.1 IU/mL is generally recognized as seroprotective, the primary endpoint was defined for subjects with and without existing pre-vaccination seroprotective titers. Response for subjects with existing anti-tetanus IgG (≥ 0.1 IU/mL) at baseline was defined as a 4-fold increase in anti-tetanus IgG titer from baseline, indicative of a booster response. Response for subjects without existing IgG (< 0.1 IU/mL) was defined as 0.2 IU/mL, a concentration 2-fold higher than the recognized seroprotection level. As subjects with already high anti-tetanus IgG titers at baseline may not achieve a 4-fold increase in IgG following vaccination, a secondary endpoint identical to the primary endpoint but with response defined as a 2-fold increase in titer for subjects with pre-existing anti-tetanus IgG was also included.

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A follow-up visit is scheduled for subject safety and will occur at the Week 24 visit (12 weeks after the last dose of study medication). The duration of the follow-up period corresponds to approximately 5 half-lives of nemolizumab, which is considered adequate to ensure subject safety.

7.3 End of Study

A subject will have fulfilled the requirements for study completion if/when the subject has completed all study periods, including the follow-up visit at Week 24 or the last scheduled visit as indicated in the schedule of assessments (Table 4).

The end of the study will be the last subject's last visit or the last subject's scheduled visit as indicated in the schedule of assessments (Table 4).

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8 SELECTION OF STUDY POPULATION

Section 7.1 provides information regarding the number of subjects planned to be randomized.

8.1 Inclusion Criteria

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

1. Male or female subjects aged ≥ 12 years through 54 years at the screening visit.

   Note: Enrollment of subjects aged 12 to 17 years will begin after an interim PK and safety analysis of data from the phase 2 study SPR.116912 are conducted by the sponsor and an IDMC to determine whether enrollment of this age group is safe. Following Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) approval, the sponsor will send a written communication to the site confirming that the study is open for enrollment of adolescents. Adolescents must not be enrolled in the study until such communication is received.

2. Chronic AD for at least 2 years before the screening visit, and confirmed according to American Academy of Dermatology Consensus Criteria (Appendix 1)[2] at the time of the screening visit.
3. EASI score ≥ 16 at both the screening and baseline visits.
4. IGA score ≥ 3 (based on the IGA scale ranging from 0 to 4, in which 3 is moderate and 4 is severe) at both the screening and baseline visits.
5. AD involvement ≥ 10% of BSA at both the screening and baseline visits.
6. Peak (maximum) pruritus NRS score of at least 4.0 at the screening and baseline visit.

   Peak pruritus (PP) NRS score at screening will be determined by a single NRS assessment (score ranging from 0 to 10) for the 24-hour period immediately preceding the screening visit.

   Baseline PP NRS score will be determined based on the average of daily NRS scores (score ranging from 0 to 10) during the 7 days immediately preceding baseline

(rounding is not permitted). A minimum of 4 daily scores out of the 7 days immediately preceding baseline is required for this calculation.

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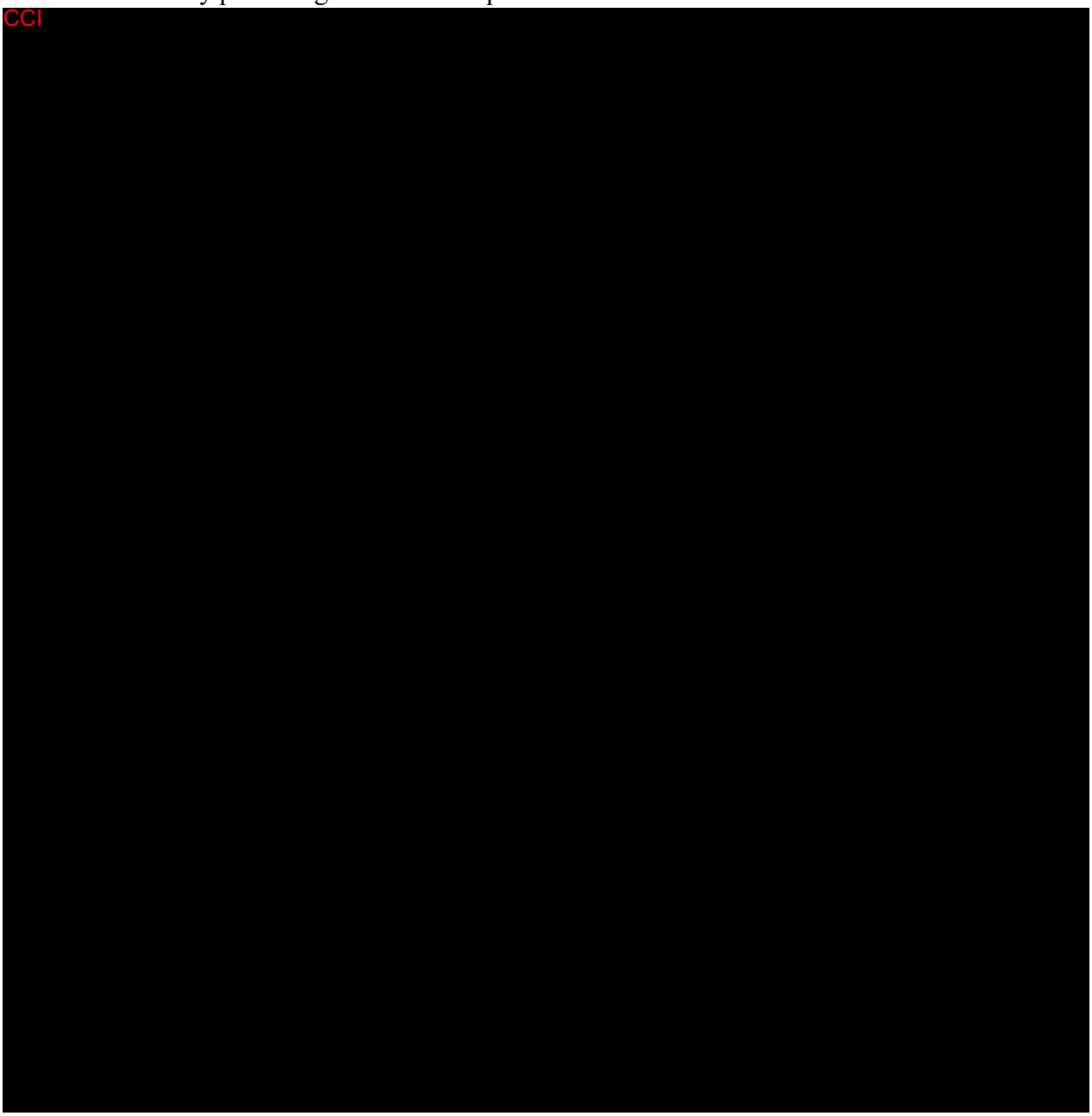

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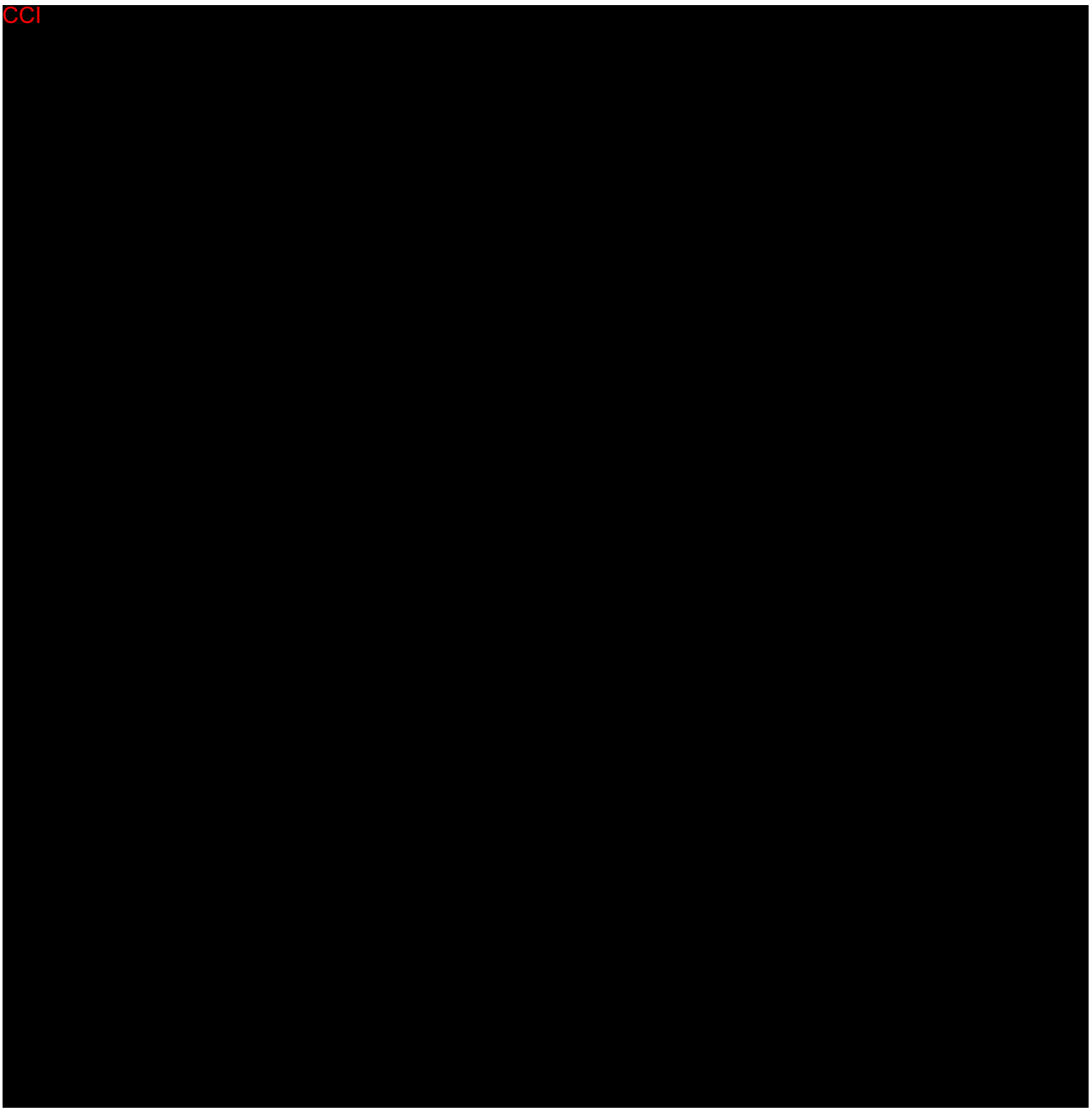

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8.2 Exclusion Criteria

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

1. Body weight < 30 kg.
2. History of hypersensitivity (including anaphylaxis) to an immunoglobulin product (plasma-derived or recombinant, eg, monoclonal antibody) or to any of the study drug excipients.
3. History of severe allergic reaction to either vaccine or to vaccine components including alum, thimerosal, phenol.
4. Subjects for whom administration of the meningococcal vaccine provided in this study is contraindicated or medically inadvisable, according to prescribing information of the commercially available vaccine.
5. Subjects for whom administration of the tetanus, diphtheria, and pertussis vaccine provided in this study is contraindicated or medically inadvisable, according to prescribing information of the commercially available vaccine, especially a history of seizures or progressive encephalopathy after previous dosing.
6. Receipt of any vaccine (except inactivated influenza vaccine) within 12 weeks prior to screening, any meningococcal vaccine within 1 year prior to screening, or any tetanus-, diphtheria-, or pertussis-containing vaccine within 5 years prior to screening.

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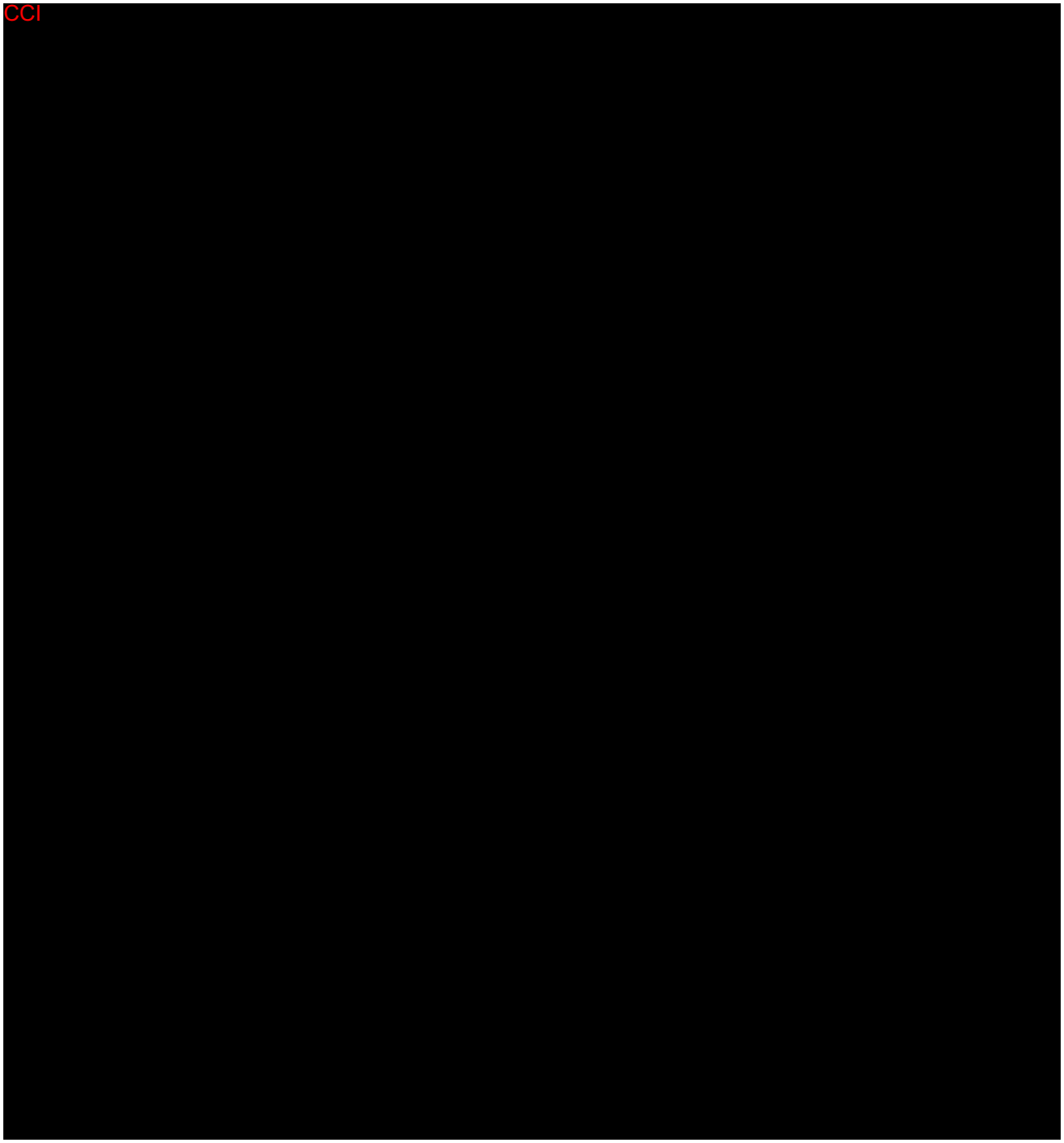

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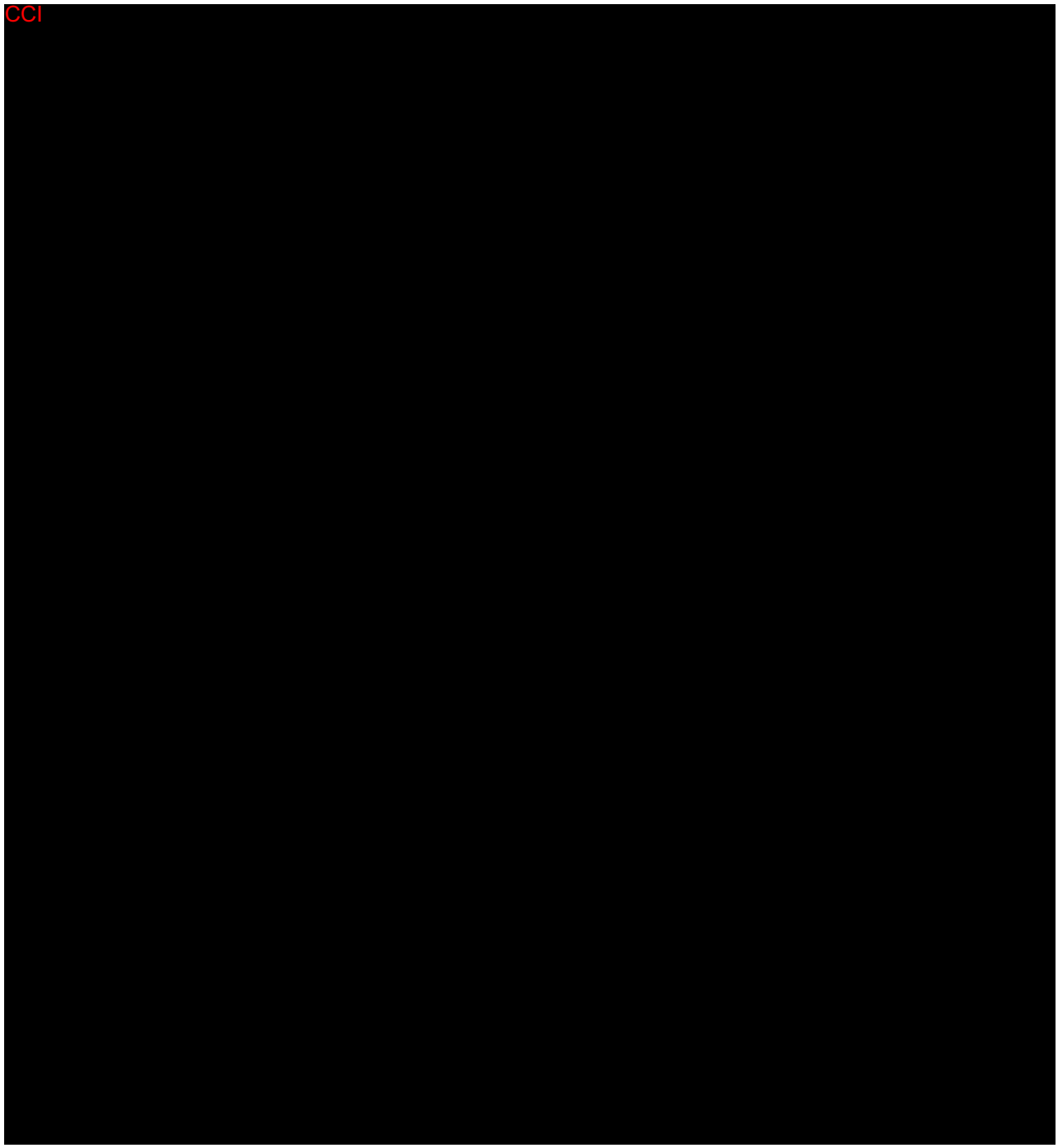

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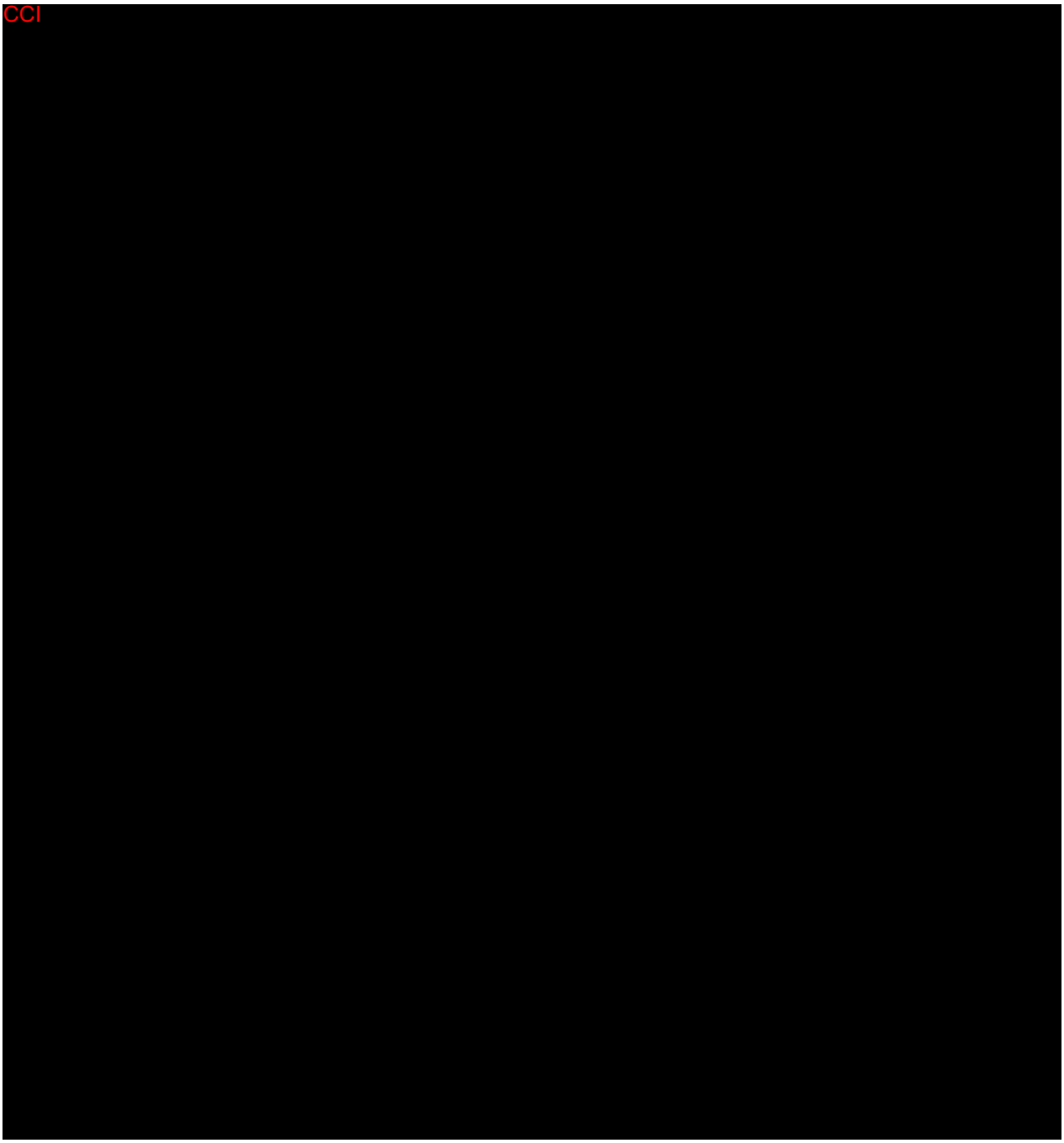

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8.3 Rescreening

Screen failures may be allowed to rescreen up to 1 time, unless the reason for screen failure is related to disease severity inclusion criteria (CCI [redacted]). Subjects who screen fail due to disease severity are not allowed to rescreen. Subjects who are rescreened must sign a new informed consent form (ICF) and be assigned a new subject identification number (SIN).

8.4 Study Withdrawal, Removal, and Replacement of Subjects

Although the importance of completing the entire clinical study will be explained to the subjects, any subject is free to discontinue his/her participation in the study at any time and for whatever reason, specified or unspecified, and without any 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 clinical study if deemed to be necessary.

If a subject discontinues study treatment or is withdrawn from the study for any reason, the study site must immediately notify the medical monitor. The date and the reason for study drug discontinuation must be recorded on the electronic case report form (eCRF). Subjects who prematurely discontinue study drug will be encouraged to complete the scheduled study visits. Subjects who complete or discontinue early from the study will be asked to return to the study site to complete the follow-up assessments as indicated in the schedule of assessments (Table 4).

In the event that a subject discontinues prematurely from the study because of a TEAE or serious TEAE, he/she will be followed up until it resolves (returns to normal or baseline values) or stabilizes, or until it is judged by the investigator to no longer be clinically significant.

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Once a subject is withdrawn from the study, the subject may not reenter the study.

Reasons for discontinuing study drug include, but are not limited to, the following:

- Subject request (ie, consent withdrawal)
- Non-compliance with the study drug or study schedule
- Lost to follow-up
- 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 the following:
  - Serious immediate-type allergic manifestations including anaphylactic reaction
  - Serious worsening of asthma considered related to study drug administration
  - 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 infection (temporary discontinuation may be acceptable; for instructions on resuming study drug administration, see Section 8.4.2)
- Pregnancy as indicated in Section 8.4.1
- Use of non-permitted concurrent therapy (unless discussed and agreed upon with the investigator and medical monitor)
- Use of systemic rescue therapy, as specified in Section 9.6.1.3 and Table 3 of Section 9.6.2
- Treatment failure

- Investigator request
- Sponsor request, including any of the above criteria

Additionally, the sponsor may stop the study at any time for safety, regulatory, legal, or other reasons aligned with Good Clinical Practice (GCP) guidelines. This study may be terminated at the discretion of the sponsor or any regulatory agency. An investigator may elect to discontinue or stop the study at his or her study site for any reason, including safety or low enrollment.

8.4.1 Pregnancy

Subjects will be instructed that a known or suspected pregnancy occurring during the study should be confirmed and reported to the investigator (see Section 13.1.5). **If a subject becomes pregnant, the investigator must withdraw the subject from the study without delay. The subject must not receive any further injection(s) of the study drug or vaccinations.**

8.4.2 COVID-19 Infection

Study drug administration will be discontinued in a subject in whom a COVID-19 infection is confirmed or suspected. COVID-19 must be specified as the reason for study drug discontinuation.

Study drug administration may resume in subjects with confirmed or suspected COVID-19 infection based on investigator judgement after discussion with the medical monitor or Sponsor and only if the following minimum conditions are met:

- 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 positive polymerase chain reaction test and no symptoms.

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

See Appendix 4 for additional guidance for management of subjects and study conduct during the COVID-19 pandemic.

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9 TREATMENTS

9.1 Details of Study Drug and Vaccines

9.1.1 Study Drug

"Study drug" or "study medication" refers to nemolizumab or placebo drug product for purposes of this double-blind study. The list of excipients are detailed in the IB.

Nemolizumab 30 mg and placebo will be provided as lyophilized powder for solution for injection for subcutaneous use only after reconstitution in a pre-filled, single-use, dual-chamber syringe (DCS).

The lyophilized nemolizumab (CD14152) powder (39 mg) and solution for reconstitution (0.595 mL) are stored in separate syringe chambers, with each DCS designed to deliver a 30-mg dose of nemolizumab (CD14152) after reconstitution.

Subjects will receive a loading dose of nemolizumab (eg, 60 mg) or placebo by 2 SC injections at baseline and a single 30-mg dose at Weeks 4, 8, and 12.

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9.1.1.2 Study Drug Injection

All study drug injections will be performed by the study center staff at the study centers, following instructions provided in the current version of the pharmacy manual and the instructions for use. After confirming that the study drug is fully reconstituted, the pharmacist (or other qualified personnel) will deliver the DCS to the investigator or other qualified personnel, for subcutaneous injection in the subject's abdomen, front upper thigh, or outer upper arm. Good hygiene practices and clean techniques must apply at all times. A different injection site should be selected for each injection. Refer to the current version of the pharmacy manual and the instructions for use for further details. The site of injection should be recorded in the subject's treatment record as well as the eCRF at each time point.

After study drug administration or vaccine administration, subjects will be monitored closely for any signs or symptoms of hypersensitivity reaction before being discharged. For the first 2 visits where study drug is administered and after vaccines are administered, subjects should remain at the study center for at least 30 minutes following the injection(s).

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9.1.2.1 Preparation of Vaccines

A pharmacist (or other qualified personnel) will prepare the vaccines for injection according to the instructions in the respective prescribing information.

9.1.2.2 Injection of Vaccines

Vaccine administration will occur at the study centers by study center/clinical staff. Intramuscular injections of vaccines will be done according to the instructions in the prescribing information. The vaccines will be administered separately (with 2 different syringes) at 2 different injection sites.

After administration of the vaccines, subjects should stay in the office for 15 to 20 minutes to observe for potential severe reactions to the vaccine including dyspnea, wheezing, dizziness, and/or rash accompanied with itching.

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9.2 Dosage Schedule

Table 2 summarizes study drug dosing for the 16 week treatment period.

Table 2: Treatment Period Dosing By Treatment Group

Treatment Group	Dose/route	Week(s)	Schedule
Nemolizumab (CD14152)	30 mg × 2 SC injections	Baseline	Baseline
	30 mg × 1 SC injections	4, 8, 12	Q4W
Placebo	Placebo× 2 SC injections	Baseline	Baseline
	Placebo× 1 SC injections	4, 8, 12	Q4W

Abbreviation(s): Q4W=every 4 weeks; Q8W=every 8 weeks; SC=subcutaneous.

Tdap and MCV4 will be administered separately each as a 0.5 mL intramuscular injection at Week 12.

Subjects requiring any rescue therapy during the screening period are ineligible for participation in the study. Subjects requiring systemic rescue therapy during the treatment period prior to Week 16 must discontinue study treatment.

9.3 Measures to Minimize Bias: Study Treatment Assignment and Blinding

9.3.1 Method of Study Treatment Assignment

At the baseline visit, a unique randomization number will be assigned to an eligible subject via interactive response technology (IRT). Subjects will be randomized in a 1:1 ratio to receive either nemolizumab or placebo. The randomization scheme will be

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stratified by baseline disease severity [redacted] to ensure appropriate distribution of assignment to the 2 treatment groups.

9.3.2 Blinding

All attempts will be made to keep the study center staff and subjects blinded throughout the study. Members of the study center staff, including those responsible for DCS preparation, will not have access to the randomized treatment assignment.

To ensure double-blind administration of study drug, the study center pharmacist(s) or other qualified personnel will prepare all nemolizumab or placebo treatments, according to the current version of the pharmacy manual, the instructions for use, and assigned DCS provided by the IRT system.

As there may be detectable differences between active and placebo during the reconstitution process, the DCS is delivered for injection after the reconstitution is complete. The pharmacist (or other qualified personnel) preparing study medication should not be involved with any study assessments and should not discuss any aspects of study drug reconstitution with the subject/caregiver or study staff involved in subject interviews or study assessments.

To maintain the integrity of the study blinding, the bioanalytical laboratory staff who process/analyze the PK/[redacted] samples will not provide any information to sponsor, clinical research organization (CRO), or investigational study center personnel directly involved with the ongoing conduct of the study that may lead to unblinding during the ongoing study.

Unblinding of a subject's individual treatment code should occur only in case of a medical emergency or in the event of a serious medical condition that necessitates identification of the study drug for the welfare of that subject, as judged by the investigator. The emergency unblinding process utilizes IRT to allow the investigator to have unrestricted, immediate, and direct access to the subject's individual study treatment. When possible (ie, when the health of the subject is not immediately at risk), the investigator or sub-investigator is encouraged to consult with the medical monitor and the sponsor before breaking the blind.

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If emergency unblinding is required:

- Only the investigator will make the decision to unblind the treatment assignment.
- Only the affected subject will be unblinded.
- The IRT system will provide the treatment assignment to the investigator.

Refer to the Randomization and Trial Supply Management (RTSM) User Guide for information on the steps for breaking the blind in the IRT system.

When the blinding code is broken, the reason must be fully documented. If the code is broken by the investigator, the subject must be withdrawn from the study and must also be appropriately followed for a minimum of 12 weeks after the last dose of study drug.

The reporting requirements for unblinding are the same for reporting an SAE (see Section 13.1.3).

The randomization code will remain blinded to all study sites and study team members until completion of the study and after the study database has been locked. Although initial treatment period results will be analyzed after all subjects have either completed the Week 16 visit, or have withdrawn or been discontinued from the study before Week 16, personnel from sponsor, CRO, and investigational sites directly involved with the ongoing conduct of the study will not have access to any information that may lead to unblinding for the ongoing maintenance evaluation.

The IDMC will review data at periodic intervals throughout the study as defined in the IDMC charter. The IDMC charter will specify the procedures for unblinding to ensure that treatment assignment remains undisclosed to all individuals involved in the direct execution and management of the study until the final database is locked.

9.4 Dosage Modification

Dose modification of the study drug and vaccines will not be permitted during the clinical study.

Any inadvertent dose modification(s) should be reported to the sponsor/CRO.

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In the event of a missed dose (ie, temporary discontinuation of the study drug), it will be documented in the eCRF that the drug has not been administered at the study visit, together with the reason (eg, for safety). Subjects will be asked to return to the study centers for all remaining visits and complete all study assessments and procedures as described in Section 10.

Dosing frequency of study drug (nemolizumab and placebo) is scheduled for Q4W, based on the baseline/Day 1 visit date. If a study visit occurs outside the visit window, study drug can be administered provided there is a minimum of 3 weeks since the last injection. Future visits should be scheduled within the required windows based on the baseline/Day 1 visit date, while maintaining the minimum 3-week interval between 2 injections. Vaccines will be administered as single separate doses at Week 12.

9.5 Accountability and Compliance

Study drug (nemolizumab and placebo) and vaccines will be provided to the investigational site. Site personnel will acknowledge receipt of the study drug using IRT 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 maintain accurate records of the study drug and vaccines 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 DCS and vaccine 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 DCS and vaccine units can be disposed of in an appropriate sharps container and according to waste regulation(s) in the country. A 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 9.6.3 for PTCs.

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The study monitor may check the study supplies at each study center at any time during the study. It is the responsibility of the study monitor to ensure that the investigator (or designee) has correctly documented the amount of the study drug and vaccines received, dispensed, and returned/destroyed on the dispensing log that will be provided. A full drug accountability log will be maintained at the study center at all times. 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 and vaccines at the close-out visit to the study center. All discrepancies must be accounted for and documented.

9.6 Prior and Concomitant Therapies

Prior therapies and medications are defined as therapies/medications that have been stopped within the 3 months before the screening visit, unless relevant to the inclusion/exclusion criteria. Whenever possible, all prior therapies/medications for AD and all prior vaccinations should be documented.

Concomitant therapies/medications are defined as follows:

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

The following 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, homeopathic preparations, and other alternative medications
- Medical and surgical procedures (eg, phototherapy, exodontia). Procedures whose sole purpose is diagnosis (non-therapeutic) are not included

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

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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 or at appropriate visits when pre-pubertal subjects begin menses.

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.

Restricted prior therapies are provided in Section 8.2.

9.6.1 Permitted Concomitant Therapy

Unless specified as prohibited therapies (see Section 9.6.2), all therapies are authorized, including basic skin care (cleansing and bathing), moisturizers, bleach baths, topical anesthetics, and antihistamines without a sedative effect.

The formation of cytochrome P450 (CYP450) metabolic enzymes can be altered by increased levels of certain cytokines (eg, IL-1, IL-6, and IL-10) during chronic inflammation. Although there is no known evidence suggesting that IL-31 affects the level or activity of CYP450 enzymes, the impact of nemolizumab on such enzymes has not been studied. Therefore, investigators should be attentive to clinical or laboratory signs that might indicate a potential effect of nemolizumab in subjects using other therapies that are CYP450 substrates and have a narrow therapeutic index.

Only the following non-live vaccinations are permitted during the study and follow-up period, besides the vaccines specifically administered in this study (ie, Tdap, MCV4):

- seasonal vaccinations (eg, inactivated influenza)
- COVID-19 vaccinations.

Wherever possible, it is recommended to avoid administration of seasonal and COVID-19 vaccinations within 1 week before or after study drug dosing, and a different anatomical location should be used for study drug administration and vaccine administration. For guidance on administration of COVID-19 vaccines and study vaccinations, see Appendix 4.

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9.6.1.1 Topical Background Therapy

At the screening visit (≥14 days prior to baseline), subjects who are using a stable regimen of medium- or low-potency TCS therapy, with or without TCI therapy, should continue their therapy regimen.

Background therapy use should be adjusted to the disease activity and tolerability of the subject, including tapering when signs and symptoms improve, discontinuation when lesions clear, and restarting if signs and symptoms recur, at the discretion of the investigator.

Subjects who are not using a stable regimen of topical therapy at the screening visit should not use topical background therapy during the study, unless required as rescue therapy (see Section 9.6.1.3).

Subjects with a history of intolerance to TCS or for whom TCS are not advisable (eg, hypersensitivity, significant skin atrophy) must not use TCS background therapy.

9.6.1.2 Moisturizer

Subjects will apply a moisturizer at least once daily, and liberally as needed, to dry skin and AD lesions beginning at screening, and throughout the study. The subject's current moisturizer or a moisturizer recommended by the investigator may be used. Use should not occur within 8 hours before each clinic/office visit. Whenever possible, subjects should use the same moisturizer throughout the study. Moisturizer used and any adjustments should be documented in the eCRF.

9.6.1.3 Rescue Therapy

If deemed to be medically necessary by the investigator (eg, to control intolerable AD signs/symptoms), topical and/or phototherapy rescue treatments can be prescribed to the subjects at any time during the study except during the screening period. Subjects receiving any rescue therapy during the screening period are ineligible for participation in the study. Subjects receiving systemic rescue during the treatment period must discontinue study treatment.

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As a general guideline and per individual investigator judgment, rescue therapy should not be prescribed within the first 2 weeks after baseline (ie, Week 2) to allow a minimum time for study drug exposure.

Permitted rescue therapies during the treatment period include:

- TCS (higher potency than used at baseline for subjects using TCS background therapy; any potency for subjects not using TCS background therapy)
- TCI (only for subjects not using TCI background therapy at baseline)
- Phototherapy

Rescue treatments are only approved and/or standard of care treatments that directly treat AD. Antihistamines, sleep aids, topical and systemic antibiotics, and anti-itch creams are not considered to be rescue therapy because they do not directly treat AD.

Whenever possible, investigators should first use topical medications as rescue therapy before escalating to systemic therapies. If subjects receive topical treatments or phototherapy as rescue therapy, study drug and vaccine administration should be continued unless there is a safety concern according to the investigator's judgment. If subjects receive systemic rescue therapy, they should permanently discontinue study treatment.

9.6.2 Prohibited Medication/Therapy

Treatment with the following concomitant medications/therapies is prohibited during the study unless otherwise specified in Table 3. "As needed" (PRN) use of TCS or TCI is not permitted.

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Table 3: Prohibited Medication/Therapy and Timeframe Prior to Baseline

Treatment(s)	Timeframe	
	Before Baseline/Day 1	Day 1 – Week 24
Coal tar products	2 weeks	Prohibited
Topical PDE-4 inhibitor	2 weeks	Prohibited
TCI, only for subjects not using stable TCI therapy ≥14 days prior to baseline	2 weeks	Prohibited*
High- or very high-potency TCS (Class I-II according to the US classification)[2] (applies to all subjects); any TCS only for subjects not using stable TCS therapy ≥ 14 days prior to baseline	2 weeks	Prohibited*
Topical medications, including TCS/TCI, with occlusive dressings (eg, wet wraps)	2 weeks	Prohibited
Systemic corticosteroids (corticosteroid inhalers are permitted)	4 weeks	Prohibited
Phototherapy	4 weeks	Prohibited*
Tanning bed use	4 weeks	Prohibited
Immunosuppressive or immunomodulatory drugs (eg, cyclosporine A, oral tacrolimus, cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil)	4 weeks or 5 half-lives (whichever is longer)	Prohibited
Biologics and their biosimilars (eg, dupilumab, etanercept, adalimumab, infliximab, omalizumab, etc)	8 weeks or 5 half-lives (whichever is longer)	Prohibited
Investigational topical and systemic medication (eg, topical or oral JAK inhibitors)	8 weeks or 5 half-lives (whichever is longer)	Prohibited
Drugs with a sedative effect such as benzodiazepines, imidazopyridines, barbiturates, or sedative anti-depressants (eg, amitriptyline), except if these treatments were taken at a stable dose for at least 3 months before screening (Stable treatment with antihistamines with sedative effect, SSRIs, or SNRIs is allowed.)	1 week	Prohibited
Gabapentinoids (eg, gabapentin, pregabalin)	4 weeks	Prohibited
Cannabinoids	2 weeks	Prohibited
Alternative medicine for AD (eg, traditional Chinese medicine)	2 weeks	Prohibited
Live (attenuated) vaccines	12 weeks	Prohibited
Non-live vaccines, except vaccines specifically administered in the study (exceptions apply; see Section 9.6.1)	12 weeks	Prohibited

Abbreviation(s): AD=atopic dermatitis; JAK=Janus kinase; PDE-4=phosphodiesterase-4; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TCI=topical calcineurin inhibitor; TCS=topical corticosteroid.
* Unless used as rescue therapy
Note: These treatments should not be discontinued for reasons related to this clinical study.

If a prohibited therapy becomes necessary for the safety of the subject, the investigator should notify the medical monitor and discuss possible alternatives. If a subject receives a prohibited therapy during the clinical study (eg, inadvertent short-term use), the investigator should also notify the medical monitor and discuss whether or not it is acceptable for the subject to continue receiving the study drug.

Vaccinations during the study and follow-up period are not permitted, except for use of vaccines specifically administered in this study (ie, Tdap, MCV4) and non-live vaccines specified in Section 9.6.1.

9.6.3 Product Technical Complaints

All DCS and vaccine units must be inspected prior to preparation/injection by the persons performing the preparation/injection to ensure absence of visual defects that could lead to a DCS or vaccine PTC. This also includes the DCS plunger rod. In case of doubt, the DCS or vaccine should not be used, and the deficiency must be reported as defined in the pharmacy manual.

All PTCs should be reported to the sponsor/designee by filing the relevant forms available in the Investigator Site File and the pharmacy manual and as required by local regulations.

Refer to the current version of the pharmacy manual for further details.

9.7 Duration of Subject Participation

The expected duration for each subject's participation in the study is up to 28 weeks, including a 2- to 4-week screening period, a 16-week treatment period, and an 8-week follow-up period (12 weeks after the last study medication injection).

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The 12-week follow-up visit is not required for subjects who will continue in the LTE study (Protocol 118163).

9.7.1 Early Termination Visit

Subjects may discontinue from the study or discontinue the study treatment only and continue to participate in the study.

Subjects who prematurely discontinue from the study should undergo final study assessments according to the following guidelines:

- Subjects discontinued from the study during the treatment period on/before the Week 16 visit should attend an early termination visit.
- A follow-up/final visit is required 12 weeks after the last study drug administration.

Subjects who prematurely discontinue the study drug will be asked to continue participation in the study; however, subjects who discontinue the study drug prior to Week 12 should not be vaccinated. Subjects will be asked to return for all remaining visits and assessments (including daily assessment of pruritus, sleep disturbance, etc). Participation will continue until the subject completes the final study visit or otherwise discontinues study participation.

9.7.2 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, for follow-up of AEs, or to conduct efficacy assessments for subjects requiring rescue medication between regularly scheduled study visits. Visits occurring 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: Any of the procedures/assessments listed in Table 4 may be conducted, but not all are required. However, blood sample collection for CCI [redacted] are required during unscheduled visits that are conducted for safety reasons.

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10 STUDY PROCEDURES

A written, signed ICF, assent form, and Health Insurance Portability and Accountability Act (HIPAA) authorization is required before any study-related procedures are performed.

Upon provision of the signed ICF/assent form, each subject will be assigned a unique SIN. For the duration of the entire clinical study, the subject will be identified using the SIN in all documentations and discussion.

The planned study assessments are in Table 4. At each visit, assessments/procedures should be performed in the following order:

1. Patient-reported safety measurements
2. Investigator assessments (including efficacy and safety)
   - Electrocardiogram (ECG) should be done before vital signs measurements and blood draws (see Section 13.7).
3. Sample collections for laboratory assessments
4. Sample collections for correlative assessments (PK, CCI vaccine response)
5. Administration of study drug injections and vaccines

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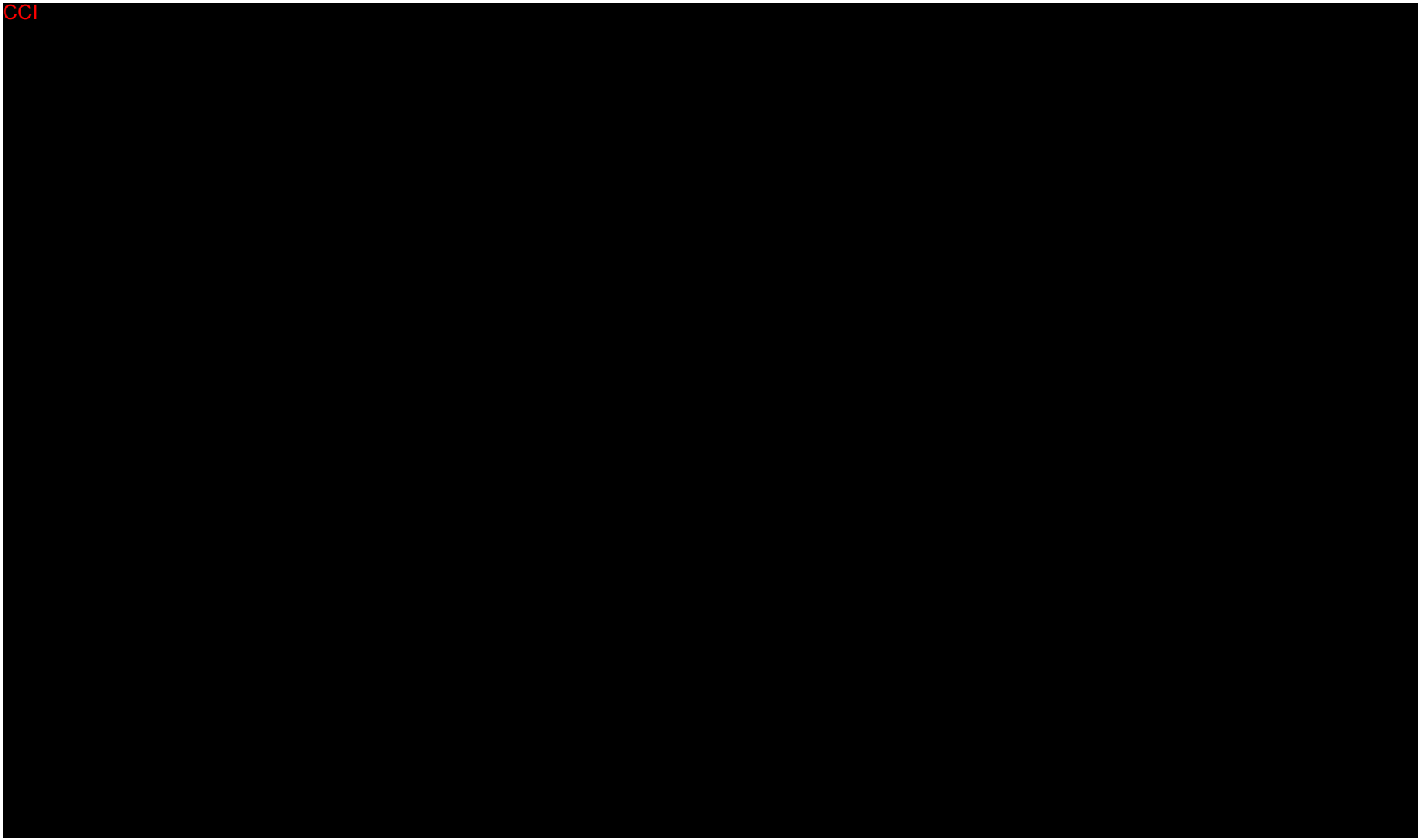

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11 IMMUNOGENICITY ASSESSMENTS

11.1 Vaccine Response

Humoral immune responses to tetanus and meningococcal vaccination will be determined using serum samples collected from all subjects according to Table 4.

11.1.1 Tetanus Toxoid IgG Antibody Concentration

Serum concentrations of anti-tetanus IgG will be assessed. The detection and characterization of antibodies to tetanus toxoid will be performed using a validated immunoassay.

11.1.2 Meningococcal Serogroup C SBA Reciprocal Titer

Immune response to meningococcal vaccination will be determined by measuring functional antibody responses using an SBA assay.

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12 EFFICACY ASSESSMENTS

Efficacy measurements should be conducted by the investigators (or trained designees) and subjects (for patient-reported efficacy measurements) according to Table 4. Whenever possible, the same evaluator should make the assessment throughout the study.

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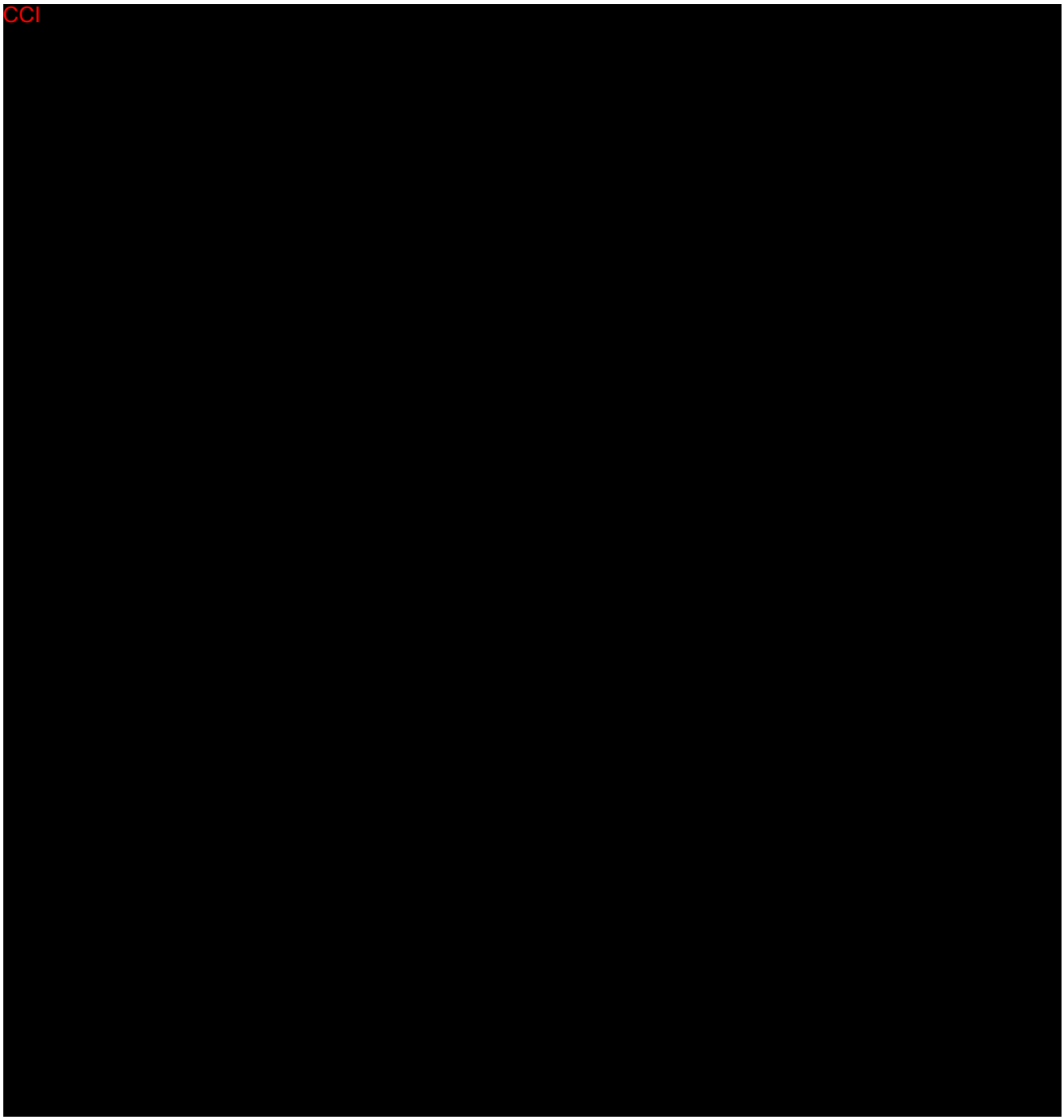

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13 SAFETY ASSESSMENTS

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

13.1 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 the use of a medicinal (investigational) product, whether or not it is related to the medicinal (investigational) product. This includes an exacerbation of preexisting conditions or events, intercurrent illnesses, drug interaction, or the significant worsening of the indication under investigation that is 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 should be reported as an AE.
- Whenever possible, 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 13.1.5.
- 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 becomes aware of any safety information that appears to be drug-related, even after the subject has completed the clinical study.

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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 as appropriate.

Any AE occurring 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 Adverse Event Form (“AE Form”) along with the date of onset, severity, relationship to the study drug(s), and outcome, without omitting any requested and known information. Additional information will be requested under certain circumstances.

Adverse events 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 as follows:

Mild: An AE that is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities.

Moderate: An AE that is 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.

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Assessment of Causality

The investigator is to determine whether there is a reasonable causal relationship between the occurrence of the AE, and exposure to the study drug (ie, nemolizumab or placebo) and/or study procedure (eg, injection, topical background therapy, blood sample collection). Medical judgment should be used to 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" is meant to convey in general that there are facts or arguments to suggest a causal relationship (International Council for Harmonisation [ICH] E2A, Section IIIA 1).

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

Reasonable possibility:

According to the reporting investigator, there is a reasonable possibility (ie, suggestive evidence or arguments) that there is a causal relationship irrespective of the dose administered:

- Between the study drug (nemolizumab) and the AE, and/or
- Between the clinical study protocol procedure (eg, 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, as follows:

- None

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- 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.

Subjects should be followed up for 12 weeks (± 5 days) after receiving the last dose of study drug, and any AEs that occur during this time should be reported according to the procedures outlined above.

Documentation and Reporting of Adverse Events

Adverse events should be reported and documented in accordance with the procedures outlined below. All AEs occurring 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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13.1.1 Adverse Events of Special Interest

An AESI is a noteworthy treatment-emergent event for the study drug that should be monitored closely and reported promptly. See Section 13.1.4 for reporting procedure. An AESI can be either serious or non-serious.

Based on the potential risks of nemolizumab and the risks associated with biologics (and their biosimilar equivalents) in general (ie, class effects), the following AEs will be considered AESIs:

- Injection-related reactions
  - Anaphylactic reactions
  - Acute allergic reactions requiring treatment
  - Severe injection site reaction (ie, lasting > 24 hours)
- Newly diagnosed asthma or worsening of asthma
  - More specifically, subjects with a medical history of asthma will be referred to the physician who manages their asthma when:
    - ACT score ≤ 19: An ACT score ≤ 19 conveys asthma that may not be adequately controlled. An AESI is reported based on the investigator's clinical judgment, including consideration of the managing physician's report.
    - PEF < 80% of the predicted value: An AESI should be reported.
    - Unexpected worsening of asthma is observed or reported. An AESI is reported based on the investigator's clinical judgment.
  - Subjects without a medical history of asthma will be referred to an appropriate respiratory physician/specialist when:
    - Signs and/or symptoms suggestive of asthma have been observed or reported. An AESI is reported based on the investigator's clinical judgment of the specialist's report.

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- Respiratory assessments (eg, examination, PEF) suggest a decline in the subject's respiratory health. An AESI is reported based on the investigator's clinical judgment of the specialist's report.

- Infections
  - Any severe infection or any infection requiring treatment with parenteral antibiotics or oral antibiotics/antivirals/antifungals for > 2 weeks
  - Any confirmed or suspected COVID-19 infection
- Peripheral edema: limbs, bilateral
- Facial edema
- Elevated ALT or AST (> 3 × ULN) in combination with elevated bilirubin (> 2 × ULN)

13.1.2 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, ie, it does not include a reaction that might have caused death if it had occurred in a more serious form).
- Requires or prolongs inpatient hospitalization. (Complications occurring during hospitalization are AEs and SAEs if they cause prolongation of the current 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 considered as an SAE if it is solely for the purpose of diagnostic tests [even if related to an AE], elective hospitalization for an intervention that was already planned before subject enrollment in the clinical study, admission to a day care facility, social admission [eg, if the subject has no place to sleep], or administrative admission [eg, for a yearly examination].

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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 subject's 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 appropriate 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.

13.1.3 Procedure for Reporting a Serious Adverse Event

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

1. Take prompt and appropriate 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 PPD group of an SAE report, by email or fax:

   PPD

   Note: Immediate SAE 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 to be related to the investigational product.

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

3. Send any relevant information or anonymized medical records (eg, laboratory test results) to the PPD (see contact details above), within 24 hours 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, complete an updated SAE report **within 24 hours** of receipt of the updated information.
5. 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.
6. When the outcome of the event is known, complete an updated SAE report, if appropriate.
7. Prompt notification of SAEs by the investigator is essential so that legal obligations and ethical responsibilities toward the safety of subjects are met. The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. The sponsor or its delegate (ie, the CRO) 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 are forwarded to investigators as necessary.

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

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

13.1.4 Procedure for Reporting an Adverse Event of Special Interest

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

1. Take prompt and appropriate 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**) the PPD of an AESI report, by email or fax. Refer to Section 13.1.1.

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

   The demographics, medical history, drugs/therapies, and medical and surgical procedures forms must also be available for review in the eCRF, at that time.
3. Send any relevant information or medical records (eg, laboratory test results) to the PPD 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.

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13.1.5 Procedure for Reporting Pregnancies

Any pregnancy occurring during clinical studies where the fetus could have been exposed to the study drug must be monitored until its outcome in order 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 not receive any further injection of the study drug.
2. Complete as fully as possible 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 the PPD Refer to Section 13.1.5.

   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 to be 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 to the PPD within 24 hours of receipt of the information. If the subject can no longer be reached (ie, 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 as fully as possible the Pregnancy Surveillance Form – Part II: Course and Outcome of Pregnancy. Print and send the form by email or fax to the PPD within 24 hours of receipt of the information.

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6. If the pregnancy leads to an abortion (ie, voluntary abortion, spontaneous abortion, or therapeutic abortion), in utero death or congenital anomaly, follow the procedure for declaration of/reporting an SAE (see Section 13.1.3).

13.1.6 Unexpected Adverse Reactions

Unexpected Adverse Reaction Definition

An unexpected adverse reaction is any untoward and unintended response that is related to the administration of the study drug at any dose, the nature or severity of which is not consistent with the applicable product information (eg, reference safety information in the IB for nemolizumab, study protocol, etc).

The sponsor or its delegate (ie, PPD 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 an SAE(s) or other specific safety information (eg, summary or listing of SAEs) from the sponsor or its delegate (ie, PPD will file it accordingly (ie, with the TMF), and will notify the IRB/IEC, if appropriate according to local requirements.

13.2 Clinical Laboratory Assessments

The hematology laboratory analyses, clinical chemistry laboratory analyses, and urinalyses will be performed at a central laboratory. Reference ranges will be supplied by the central 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 in a timely manner. Study centers should refer to the current version of the laboratory manual for laboratory values outside of normal limits. For each out-of-range laboratory result, the investigator or designee will evaluate whether

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he/she considers it to be clinically significant, defined as meeting at least 1 of the following conditions:

- The abnormality suggests a disease and/or organ toxicity, or
- The abnormality is of a degree that requires additional active management, eg, 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 as soon as possible and the subject will be monitored until the value returns to normal and/or an adequate explanation for the abnormality is found.

Investigators will also be allowed to repeat specific laboratory test(s) or procedure(s) where the investigator suspects an inaccuracy or false result and that which may impact the safety of the subject or the interpretation of the trial 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 whenever possible). 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 (ie, changed significantly from the screening visit). Whenever possible, the investigator should provide a diagnosis of an AE when reporting the abnormal laboratory value.

Subjects should be reminded to be well hydrated before all visits for phlebotomy purposes. 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 nonfasting state will not be a protocol deviation.

Total blood volumes to be drawn at each visit are provided in the clinical laboratory manual. Additional samples may be required if medically indicated (eg, at unscheduled visits for safety reasons, when an abnormal laboratory value is observed and requires a re-test).

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See Sections 13.2.4, 13.2.5, and 13.2.6 for details regarding pregnancy testing, virology, and TB testing samples, respectively.

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

13.2.1 Hematology

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

13.2.2 Clinical Chemistry

Subjects should fast for at least 8 hours before the visits when blood chemistry is planned, except the screening visit.

Creatinine, ALT, AST, gamma glutamyltransferase, 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), and CPK isoenzyme.

13.2.3 Urinalysis

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

13.2.4 Pregnancy Testing

All women of childbearing potential will have a serum pregnancy test at the screening visit and urine pregnancy tests (UPTs) at subsequent visits according to Table 4. Pregnancy test results must be available prior to the administration of the study drug.

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

Urine pregnancy tests with a sensitivity < 25 IU/L will be provided to the study centers for use in the trial.

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

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If the result of a UPT is positive, it must be confirmed with a serum pregnancy test, and no study drug or vaccine should be administered pending the serum pregnancy test result. Subjects with a positive serum pregnancy test result during the trial must discontinue treatment and be withdrawn from the trial.

13.2.5 Virology

Virology including HBsAg, HBcAb, hepatitis C, HIV-1, and HIV-2 antibody will be assessed at the screening visit. Subjects with a positive HBcAb and a negative HBsAg will also be assessed for hepatitis B surface antibody.

13.2.6 Tuberculosis Testing

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

13.2.6.1 Active/Latent Tuberculosis 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 M tuberculosis, as evidenced by a positive Interferon Gamma Release Assay, 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.

13.2.6.2 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-

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Guérin (or BCG) 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 (eg, 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 appropriate follow-up. 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.

13.3 Vital Signs

Vital signs will be evaluated at the screening visit and at each subsequent visit according to Table 4. 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.

13.4 Height and Weight

Height and weight will be measured, according to Table 4.

Subjects must be at least 30 kg at both screening and baseline visits in order to be enrolled into this clinical study.

After the screening visit, additional height assessments will only be conducted for adolescent subjects (aged 12 to 17).

13.5 Physical Examination

Complete physical examination should be performed at the screening, and certain subsequent scheduled visits, according to Table 4. A complete physical examination will include assessments of the head, ears, eyes, nose, throat, neck (including thyroid),

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skin/integumentary system, cardiovascular system, respiratory system (for additional respiratory assessments), gastrointestinal system, musculoskeletal system, lymph nodes, extremities, and nervous system.

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.

13.6 Respiratory Assessments

At screening, the investigator should specifically question all subjects about any medical history of asthma and their respiratory health (eg, wheezing, coughing, allergies, and infections). Subjects with a history of asthma will be questioned about the seasonality of their asthma and known triggers, such as allergens. Newly diagnosed asthma or worsening of asthma during the study will be reported as an AESI.

13.6.1 Asthma Control Test

Subjects with a medical history of asthma will take the ACT at visits according to Table 4 before questioning and physical examination by the investigator. Subjects with a new (de novo) diagnosis of asthma will take the ACT beginning at the visit the diagnosis was first confirmed and at all subsequent study visits thereafter. Subjects with an ACT score ≤ 19 will be referred to the physician managing their asthma.

The ACT is an assessment to determine if a subject's asthma symptoms are well-controlled. The ACT is designed for adults and adolescents 12 years or older, and is composed of 5 questions. For each question, the subject will choose the best answer out of 5 possible answers. The test provides a numerical score ranging from 5 to 25 to assess asthma control; a higher score indicates better asthma control while a score of 19 or less indicates the subject's asthma may not be under control (Appendix 9).

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13.6.2 Respiratory Examination

A respiratory examination will be required to be performed for all subjects at all scheduled visits, according to Table 4. The ACT will aid the investigator's questioning of subjects with a medical history of asthma and should be completed before the clinical questioning. After the screening visit, all subjects will be asked non-leading questions about any respiratory changes. The investigator or designee will then perform a respiratory examination of all subjects at all visits.

Subjects with a medical history of asthma will be referred to the physician managing their asthma if unexpected worsening of asthma is observed or reported. Subjects without a medical history of asthma who experience respiratory changes (examination findings or newly reported signs and/or symptoms suggestive of asthma) should be referred to a respiratory specialist.

13.6.3 Peak Expiratory Flow

All subjects will undergo PEF testing at screening, baseline, and specified visits according to Table 4. For subjects reporting a medical history of asthma, PEF will be conducted at all visits.

Subjects with a new (de novo) diagnosis of asthma will be evaluated by PEF at all visits after the diagnosis is first made according to Table 4.

PEF testing during the clinical study will be performed under the supervision of qualified study personnel. Peak expiratory flow measurements should consist of 3 good efforts, with the best result documented. It is preferable that the PEF measurement be performed before noon or at the same time during each study visit whenever possible. Obtained PEF values will be compared to predicted values based on the subject's age, sex and height.[27,28]

Subjects should be asked to withhold asthma medication on study visit days until after PEF testing is complete, to the extent it does not pose an undue risk to the subject, to avoid interference with PEF measurements.

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Subjects with a medical history of asthma will be referred to the physician managing their asthma if PEF < 80% of the predicted value.

13.6.4 Respiratory Referrals

Subjects with a medical history of asthma will be referred to the physician who manages their asthma when:

- PEF < 80% of the predicted value.
- ACT score ≤ 19 (an ACT score ≤ 19 conveys asthma that may not be adequately controlled).
- Unexpected worsening of asthma is observed or reported at any time during the study.

At any study visit, subjects without a medical history of asthma will be referred to an appropriate specialist physician whenever:

- Signs and/or symptoms suggestive of asthma are newly observed or reported.
- Respiratory assessment suggests a decline in the subject's respiratory health.

13.7 Electrocardiogram

A 12-lead Electrocardiogram (ECG) will be performed and read centrally according to visits specified in Table 4 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 (refer to the current version of the central laboratory manual). Tests with abnormal results that are 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 to be clinically significant after the screening visit are to be recorded as AEs and discussed with the medical monitor, as needed.

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15 OTHER ASSESSMENTS

15.1 Independent Data Monitoring Committee

An IDMC will review and monitor subject safety throughout the study. The IDMC will provide recommendations on the safety of subjects. Details on the IDMC, including the plan of analysis for IDMC outputs, the composition of the IDMC, the procedures, roles, responsibilities, and their communications are provided in the IDMC charter.

15.2 Independent Adjudication Committee

An IAC will review all asthma-related AEs throughout the study. Details on the IAC, including the plan of analysis for IAC outputs, the composition of the IAC, the procedures, roles, responsibilities, and their communications are provided in the IAC charter.

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16 STATISTICAL ANALYSIS

A statistical analysis plan (SAP) will be created and finalized before database lock. This document will provide details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will contain further detailed and technical descriptions of specific data conventions, calculations and of statistical procedures for executing the analyses that are specified in this protocol. Any changes made to the analysis after finalization of the SAP (ie, post-database lock) will be discussed and documented in the clinical study report.

The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided. 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.

Unless otherwise stated, the baseline value for any variable will be the last non-missing value taken prior to the receipt of study treatment at the Baseline visit (Day 1).

Unless otherwise stated, all statistical tests other than the primary vaccine response endpoint will be 2-sided and conducted at the 5% level. All presented confidence intervals will be 2-sided 95% confidence intervals.

A full discussion of inclusion/exclusion of subjects into the analysis populations described here will be provided close to database lock, including any decisions on data handling and other topics, and will be documented in the Blind Data Review Meeting (BDRM) Plan and subsequently in the BDRM Report. No Per-Protocol population is included in this study.

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16.1 Analysis Populations

Screened Population

The Screened population comprises all subjects who signed the ICF. This population includes screen failures, and randomized subjects. For clarity, screen failed subjects are defined as are those subjects who fail to meet inclusion criteria or meet exclusion criteria and discontinued the study prior to randomization. Subjects that are re-screened will only be counted once, under the subject ID assigned for the repeat screening.

Intent-to-Treat Population (ITT)

The ITT population will consist of all randomized subjects. The ITT population will be the primary population for efficacy analyses. All analyses under the ITT population will be analyzed under the treatment group as randomized.

Modified Intent-to-Treat Population (mITT)

The mITT population will consist of all randomized subjects who received at least one administration of study drug and vaccine injection, have an evaluable vaccine response and did not receive any systemic rescue therapy prior to the post-vaccination vaccine response assessment. The mITT will be the primary population for vaccine response. All analyses under the mITT will be analyzed under the treatment group actually received.

Safety Population (SAF)

The SAF will consist of all randomized subjects who received at least one administration of study drug. The treatment group assignment in this population will be defined by the treatment actually received. This population will be used for the analyses of safety.

Pharmacokinetic Analysis Population (PKAP)

The PK analysis population (PKAP) will consist of all subjects included in the SAF, with at least one measurable post-baseline PK assessment. Similar to SAF, the treatment group assignment in this population will be defined by the treatment actually received. This population will be used for the analyses of PK.

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16.2 Subject Disposition

The number of subjects included in each analysis population and the reasons for discontinuation will be summarized. In addition, subjects' status with regard to study treatment and follow-up will also be summarized.

16.3 Demographics and Other Baseline Characteristics

Demographic and other baseline characteristics (e.g., age, sex, race, height, body weight, body mass index, and applicable baseline data for primary and key secondary efficacy assessments) will be summarized for the ITT, mITT, and SAF populations. Medical history, plus prior and concomitant therapies (including prohibited therapies) will be summarized for the ITT, mITT, and SAF populations.

16.4 Vaccine Response Analysis

Unless otherwise stated, vaccine response analyses will be performed on the mITT population, and where appropriate on the ITT.

16.4.1 Definition of Primary Vaccine Response Endpoint

The primary endpoint for this study is the proportion of subjects with a positive serum IgG response to tetanus toxoid at Week 16 (4 weeks post-vaccination), defined as:

1. ≥ 4-fold increase in anti-tetanus IgG concentration from baseline in subjects with pre-vaccination anti-tetanus IgG concentrations ≥ 0.1 IU/mL, OR
2. ≥ 0.2 IU/mL anti-tetanus IgG concentrations in subjects with pre-vaccination anti-tetanus IgG concentrations < 0.1 IU/mL.

Subjects in receipt of systemic rescue medication will not be vaccinated, and so will thus not be included in the mITT. Thus, for the primary analysis of the primary vaccine response endpoint, no imputation is required as all subjects included in the mITT are required to have an evaluable vaccine (IgG) response.

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16.4.2 Analysis of Primary Vaccine Response Endpoint

The estimate of the corresponding proportion for the endpoint will be adjusted for the randomization strata baseline CCI [redacted] using the Cochran-Mantel-Haenszel (CMH) estimate of the risk difference and corresponding 2-sided 90% CI. This primary analysis will be conducted on the mITT population.

16.4.3 Sensitivity Analyses of the Primary Vaccine Response Endpoint

Sensitivity analyses for the primary analysis of the primary endpoint will also be conducted in order to test for the robustness of the primary analysis. The primary analysis above will be repeated on the ITT population as sensitivity, whereby any subjects without an evaluable vaccine response will be regarded as a Non-Responder. Further to this, an observed case analysis on the ITT population will also be performed, with no imputation for missing data at Week 16.

16.4.4 Secondary Vaccine Response Endpoints

The following secondary vaccine response endpoints are to be analyzed, in any order:

- Proportion of subjects with a positive serum IgG response to tetanus toxoid at Week 16 (≥ 2-fold increase in anti-tetanus IgG concentration from baseline in subjects with pre-vaccination anti-tetanus IgG concentration ≥ 0.1 IU/mL OR ≥ 0.2 IU/mL anti-tetanus IgG concentrations in subjects with pre-vaccination anti-tetanus IgG concentrations < 0.1 IU/mL)
- Proportion of subjects with serum anti-tetanus IgG concentrations of ≥ 0.1 IU/mL at Week 16
- Proportion of subjects with serum anti-tetanus IgG concentrations of ≥ 1.0 IU/mL at Week 16
- Proportion of subjects with a positive serum bactericidal antibody response to meningococcal serogroup C polysaccharide at Week 16 (4 weeks post-vaccination) defined as ≥ 4-fold increase in SBA reciprocal titer from baseline

- Proportion of subjects with a positive serum bactericidal antibody response to meningococcal serogroup C polysaccharide at Week 16 defined as SBA reciprocal titer ≥ 8

All secondary vaccine response endpoints will be analyzed on the mITT population.

For all secondary vaccine response endpoints, the same analysis methods as for the primary vaccine response endpoint will be utilized.

Subgroup analyses may be conducted based on selected demographic variables of interest, and by vaccine response for the endpoints described in Section 16.4, if needed.

Further details on all vaccine response endpoints and analyses will be included in the SAP.

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[redacted]

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Discrete binary secondary efficacy endpoints will be analyzed in the same manner as the primary vaccine response endpoint, using a CMH method to estimate the risk difference and two-sided 95% CI, stratified by baseline [redacted] Given that the population for efficacy is the ITT population, the analysis will be conducted with any missing data at the time point imputed as Non-Responder.

Continuous secondary endpoints will be analyzed primarily as observed (ie, non-imputed) using a mixed-effect model for repeated measures approach, including baseline [redacted] as factor and baseline result for the endpoint as covariate. The estimated treatment difference for each endpoint at each visit will be displayed in the summary of statistical analysis together with the two-sided 95% confidence interval and associated p-value. An unstructured covariance matrix will be used to model the correlation among repeated measurements, and the Kenward-Roger adjustment will be used with restricted maximum likelihood for statistical inference.

Additionally, an analysis of covariance approach, including baseline [redacted] as factor and baseline result as covariate will be conducted for the specific secondary endpoint, based on data as observed.

Further to the above efficacy analyses, for all secondary efficacy endpoints, any missing data at any post-baseline visit (including Week 16) will be imputed utilizing multiple imputation (MI) using missing not at random (MNAR) with a controlled-based pattern mixture approach.

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The MI will be carried out as follows:

1) Fifty (50) imputed datasets with a monotone missing pattern will be multiply created using SAS MI procedure based on the observed data (Markov-Chain-Monte-Carlo method). The seed to be used is 118380 (the protocol number).
2) Each of the imputed datasets will be used to generate 50 complete datasets, using a regression method and the profiles from placebo subjects to impute the missing data of subsequent visits, including factors for treatment and randomization strata, and any applicable baseline as covariate.
3) The complete datasets will be modelled for the endpoint as specified above for discrete binary or continuous endpoints
4) The results from the analysis of the multiple imputed datasets will be combined by the MIANALYZE procedure of the SAS system.

Further details will be provided in the SAP.

For subjects in receipt of rescue medication at any point during the study, their data collected post-rescue intake will be set to missing, and analyzed in the manner above as observed and/or imputed. An additional analysis including all collected data as observed will also be conducted, with no adjustment for data collected post-rescue medication intake.

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A summary of the approach for analysis of the secondary efficacy endpoints on the ITT population is as follows:

Endpoint Type	Analysis	Imputation Method	Adjustment for Data Post-Rescue Med Intake
Binary	CMH	Non-Responder	Set to missing and impute
		MI	Set to missing and impute
		OC	Set to missing (with no imputation)
			Analyzed as seen (OC)
Continuous	MMRM	OC	Set to missing (with no imputation)
			Analyzed as seen (OC)
	ANCOVA	MI	Set to missing and impute

Abbreviation(s): ANCOVA= analysis of covariance; CMH= Cochran-Mantel-Haenszel; MI= multiple imputation; MMRM= mixed-effect model for repeated measures; OC=observed case.

Further details will be included in the SAP.

16.6 Safety Analysis

All safety analyses will be conducted on the SAF, by treatment group.

All reported AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 22.0 or later. The treatment-emergent period will be defined as the period of time from the first dose date of study treatment through 12 weeks (84 days) after the last dose of study treatment (ie, up to the follow-up visit for completers), or the date of rollover to the LTE study (SPR.118163), whichever is earlier. The incidence of TEAEs (events with onset dates on or after the start of the study drug), drug-related TEAEs, SAEs, TEAEs leading to study drug discontinuation and treatment-emergent AESIs will be included in incidence tables, summarized by System Organ Class (SOC) and Preferred Term (PT). Events with missing onset dates (and no data to suggest the

event stopped prior to study treatment start) will be included as treatment-emergent. The incidence of TEAEs by severity, counting multiple AEs under SOC and PT for a subject at the maximum severity will be presented. All AEs will be listed by subject, along with information regarding onset, duration, relationship and severity to study drug, action taken with study drug, treatment of event, and outcome.

Clinical laboratory data and vital signs will be summarized using descriptive statistics, including observed values and change from baseline values, as well as numbers of subjects with values outside limits of the normal range, including shifts from baseline at each time point.

Summary tables will be provided for 12-Lead ECG, Physical Examination (Full and Symptom-oriented), ACT, PEF, and Respiratory Exam, by treatment group and visit where appropriate. Listings will also be provided.

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16.9 Determination of Sample Size

Approximately 245 subjects will be randomized (~123 per arm) to show that the 90% confidence interval of the proportion difference between treatment groups will exclude a difference of more than 10%.

16.10 Protocol Deviations

Protocol deviations may be categorized into the following main categories (not exhaustive):

- Inclusion or Exclusion Criteria
- Investigational Product (Incorrect kit, Dosing, Storage issues etc.)
- Randomization
- Study Procedure compliance

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- Concomitant Medication / Administration of prohibited medication
- Visit Window (adherence)

All protocol deviations will be identified, evaluated, and closed before the respective database lock (final analysis) and will be discussed in the clinical study report. Protocol deviations occurring during the study will be listed. Protocol deviations incurred as a direct result 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.

16.11 Interim Analysis

No interim analysis will be performed.

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17 STUDY MANAGEMENT

17.1 Approval and Consent

17.1.1 Regulatory Guidelines

This study will be conducted in accordance with 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 ICH and GCP guidelines, and according to the appropriate regulatory requirements in the countries where the study was conducted.

17.1.2 Institutional Review Board/Independent Ethics Committee

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.

17.1.3 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 that is required by local regulations and guidelines for ICH. The PI will provide the sponsor or its representative with a copy of the IEC-/IRB-approved ICF before the start of the study.

17.2 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 appropriate validation of data and

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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.

17.3 Source Documents

Source documents are considered to be 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 trial-related monitoring, audits, review by IECs/IRBs, and regulatory inspections.

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

17.4 Record Retention

Study records and source documents must be preserved for at least 15 years after the completion or discontinuation of/withdrawal from the study, at least 2 years after the drug being studied has received its last approval for sale, or at least 2 years after the drug development has stopped, and in accordance with the applicable local privacy laws, whichever is the longer period.

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The investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subject health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR, Parts 160 and 164 (HIPAA Privacy Regulation). The investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the sponsor.

17.5 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 in order to check the completeness, clarity, and consistency of the data recorded in the eCRFs for each subject.

The investigator will make available 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 in accordance with the protocol, applicable regulations, and GCP guidelines.

17.6 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.

The sponsor will arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, standard operating procedures, GCP, and all applicable regulatory requirements. Audits will be

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independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at study sites and during data management to assure that safety and efficacy data are adequate and well documented.

17.7 Protocol Amendment and Protocol Deviation

17.7.1 Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no effect on 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 acknowledgement is received and filed. Amendments that are 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 in the case of an urgent safety measure.

17.7.2 Protocol Deviations

Should a protocol deviation occur, the sponsor must be informed as soon as possible. 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 in accordance with applicable regulatory authority mandates.

17.8 Ethical Considerations

This study will be conducted in accordance with this protocol, the accepted version of the Declaration of Helsinki and/or all relevant 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 are required to give written informed consent before participation in the study.

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17.9 Financing and Insurance

Before the study commences, the sponsor (or its designee) and the investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the investigator (or the institution signatory) and the sponsor (or its designee).

The investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The sponsor will provide no-exclusion insurance coverage for the clinical study as required by national regulations.

17.10 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 that will be agreed between the institution and the sponsor or their designee. With respect to 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. In order to facilitate such ownership, investigators will be required to assign all such inventions either to their institution or directly to the sponsor or its designee, as will be set forth in the clinical study agreement.

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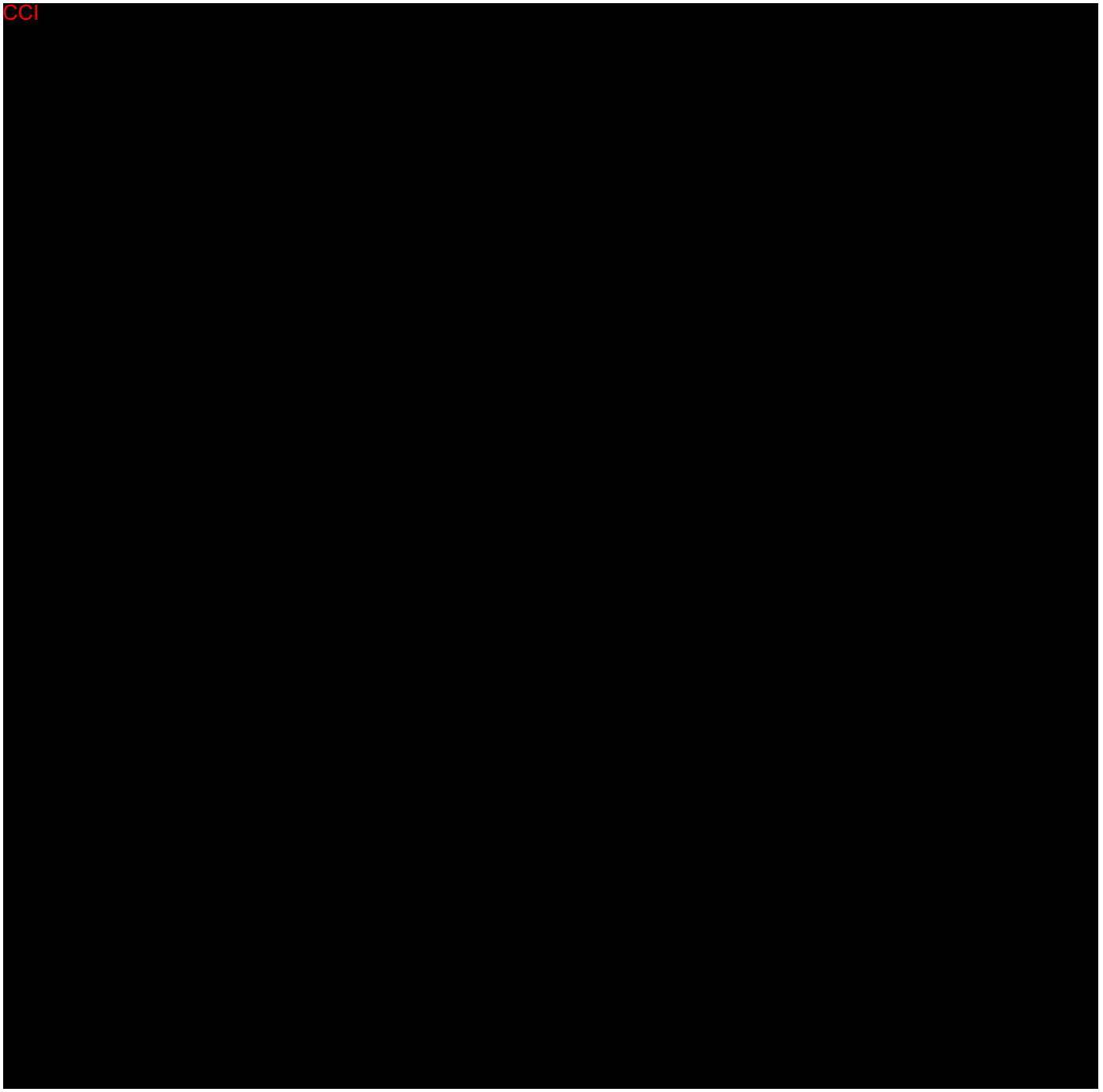

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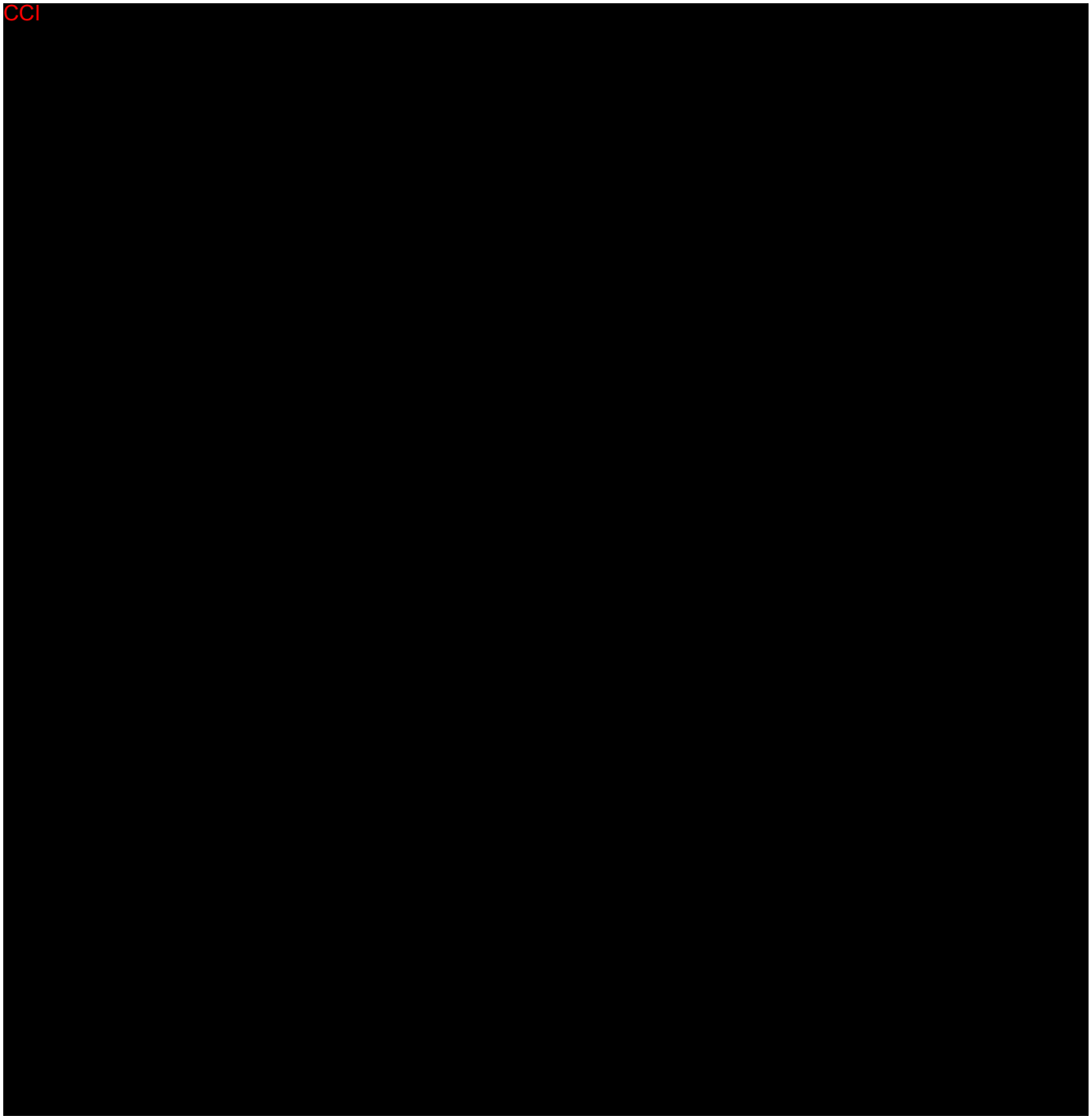

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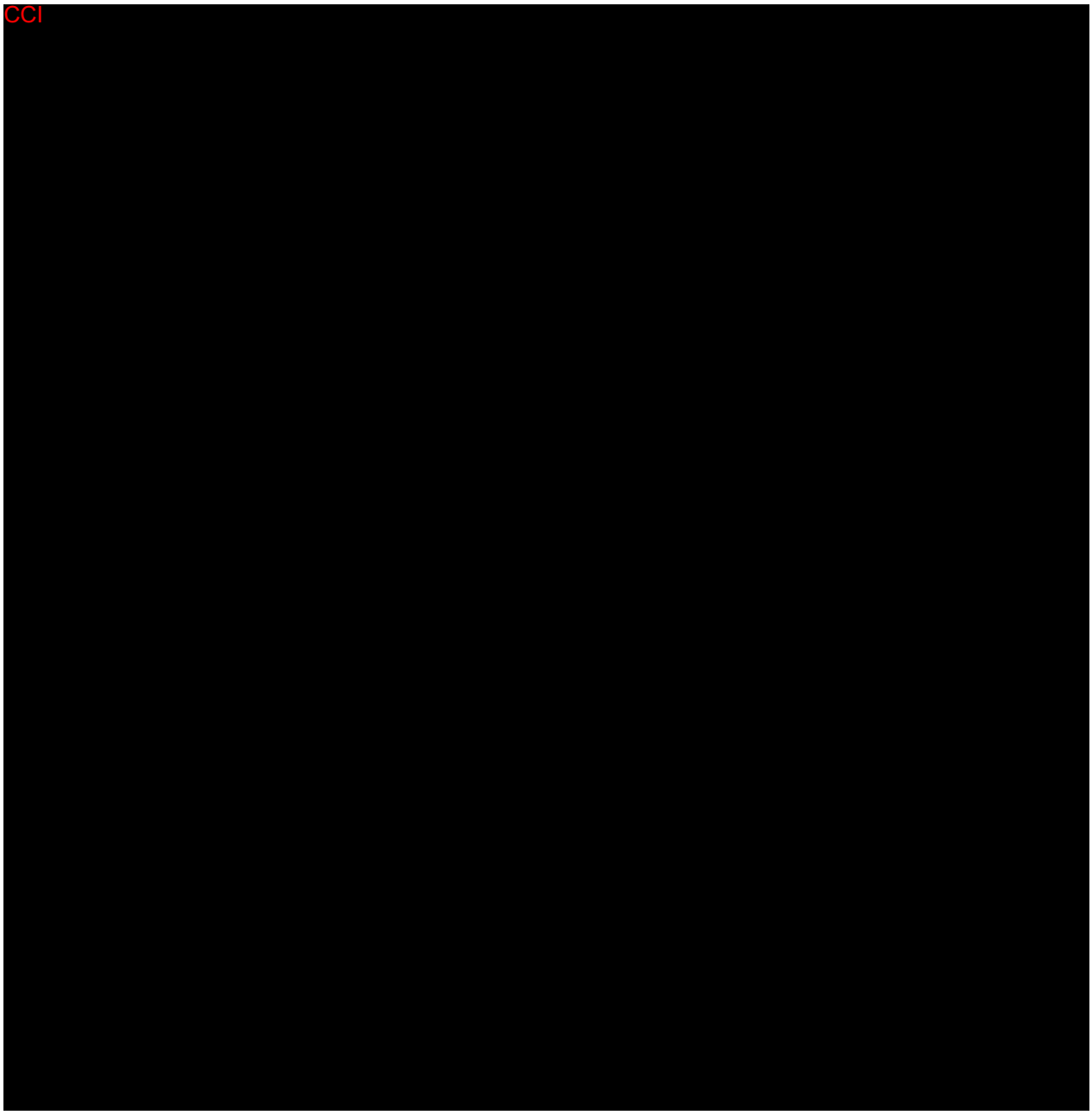

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Appendix 4 Specific Guidance for Study Conduct and Subject Safety During the Covid-19 Pandemic

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

Section 5.3 Clinical Risks/Benefits

During the COVID-19 pandemic, additional risks to participants may exist, including generic 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 infection are ineligible for study enrollment until the infection has resolved. Furthermore, potential new subjects in a high-risk population for COVID-19 (e.g., 60 years and older or with comorbidities), should be temporarily deferred until the COVID-19 risk has subsided at the location of the enrolling site, according to investigator judgement. 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 a known or suspected COVID-19 infection will immediately discontinue study drug; instructions for resuming treatment are described in Section 8.4.2. Known or suspected COVID-19 infection will also be followed as an AESI.

New Subsection to Section 7.1, Overall Study Design and Plan: Additional Measures for Subjects Amidst COVID-19 Pandemic

All investigational sites should act according to applicable 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 currently in place must be followed when evaluating eligibility of subjects to participate in the study during the COVID-19 pandemic.

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For potential subjects in a high-risk population for COVID-19 as defined by the American Academy of Dermatology (AAD)[1] (e.g., 60 years and older or with comorbidities) or local guidelines, 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 on a case by case basis.

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 all of 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, the following measures should be taken:

- Implement and document in the subject records regular communication with the subject between visits to attempt to ensure early detection of potential signs/symptoms of COVID-19 infection, and provide adequate advice, as per local medical practice and public health guidelines for suspected COVID-19 infection. Please refer to the Centers for Disease Control (CDC; https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html) and applicable local guidelines for assessment of subjects' COVID-19 status.

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- Following the same guidelines, implement and document in the subject records an additional communication to the subject just before the scheduled visit.
- Discontinue study drug administration in case of confirmed or suspected COVID-19 infection until the infection is resolved. See Section 8.4.2.
- Report any COVID-19 infection (confirmed or suspected) as an AE:
    - if any seriousness criterion is met, also report as an SAE (see Section 13.1.3).
    - if it occurs during the clinical study following the first dose of study drug administration, also report as AESI (see Section 13.1.4).
- Implement preventive infection control measures against COVID-19 infection following local guidelines (i.e. good hygiene practice, clean techniques, and use of personal protective equipment such as gloves, goggles, and masks).
- Implement preventive measures in handling all subject-facing study-mandated assessment devices and parts:
    - PEF meter device body is to be cleaned after each use, with recommended wipes, as per user manual
    - PEF meter flow sensor is to be disposed of after each set of measurements is taken
    - Approved bacterial/virus filters may be used; if used, they must be disposed of after each set of measurements is taken

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- Offer protective gloves to subjects for use while filling out assessments on a tablet and provide training on hygienic removal and disposal of gloves

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. All assessments should be conducted if possible. Specific efforts should be made to administer vaccines and collect all immunogenicity assessments at the scheduled visits. Subject-reported assessments that would usually be collected on the site tablet (e.g., ACT) may be collected remotely (e.g., completed over the phone), as available.

Taking into account the local situation and risk of exposure to COVID-19, subjects can be dosed with study drug and vaccines only if 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 an independent pharmacist or other qualified personnel.
- Vaccine injections can be performed and vaccine response samples collected at the investigational site according to the instructions in the protocol, pharmacy manual and instruction for use
  - In the event a subject cannot receive the vaccinations or provide vaccine response samples according to the Schedule of Assessments (protocol Section 10, Table 4), contact the Sponsor
- ACT (for subjects with a medical history of asthma) and PEF (for all subjects) can be performed according to the protocol.
- All other safety assessments are to be performed as per protocol: physical exam, vital signs, ECG, laboratory assessments, pregnancy test, monitoring of AEs and concomitant medications.
- All missing assessments should be appropriately documented with COVID-19 recorded as the reason, where applicable.

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

- See New Subsection to Section 9.4, Dosage Modification: **Management of Subjects with Missed Doses of Study Drug due to COVID-19 Pandemic** (below) for guidance on further dosing of subjects.
- Remote collection of data by Investigator or delegate is still to be done for the following assessments at the regularly scheduled visit time, by phone or video call:
  - AE collection
  - ACT (for subjects with a history of asthma)
  - Concomitant therapies used,
  - Moisturizer use/background topical therapy
  - UPT results (for WOCBP),
- All laboratory samples should be collected at the site and analyzed at the central lab. Only in exceptional situations 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.
- Subject-reported assessments that would usually be collected on the site tablet (e.g., ACT), may be completed over the phone, as available.

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

New Subsection to Section 9.4, Dosage Modification:
Management of Subjects with Missed Doses of Study Drug due to COVID-19 Pandemic

If a subject misses a dose of study drug due to the COVID-19 pandemic, study drug administration may be continued. Study drug can be administered provided that there is a minimum 3-week interval between injections. If a subject cannot come to a planned visit due to COVID-19, the visit should be conducted remotely according to **Additional**

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Measures for Subjects Amidst COVID-19 Pandemic. If a subject misses a dose of study drug or cannot receive the vaccinations or provide vaccine response samples according to the Schedule of Assessments (protocol Section 10, Table 4), the investigator must contact the Sponsor for further guidance.

Subjects with missed doses of study drug may still be eligible to enter the LTE study SPR.118163 after the Week 16 visit has been completed, even if done remotely. Enrolment of subjects into the LTE study must be done in accordance with the LTE study protocol. Subjects who decline or are not eligible to enter into the LTE study will complete a follow-up visit 12 weeks after the last study drug injection.

9.6.1 Permitted Concomitant Therapy

COVID-19 vaccination and study vaccinations should be administered according to current CDC guidelines for co-administration of COVID-19 vaccines with other vaccines (https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html).

17.5 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.

[1]https://assets.ctfassets.net/1ny4yoiyrqia/PicgNuD0IpYd9MSOwab47/2461e6c12cd88953632a13cd68952b71/Guidance_on_medications__10-12-20.pdf

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Appendix 9 Asthma Control Test (ACT)

This survey was designed to help you describe your asthma and how your asthma affects how you feel and what you are able to do. To complete it, please mark an ☒ in the one box that best describes your answer.

1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. During the past 4 weeks, how often have you had shortness of breath?

More than once a day	Once a day	3 to 6 times a week	Once or twice a week	Not at all
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

4 or more nights a week	2 to 3 nights a week	Once a week	Once or Twice	Not at all
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as Albuterol, Ventolin®, Proventil®, or Maxair®)?

3 or more times per day	1 or 2 times per day	2 or 3 times per week	Once a week or less	Not at all
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. How would you rate your asthma control during the past 4 weeks?

Not Controlled at all	Poorly Controlled	Somewhat Controlled	Well Controlled	Completely Controlled
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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