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Name	Reason for Signature	Date
PPD	Approver	15-Jul-2024 07:33:13 UTC

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1 CLINICAL STUDY PROTOCOL

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An Open-label Drug-Drug Interaction Study to Assess the Effects of Nemolizumab on Cytochrome P450 Substrates in Subjects with Moderate-to-Severe Atopic Dermatitis

Protocol Number:	RD.06.SPR.201593
EudraCT Number:	2020-000229-24
IND Number:	117122
Investigational Product:	Nemolizumab (CD14152)
Indication:	Moderate-to-severe atopic dermatitis
Phase:	2
Sponsor:	Galderma S.A. Avenue Gratta-Paille 2 1018 Lausanne Switzerland Galderma Research & Development, LLC 14501 North Freeway Fort Worth, TX 76177 United States
Protocol Date:	14SEPT2021
Protocol Version:	5.0

CONFIDENTIAL

PROTOCOL APPROVAL SIGNATURES

Protocol Title: An Open-label Drug-Drug Interaction Study to Assess the Effects of Nemolizumab on Cytochrome P450 Substrates in Subjects with Moderate-to-Severe Atopic Dermatitis

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Protocol Number: RD.06.SPR.201593

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

Sponsor Signatory

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2 SYNOPSIS

Title of Study:	An Open-label Drug-Drug Interaction Study to Assess the Effects of Nemolizumab on Cytochrome P450 Substrates in Subjects with Moderate-to-Severe Atopic Dermatitis
Investigational Product:	Nemolizumab (CD14152)
Protocol Number:	RD.06.SPR.201593
Investigators / Study Sites / Centers:	At least 2 study sites are planned.
Phase of Development:	Phase 2
Primary Objective:	The primary objective is to evaluate the effect of nemolizumab (CD14152) on the pharmacokinetics (PK) of a drug "cocktail" representative of Cytochrome P450 (CYP) 1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 sensitive index substrates in adult subjects with moderate-to-severe atopic dermatitis (AD).
Secondary Objective:	The secondary objective is to assess the safety of nemolizumab.
Study Endpoints:	Primary endpoint: The primary endpoint of this study is the change of PK parameters ($AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, C_{max}) in the 5 probe drugs administered concomitantly (Caffeine, Warfarin Sodium, Omeprazole, Metoprolol Tartrate, and Midazolam) derived from the plasma concentration-time profile before and after 9-weeks of nemolizumab treatment. Secondary endpoint: • Incidence and severity of adverse events (AEs), including treatment-emergent AEs (TEAEs), AEs of special interest (AESIs), and serious AEs (SAEs) CCI [redacted]
Study Design:	This is an open-label, single sequence drug-drug interaction study in approximately 25 adult subjects aged ≥ 18 years with moderate-to-severe AD. Eligible subjects must have a documented history of inadequate response to topical AD medication(s) within 6 months of screening visit. The study consists of a 2 to 4 week screening period, a 1-week predose period, a 12-week nemolizumab treatment period, and an 8-week follow-up period (12 weeks after last study drug injection). Refer to Figure 1 below for an overview of the treatment/study design. Subjects will apply a moisturizer at least once daily, beginning at screening and throughout the study. Subjects using a stable regimen of low- or medium-potency topical corticosteroid (TCS) with or without topical calcineurin inhibitor (TCI) at the screening

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	visit (i.e., ≥ 14 days prior to the baseline visit) should continue their therapy regimen in the study. 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. Subjects will receive 1 single oral dose of the selected, commercially available, CYP substrates [Caffeine100 mg, Warfarin Sodium 10 mg, Midazolam 2 mg (diluted with water, a sugar or sugar substitute may be added), Omeprazole 20 mg, and Metoprolol Tartrate 100 mg] administered 1 at a time in sequence at Baseline/Day 1 under fasted conditions for at least 10 hours. After a 1 week wash-out period, subjects will receive nemolizumab by subcutaneous (SC) injection every 4 weeks (Q4W) for a treatment period of 12 weeks. Subjects will receive a 60 mg loading dose of nemolizumab (given via 2 consecutive SC 30 mg injections) at Week 1, followed by a single 30 mg dose at Week 5 and Week 9 of the study. Subjects will receive a second oral dosing of CYP substrates, administered 1 at a time in sequence, 9 weeks after initiation of nemolizumab treatment (at Week 10) under fasted conditions for at least 10 hours at the anticipated peak serum concentration of nemolizumab (i.e., 1 week after the last nemolizumab administration). Blood samples will be collected at Baseline and at Week 10 before and after each oral dosing of CYP probe substrates up to 120 hours postdose for the determination of the complete plasma PK profile of each CYP probe. A total of 14 blood samples will be collected at each visit before and after each oral dose (i.e., predose, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 72 and 120 hours postdose) for a total of 28 samples. In addition, blood samples will be collected for the assessment of nemolizumab serum concentrations during the treatment period at Weeks 0, 5, 9, 10 and 13. Subjects who complete the Week 13 visit may be eligible to enroll into the long-term extension (LTE) study (SPR.118163). The follow-up period including 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 21 (12 weeks after their last study drug injection). If deemed to be medically necessary by the investigator (eg, to control intolerable AD signs/symptoms), rescue therapies can be prescribed to any subject at any time during the study, except during the screening period. 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 events throughout the study. The IDMC and IAC charters provide details on the IDMC and IAC, including the plan of analysis for output, the composition of the committees, procedures, roles, responsibilities, and communications.

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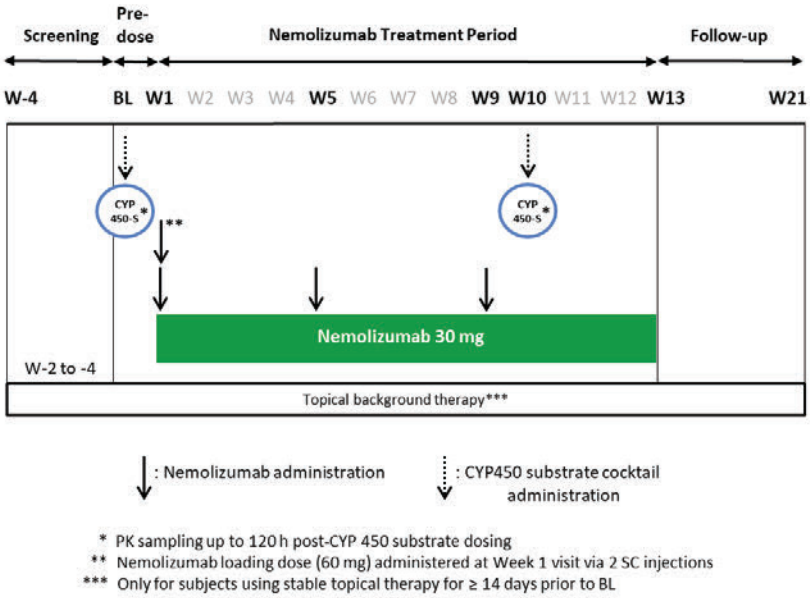
Figure 1 Study Design Schematic



Abbreviations: BL=baseline; CYP450-S=cytochrome P450 substrates; SC=subcutaneous; W=week.

Selection of Subjects:

Inclusion Criteria:

1. Subjects aged ≥ 18 years at the time of screening.
2. Chronic AD for at least 2 years before the screening visit, and confirmed according to American Academy of Dermatology Consensus Criteria (Appendix 1) at the time of the screening visit.
3. EASI score ≥ 16 (Appendix 2) at both the screening and baseline visits.
4. Investigator's Global Assessment (IGA) score ≥ 3 (based on the IGA scale ranging from 0 to 4, in which 3 is moderate and 4 is severe) (Appendix 3) at both the screening and baseline visits.
5. AD involvement ≥ 10% of body surface area (BSA) at both the screening and baseline visits.
6. Peak (maximum) pruritus numeric rating scale (PP NRS) score of at least 4.0 at both the screening and baseline visit (Appendix 4):

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7. Documented recent history (within 6 months before the screening visit) of inadequate response to topical medications (TCS with or without TCI). All subjects must demonstrate inadequate response to TCS. All subjects who have used TCI within 6 months of the screening visit must also demonstrate inadequate response to TCI. Acceptable documentation includes subject records with information on TCS (with

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or without TCI) prescription and treatment outcome, or written documentation of the conversation with the subject's treating physician, if different than the investigator. If documentation is inadequate, subjects may be rescreened after such documentation is obtained.

Inadequate response to TCS treatments (with or without TCI) is defined as:

a. Failure to achieve or maintain remission or low disease activity (equivalent to IGA ≤ 2) despite treatment with a regimen of a medium-, high-, or very high-potency TCS (Class I to III according to the US classification) (Eichenfield 2014) (with or without TCI), applied for at least 4 weeks or for the maximum duration per prescribing information;

or

b. Requirement of a long-term treatment (> 4 weeks) with a high- or very high-potency TCS (Class I to II according to the US classification) (Eichenfield 2014) (with or without TCI) to achieve or maintain remission or low disease activity (equivalent to IGA ≤ 2);

or

c. If documentation of inadequate response to topical treatments is not available, subjects with a documented recent course of systemic treatment or phototherapy for AD (within 6 months before the visit) will also be considered as inadequate responders to topical treatments.

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Note: "Double barrier methods" refers to simultaneous use of a physical barrier

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Exclusion Criteria:

Subjects will be excluded from the study if 1 or more of the following criteria are applicable:

1. Body weight < 45 kg
2. Subjects meeting 1 or more of the following criteria at screening or baseline:
   a. Had an exacerbation of asthma requiring hospitalization in the preceding 12 months.
   b. Reporting asthma that has not been well-controlled (i.e., symptoms occurring on > 2 days per week, night-time awakenings 2 or more times per week, or some interference with normal activities) during the preceding 3 months.
   c. Asthma Control Test (ACT) ≤ 19 (only for subjects with a history of asthma) (Appendix 5).
   d. Peak expiratory flow < 80% of the predicted value.

   Note: In the event that PEF is < 80% of the predicted value at the screening visit, PEF testing can be repeated once within 48 hours:

   - For subjects without a history of asthma
   - For subjects with a history of asthma but if the ACT score is >19 at screening
3. Subjects with a current medical history of chronic obstructive pulmonary disease and/or chronic bronchitis.

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4. Cutaneous infection within 1 week prior to the baseline visit, any infection requiring treatment with oral or parenteral antibiotics, antivirals, antiparasitics or antifungals within 2 weeks prior to the baseline visit, or any confirmed or suspected coronavirus disease (COVID)-19 infection within 2 weeks before the screening or baseline visit. Subjects may be rescreened once the infection has resolved. Resolution of COVID-19 infection can be confirmed by recovery assessment methods, as described in Section 8.7.

   Note: Subjects with chronic, stable use of prophylactic treatment for recurrent herpes viral infection can be included in this clinical study.

5. Requiring rescue therapy for AD during the screening period or expected to require systemic rescue therapy during the treatment period.

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

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

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

7. CCI [redacted]

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8. Previous treatment with nemolizumab.

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[redacted]

15. Consumption of any 1 or more of the following food items and/or beverages within 1 week prior to baseline:

- Grapefruit or grapefruit juice, apple or apple juice, orange or orange juice, lemons or lemon juice, limes or lime juice, cranberries or cranberry juice
- Vegetables from the mustard green family (eg, broccoli, kale)
- Charbroiled meats
- Beverages, foods, or drugs containing caffeine

	Subjects who are not willing to abstain from the consumption of these food items and/or beverages for 7 days before and 7 days after administration of CYP substrates will also be excluded. 16. Subjects with international normalized ratio (INR) > 1.5. CCI 24. Current smokers. CCI
Planned Sample Size:	Approximately 25 subjects are planned to be enrolled in this study.
Therapies:	Investigational therapy Nemolizumab (CD14152) 30 mg 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) by 2 SC injections at the Week 1 visit, followed by a single 30 mg injection Q4W at Week 5 and Week 9.

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CYP Substrates

At Baseline/Day 1 and Week 10, subjects will receive a cocktail of Midazolam 2 mg, Omeprazole 20 mg, Warfarin Sodium 10 mg, Caffeine 100 mg, and Metoprolol Tartrate 100 mg.

All drugs contained in the cocktail are listed as sensitive substrates in the US Food and Drug Administration (2017) and European Medicines Agency (2012) guidances. The probe doses were chosen based on the clinical tolerability of these drugs and the ability to reliably assess their PK parameters.

- Caffeine (CYP1A2 substrate) 100 mg was chosen as it is approximately the amount found in 1 cup of coffee.
- Warfarin Sodium (CYP2C9 substrate) 10 mg is often used as a maintenance dose.
- Omeprazole (CYP2C19 substrate) dose of 20 mg once daily is used in the treatment of symptomatic gastro-esophageal reflux disease and duodenal ulcer.
- Metoprolol Tartrate (CYP2D6 substrate) is currently used in clinic at a daily dose of 100 mg.
- Midazolam (CYP3A4/5 substrate), with an absolute bioavailability of 74.5%, a dose of 0.03 mg/kg of the intravenous formulation given orally should lead to significant systemic exposure without major sedative effect. This dose corresponds to approximately a 2 mg dose in a 70 kg subject.

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 will not be sourced by the sponsor. 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. "As needed" (PRN) use of TCS or TCI is not permitted.

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 Therapies

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 any subject at any time during the study, except during the screening period.

Permitted rescue therapies include:

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	• 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. Subjects receiving any systemic rescue during the treatment period must permanently discontinue study drug and CYP substrate administration.
Treatment Duration:	The expected duration of each subject's participation in the study is up to 25 weeks, including an up to 4-week screening period, a 1-week predose period, a 12-week treatment period, and an 8-week follow-up period (12 weeks after the last study drug injection). The 8-week follow-up period is not required for subjects who will continue in the LTE study (SPR.118163). The reduction in pruritus (as measured using the PP-NRS) after treatment with nemolizumab reflects the blockade of interleukin (IL)-31 receptor signaling. For this reason, a change in pruritus NRS can be viewed as a relevant metric for clinical efficacy in both AD and prurigo nodularis (PN) patient populations. In subjects with AD (Study SPR.114322), a highly significant effect on pruritus was observed from Week 8 of treatment (mean percent change from baseline of -61.5% in nemolizumab treated subjects compared with -23.0% in the placebo group [P <0.001]). Similarly in subjects with PN (Study SPR.115828), a highly significant effect on pruritus was also observed from Week 8 of treatment (percent change from baseline of -56.5% in nemolizumab treated subjects compared with -19.7% in the placebo group [P <0.001]). Based on these considerations, assessment of the perpetrator potential of nemolizumab on CYP enzymes following 9 weeks of nemolizumab treatment was considered appropriate.
Efficacy:	CCI [redacted]
Safety:	The following safety assessments are planned according to the schedule of assessments (Table 1): • AEs, including TEAEs, AESIs, and serious AEs • Physical examination and vital signs • Clinical laboratory tests • Electrocardiogram • Respiratory examination and assessments
Pharmacokinetics:	The following PK assessments are planned according to the schedule of assessments (Table 1): • Midazolam, Omeprazole, Warfarin Sodium, Caffeine (Jet-Alert Regular Strength Caffeine), and Metoprolol Tartrate plasma concentrations • Serum nemolizumab concentrations

	• Anti-drug antibody (ADA) serum concentrations
Statistical Methods and Planned Analyses:	The safety population will include all subjects who receive at least 1 dose of nemolizumab. All safety and efficacy data will be summarized using the safety population. The per-protocol population will consist of all subjects who complete the study without any major protocol deviations or any other event which could render the probe drugs plasma concentration-time profiles unreliable, especially (but not limited to): • vomiting and diarrhea which could render the plasma concentration-time profiles unreliable i.e., after probe drugs intake and/or before 2 times median t_{max} • other AEs which could render the plasma concentration-time profile unreliable • intake of concomitant medications which could render the plasma concentration-time profile unreliable • administration errors which could render the plasma concentration-time profile unreliable. The primary endpoint will be analyzed using the per-protocol population. For the primary endpoint analysis, a linear mixed-effect model will be used to the log-transformed PK parameters ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$ and C_{max}) of each CYP substrate, with treatment (with or without nemolizumab) as a fixed effect and subject as a random effect. Some clinically important baseline characteristics may also be included in the model as appropriate. The geometric mean ratio between treatments (substrates with [test] or without [reference] nemolizumab) after back-transformation and the corresponding 90% confidence interval (CI) will be provided. According to the calculated 90% CI for AUC, the following will be claimed: • If the lower limit of the 90% CI is > 80%, no interaction is present • If the lower limit of the 90% CI is ≤ 80% and > 50%, a weak interaction is present • If the lower limit of the 90% CI is ≤ 50% and > 20%, a moderate interaction is present • If the lower limit of the 90% CI is ≤ 20%, a strong interaction is present A weak interaction will not be considered clinically meaningful. Approximately 25 subjects will be enrolled to have 15 completed subjects in the per-protocol population to provide a reliable estimate of the magnitude and variability of the interaction.

3 TABLE OF CONTENTS

CCI

TABLE OF FIGURES

TABLE OF TABLES

4 LIST OF ABBREVIATIONS

CCI

ACT	Asthma Control Test
AD	atopic dermatitis
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BLQ	below the lower quantification limit
BSA	body surface area
COVID-19	coronavirus disease-19
CPK	creatinine phosphokinase
CRO	contract research organization
CYP	Cytochrome
CYP450	cytochrome P450
DCS	dual-chamber syringe
DDI	drug-drug interaction
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
eCRF	electronic case report form
ET	early termination
FSH	follicle-stimulating hormone
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
IGA	Investigator's Global Assessment
IgE	immunoglobulin E
IL	Interleukin
INR	international normalized ratio
IRB	Institutional Review Board
IRR	injection-related reaction
LTE	Long-Term Extension
NRS	numeric rating scale
PAS	Prurigo Activity Score
PDE	Phosphodiesterase
PEF	peak expiratory flow
PK	Pharmacokinetics
PN	prurigo nodularis
PP NRS	peak pruritus numeric rating scale
PTC	product technical complaint
Q4W	every 4 weeks
RA	receptor A
SAE	serious adverse event

SAP	statistical analysis plan
SC	Subcutaneous
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
TMF	Trial Master File
ULN	upper limit of normal
UPT	urine pregnancy test

5 INTRODUCTION

5.1 Background and Rationale

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Atopic dermatitis (AD) is a chronic inflammatory skin disease estimated to occur in 10% to 20% of the population (Weidinger 2016) and in up to 25% of children (Eichenfield 2014). The disease is characterized by pruritus (itching), xerosis (skin dryness), and eczematous lesions whose features include erythema, infiltration/papulation, oozing with crusting, excoriations, and lichenification.

Prurigo nodularis (PN) is characterized by the presence of symmetrically distributed multiple, highly pruritic, hyperkeratotic, erosive or crusted nodules and papules (Hyde 1909). This leads to an impaired quality of life and high burden due not only to the severe itch but also the chronic skin lesions and lack of treatment options (Warlich 2015).

The scratching behavior associated with pruritus is believed to exacerbate AD and PN lesions by causing mechanical damage to the skin, allowing the penetration of foreign antigens, triggering inflammatory responses, and leading to further aggravation of dermatitis and itching.

Interleukin (IL)-31 is considered to play a bridging role between itch induction and maintenance of inflammation in pruritic skin disorders. Therefore, IL-31 seems to be an important cytokine for the regulation of PN and AD and a potential therapy target. Nemolizumab, a humanized anti-human IL-31 receptor A (RA) monoclonal antibody, inhibits the binding of IL-31 to IL-31 RA and subsequent signal transduction.

Study SPR.114322 (conducted in patients with AD) and Study SPR.115828 (conducted in patients with PN) demonstrated that nemolizumab showed clinically and statistically significant differences compared with placebo for all the primary endpoints of these 2 clinical studies.

5.1.1 Justification of Study

Cytochrome P450 (CYP450) isozymes are down-regulated in response to inflammation and infection leading to altered metabolism of small molecule drugs. In patients with inflammatory diseases associated with systemic inflammation, down-regulation of CYP450 can affect drug disposition with increased exposure of small molecules. Treatment with a biologic agent with an anti-inflammatory effect may indirectly upregulate CYP450 expression by decreasing cytokine levels thereby interfering with metabolism of co-administered small molecules. Emerging data suggest that patients with AD harbor chronic systemic inflammation, similarly to chronic plaque-type psoriasis, another chronic inflammatory skin disease (Silverberg 2017).

Thus, patients with inflammatory diseases such as AD or PN undergoing biologic treatment may have changes in CYP450 activity due to combined effects of the disease and treatment (i.e., disease-drug interaction) that may affect concomitant treatments with small molecules.

Previous drug interaction studies have shown that cytokine modulators can indirectly alter the pharmacokinetics (PK) of concomitantly administered drugs that are substrates of the affected CYP450 enzymes. For example, in patients affected by rheumatoid arthritis, which is also associated with chronic systemic inflammation, intravenous infusion of tocilizumab

(IL-6 receptor blocker) was associated with a significant decrease in systemic exposure to orally administered simvastatin, a CYP3A4 substrate (Schmitt 2011). Such interaction was not observed in patients with chronic moderate-to- severe psoriasis who underwent treatment with secukinumab (IL-17A blocker) or tildrakizumab (IL23p19 blocker) (Bruin 2019; Khalilieh 2018). Likewise, blockade of IL-4/IL-13 signaling by dupilumab in patients with type 2 inflammation did not significantly affect CYP450 enzyme activity in patients with AD (Davis 2018).

Mechanisms for biologic-small drug interactions are likely to be complex and only partially understood. Evaluation of disease-drug interaction from in vitro systems is difficult, so only clinical studies are commonly used.

5.1.2 Justification of Patient Population

The proposed study design includes 3 important elements: a perpetrator (nemolizumab), victim drugs (small molecules), and a mediator (AD disease state). Because of the low immunogenicity potential of nemolizumab, immunogenicity is not considered a potential mediator of interaction. The inflammatory state is a key element; therefore, this study will be conducted in patients with moderate-to-severe AD as they have significant inflammation which would have the greatest potential for an effect on CYP450 activity. Although IL-31 is an important cytokine for the regulation of PN and AD, considering the low prevalence of PN subjects, the study will be conducted only in patients with moderate-to-severe AD not adequately controlled by topical corticosteroid (TCS).

5.1.3 Justification of Substrates

CYP450 isozymes are the major drug metabolizing enzymes in the liver. Although this class has more than 50 enzymes, 6 of them (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5) metabolize approximately 90% of all drugs (Pinto 2011). Therefore, the patients in this study will receive single oral doses of Midazolam (primarily metabolized by CYP3A4/5), Omeprazole (CYP2C19), Warfarin Sodium (CYP2C9), Caffeine (CYP1A2), and Metoprolol Tartrate (CYP2D6) before and after nemolizumab treatment.

There are different CYP450 isoform-selective probe drug cocktails that have been reported in the investigation of drug-drug interaction (DDI) in vivo. The cocktail described above for the current study was selected because no PK interaction was evidenced between probe drugs when administered in combination as a cocktail when compared to the probes administered alone (Turpault 2009). The 5 selected probe drugs are listed as index substrates by the Food and Drug Administration or European Medicines Agency, i.e., they predictably exhibit exposure change because of regulation of a given metabolic pathway and are commonly used in clinical DDI studies.

5.1.4 Justification of Study Duration

The reduction in pruritus (as measured using the peak pruritus numeric rating scale [PP NRS]) after treatment with nemolizumab reflects the blockade of IL-31 receptor signaling. Furthermore, similar effects on PP NRS was observed in both patients with AD and patients with PN:

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- In patients with AD (Study SPR.114322), approximately 90% of the maximal average improvement in peak pruritus was seen by Week 8 of treatment (mean percent change of PP NRS from baseline of -61.5% in nemolizumab treated patients compared with -23.0% in the placebo group [P <0.001]).

- Similarly, in patients with PN (SPR.115828), approximately 90% of the maximal average improvement in peak pruritus was seen by Week 8 of treatment (percent change of PP NRS from baseline of -56.5% in nemolizumab treated patients compared with -19.7% in the placebo group [P <0.001]).

Based on these findings, a change in pruritus can be viewed as a relevant metric for clinical efficacy in both patients with AD and patients with PN.

Likewise, the effect of nemolizumab on lesions in both AD and PN was demonstrated after 8 weeks of treatment. Eczema Area and Severity Index (EASI) score is used to measure the extent and severity of AD. In patients with AD (Study SPR114322), EASI scores improved in the nemolizumab 30-mg group over time beginning at Week 1. The least-square mean difference in percent change from baseline in EASI score between nemolizumab and placebo treated subjects reached a peak at Week 8 (least -square mean difference -23.4 [P = 0.003]). In PN (Study SPR.115828), a highly significant difference in IGA score and the Prurigo Activity Score (PAS) for healed lesions (P <0.001) was observed from Week 8 of treatment.

Overall, an 8-week nemolizumab treatment is considered sufficient for sustained nemolizumab efficacy for both patients with PN and patients with AD. PP NRS and EASI will be assessed to confirm the nemolizumab effect during the treatment period. Of note, CYP450 substrates are administered one week after the last injection of Nemolizumab i.e., at week 10, which is the anticipated peak serum concentration of nemolizumab. Based on these considerations, assessment of the perpetrator potential of nemolizumab on CYP enzymes after 9 weeks of nemolizumab treatment is considered appropriate.

5.2 Nonclinical Studies

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

5.3 Clinical Studies

The IB contains detailed information on clinical studies. Results of 2 completed Phase 2 clinical studies of nemolizumab in patients with AD and patients with PN and summaries of ongoing Phase 3 studies of nemolizumab in AD are included below.

Phase 2b Dose-Ranging Study in Atopic Dermatitis

This Phase 2b study was a randomized, placebo-controlled, double-blind, parallel-group, dose-ranging study to evaluate the efficacy, safety, and PK of various doses of nemolizumab in patients with moderate-to-severe AD with severe pruritus (PP NRS ≥ 7). A total of 226 adult subjects were randomized—57 subjects to placebo, 55 subjects to 10 mg nemolizumab, 57 subjects to 30 mg nemolizumab, and 57 subjects to 90 mg nemolizumab arms. Overall, all demographic and baseline disease characteristics were similar in all treatment groups. The primary efficacy endpoint was percent change from baseline in EASI to Week 24. At the Week 24 visit, a greater percent change reduction in the EASI 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 with placebo. The nemolizumab 10-mg dose showed marginally significant difference versus 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 PP NRS responder (PP NRS improvement ≥ 4) rate was statistically significant ($P < 0.05$) for all nemolizumab doses at all timepoints from Week 2.

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 group compared with the placebo group, 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 events in subjects with pre-existing asthma (1 [1.8%], 2 [3.6%], 7 [12.3%], and 10 [17.5%] in placebo; 10 mg, 30 mg, and 90 mg, respectively). Events were mostly mild (1 severe event with highest dose), manageable, and reversible under treatment with study drug. Treatment for asthma was prescribed in 16 of the 24 asthma events. Further, a higher incidence of AD exacerbation in the placebo arm compared with the nemolizumab treatment arms was observed. Local and systemic injection-related reactions (IRRs) occurred more frequently in the placebo group than in 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 1 non-related serious adverse event (SAE) with a fatal outcome (a patient aged 82 years, treated with the 10-mg dose, died because of 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 (5 [8.9%], 3 [5.5%], 5 [8.8%], and 2 [3.5%] in placebo; 10 mg, 30 mg, and 90 mg, respectively) when compared with placebo.

Incidence of ADA formation was limited. Among the 5 subjects with ADA at Week 16 and the 9 subjects with ADA at Week 24, ADA in only 2 (1%) and 4 (2.2%) subjects, respectively, was observed after nemolizumab treatment and therefore considered treatment-emergent. None of the subjects developed neutralizing ADA at any study time point.

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.

Phase 2a Safety and Efficacy Study in Prurigo Nodularis

The Phase 2a study was a randomized, placebo-controlled, double-blind, parallel-group, multicenter 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

PAS at baseline, which was slightly higher in the placebo group than in the nemolizumab group, and more subjects in the nemolizumab group had a severe Investigator Global Assessment (IGA) score compared with the placebo group.

CCI

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

The proportion of subjects with IGA success, a secondary endpoint, was higher in the nemolizumab group than in 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 PP NRS scores at other time points, Average Pruritus NRS, PP and Average Pruritus 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%) than in the nemolizumab group (2 subjects, 5.9%). The incidence of AD was higher in the nemolizumab group (3 subjects, 8.8%) than in the placebo group (0 subjects). The percentage of subjects with severe TEAEs was higher in the nemolizumab group (5 subjects, 14.7%) than in 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 serious AEs (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.

A total of 2 confirmed ADA-positive subjects were reported in the study. Only 1 subject developed positive ADA after nemolizumab treatment, which was and therefore was considered as treatment-emergent. No subjects had positive ADA that included immunoglobulin E (IgE), and no subjects developed neutralizing antibodies.

Phase 3 Pivotal Studies in Adult and Adolescent Subjects

CCI

Two ongoing Phase 3 studies (SPR.118161 and SPR.118169) are randomized, double- blind, placebo-controlled, parallel-group studies in adult and adolescent subjects with moderate-to-severe AD to evaluate the safety and efficacy of nemolizumab administered concomitantly with background topical therapy.

Subjects are given subcutaneous injections of nemolizumab (30 mg) or placebo Q4W over a 16-week treatment period, with a loading dose of 60 mg (two 30-mg injections) on Day 1/Baseline. Clinical responders at Week 16 (ie, the end of initial treatment/beginning of maintenance) are re-randomized (1:1:1) to different treatment regimens (injections Q4W or every 8 weeks [Q8W] of nemolizumab or placebo Q4W) up to Week 48 (maintenance period). The study is being conducted in Europe, the Americas, and Asia-Pacific. Subjects who complete this study may be eligible to enter the planned Phase 3 long-term extension study.

Phase 3 Long-Term Efficacy and Safety Study in Adults and Adolescents

A prospective, multicenter, long-term study (SPR.118163) to assess the safety and efficacy of nemolizumab in subjects with moderate-to-severe AD who had been previously enrolled in a nemolizumab study for AD is ongoing. The study is designed to evaluate long-term safety and efficacy of nemolizumab 30 mg Q4W when administered with background TCS, with or without TCI

5.4 Risk/Benefit Assessment

5.4.1 Nemolizumab

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

Based on the currently available information on nemolizumab and the risks associated with biologic agents in general, the potential risks of nemolizumab treatment include local and systemic injection related reaction (IRRs), newly diagnosed asthma or worsening of asthma, exacerbation of AD, and skin and non-skin infections. AESIs, which also include facial and peripheral (bilateral of the extremities) edema and elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (> 3 × upper limit of normal [ULN]) in combination with elevated bilirubin (> 2 × ULN), will be followed as a safety measure (see Section 9.4.1.1). An independent data monitoring committee (IDMC) will monitor the safety data regularly throughout the study.

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.

5.4.2 CYP Substrates

CCI

During the study, subjects will also receive CYP substrates (Caffeine 100 mg, Warfarin Sodium 10 mg, Midazolam 2 mg, Omeprazole 20 mg, and Metoprolol Tartrate 100 mg). Contraindications, risks, warnings, and precautions of CYP substrates are as outlined in their respective prescribing information. See Section 8.9.1.1.

5.5 Study Drug Profile

Nemolizumab is a humanized monoclonal modified immunoglobulin G2 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. Study drug will be supplied as a lyophilized powder for solution in a pre-filled, dual-chamber, single-use syringe (DCS). The DCS is a self-contained system that holds the lyophilized nemolizumab (CD14152) and the sterile water for injection, separately. The concentration of nemolizumab in the DCS is 61.5 mg/mL once reconstituted, with an injection volume of 0.49 mL for a 30 mg dose (for the loading dose, 2 injections of 0.49 mL)

5.6 Dose Selection Rationale

The nemolizumab PK profile was extensively assessed in subjects with AD in multiple clinical studies after single and repeated doses (Studies CIM001JP, CIM003JG, and SPR.114322). The nemolizumab PK profile was also assessed after multiple doses in subjects with PN (Study SPR.115828). Similar nemolizumab systemic exposures were observed in vivo in subjects with AD and in subjects with PN when treated with the same dose (0.5 mg/kg). The similarity in nemolizumab exposure between the subjects with PN and the subjects with AD was also confirmed using population PK modelling.

Based on the outcome of the Phase 2b dose-ranging study in adults (Study SPR.114322), 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 evaluated and was therefore selected as the final dose to be developed for the treatment of AD.

After completing the Phase 2b study, the administration of 30 mg (with 60-mg loading dose) of nemolizumab also resulted in comparable through concentrations to those observed in the Phase 2a Study CIM003JG, in which a dose of 0.5 mg/kg was administered. The results confirmed the population PK modelling approach used to support the change from body weight-based dose administered during Phase 2a study to a flat dose administered during Phase 2b in subjects with AD. The same modelling approach was used to select the final dose to be developed for the treatment of PN (30 mg with a 60-mg loading dose, Q4W), switching from body weight-based dosing administered in the Phase 2a study (Study SPR.115828). This approach is justified by the absence of disease effect on the nemolizumab PK profile, which supported the transposition of results and considerations derived from data collected or simulated in patients with AD to patients with PN.

For further details, see the nemolizumab IB.

CYP substrates (Caffeine 100 mg, Warfarin Sodium 10 mg, Midazolam 2 mg, Omeprazole 20 mg, and Metoprolol Tartrate 100 mg) are identified as sensitive substrates in the Food and Drug Administration (2017) and European Medicines Agency (2012) guidances and are responsible for the metabolism of most small molecule drugs. The doses given are commonly

used in drug interaction studies and were chosen based on the clinical tolerability of these drugs and the ability to reliably assess their PK parameters.

CCI

- Caffeine (CYP1A2 substrate) 100 mg was chosen as it is approximately the amount found in 1 cup of coffee.
- Warfarin Sodium (CYP2C9 substrate) 10 mg is often used as a maintenance dose.
- Omeprazole (CYP2C19 substrate) dose of 20 mg once daily is used in the treatment of symptomatic gastro-oesophageal reflux disease and duodenal ulcer.
- Metoprolol Tartrate (CYP2D6 substrate) is currently used in clinic at a daily dose of 100 mg.
- Midazolam (CYP3A4/5 substrate), with an absolute bioavailability of 74.5%, a dose of 0.03 mg/kg of the intravenous formulation given orally should lead to significant systemic exposure without major sedative effect. This dose corresponds to approximately a 2 mg dose in a 70 kg subject.

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 Primary Objective(s)

The primary objective is to evaluate the effect of nemolizumab (CD14152) on the PK of a drug "cocktail" representative of CYP450 (CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 sensitive index substrates) in adult subjects with moderate-to-severe AD.

6.2 Secondary Objective

The secondary objective is to assess the safety of nemolizumab.

6.3 Primary Endpoint(s)

The primary endpoint(s) include:

- Change of PK parameters ($AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$ and C_{max}) in the 5 probe drugs administered concomitantly [Caffeine (Jet-Alert Regular Strength Caffeine), Warfarin Sodium, Omeprazole Metoprolol Tartrate and Midazolam] derived from the plasma concentration-time profile before and after 9-week nemolizumab treatment.

6.4 Secondary Endpoint(s)

Secondary endpoint(s) include:

- Incidence and severity of AEs, including TEAEs, AESIs, and SAEs.

6.5 CCI

7 INVESTIGATIONAL PLAN

7.1 Overall Study Design and Plan: Description

CCI

This is an open-label, single sequence drug-drug interaction study in approximately 25 adult subjects aged ≥ 18 years with moderate-to-severe AD. Eligible subjects must have a documented history of inadequate response to topical AD medication(s) within 6 months of screening visit. At least two study sites are planned.

The study consists of a 2 to 4 week screening period, a 1-week predose period, a 12 week nemolizumab treatment period, and an 8-week follow-up period (12 weeks after last study drug injection). Refer to Figure 2 for an overview of the treatment/study design.

Subjects will apply a moisturizer at least once daily, beginning at screening and throughout the study. Subjects using a stable regimen of low- or medium-potency TCS with or without topical calcineurin inhibitor (TCI) at the screening visit (i.e., ≥ 14 days prior to the baseline visit) should continue their therapy regimen in the study. 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. See Sections 8.11.2 and 8.11.3 for further details.

Subjects will receive 1 single oral dose of selected, commercially available, CYP substrates (Caffeine (Jet-Alert Regular Strength Caffeine) 100 mg, Warfarin Sodium 10 mg, Midazolam 2 mg, Omeprazole 20 mg, and Metoprolol Tartrate 100 mg) administered 1 at a time in sequence at Baseline/Day 1 under fasted conditions for at least 10 hours.

After a 1-week wash-out period, subjects will receive nemolizumab by subcutaneous (SC) injection Q4W for a treatment period of 12 weeks. Subjects will receive a 60-mg loading dose of nemolizumab (given via 2 consecutive SC 30-mg injections) at Week 1, followed by a single 30-mg dose at Week 5 and Week 9 of the study.

Subjects will receive a second oral dosing of CYP substrates administered one at a time in sequence 9 weeks after initiation of nemolizumab treatment (at Week 10) under fasted conditions (at least 10 hours) at the anticipated peak serum concentration of nemolizumab (i.e., 1 week after the last nemolizumab administration). Blood samples will be collected at Baseline and at Week 10 before and after each oral dosing of CYP probe substrates up to 120 hours postdose for the determination of the complete plasma PK profile of each CYP probe. A total of 14 blood samples will be collected before and after each oral dose (i.e., predose, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 72 and 120 hours postdose) for a total of 28 samples. Further details provided in Sections 7.1.1 and 7.1.2.

In addition, blood samples will be collected for the assessment of nemolizumab serum concentrations during the treatment period at Weeks 0, 5 (predose), 9 (pre-dose), 10 and 13.

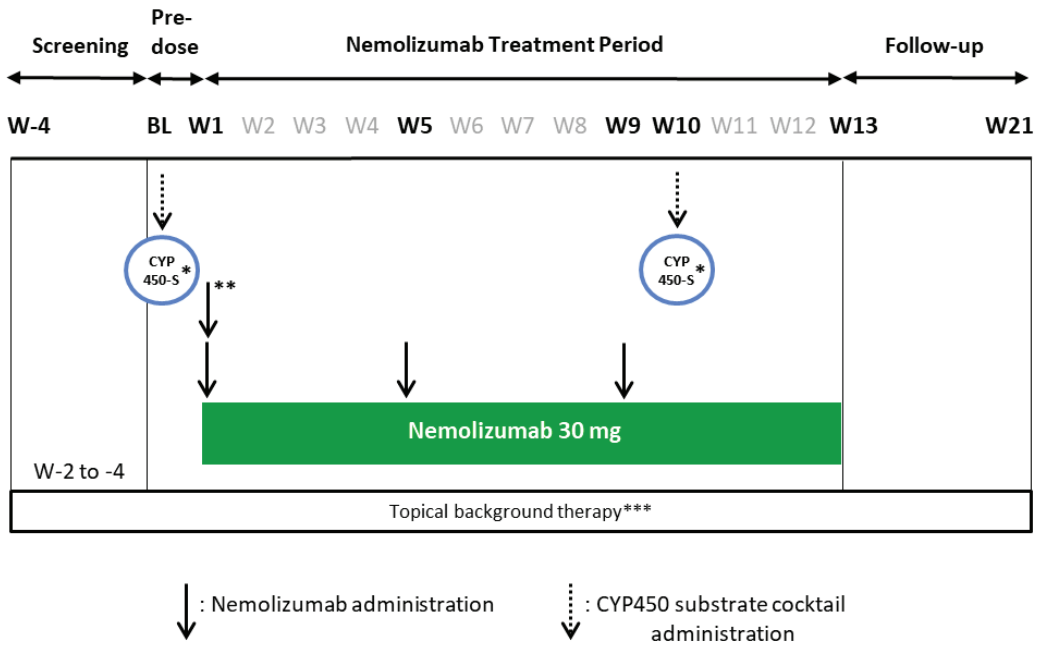
Subjects who complete the Week 13 visit may be eligible to enroll into the long-term extension (LTE) study (SPR.118163). The follow-up period including the follow-up visit is not required for subjects who participate in the LTE study. Subjects who decline or are not eligible to enter into the LTE study will complete a follow-up visit at Week 21 (12 weeks after their last study drug injection). Subjects who discontinue the study prematurely should complete an ET visit and a follow-up visit 12 weeks after the last study drug injection.

If deemed to be medically necessary by the investigator (eg, to control intolerable AD signs/symptoms), rescue therapies can be prescribed to any subject at any time during the study, except during the screening period. See Section 8.11.4 for further details.

CCI

An IDMC will review and monitor subject safety throughout the study, and an independent adjudication committee (IAC) will review all asthma-related events throughout the study. The IDMC and IAC charters will provide details on the IDMC and IAC, including the plan of analysis for output, the composition of the committees, and the procedures, roles, responsibilities, and communications.

Figure 2 Study Visit Schematic



* PK sampling up to 120 h post-CYP 450 substrate dosing
** Nemolizumab loading dose (60 mg) administered at Week 1 visit via 2 SC injections
*** Only for subjects using stable topical therapy for ≥ 14 days prior to BL

Abbreviations: BL=baseline; CYP450-S=cytochrome P450 substrate; SC=subcutaneous; W=week.

7.1.1 Restrictions

During the baseline period, subjects will be confined from the evening preceding the CYP substrates administration (Study Day -1) until the morning of Day 2 (after the 24-hour blood sample collection).

During the treatment period, subjects will be confined from the evening preceding the CYP substrates administration (Study Day 70) until the morning of Day 72 (after the 24-hour blood sample collection).

When not confined, subjects will return to the clinical facility for required study drug administration and scheduled assessments (Table 1).

For the 4 hours following the CYP substrates administration, when not involved in study activities, the subjects will remain seated or standing. They will not be allowed to lie down.

During confinement, hazardous, strenuous, or athletic activities will not be permitted.

7.1.2 Diet and Lifestyle

CCI

During confinement, subjects will not take any food or drinks (except water) for at least 10 hours (i.e., overnight) before CYP substrates administration.

A standardised low-fat dinner will be served at approximately 20:00 on Day -1 and Day 70.

The subjects will remain fasted up to 5 hours postdose.

Water will be allowed as desired, except for 1 hour before and 1 hour after investigational product administration. In order to maintain an adequate hydration, subjects will be encouraged to drink at least 180 mL of still mineral water every 2 hours for 5 hours postdose, starting at 1 hour postdose. At all other times during the study, subjects may consume water on an ad libitum basis.

On Day 1 and Day 71, standardized lunch and dinner will be served at 5 hours (approximately at 13:00) and 12 hours (approximately at 20:00) after investigational product administration, respectively. No other meals will be served during the study.

Coffee, alcohol, and other drinks and food listed in Exclusion Criteria 13 (Section 8.3) will be forbidden during confinement.

Smoking will not be allowed.

During confinement, routine ambulant daily activities will be strongly recommended.

Table 1 Schedule of Assessments

	Screening Period	Predose Period					Treatment Period									Follow-up	Early Termination Visit [a] (if applicable)	Unscheduled Visit [b] (if applicable)
Visit	Visit 1	Visit 2/ Baseline					Visit 3	Visit 4	Visit 5	Visit 6					Visit 7	Visit 8/ Final [a]		
Week	-4 to 0	0					1	5	9	10					13	21		
Day(s)	-28 to -1	-1	1	2	4	6	8	36	64	70	71	72	74	76	92	148		
Window		0	0	0	0	0	+2	±2	±2	0	0	0	0	0	+2	±5		
Inpatient or Outpatient	O	I	I	I[c]	O	O	O	O	O	I	I	I[c]	O	O	O	O		
Informed consent form	X																	
Inclusion/exclusion criteria	X		X															
Demographic data	X																	
Medical history, previous therapy	X																	(X)
EFFICACY ASSESSMENTS																		
[redacted]																		
IGA	X		X															(X)
[redacted]																		
BSA	X		X															(X)
SAFETY ASSESSMENTS [e]																		
ACT [f]	X		X					X	X						X	X	X	(X)
Respiratory exam [g]	X		X					X	X						X	X	X	(X)
PEF testing [h]	X		X					X[h]	X[h]						X	X	X	(X)
Vital signs	X		X					X	X						X	X	X	(X)
Full physical exam	X		X						X						X	X	X	(X)
Height	X																	(X)
Weight	X														X	X	X	(X)
ECG [i]	X		X												X	X	X	(X)
Contraceptive counselling	X																	(X)
Adverse event reporting [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)
Concomitant therapies/ procedures [e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)

	Screening Period	Predose Period					Treatment Period									Follow-up	Early Termination Visit [a] (if applicable)	Unscheduled Visit [b] (if applicable)
Visit	Visit 1	Visit 2/ Baseline					Visit 3	Visit 4	Visit 5	Visit 6					Visit 7	Visit 8/ Final [a]		
Week	-4 to 0	0					1	5	9	10					13	21		
Day(s)	-28 to -1	-1	1	2	4	6	8	36	64	70	71	72	74	76	92	148		
Window		0	0	0	0	0	+2	±2	±2	0	0	0	0	0	+2	±5		
LABORATORY ASSESSMENTS																		
Blood sample for CYP genotyping	X																	
Blood sample for serology (HIV, Hepatitis B and C test)	X																	(X)
Blood samples for TB test [j]	X																	(X)
Blood samples for hematology and biochemistry [k,l]	X		X [k]												X [k]	X [k]	X [k]	(X)
Urinalysis	X		X												X	X	X	(X)
Drug and alcohol testing [m]	X																	(X)
Pregnancy test [n]	Serum		U				U	U	U		U				U	U	U	(U)
FSH [o]	X																	(X)
PK, ADA ASSESSMENTS																		
Nemolizumab serum samples [p,q,r]			X					X	X		X				X			(X)
CYP substrates plasma samples [s]			X	X	X	X					X	X	X	X				(X)
INR Sampling	X		X	X	X							X	X					
ADA samples [p]							X		X						X			(X)
STUDY DRUG ADMINISTRATION																		
Study drug injection [t,u]							X [v]	X	X									(X)
CYP substrate administration [w]			X								X							(X)
CONCOMITANT THERAPY																		
Moisturizer use [x]	X----------X																	(X)
Background topical therapy use [y]	X----------X																	(X)

[redacted]

x [redacted] cci

Table 2 Schedule of PK and ADA Sample Collection

	Baseline/Week 0	Week 1	Week 5	Week 9	Week 10	Week 13
CYP probes (plasma)	Predose[a], 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 72[c] and 120[c] hours post-dose				Predose[a], 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 72[c] and 120[c] hours post-dose	
Nemolizumab (serum)	1 sample during visit		predose[b]	predose[b]	1 sample during visit	1 sample during visit
ADA (serum)		predose[b]		predose[b]		1 sample during visit

[a] Before administration of CYP probes
[b] Before Nemolizumab administration
[c] For Warfarin Sodium only

7.2 Discussion of Study Design

7.2.1 Study Design

CCI

Based on the results of the prior Phase 2b study, the fixed dose of 30 mg (with a loading dose of 60 mg) was chosen to be administered Q4W in this clinical trial. The selected dose provided the best risk/benefits ratio in adults and is expected to provide a similar efficacy and safety profile in this study. The treatment period of 12 weeks with nemolizumab is considered adequate based on the efficacy results of the Phase 2 studies in AD (Study SPR.114322 and CIM003JG).

Significant reduction in pruritus (as measured using the PP NRS) was observed after treatment with nemolizumab for 8 weeks in prior AD and PN studies (see Section 5.1); therefore, assessment of the perpetrator potential of nemolizumab on CYP enzymes after 8 weeks of nemolizumab treatment was considered appropriate.

PK sampling schedules for CYP substrates is based on the relative half-lives of each substrate.

8 SELECTION OF STUDY POPULATION

8.1 Number of Planned Subjects

Approximately 25 subjects aged ≥ 18 years are planned to be enrolled in this study.

8.2 Inclusion Criteria

To be eligible for study entry, subjects must satisfy all of the following criteria:

1. Subjects aged ≥ 18 years at the time of screening.
2. Chronic AD for at least 2 years before the screening visit, and confirmed according to American Academy of Dermatology Consensus Criteria (Appendix 1) at the time of the screening visit.
3. EASI score ≥ 16 (Appendix 2) 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) (Appendix 3) at both the screening and baseline visits.
5. AD involvement ≥ 10% of body surface area (BSA) at both the screening and baseline visits.
6. Peak (maximum) pruritus numeric rating scale (PP NRS) score of at least 4.0 (Appendix 4) at both the screening and baseline visit:

7. Documented recent history (within 6 months before the screening visit) of inadequate response to topical medications (TCS with or without TCI). All subjects must demonstrate inadequate response to TCS. All subjects who have used TCI within 6 months of the screening visit must also demonstrate inadequate response to TCI. Acceptable documentation includes subject records with information on TCS (with or without TCI) prescription and treatment outcome, or written documentation of the conversation with the subject's treating physician, if different than the investigator. If documentation is inadequate, subjects may be rescreened after such documentation is obtained.

   Inadequate response to TCS treatments (with or without TCI) is defined as:

   a. Failure to achieve or maintain remission or low disease activity (equivalent to IGA ≤ 2) despite treatment with a regimen of a medium-, high-, or very high-potency TCS (Class I to III according to the US classification) (Eichenfield 2014) (with or without TCI), applied for at least 4 weeks or for the maximum duration per prescribing information;

   or

   b. Requirement of a long-term treatment (> 4 weeks) with a high- or very high-potency TCS (Class I to II according to the US classification) (Eichenfield 2014) (with or without TCI) to achieve or maintain remission or low disease activity (equivalent to IGA ≤ 2);

   or

   c. If documentation of inadequate response to topical treatments is not available, subjects with a documented recent course of systemic treatment or phototherapy for AD (within 6 months before the visit) will also be considered as inadequate responders to topical treatments.

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8.3 Exclusion Criteria

Subjects will be excluded from the study if 1 or more of the following criteria are applicable:

1. Body weight < 45 kg
2. Subjects meeting 1 or more of the following criteria at screening or baseline:

   a. Had an exacerbation of asthma requiring hospitalization in the preceding 12 months.

   b. Reporting asthma that has not been well-controlled (i.e., symptoms occurring on > 2 days per week, night-time awakenings 2 or more times per week, or some interference with normal activities) during the preceding 3 months.

   c. Asthma Control Test (ACT) ≤ 19 (only for subjects with a history of asthma) (Appendix 5)

   d. Peak expiratory flow < 80% of the predicted value.

   Note: In the event that PEF is < 80% of the predicted value at the screening visit, PEF testing can be repeated once within 48 hours:

   - For subjects without a history of asthma
   - For subjects with a history of asthma but if the ACT score is >19 at screening

3. Subjects with a current medical history of chronic obstructive pulmonary disease and/or chronic bronchitis.
4. Cutaneous infection within 1 week prior to the baseline visit, any infection requiring treatment with oral or parenteral antibiotics, antivirals, antiparasitics or antifungals within 2 weeks prior to the baseline visit, or any confirmed or suspected coronavirus disease (COVID)-19 infection within 2 weeks before the screening or baseline visit. Subjects may be rescreened once the infection has resolved. Resolution of COVID-19 infection can be confirmed by recovery assessment methods, as described in Section 8.7.

   Note: Subjects with chronic, stable use of prophylactic treatment for recurrent herpes viral infection can be included in this clinical study.
5. Requiring rescue therapy for AD during the screening period or expected to require systemic rescue therapy during the treatment period.
6. Positive serology results (hepatitis B surface antigen [HBsAg] or hepatitis B core antibody [HBcAb], hepatitis C [HCV] antibody with positive HCV RNA or human immunodeficiency virus [HIV] antibody) at the screening visit.

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

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

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8. Previous treatment with nemolizumab.

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15. Consumption of any 1 or more of the following food items and/or beverages within 1 week prior to baseline:

    - Grapefruit or grapefruit juice, apple or apple juice, orange or orange juice, lemons or lemon juice, limes or lime juice, cranberries or cranberry juice
    - Vegetables from the mustard green family (eg, broccoli, kale)
    - Charbroiled meats
    - Beverages, foods, or drugs containing caffeine

    Subjects who are not willing to abstain from the consumption of these food items and/or beverages for 7 days before and after administration of CYP substrates will also be excluded.

16. Subjects with international normalized ratio (INR) > 1.5.

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24. Current smokers.

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8.4 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 (IGA, EASI, BSA, and PP NRS). The latter subjects are not permitted to rescreen. Subjects who are rescreened must sign a new ICF and be assigned a new subject identification number (SIN).

8.5 Removal of Subjects From Therapy or Assessments

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.

Reasons for discontinuing study drug include:

- Subject request (i.e., 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 in situ (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 8.7.

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- Pregnancy
- Use of non-permitted concurrent therapy (unless discussed and agreed upon with the Investigator and Medical Monitor)
- Use of systemic rescue therapy during the treatment period
- Treatment failure
- Investigator request
- Sponsor request, including any of the above criteria

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

When a subject discontinues study drug, he/she will be fully assessed whenever possible and followed according to ET guidelines presented in Section 8.12.1 (Early Termination Visit).

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

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

8.6 Pregnancy

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

Subjects will be instructed that known or suspected pregnancy occurring during the study should be confirmed and reported to the investigator. **If a subject becomes pregnant, the investigator must withdraw the subject from the study without delay. The subject must not receive any further injection(s) of the study drug.** See Section 9.4.1.5 for further reporting and monitoring details.

Full details will be recorded on the withdrawal page (exit form), or an SAE report will be completed if the subject has completed the study.

Pregnancy is not to be considered an AE; however, it must be monitored and reported as described in Section 9.4.1.5.

8.7 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:

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- 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 PCR test and no symptoms.
- Note: The above should be considered minimum criteria. Where the local guidelines are more stringent for infection resolution criteria, those must be applied.

See Appendix 6 for additional guidance for management of subjects and study conduct during the COVID-19 pandemic.

8.8 Investigational Product

"Study drug" refers to nemolizumab (CD14152) for purposes of this open-label study. The list of excipients are detailed in the IB.

8.8.1 Investigational Product Administration

Nemolizumab (CD14152) 30 mg will be provided as lyophilized powder for solution for subcutaneous use only after reconstitution in a pre-filled, single-use, DCS. Each DCS is designed to deliver a 30-mg dose of CD14152 after reconstitution. Subjects will receive a loading dose of nemolizumab (eg, 60 mg) by 2 SC injections at the Week 1 visit, followed by a single 30-mg injection Q4W at Week 5 and Week 9.

8.8.1.1 Investigational Product Preparation and Injection

Dosage utilizes open-label study drug (refer to Table 3).

Beginning at the Week 1 visit, the study center staff will prepare and perform all injections according to instructions provided in the current version of the pharmacy manual and the instructions for use. Good hygiene practices and clean techniques must apply at all times.

The study drug does not contain preservatives. From a microbiological point of view, the preparation of the study drug has to be done as close to subject administration as possible, and the study drug should be used immediately after reconstitution. If not used immediately, the study drug has to be used within 1 hour maximum after reconstitution stored at room temperature (below 30°C).

Injections are performed after confirming study drug is fully reconstituted, with SC injection in the subject's abdomen or alternative injection site. A different injection site should be selected for each injection. The instructions for use and the current version of the pharmacy manual

contain 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, subjects will be monitored closely for any signs or symptoms of hypersensitivity reaction before being discharged. Subjects should remain at the study center for at least 30 minutes after the first 2 injections during the study.

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8.8.2 Identity of Investigational Products

Table 3 pprovides a description and overview of open-label study drug administered under this protocol.

Table 3 Description of Nemolizumab (CD14152)

Name	Nemolizumab (CD14152)
Internal code	CD14152
Pharmaceutical form	Lyophilized powder and water for injection for solution for injection in a dual-chamber syringe.
Packaging	Single-Use Dual-chamber syringe (DCS)
Storage conditions[a]	Stored at room temperature; do not store above 30°C; protected from freezing, protected from light; until current stock is depleted. Then newer stock should be stored between 2 to 8°C (36 to 46°F); protected from freezing; protected from light, as per product label.
Dosage	60 mg loading dose of Nemolizumab (given via 2 consecutive SC 30 mg injections) at baseline.
Route[b]	Only Subcutaneous use by clinic staff after reconstitution
Dose schedule	60 mg loading dose at Week 1, followed by a single 30-mg dose Q4W at Week 5 and Week 9 of the study; refer to Table 1 for study dosing schedule.
Treatment duration	12-week nemolizumab treatment period

[a] Refrigeration is not required for current stock.
[b] All injections are performed at the clinic office by clinical site staff.

8.8.3 Investigational Products Packaging and Labeling

All packaging and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products in the local language, national regulations/guidelines, and the relevant regulatory requirements, specifying that the drug is for use in a clinical trial. Each DCS will be provided as open-label study drug, packaged in an individual carton, including a 27G 1/2" needle and a plunger rod (not assembled). Local adaptation of the kit design may be required; specific details for each country are provided in the pharmacy manual.

8.8.4 Investigational Products Management

8.8.4.1 Storage

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All DCS units must be stored together in a safe and secure area with restricted access. Upon receipt, the DCS must be removed from the shipper, kept in the outer carton until use, and stored securely at room temperature complying with the following storage conditions:

Stored at room temperature; do not store above 30°C; protected from freezing, protected from light; until current stock is depleted. Then the newer stock should be stored between 2 to 8°C (36 to 46°F); protected from freezing; protected from light, as per product label.

The storage area must be monitored daily, and if a temperature excursion occurs, the designated personnel should promptly inform the study monitor, as specified in the current version of the pharmacy manual.

8.8.4.2 Accountability

Study drug will be provided to the investigational study center and site personnel will acknowledge receipt of the study drug as defined in the current version of the pharmacy manual to confirm the shipment condition and content. Upon receipt of the investigational drug and CYP substrates, the designated site personnel will visually inspect the shipment and verify the contents and condition of the items received, and confirm receipt as described in the pharmacy manual. If a damaged shipment is received and/or a temperature excursion has been experienced, he/she will notify the sponsor/contract research organization (CRO) and follow the guidelines according to the current version of the pharmacy manual. The designated personnel will also maintain accurate records of the study drug throughout the clinical study, including the inventory delivered to the site, 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 units will be properly documented in drug accountability records. Unless a product technical complaint (PTC) is detected, the used DCS can be disposed 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 8.8.9 for PTCs.

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 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 at the close-out visit to the study center. All discrepancies must be accounted for and documented.

8.8.4.3 Dispensing and Return

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All drug preparation must be appropriately performed and documented by the designated personnel as defined in the current version of the Pharmacy Manual. Any error in the preparation of dosing solution must be reported to the study monitor promptly and be properly documented. At the end of the study, the reconciliation/return/destruction processes for all unused study drug will be conducted according to the sites' SOPs, local regulations, and best practices, as described in the current version of the pharmacy manual. If the site does not have the capability to destroy drug, then the unused study drug will be returned to the CRO/drug depot for destruction.

8.8.5 Method of Assigning Subject Numbers

Upon confirmation of eligibility for a given subject to participate in the study, a unique SIN for that subject will be assigned via an electronic data capture system.

All study treatment will occur with open-label study drug.

8.8.6 Selection of Doses in the Study

The 30-mg dose proposed for this study is supported by the results of the Nemolizumab Phase 2b study (Study SPR.114322). Refer to Section 7.2.1 for further details.

8.8.7 Dose Modification

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

Any inadvertent dose modifications should be reported to the sponsor/CRO.

In the event of a missed dose (i.e., 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 investigational study centers for all remaining visits and complete all study assessments and procedures as described in Section 7.1.

8.8.8 Treatment Compliance

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

As study drug is administered in the clinic, treatment compliance will be overseen and documented by the investigator and study staff (using the treatment records and drug accountability records). At a minimum, date, time, injector (study center staff) and site of injection should be accurately recorded to confirm that each dose of study treatment was properly administered as define in the current version of the Pharmacy Manual.

8.8.9 Product Technical Complaints

All DCS units, including plunger rod, 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 PTC as required by the Instruction for Use and the current version of the Pharmacy

Manual. In case of doubt, the DCS should not be used, and the deficiency must be reported as defined in the pharmacy manual.

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8.9 Probe Drugs - CYP Substrates

At the baseline and Week 10 visits, subjects will receive 1 single oral dose of selected, commercially available, CYP substrates [Caffeine (Jet-Alert Regular Strength Caffeine) 100 mg, Warfarin Sodium 10 mg, Midazolam 2 mg, Omeprazole 20 mg, and Metoprolol Tartrate 100 mg] administered 1 at a time in sequence at Baseline/Day 1 under fasted conditions for at least 10 hours. For further details, refer to the prescribing information.

8.9.1 Preparation and Administration of CYP Substrates

Study staff will administer the CYP substrates at the study center according to the respective commercially available prescribing information, except for Midazolam. Midazolam solution for injection will be administered orally, mixing 2 mL of solution with 120 mL of water sugar or sugar substitute may be added (Turpault 2009). A hand and mouth check will be performed to verify that the dose administered was swallowed.

8.9.1.1 Contraindications, Warnings, and Risks of CYP Substrates

Preparation and administration of CYP substrates as well as specific contraindications, warnings, and risks for each product are provided in the product information links below as follows:

1. Warfarin Sodium will be administered as one 10-mg tablet: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c0cc4511-e656-4b6d-96cd-e02e76173b9d

2. Caffeine will be provided as Jet-Alert® Regular Strength Caffeine and administered as one 100-mg tablet: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=cd7366f9-6ee9-4f1d-bfd2-3ce067f59b2d

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3. Midazolam will be administered as a 2 mL solution (2 mg/2 mL): https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=575d8bf0-7af7-427c-a231-966e2a5e070d

4. Omeprazole will be administered as 20 mg tablets: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=fe0bb8c5-9965-46f6-b675-773f2730d9f0

5. Metoprolol Tartrate will be administered as 100 mg tablets: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=6ae551f6-b6cc-46df-b3d7-eb2963295e0a

8.9.1.2 Packaging, Labeling, and Storage of CYP Substrates

Commercially available CYP substrates will be supplied to the sites and stored as described according to their respective storage and handling information:

1. Warfarin Sodium: Warfarin Sodium is manufactured by Exelon Pharmaceutical Inc. 10 mg tablets will be supplied in a bottle of 100 tablets. Store at 20ºC to 25ºC (68ºF to 77ºF). Protect from light and moisture. Do not use after the expiry date which is stated on the folding carton and the container after "Expiry date."

2. Jet-Alert Regular Strength Caffeine (Caffeine): Jet-Alert Regular Strength Caffeine is manufactured by Bell Pharmaceutical, Inc. 100 mg tablets will be supplied in bottles of 120 tablets. Jet-Alert Regular Strength Caffeine 100 mg tablets are white in color. Do not use after the expiry date which is stated on the folding carton and the container after "Expiry date". The expiry date relates to the last day of the indicated month. Store at room temperature between 59°-86°F (15°C-30°C). Protect from excessive moisture.

3. Midazolam: Midazolam is manufactured by Hikma Pharmaceuticals (West-Ward Pharmaceuticals). 2 mg/2 mL (2 mL of liquid contains 2 mg of midazolam) will be supplied as a clear and colorless solution in clear glass vials. Do not use this medicine after the expiry date which is stated on the label/carton after "EXP:". The expiry date refers to the last day of that month. Store at 20°-25°C (68°-77°F) and do not freeze.

4. Omeprazole: Omeprazole is manufactured by Sunmark; 20 mg tablets will be supplied in a blister with 14 tablets. Store at 20-25°C (68-77°C) and protect from moisture. The shelf-life of the drug is indicated on the packaging. Do not take after the expiry of the deadline date. Do not use this medicine after the expiry date which is stated on the label/carton after "EXP:".

5. Metoprolol Tartrate: Metoprolol Tartrate is manufactured by Sun Pharmaceutical Industries, Inc. 100 mg tablets will be supplied in 100-tablet bottles. The deadline date is printed on the bottle. Do not use after this date. Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F).

The storage area must be monitored daily, and if a temperature excursion occurs, the designated personnel should promptly inform the study monitor, as specified in the current version of the pharmacy manual.

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8.9.2 CYP Substrate Accountability and Compliance

CYP substrates will be provided to the investigational study center. If a damaged shipment is received and/or a temperature excursion has been experienced, site personnel will notify the sponsor/contract research organization (CRO) and follow the guidelines according to the current version of the pharmacy manual.

The designated personnel will also maintain accurate records of the CYP substrates throughout the clinical study, including the inventory delivered to the site, the use by each subject, the reconciliation of all delivered and received units, and the return of unused units as specified in the current version of the pharmacy manual. No unauthorized use is permitted.

Treatment compliance will be overseen and documented by the investigator and study staff (using the treatment records and drug accountability records). At a minimum, date, time, and administrator of drugs (study center staff) should be accurately recorded to confirm that each drug was properly administered.

The study monitor may check the study supplies, treatment records, and drug dispensation logs at each study center at any time during the study. A full drug accountability log will be maintained at the study center at all times.

8.10 Blinding

This is an open-label study.

8.11 Prior and Concomitant Therapy

Previous therapies are defined as therapies that have been stopped within the 3 months before the screening visit, unless relevant to the inclusion/exclusion criteria. Whenever possible, previous therapies for AD 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 (eg, changes in dose, formulation or application frequency) during the course of the clinical trial
- any new therapies received by the subject since the screening visit

The following 2 categories are to be considered for previous and concomitant therapies:

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

Previous and concomitant therapies for drugs/therapies or for medical/surgical procedures are to be recorded in the appropriate eCRF. Concomitant therapies are to be recorded, reviewed, and updated at each visit. At each visit, investigators should also confirm concomitant therapies for contraception. Contraceptive counseling will occur at screening.

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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, except in some cases such as dose modification for a chronic condition (see Section 8.8.7), in which case the medication will be linked to an item in the medical history.

8.11.1 Permitted Concomitant Therapy

Unless specified as prohibited therapies (see Section 8.11.5), 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, IL-10, TNFα, IFN) during chronic inflammation.

Although there is no known evidence suggesting that IL-31 affects the level or activity of CYP450 enzymes, the effect of nemolizumab (CD14152) 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 (CD14152) in subjects using other therapies that are CYP450 substrates and have a narrow therapeutic index.

8.11.2 Moisturizer

Subjects will apply a moisturizer at least once daily, and liberally as needed, to dry skin and AD lesions, beginning at screening/baseline, 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 clinic/office visits involving AD clinical assessments (eg, EASI). Whenever possible, subjects should use the same moisturizer throughout the study. Moisturizer use and any adjustments should be documented in the eCRF.

8.11.3 Background Topical 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 will not be sourced by the sponsor. 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. The prescribed use of

background therapies and any adjustments should be documented in the eCRF. “As needed” (PRN) use of TCS or TCI is not permitted.

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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 8.11.4).

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.

8.11.4 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.

Permitted rescue therapies 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 administration should be continued unless there is a safety concern according to the investigator’s judgment. Subjects receiving any systemic rescue during the treatment period must permanently discontinue study drug and CYP substrate administration.

8.11.5 Prohibited Medication/Therapy

Treatment with the following concomitant medications/therapies is prohibited during the study unless otherwise specified in Table 4. “As needed” (PRN) use of background topical therapy is not permitted.

Table 4 Prohibited Medication/Therapy

	Timeframe	
Treatment(s)[a]	**Prior to Day 1/ Baseline**	**Day 1 – Week 21**
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 (all subjects); any TCS only for subjects not using stable TCS therapy ≥14 days prior to baseline	2 weeks	Prohibited*
Topical medications, including TCS and TCI, with occlusive dressings (eg, wet wraps)	2 weeks	Prohibited
Systemic corticosteroids (corticosteroid inhalers are permitted)	4 weeks	Prohibited*
Phototherapy	4 weeks	Prohibited*
Tanning beds	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)	8 weeks or 5 half-lives (whichever is longer)	Prohibited*
Dupilumab	10 weeks	Prohibited
Live attenuated vaccine	12 weeks	Prohibited
Non-live vaccine	4 weeks	Prohibited
Medication that is a known inducer, inhibitor, or competitive substrate of one or more of the following CYP enzymes: CYP3A4/5, CYP2C19, CYP2C9, CYD2D6, and CYP1A2 [b,c]	2 weeks or 5 half-lives (whichever is longer)	Prohibited
Midazolam, Omeprazole, Warfarin Sodium, Metoprolol Tartrate	2 weeks or 5 half-lives (whichever is longer)	Prohibited
Caffeine (eg, coffee, tea, chocolate, energy drinks, soft drinks, supplements)	1 week	Prohibited
Anticoagulants or drugs that may affect INR (eg, aspirin, clopidogrel, ticlopidine, and dipyridamole)	2 weeks	Prohibited
Drugs with a sedative effect such as benzodiazepines, imidazopyridines, barbiturates, or sedative anti-depressants (eg, amitriptyline) (Stable treatment with antihistamines with sedative effect, is allowed at a dose that, based on previous experience, is well tolerated by the subject.)	1 week	Prohibited

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Treatment(s)[a]	Timeframe	
	Prior to Day 1/ Baseline	Day 1 – Week 21
Gabapentinoids (eg, gabapentin, pregabalin)	4 weeks	Prohibited
Cannabinoids	2 weeks	Prohibited
Alternative medicine for AD (eg, traditional Chinese medicine)	2 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.
Note: *Unless used as rescue therapy during the study.
[a] Subjects should not interrupt ongoing treatment with medications important for the subject's health for the sole purpose of participating in this study.
[b] https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers
[c] https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-drug-interactions_en.pdf

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 trial (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.

Immunization with non-live COVID-19 vaccine is permitted during the study. Wherever possible, it is recommended to avoid administration of COVID-19 vaccinations within 1 week of study drug dosing. A different anatomical location should be used for study drug administration and vaccine administration.

8.12 Duration of Subject Participation

The expected duration for each subject's participation in the study will be approximately 25 weeks, including up to a 4-week screening period, a 1-week predose period, a 12-week treatment period, and an 8-week follow-up period (12 weeks after the last study drug injection).

8.12.1 Early Termination Visit

Subjects who discontinue prematurely from the study should complete an ET visit and a follow-up visit (12 weeks after the last study drug injection).

8.12.2 Unscheduled Visit

The subject should be reminded to adhere to the study schedule. Unscheduled visits may include but are not limited to repeat testing for abnormal laboratory results or follow-up of AEs. PK and ADA analyses are obligatory only at unscheduled visits that are conducted for safety reasons. 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.

9 STUDY ASSESSMENTS

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Subjects will provide written informed consent, assent, and Health Insurance Portability and Accountability Act (HIPAA) authorization before any study-related procedures are performed. Upon provision of the signed ICF, 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 provided in Table 1.

At each visit, assessments/procedures should be performed in the following order, when applicable:

1. Investigator assessments (including efficacy and safety)
   - Electrocardiograms (ECGs) should be done before vital signs measurements (and blood draws) (see also Section 9.4.10)
2. Sample collections for laboratory assessments
3. Patient-reported efficacy and safety measurements
4. Sample collections for predose primary PK assessments (probe drugs)
5. Administration of probe drugs at baseline and week 10
6. Sample collections for postdose primary PK assessments (probe drugs) (at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 72 and 120 hours)
7. Sample collections for correlative PK assessments (study drug and ADA)
8. Administration of study drug injections

9.1 Efficacy Assessments

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9.1.1

CCI [redacted]

CCI [redacted]

9.1.2 [redacted]

[redacted]

9.2 [redacted]

9.2.1 [redacted]

[redacted]

9.2.2 [redacted]

[redacted]

9.3 Pharmacokinetics

9.3.1 Blood Sampling

Nemolizumab/ADA: Blood samples will be collected according to the schedule of assessments (Table 1 and Table 2), Appendix 7, and the clinical laboratory manual to determine the PK profile of nemolizumab and ADA. At each sampling time point for PK assessment, collected blood will be placed to clot at room temperature (no more than 30 minutes after collection) and then centrifuged. The serum will be collected into storage tubes.

Nemolizumab PK samples should be collected at approximately the same time of day throughout the study, to the extent possible, before study drug injection (predose samples) and at Week 10.

CYP probes: Blood samples will be collected according to the schedule of assessments (Table 1 and Table 2), Appendix 7, and the clinical laboratory manual to determine the PK profile of CYP substrates. At each sampling time point for PK assessment, blood will be collected with appropriate anticoagulant and then centrifuged. The plasma will be collected into storage tubes.

CYP substrates PK samples should be collected exactly at the scheduled sampling time points throughout the study, to the extent possible. The date and the time of each sample collection will be recorded in the eCRF, together with the time of study drug injection at the same visit (or missed injection if applicable).

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9.3.1.1 CD14152 and CYP Substrates Quantification in Blood Sampling

Concentration of nemolizumab (CD14152) in the serum will be determined by the designated CRO using a validated enzyme-linked immunosorbent assay method.

Concentration of CYP substrates in plasma will be determined up to 120 hours for Warfarin Sodium and up to 24 hours for the other substrates using a fully validated LC-MS/MS methods.

Details related to the processing of serum and plasma samples and the assessments of nemolizumab and CYP substrates will be described in the bioanalytical plans, which will be finalized before the beginning of sample analysis. Results will be described in a bioanalytical report for nemolizumab and for each CYP substrate probe, which will be included as an appendix in the final clinical study report.

9.3.2 Pharmacokinetic Parameters

No PK parameter for nemolizumab (CD14152) will be calculated. Only trough concentrations will be reported as proof of exposure.

The following individual PK parameters will be measured and/or calculated for each CYP substrates with a Non-Compartmental Analysis (NCA), using a suitable validated software (actual software used and version will be stated in the final report):

C_{max}	Observed maximum plasma concentration
t_{max}	Time to achieve C_{max}
λ_z	Terminal elimination rate constant, calculated, if feasible, by log-linear regression using at least 3 points excluding C_{max}
$t_{1/2}$	Half-life, calculated, if feasible, as $\ln 2/\lambda_z$
$AUC_{0\text{-last}}$	Area under the concentration-time curve from administration to the last observed concentration-time t, calculated with the linear trapezoidal method
$AUC_{0\text{-inf}}$	Area under the concentration-time curve extrapolated to infinity, calculated, if feasible, as $AUC_{0\text{-last}} + C_{last}/\lambda_z$, where C_{last} is the last measurable drug concentration
$\%AUC_{extra}$	Percentage of the residual area (C_{last}/λ_z) extrapolated to infinity in relation to the total $AUC_{0\text{-inf}}$, calculated, if feasible, as $100\times[(C_{last}/\lambda_z)/AUC_{0\text{-inf}}]$
Cl	Systemic clearance, calculated, if feasible, as $DOSE/AUC_{0\text{-inf}}$

The sampling schedule is considered adequate if the ratio $AUC_{0\text{-last}}/AUC_{0\text{-inf}}$ equals or exceeds a factor of 0.8 (i.e., if $\%AUC_{extra}$ is < 20%) for more than 80% of the individual PK profiles. This assures that the primary variable $AUC_{0\text{-t}}$ covers a sufficient percentage of the theoretical total extent of exposure. If $\%AUC_{extra}$ is > 20%, $AUC_{0\text{-inf}}$ will not be reported.

The quality of log-linear regression (and, consequently, the reliability of the extrapolated PK parameters) should be demonstrated by a determination coefficient $R^2 \geq 0.8$. Individual extrapolated parameters (i.e., λ_z, $t_{1/2}$, $AUC_{0\text{-inf}}$, $\%AUC_{extra}$ and Cl), when considered unreliable, will not be reported.

The calculations of PK parameters will be based on the actual sampling times.

For the calculation of the PK parameters, concentrations below the lower quantification limit (BLQ) will be treated as follows:

- BLQ plasma concentrations occurring before the first measurable concentration will be treated as zero;
- BLQ plasma concentrations occurring after the first measurable concentration will be omitted from the calculation of PK parameters.

9.3.3 Immunogenicity

According to the schedule of assessments (Table 1) and the clinical laboratory manual, blood samples will be collected to assess anti-nemolizumab ADA, which will be determined at these time points by the designated CRO using a validated enzyme-linked immunosorbent assay screening assay. The serum concentration will be assessed using a multi-tiered approach.

Details related to the processing of serum samples and the assessments of ADA will be described in the bioanalytical plan, which will be finalized before the beginning of sample analysis. Results will be described in the bioanalytical report, which will be included as an appendix in the final clinical study report.

If serum circulating ADA is detected, presence will be confirmed and characterized (eg, for neutralizing potential) using a validated assay. Incidence of positive ADA results will be summarized (absolute occurrence and percent of subjects).

9.4 Safety Assessments

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

9.4.1 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 pre-existing 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.

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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 9.4.1.5.
- 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.

At each post-enrollment visit, the investigator (or sub-investigator) will question the subject about AEs using open non-persuasive questions 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”) of the eCRF 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.

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

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

Assessment of Severity

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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.

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 and/or study procedure (eg, injection, background topical 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 (i.e., 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, background topical 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
- 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

AEs 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])

9.4.1.1 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 9.4.1.4 for reporting procedures. An AESI can be either serious or non-serious.

Based on the potential risks of nemolizumab (CD14152) and the risks associated with biologics (and their biosimilar equivalents) in general (i.e., class effects), the following AEs will be considered AESIs:

- Injection Related Reaction (IRRs)
  - Anaphylactic reactions
  - Acute allergic reactions requiring treatment
  - Severe injection site reaction (i.e., lasting > 24 hours)
- Newly diagnosed asthma or worsening of asthma

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- 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.
  - Peak expiratory flow (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.
  - 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)

9.4.1.2 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, i.e., 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]. 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.

9.4.1.3 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 CCI Safety and Pharmacovigilance group of an SAE report, by email or fax:

   CCI [redacted]
   CCI [redacted]

   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.

   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 CCI Safety and Pharmacovigilance group (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 (i.e., the CRO) will comply with country-specific regulatory requirements relating to safety reporting to regulatory authorities, institutional review board (IRB)/independent ethics committee (IEC) and investigators. Investigator safety reports are prepared for SUSARs according to local regulatory requirements, and are forwarded to investigators as necessary.

   An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (eg, summary or listing of SAEs) from the sponsor or its delegate (i.e., the CRO) will file it accordingly (i.e., 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.

9.4.1.4 Procedure for Reporting Adverse Events 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 CCI Safety and Pharmacovigilance group of an AESI report, by email. Refer to Section 9.4.1.3.

   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 eCRF, at that time.

3. Send any relevant information or medical records (eg, laboratory test results) to the CCI Safety and Pharmacovigilance group 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 report 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 report, if appropriate.

9.4.1.5 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 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 along with the exit form within 24 hours of receipt of the information, to the CCI Safety and Pharmacovigilance group. Refer to Section 9.4.1.3. 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 to the CCI Safety and Pharmacovigilance group within 24 hours of receipt of the information. If the subject can no longer be reached (i.e., lost to follow-up), documentation of the non-response/contact with 2 phone calls and a letter (certified with return receipt) is required.

5. At the outcome of the pregnancy, complete as fully as possible the Pregnancy Surveillance Form – Part II: Course and Outcome of Pregnancy. Print and send the form by email to the CCI Safety and Pharmacovigilance group within 24 hours of receipt of the information.

6. If the pregnancy leads to an abortion (i.e., voluntary abortion, spontaneous abortion, or therapeutic abortion), in utero death, or congenital anomaly, follow the procedure for declaration of ~~reporting~~ an SAE (see Section 9.4.1.3).

9.4.1.6 Unexpected Adverse Reactions

Unexpected Adverse Reaction Definition

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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).

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

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

9.4.2 Clinical Laboratory Evaluation

The hematology laboratory analyses, clinical chemistry laboratory analyses, and urinalyses will be performed by the sites local laboratory while the CYP metabolism genotyping we be done by a designated lab.

Reference ranges will be supplied by 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 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 effect the safety of the subject or the interpretation of the trial results. This should occur 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 (i.e., 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 scheduled 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 non-fasting 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).

See Sections 9.4.3, 9.4.4, and 9.4.5 for details regarding pregnancy testing, virology, and TB testing samples, respectively. (See Section 9.3, Appendix 7, and the clinical laboratory manual for details regarding PK and ADA sampling.)

The following laboratory safety tests will be performed as specified in Table 1.

9.4.2.1 CYP Metabolism Genotyping

Poor metabolizers of CYP2C9, CYP2C19, or CYP2D6 will be identified based on genotype.

9.4.2.2 Hematology

Testing will include hemoglobin, hematocrit, white blood cell count (with differential including eosinophils), red blood cell count, platelet count, mean cell volume, and INR.

9.4.2.3 Clinical Chemistry

Testing will include creatinine, AST, ALT, 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, and creatinine phosphokinase (CPK). CPK isoenzyme test will be performed only if CPK is elevated to > 2.5 × ULN. The investigator should also contact the Medical Monitor in such situations.

The postmenopausal status is defined as no menses for 12 consecutive months, and will be confirmed with a high follicle-stimulating hormone (FSH) level in the postmenopausal range at the screening visit.

9.4.2.4 Urinalysis

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

A 12-panel drug test at screening will include: marijuana, opiates, PCP, cocaine, amphetamines, benzodiazepines, barbiturates, methadone, methaqualone, propoxyphene, ecstasy, and oxycodone.

9.4.3 Pregnancy Testing

A serum pregnancy test is required at screening for women of childbearing potential (WOCBP). 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.

UPTs 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. If the result of a UPT is positive, it must be confirmed with a serum pregnancy test, and no study drug 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.

9.4.4 Virology

Virology including HBsAg, HBcAb, hepatitis C, human immunodeficiency virus (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.

9.4.5 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. Subjects will be screened for active or latent TB before entry into this study.

9.4.5.1 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 (Centers for Disease Control and Prevention [CDCP] guidelines 2010), such as QuantiFERON-TB Gold, but is asymptomatic and has no evidence of active infection on screening pathology or radiographic tests. Such individuals do not pass the

disease to others and should commence a course of prophylactic antimycobacterial treatment to eliminate the infection and commit to completing the course of treatment.

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9.4.5.2 Tuberculosis Screening

Ideally, as part of the medical history, the subject should be asked if they have presented with active or latent TB in the past and whether they have received a bacillus Calmette-Guérin (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. If confirmed indeterminate, the subject should then be managed as though he/she has a positive test result.

9.4.6 Vital Signs

Vital signs will be evaluated at the screening visit and at subsequent visits according to Table 1.

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

9.4.7 Height and Weight

Height and weight will be measured according to Table 1.

9.4.8 Physical Examination

A complete physical examination will include assessments of the head, ears, eyes, nose, throat, neck (including thyroid), skin/integumentary system, cardiovascular system, respiratory system (see Section 9.4.9 for additional respiratory assessments), gastrointestinal system, musculoskeletal system, lymph nodes, nervous system, and extremities.

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.

9.4.9 Respiratory Assessments

At screening/baseline, the investigator should specifically question all subjects about any medical history of asthma and their respiratory health (eg, wheezing, coughing, allergies, 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.

9.4.9.1 Asthma Control Test

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Subjects with a medical history of asthma will take the ACT at designated visits according to Table 1.

Subjects with a new (de novo) diagnosis of asthma will take the ACT beginning at the visit the diagnosis was first confirmed and at designated visits thereafter. The ACT should be completed before questioning and physical examination by the investigator. 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. See Appendix 5.

9.4.9.2 Respiratory Examination

A respiratory examination will be performed for all subjects at designated visits according to Table 1.

The ACT will aid the investigator's questioning of subjects with a medical history of asthma and should be completed before the clinical questioning. At all designated visits, all subjects will be asked non-leading questions about any respiratory changes. The investigator or designee will then perform a respiratory examination.

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) will be referred to a respiratory specialist.

9.4.9.3 Peak Expiratory Flow

PEF measurements will be performed for all subjects at screening, baseline, Week 13, and follow-up visits. For subjects reporting a medical history of asthma, PEF measurements will be conducted at additional designated visits, including Weeks 5 and 9 (see Table 1).

Subjects with a new (de novo) diagnosis of asthma will undergo PEF testing at all designated visits after the diagnosis is first made.

PEF testing during the clinical study will be performed under the supervision of qualified study personnel. PEF 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 (Quanjer 1993; Polgar 1979).

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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9.4.9.4 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 because 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 assessments (eg, examination, PEF) suggests a decline in the subject's respiratory health.

9.4.10 Electrocardiogram

A 12-lead ECG will be performed and read at the site according to visits and time points specified in Table 1. ECGs will be performed in the supine position 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.

9.5 Independent Data Monitoring Committee

An IDMC will review and monitor subject safety throughout the study, and an IAC will review all asthma-related events throughout the study. The IDMC and IAC charters will provide details on the IDMC and IAC, including the plan of analysis for output, the composition of the committees, and the procedures, roles, responsibilities, and communications.

10 STATISTICAL METHODS

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A statistical analysis plan (SAP) will be developed as a separate document. The SAP will contain detailed and technical descriptions of specific data conventions, calculations, and statistical procedures for executing the analyses that are specified in the sections of the clinical study protocol below.

All PK, efficacy, and safety data will be summarized descriptively. The categorical variables will be summarized by frequency and percentage for each response category. The continuous variables will be summarized descriptively using mean, median, minimum, maximum, and standard deviations.

10.1 Analysis Populations

The safety population will include all subjects who receive at least 1 dose of nemolizumab. All safety and efficacy data will be summarized using the safety population.

The per-protocol population will consist of all subjects who complete the study without any major protocol deviations or any other event which could render the probe drugs plasma concentration-time profiles unreliable, especially (but not limited to):

- vomiting and diarrhea which could render the plasma concentration-time profiles unreliable i.e., after probe drugs intake and/or before 2 times median t_{max}
- other AEs which could render the plasma concentration-time profile unreliable
- intake of concomitant medications which could render the plasma concentration-time profile unreliable
- administration errors which could render the plasma concentration-time profile unreliable

The samples from the subjects excluded from the per-protocol population should still be assayed and the results will be listed.

The primary endpoint will be analysed using the per-protocol population.

10.2 Demographic and Other Baseline Characteristics

Subject disposition, demographics, baseline characteristics, previous therapies and concomitant therapies, and medical history will be summarized descriptively on the safety population and per-protocol populations.

10.3 Pharmacokinetic Analysis

The plasma concentrations and PK parameters for the 5 selected CYP substrates and serum nemolizumab concentrations will be summarized descriptively on the per-protocol and safety populations and fully described in the SAP.

The primary endpoints are the PK parameters ($AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max}) in the 5 probe drugs (Caffeine, Warfarin Sodium, Omeprazole, Metoprolol Tartrate and Midazolam) derived from the plasma concentration-time profile before and after 9-week nemolizumab treatment.

For the primary endpoint analysis, a linear mixed-effect model will be used to the log-transformed PK parameters ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$ and C_{max}) of each CYP substrate, with treatment (with or without nemolizumab) as a fixed effect and subject as a random effect. Some clinically important baseline characteristics may also be included in the model as appropriate. The geometric mean ratio between treatments (substrates with [test] or without [reference] nemolizumab) after back-transformation and the corresponding 90% CI will be provided.

Subjects can be excluded from the analysis of each CYP substrate on the basis of pharmacokinetic reasons only for:

- lack of any measurable concentrations or only very low plasma concentrations of the probe drug at visit 2. A subject is considered to have very low plasma concentrations if his/her AUC is less than 5% of the geometric mean AUC of the probe drug at visit 2 (which should be calculated without inclusion of data from the outlying subject)
- non-zero baseline concentrations > 5% of C_{max}

Subjects should not be excluded from the statistical test if their individual $AUC_{0\text{-}t}$ covers less than 80% of their individual $AUC_{0\text{-}inf}$ (see Section 9.3.2)

According to the calculated 90% CI for AUC, the following will be claimed:

- If the lower limit of the 90% CI is > 80%, no interaction is present
- If the lower limit of the 90% CI is ≤ 80% and > 50%, a weak interaction is present
- If the lower limit of the 90% CI is ≤ 50% and > 20%, a moderate interaction is present
- If the lower limit of the 90% CI is ≤ 20%, a strong interaction is present

A weak interaction will not be considered clinically meaningful.

10.4 Efficacy Variables

For each visit, the maximum itch intensity (PP NRS) will be calculated based on the average of daily PP NRS during 7 days immediately preceding that visit. A minimum of 4 daily scores out of the 7 days immediately preceding that visit are required for this calculation. The PP NRS and their percent change from baseline will be summarized descriptively by visit.

The EASI score and percent change from baseline will be summarized by visit.

10.5 Safety Variables

All safety analyses will be based on the safety population.

Further details of safety analyses, including extent of exposure, will be provided in the SAP.

10.5.1 Treatment-Emergent Adverse Events

A TEAE is defined as an AE that occurs on or after the first date of study drug(s) administration until the date of last study visit. TEAEs will be tabulated in frequency tables by system organ class and preferred term based on the Medical Dictionary for Regulatory Activities (MedDRA).

Additional summary tables will be provided for SAEs, AEs related to the study drug(s), AESIs, and AEs leading to treatment discontinuation and study withdrawal. For a given AE, a subject will be counted once even if he/she has experienced multiple episodes of that particular AE.

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In addition, AEs with an onset before the first dosing of study drug will be listed.

10.5.2 Clinical Laboratory

Laboratory data (absolute values and change from baseline) will be summarized by visit. Shift tables for each visit will be summarized for each laboratory parameter. Reference ranges will be provided in the laboratory manual.

10.5.3 Vital Signs

All vital signs and weight data (absolute values and change from baseline) will be summarized descriptively by visit. In addition, shift from baseline will be summarized by visit.

10.5.4 Other Safety Data

Other safety data including PEF, ACT, ECG, pregnancy test, ADA will be listed. Summary tables may be provided where appropriate.

10.6 Interim Analyses

Not applicable.

10.7 Handling of Missing Data

No missing imputation will be used in this study.

10.8 Determination of Sample Size

Approximately 25 subjects will be enrolled to have 15 completed subjects in the per-protocol population to provide a reliable estimate of the magnitude and variability of the interaction.

10.9 Protocol Deviations

All protocol deviations will be identified, evaluated, and closed before the database lock and will be described in the Protocol Deviation Management Plan and clinical study report.

11 QUALITY ASSURANCE AND QUALITY CONTROL

11.1 Audit and Inspection

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Study centers and study documentation may be subject to Quality Assurance audit during the course of the study by the sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

11.2 Monitoring

Data for each subject will be recorded on eCRFs. Data collection must be completed for each subject who signs an ICF and is administered study drug.

In accordance with current GCP and ICH guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable.

The investigator must permit the monitor, the IEC/IRB, the sponsor's internal auditors, and representatives from regulatory authorities direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the eCRFs.

11.3 Personnel Training

Study monitors and all relevant personnel will be trained before study initiation on the condition to be treated, the standard operating procedures to be used in this clinical study, the protocol, and all study-specific procedures. Team organization, communication, and operational issues will also be discussed and agreed upon.

Investigators, evaluators, study coordinators, pharmacists, and other applicable personnel are recommended to attend an investigator meeting. During the meeting, participants will be trained on the protocol, ICH/GCP, study-specific procedures (including efficacy assessment scales and instruction for use of the study drug), and eCRF completion.

All personnel involved in the study conduct will receive training before participating in any procedure and/or evaluation. Each study center will have a training record as part of the site file and TMF.

11.4 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 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 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, or remotely if applicable. 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 electronic data capture system will be recorded in the audit trail.

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11.5 Clinical Study Conduct

With the exception of avoiding an immediate risk to a subject, the investigator should not deviate from the clinical study protocol or implement any changes without written approval from the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of a protocol amendment.

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

11.6 Amendments

The sponsor may modify the clinical study protocol at any time for ethical, medical, or scientific reasons. Any amendments will be handled according to applicable local regulations.

The sponsor does not have to notify non-substantial amendments to the competent authorities or IRB/IEC. However, non-substantial amendments will be recorded and detailed in subsequent submissions (eg, in the subsequent notification of a substantial amendment).

11.7 Quality Management and Risk Evaluation

Details will be provided in a separate Integrated Quality Risk Management Plan.

12 ETHICS

12.1 Independent Ethics Committee or Institutional Review Board

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the subjects, and any other relevant study documentation will be submitted to the appropriate IEC/IRB. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the study drug is released to the investigator. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study such as amendments to the protocol, the ICF or other study documentation. The written approval of the IEC/IRB together with the approved ICF must be filed in the study files.

The investigator will promptly report to the IEC/IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The investigator will submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

12.2 Regulatory Authorities

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

12.3 Ethical Conduct of the Study

The investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines, and the applicable national and local laws and regulatory requirements.

12.4 Informed Consent

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to GCP guidelines.

The investigator is responsible for ensuring that no subject undergoes any study-related examination or activity before that subject has given written informed consent to participate in the study.

The investigator or designated personnel will inform the subject of the objectives, methods, anticipated benefits and potential risks and inconveniences of the study. The subject should be given every opportunity to ask for clarification of any points she/he does not understand and, if necessary, ask for more information. At the end of the interview, the subject will be given ample time to consider the study. Subjects will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the investigator in the investigator's study file. A signed and dated copy of the subject ICF will be provided to the subject or his/her authorized representative.

It should be emphasized that the subject may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the study, a new ICF will be approved by the IEC(s)/IRB(s) (and regulatory authorities, if required). The study subjects will be informed about this new information and reconsent will be obtained.

12.5 Subject Confidentiality

Monitors, auditors, and other authorized agents of the sponsor and/or its designee, the IEC(s)/IRB(s) approving this research, and the US Food and Drug Administration, as well as that of any other applicable agency(ies), will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any

presentations of the results of this study or in publications, the subjects' identities will remain confidential.

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All personal data collected and processed for the purposes of this study should be managed by the investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the applicable national and/or local laws and regulations (HIPAA for the United States) on personal data protection.

12.6 Financing and Insurance

Financing and insurance of this study will be outlined in a separate agreement between the designated CRO and the sponsor.

13 REPORTING AND PUBLICATION, INCLUDING ARCHIVING

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study (end of study defined as the date of the last visit of the last subject), all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file. This file will be available for inspection by the sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval in an ICH region or for at least 2 years since the discontinuation of clinical development of the investigational product. It is the responsibility of the sponsor to inform the study center when these documents no longer need to be retained. The investigator must contact the sponsor before destroying any study-related documentation. In addition, all subject medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

The sponsor must review and approve any results of the study or abstracts for professional meetings prepared by the investigator(s). Published data must not compromise the objectives of the study. Data from individual study centers in multicenter studies must not be published separately.

14 REFERENCES

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15 APPENDICES

Appendix 1: American Academy of Dermatology Consensus Criteria for AD Diagnosis

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Features to be considered in diagnosis of patients with atopic dermatitis:

ESSENTIAL FEATURES; must be present:

- Pruritus
- Eczema (acute, subacute, chronic):
  - Typical morphology and age-specific patterns*
  - Chronic or relapsing history

*_Patterns include_:

1) *Facial, neck, and extensor involvement in infants and children;*
2) *Current or prior flexural lesions in any age group;*
3) *Sparing of groin and axillary regions.*

IMPORTANT FEATURES; seen in most cases, adding support to the diagnosis:

- Early age of onset
- Atopy
  - Personal and/or family history
  - Immunoglobulin (IgE) reactivity
- Xerosis

ASSOCIATED FEATURES; these clinical associations help to suggest the diagnosis of AD but are too non-specific to be used for defining or detecting AD for research and epidemiologic studies:

- Atypical vascular responses (eg, facial pallor, white dermographism, delayed blanch response)
- Keratosis pilaris / pityriasis alba / hyperlinear palms / ichthyosis
- Ocular / periorbital changes
- Other regional findings (eg, perioral changes / periauricular lesions)
- Perifollicular accentuation / lichenification / prurigo lesions

EXCLUSIONARY CONDITIONS; it should be noted that a diagnosis of AD depends on excluding conditions such as:

- Scabies
- Seborrheic dermatitis
- Contact dermatitis (irritant or allergic)
- Ichthyoses
- Cutaneous T-cell lymphoma
- Psoriasis
- Photosensitivity dermatoses
- Immune deficiency diseases
- Erythroderma of other causes

Source: Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol*. 2014;71(1):116-32.

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Appendix 6: Specific Guidance for Study Conduct and Subject Safety during the COVID-19 Pandemic.

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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 5.4.1 Risk/Benefit Assessment

During the COVID-19 pandemic, additional risks to participants may exist, including general environmental risks (e.g., being outside the home, possible contact with unsanitized surfaces) and study-related activities (e.g., interaction with study staff). Potential new subjects with known or suspected COVID-19 infection are ineligible for study enrolment 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 8.7 and below in Guidance for Existing Subjects. 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.

For potential subjects in a high-risk population for COVID-19 as defined by the American Academy of Dermatology (AAD) (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.

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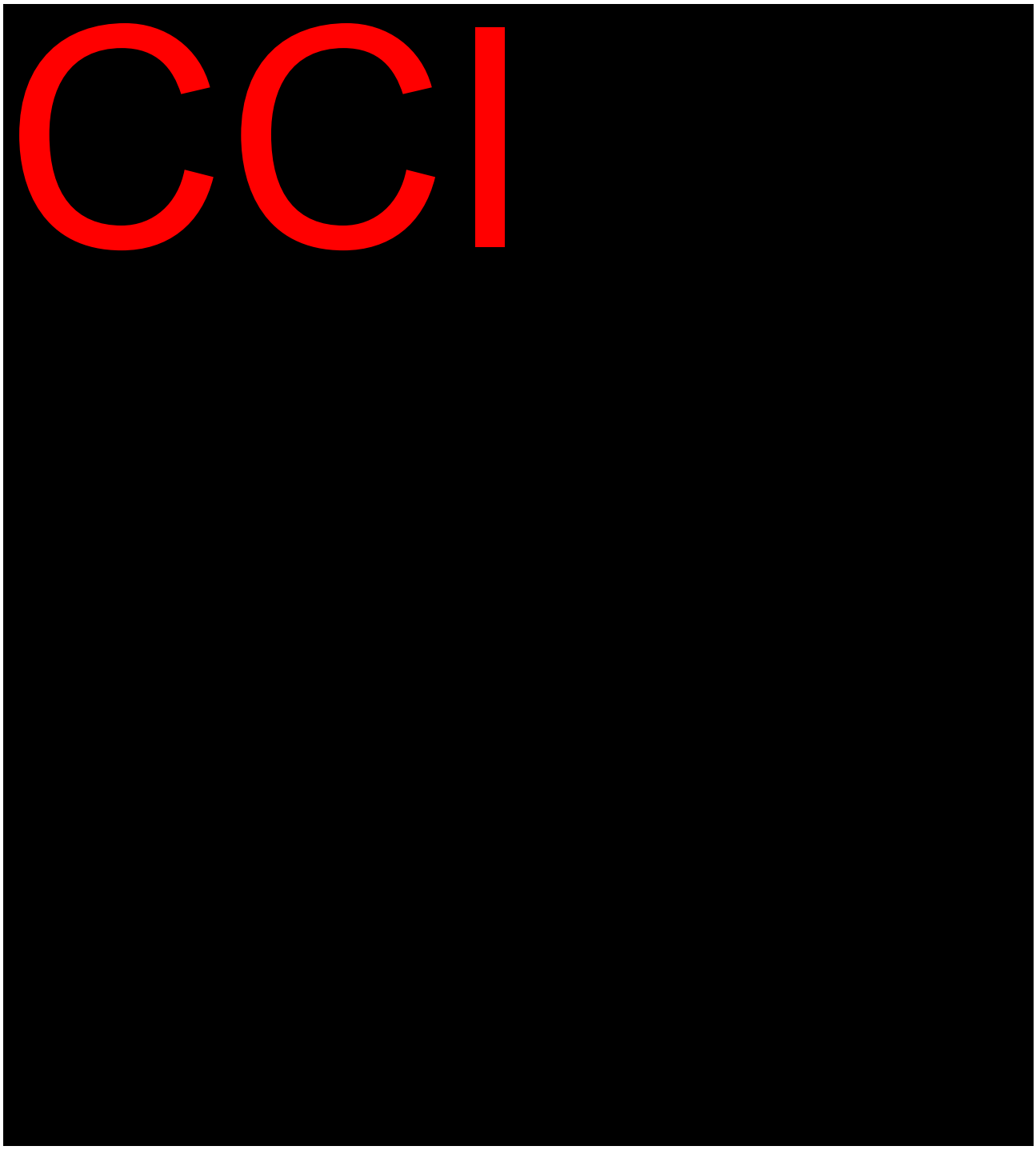

Appendix 7: Total Number of Samples and Blood Volume Withdrawn

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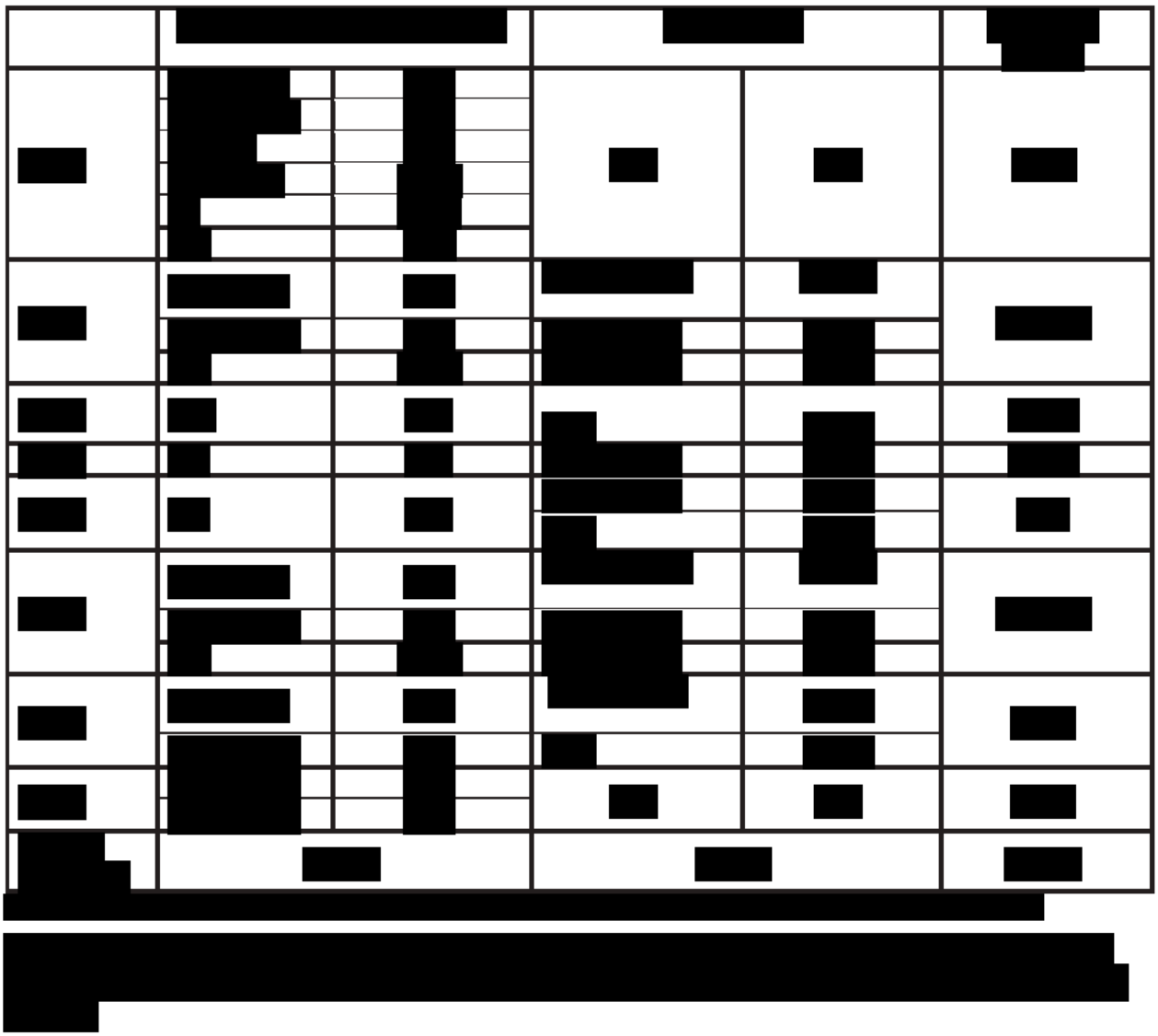

INVESTIGATOR SIGNATURE PAGE

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Protocol Title: An Open-label Drug-Drug Interaction Study to Assess the Effects of Nemolizumab on Cytochrome P450 Substrates in Subjects with Moderate-to-Severe Atopic Dermatitis

Protocol Number: RD.06.SPR.201593

Confidentiality and Current GCP Compliance Statement

I, the undersigned, have reviewed this protocol (and amendments), including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), GCP, and relevant ICH guidelines.

Once the protocol has been approved by the IEC/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 ICF modifications to Galderma S.A./Galderma R&D, LLC and the IEC/IRB, and approval will be obtained before any amendments are implemented.

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 eCRFs, 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.

Investigator Signature	Date
Printed Name	Title
Institution	Study Center Number