Statistical Analysis Plan for Interventional Studies

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Protocol Number: RD.06.SPR.118169

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Nemolizumab (CD14152) in Subjects with Moderate-to-Severe Atopic Dermatitis

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CCI [redacted]

Authors: PPD

Notice of Confidential and Proprietary Information:

Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
1.0	09-Nov-2022	PPD	Final Version

I confirm that I have reviewed this document and agree with the content.

Approvals		
Syneos Health Approval		
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Table of Contents

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1. Glossary of Abbreviations

Abbreviation	Description
ACT	Asthma Control Test
AD	Atopic dermatitis
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
CCI	
BSA	Body surface area
CCI	
CI	Confidence interval
COVID-19	Coronavirus disease-19
CPK	Creatinine phosphokinase
CRF	Case report form
CRO	Contract research organization
CS	Clinically significant
CSR	Clinical study report
DCS	Dual-chamber, single-use syringe
CCI	
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
CCI	
ET	Early termination
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
CCI	
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
IAC	Independent adjudication committee
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent data monitoring committee
IGA	Investigator's Global Assessment
IgE	Immunoglobulin E
IL	Interleukin
IRT	Interactive Response Technology
ITT	Intent-to-treat
JAK	Janus Kinase
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
LTE	Long term extension
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Description
MI	Multiple imputation
MMRM	Mixed-effect model for repeated measures
NCA	Non-compartmental analysis
NCS	Not clinically significant
NRS	Numeric rating scale
OC	Observed case
CCI [redacted]	
PD	Pharmacodynamics
PEF	Peak expiratory flow
CCI [redacted]	
PGx	Pharmacogenomics
CCI [redacted]	
POEM	Patient-Oriented Eczema Measure
PK	Pharmacokinetics
PP NRS	Peak pruritus numeric rating scale
CCI [redacted]	
PROMIS	Patient-Reported Outcomes Measurement Information System
Q4W	Every 4 weeks
Q8W	Every 8 weeks
QoL	Quality of Life
RTSM	Randomization and Trial Supply Management
SAE	Serious adverse event
SAP	Statistical Analysis Plan
sc	subcutaneous
CCI [redacted]	
SNRI	Serotonin-norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TB	Tuberculosis
TCI	Topical calcineurin
TCS	Topical corticosteroid
TEAE	Treatment-emergent adverse event
TFLs	Tables, figures and listings
UPT	Urine pregnancy test
US	United States
VAS	Visual analytic scale
WASO	Wakefulness after sleep onset
CCI [redacted]	

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives. The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts. Exploratory analyses not identified or defined in this SAP may be performed to support the clinical development program. Any post-hoc or unplanned analyses performed and not identified in this SAP will be documented in the respective clinical study report (CSR).

2.1. Responsibilities

Syneos Health will perform the statistical analyses and is responsible for the production and quality control of all tables, figures and listings.

Detailed PK and PKPD modeling and Biomarker analysis will be performed by the designated Contract research organization (CRO). Only the summary and listing of PK concentrations and listing of Biomarker data will be provided by Syneos Health.

2.2. Timings of Analyses

The final analysis will be performed after all subjects completed the study.

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 adverse events throughout the study.

Details on the IDMC and IAC, including the plan of analysis for outputs; the composition of the committees; and the procedures, roles, responsibilities, and communications are provided in the respective IDMC and IAC charters.

3. Study Objectives

3.1. Primary Objective

The primary objective is to assess the efficacy and safety of nemolizumab (CD14152) after a 16-week treatment Period in adult and adolescent subjects with moderate-to-severe atopic dermatitis (AD) not adequately controlled with topical treatments.

3.2. Secondary Objective(s)

The secondary objective is to evaluate the efficacy and safety of Maintenance treatment with nemolizumab (CD14152) for up to 32 weeks.

4. Study Details/Design

4.1. Brief Description

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

Approximately 750 total subjects will be randomized (2:1) to receive either nemolizumab (CD14152) or placebo, stratified by Baseline disease severity (Investigator's Global Assessment [IGA]; moderate: IGA = 3; severe: IGA = 4) and peak pruritus numeric rating scale (PP NRS) severity (PP NRS ≥ 7; PP NRS < 7). A minimum of 250 subjects will be randomized in each PP NRS strata. Clinical responders at Week 16 who were treated by Nemolizumab during Initial Period (i.e., the end of Initial treatment/beginning of Maintenance) will be re-randomized (1:1:1) to different treatment regimens (injections every 4 weeks [Q4W] or every 8 weeks [Q8W] of nemolizumab [CD14152] or placebo Q4W). All placebo-treated subjects (i.e., subjects in placebo from the Initial Period) who responded to placebo during the Initial Period will continue to receive placebo Q4W in the Maintenance Period.

The study consists of 4 Periods over approximately 60 weeks: Screening (including run-in), Initial, Maintenance, and Follow-up (unless the subject is a non-responder at Week 16, at which their participation could last up to 28 weeks).

Screening Period:

The Screening Period (approximately 2-4 weeks before planned Day 1/Baseline) will evaluate subject eligibility and introduce standardized background topical therapy over a Run-in Period of at least 2 weeks (i.e., 14 days) before Day 1/Baseline. Subjects may be rescreened once 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.

Initial Period:

The Initial Period is defined as Day 1/Baseline through Week 16 (before the Week 16 dose, with last dose at Week 12). Eligible subjects will be randomized in a ratio of 2:1 at Baseline to receive subcutaneous injections of nemolizumab (CD14152) (i.e., group 1) or placebo Q4W (i.e., group 2).

Clinical assessments will occur according to the schedule of assessments through the Week 16. Subjects who are clinical responders at Week 16 will continue to the Maintenance Period. Subjects who discontinue the Initial Period prematurely should complete an Early termination (ET) visit and a Follow-up visit 12 weeks after the last study drug injection. Subjects who are non-responders at Week 16 may be eligible to enroll into the LTE study (Protocol 118163). Subjects who require rescue therapy for clinical worsening of AD before Week 16 may also be considered for LTE study participation but will be required to continue with study visits until the Week 16 visit is due. The Follow-up visit is not required for subjects who participate in the LTE study.

Maintenance Period (Re-Randomization: Week 16 to Week 48):

The Maintenance Period is defined as Week 16 (Maintenance Baseline) to Week 48. All nemolizumab (CD14152)-treated subjects (i.e., group 1) who are clinical responders at Week 16 will be re-randomized (1:1:1) to study medication, as follows: group 1A, nemolizumab (CD14152) 30 mg Q4W; group 1B, nemolizumab (CD14152) 30 mg Q8W; or group 1C, placebo Q4W.

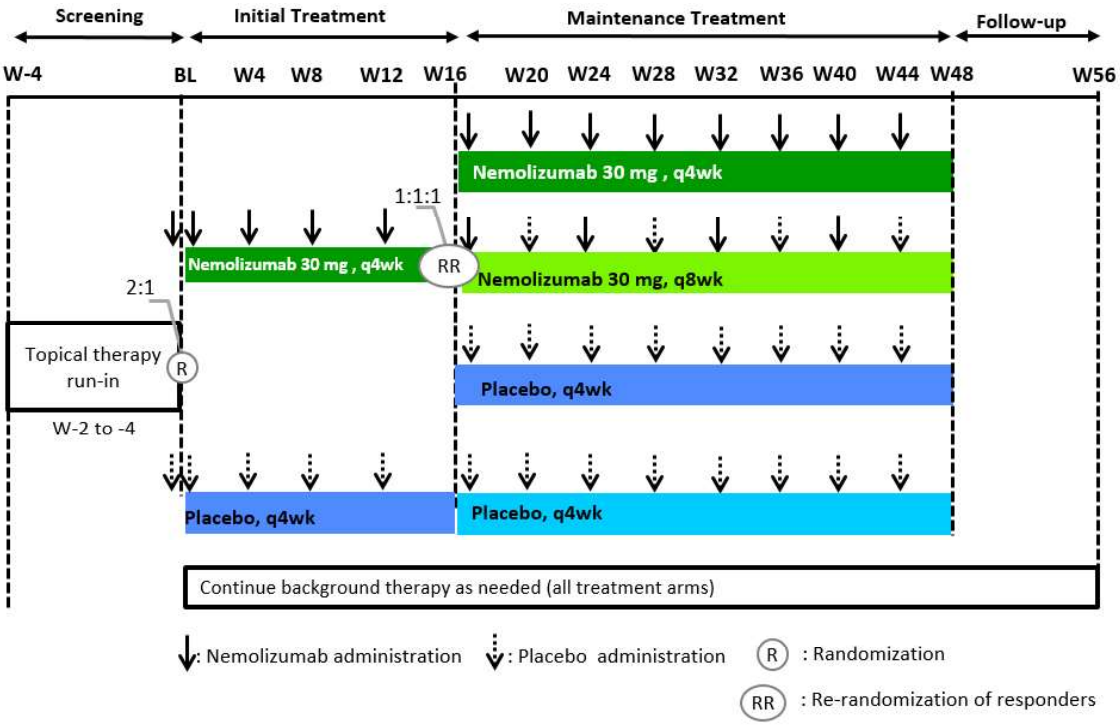
All placebo-treated subjects (i.e., subjects in group 2 from the Initial Period) who responded to placebo during the Initial Period will continue to receive placebo Q4W in the Maintenance Period. Beginning at Week 16, subjects in group 1A will receive active (i.e., nemolizumab [CD14152]) study drug injections Q4W up to Week 44. Subjects in group 1B will receive active (i.e., nemolizumab [CD14152]) study drug injections Q8W, with placebo at alternating visits to maintain the blind. Group 1B subjects will receive the last active study drug injection at Week 40 (final injection at Week 44 will be placebo). Group 1C subjects will receive placebo Q4W (i.e., through Week 44).

Clinical assessments will occur according to the schedule of assessments through the Week 48 visit. Subjects should continue the same background topical therapy used in the Initial Period leading up to the Week 16 visit, including tapering or complete cessation (no use), if applicable. Throughout the Maintenance Period, adjustments to background topical therapy, as determined by the investigator, are permitted based on the subject's clinical response. Subjects who complete the Week 48 visit may be eligible to enroll into the LTE study (Protocol 118163). The Follow-up visit is not required for subjects who participate in the LTE study. Subjects who discontinue the Maintenance period prematurely should complete an Early termination (ET) visit and a Follow-up visit 12 weeks after the last study drug injection.

Follow-up

The Follow-up visit will be conducted 12 weeks after the last study drug injection for subjects who decline or are not eligible to enter the LTE study. The Follow-up visit is not required for subjects who participate in the LTE study. (Twelve weeks corresponds to approximately 5 half-lives when nemolizumab 30 mg is dosed subcutaneously Q4W.)

Figure 4-1: Study Visit Schema



Abbreviations: BL=Baseline; q4wk=every 4 weeks; q8wk=every 8 weeks; W=week.

4.2. Subject Selection

Subjects will be selected based on the inclusion criteria, exclusion criteria and removal of subjects from therapy or assessments in Protocol Sections 8.3.2, 8.3.3 and 8.3.4.

4.3. Determination of Sample Size

With a 2:1 randomization, 180 subjects in nemolizumab and 90 subjects in placebo required to detect the differences in both co-primary endpoints to achieve 90% power.

IGA Success: To detect a difference of 18%, assuming IGA response for nemolizumab 30% and placebo 12% at Week 16.

EASI-75 Response: To detect a difference of 30%, assuming EASI-75 response for nemolizumab 49% and placebo 19% at Week 16.

To ensure sufficient exposure with nemolizumab and to ensure sufficient size of the safety database, the sample size increased to 750 subjects in total with randomization ratio 2:1. This sample size will provide more than 99% power to detect the treatment difference for both co-primary endpoints at 2.5% significance level.

4.4. Treatment Assignment and Blinding

Upon confirmation of eligibility for a given subject to participate in the study, a unique randomization number will be assigned to that subject via Interactive Response Technology (IRT) at the Baseline visit. Subjects will be randomized (2:1) to receive treatment of nemolizumab (CD14152) every 4 weeks (Q4W) or placebo. Randomization will be stratified by disease severity (Investigator's Global Assessment [IGA]=3, IGA=4) and pruritus severity (PP NRS ≥ 7, PP NRS < 7).

Subjects who were randomized to nemolizumab in the Initial Period and achieved clinical response (EASI-75 or IGA 0/1) at Week 16 will be re-randomized (1:1:1) to receive nemolizumab Q4W, nemolizumab every 8 weeks (Q8W), or placebo via IRT in the Maintenance Period.

All placebo-treated subjects who were randomized to placebo in the Initial Period and responded to placebo during the Initial Period will continue to receive placebo in the Maintenance Period.

The randomization code will remain blinded to all study sites and study team members until completion of the study and after the study database has been locked. Details about emergency unblinding are in Protocol Section 8.4.8.

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

4.5. Administration of Study Medication

Study drug will be supplied as a lyophilized powder for solution for injection for subcutaneous use only after reconstitution in a pre-filled, dual-chamber, single-use syringe (DCS). The lyophilized nemolizumab (CD14152) powder (39 mg) and solution for reconstitution (0.595 mL) are stored in separate syringe chambers, with each DCS designed to deliver a 30-mg dose of nemolizumab (CD14152) after reconstitution.

4.5.1. Study Drug Dosing – Initial Period

Table 4-1 summarizes study drug dosing for the Initial Period, which includes Day 1/Baseline to Week 16.

Table 4-1: Initial Period Dosing By Treatment Group

Group	Treatment	Loading Dose (Day 1/Baseline)	Dose at Week 4, 8, 12	Route	Schedule
1	Nemolizumab (CD14152)	60 mg (two 30 mg injections)	30 mg	sc	Q4W
2	Placebo	Placebo (2 placebo injections)	Placebo	sc	Q4W

Abbreviation(s): Q4W = every 4 weeks; sc = subcutaneous.

4.5.2. Study Drug Dosing – Maintenance Period

At Week 16, subjects who are clinical responders to nemolizumab (CD14152) treatment will be re-randomized (1:1:1) for participation in the Maintenance Period, and assigned by IRT to nemolizumab (CD14152) 30 mg Q4W, nemolizumab (CD14152) 30 mg Q8W, or placebo Q4W. The Q8W group will receive alternating injections of placebo to maintain the blind.

All placebo-treated subjects who responded to Placebo during the Initial Period will continue to receive placebo in the Maintenance Period.

Table 4-2 summarizes study drug dosing for the Maintenance Period after re-randomization, which spans the Week 16 to Week 48 visits.

Table 4-2: Maintenance Period Dosing By Re-randomized Treatment Group

Group	Treatment	Dose	Week(s)	Route	Schedule
1A	Nemolizumab (CD14152)	30 mg	16, 20, 24, 28, 32, 36, 40, 44	sc	Q4W
1B	Nemolizumab (CD14152)	30 mg	16, 20*, 24, 28*, 32, 36*, 40, 44*	sc	Q8W
1C	Placebo	Placebo	16, 20, 24, 28, 32, 36, 40, 44	sc	Q4W

**with placebo injections at Week 20, 28, 36, and 44 to maintain blind*
Abbreviation(s): Q4W = every 4 weeks; Q8W = every 8 weeks; sc = subcutaneous.

4.6. Study Procedures and Flowchart

The study procedures are described in Table 4-3 below:

Table 4-3: Schedule of Assessments:

Periods	Screening	Initial Treatment						Maintenance								*Unscheduled Visit* [a,b]	Follow-up [a,d,e]
Visit	1	2[a]	3	4[a]	5	No visit [c]	6[a]/ (ET)[d]	7	8	9	10[a,d]	11	12	13	14[a]/ (ET)[d]	(as applicable)	(12 weeks after last injection)
Week (relative to baseline)	(2 to 4 weeks before Day 1)[f]	(Day 1)/ Baseline	4	8	12	15	16	20	24	28	32	36	40	44	48		
Window (± days)		0	±3	±3	±5	±0	±5	±5	±5	±5	±5	±5	±5	±5	±5		±5
Informed consent and assent form	X															(X)	
PGx, subject interview, photography consent form(s) (if applicable)	X															(X)	
Inclusion/exclusion criteria	X	X														(X)	
Demographic data	X															(X)	
Medical history, previous therapy, smoking status	X															(X)	
PATIENT-REPORTED OUTCOME ASSESSMENTS																	
CCI [redacted]																	

Periods	Screening	Initial Treatment						Maintenance								*Unscheduled Visit* [a,b]	Follow-up [a,d,e]
Visit	1	2[a]	3	4[a]	5	No visit [c]	6[a]/ (ET)[d]	7	8	9	10[a,d]	11	12	13	14[a]/ (ET)[d]	(as applicable)	(12 weeks after last injection)
Week (relative to baseline)	(2 to 4 weeks before Day 1)[f]	(Day 1)/ Baseline	4	8	12	15	16	20	24	28	32	36	40	44	48		
Window (± days)		0	±3	±3	±5	±0	±5	±5	±5	±5	±5	±5	±5	±5	±5		±5
CCI [redacted]																	
CLINICAL PHOTOGRAPHS																	
Clinical photographs (optional) [m]		X					X								X	(X)	
EFFICACY ASSESSMENTS																	

Periods	Screening	Initial Treatment						Maintenance								*Unscheduled Visit* [a,b]	Follow-up [a,d,e]
Visit	1	2[a]	3	4[a]	5	No visit [c]	6[a]/ (ET)[d]	7	8	9	10[a,d]	11	12	13	14[a]/ (ET)[d]	(as applicable)	(12 weeks after last injection)
Week (relative to baseline)	(2 to 4 weeks before Day 1)[f]	(Day 1)/ Baseline	4	8	12	15	16	20	24	28	32	36	40	44	48		
Window (± days)		0	±3	±3	±5	±0	±5	±5	±5	±5	±5	±5	±5	±5	±5		±5
EASI	X	X	X	X	X		X	X	X	X	X	X	X	X	X	(X)	
IGA	X	X	X	X	X		X	X	X	X	X	X	X	X	X	(X)	
CCI [redacted]																	
SAFETY ASSESSMENTS																	
ACT [g,n]	X[n]	X[n]	X[n]	X[n]	X[n]		X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	(X)[n]	X[n]
Respiratory examination [o]	X	X	X	X	X		X	X	X	X	X	X	X	X	X	(X)	X
PEF testing [p]	X	X	X[p]	X	X[p]		X	X[p]	X[p]	X[p]	X	X[p]	X[p]	X[p]	X	(X)	X
Physical examination [q]	X	X		X			X		X		X		X		X	(X)	X
Contraceptive counseling [r]	X															(X)	
Height [s]	X			X[s]			X[s]		X[s]		X[s]		X[s]		X[s]	(X)[s]	X[s]
Weight	X	X					X				X				X	(X)	X
12-lead ECG [t]	X						X								X	(X)	X
Vital signs [u]	X	X	X	X	X		X	X	X	X	X	X	X	X	X	(X)	X
Adverse event reporting [g]	X	X	X	X	X		X	X	X	X	X	X	X	X	X	(X)	X
Concomitant therapy (including contraception)/ medications [g]	X	X	X	X	X		X	X	X	X	X	X	X	X	X	(X)	X

Periods	Screening	Initial Treatment						Maintenance								*Unscheduled Visit* [a,b]	Follow-up [a,d,e]
Visit	1	2[a]	3	4[a]	5	No visit [c]	6[a]/ (ET)[d]	7	8	9	10[a,d]	11	12	13	14[a]/ (ET)[d]	(as applicable)	(12 weeks after last injection)
Week (relative to baseline)	(2 to 4 weeks before Day 1)[f]	(Day 1)/ Baseline	4	8	12	15	16	20	24	28	32	36	40	44	48		
Window (± days)		0	±3	±3	±5	±0	±5	±5	±5	±5	±5	±5	±5	±5	±5		±5
LABORATORY ASSESSMENTS																	
Urinalysis [v]	X	X		X			X				X				X	(X)	X
Hematology [v]	X	X		X			X				X				X	(X)	X
Blood chemistry [v]	X	X		X			X				X				X	(X)	X
TB test [w]	X															(X)	
Hepatitis B and C test	X															(X)	
HIV test	X															(X)	
Pregnancy test [x]	X	X	X	X	X		X	X	X	X	X	X	X	X	X	(X)	X
FSH [y]	X															(X)	
PK, ADA, PD/BIOMARKERS, and OPTIONAL PGx ASSESSMENTS																	
CCI [redacted]																	
D-Squames samples [aa]		X					X									(X)	
PGx samples (optional) [bb]		X														(X)	
STUDY DRUG ADMINISTRATION																	
Randomization		X					X[cc]									(X)	
Study drug injection and training [dd,ee]		X[ff]	X	X	X		X	X	X	X	X	X	X	X		(X)	

Periods	Screening	Initial Treatment						Maintenance								*Unscheduled Visit* [a,b]	Follow-up [a,d,e]
Visit	1	2[a]	3	4[a]	5	No visit [c]	6[a]/ (ET)[d]	7	8	9	10[a,d]	11	12	13	14[a]/ (ET)[d]	(as applicable)	(12 weeks after last injection)
Week (relative to baseline)	(2 to 4 weeks before Day 1)[f]	(Day 1)/ Baseline	4	8	12	15	16	20	24	28	32	36	40	44	48		
Window (± days)		0	±3	±3	±5	±0	±5	±5	±5	±5	±5	±5	±5	±5	±5		±5
CONCOMITANT THERAPY																	
Moisturizer use	X[gg] ----------																X[gg]
Background topical therapy use	X[hh] ----------																X[hh]
TCS ± TCI accountability [ii,jj]	X	X	X	X	X		X	X	X	X	X	X	X	X	X	(X)	X[ij]

Abbreviations: ACT = Asthma Control Test; AD = atopic dermatitis; ADA = anti-drug antibody; BSA = body surface area; CCI EASI = Eczema Area and Severity Index; ECG = electrocardiogram; CCI FSH = follicle-stimulating hormone; HADS = Hospital Anxiety and Depression Scale; HIV = human immunodeficiency virus; IGA = Investigator's Global Assessment; IRR = injection-related reaction; LTE = long-term extension; PCS = pruritus categorical scale; CCI CCI CCI , PGx = pharmacogenomics; CCI = peak pruritus numeric rating scale; CCI CCI ; TB = tuberculosis; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid; UPT = urine pregnancy test; WOCBP = women of childbearing potential; WPAI:AD = Work Productivity and Activity Impairment: Atopic Dermatitis.

Notes:

[a] Subjects should fast for at least 8 hours before the visit(s) when blood chemistry testing is planned, except for the screening visit.

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[d] Subjects discontinued prematurely should complete ET assessments according to: Visit 6/Week 16 if during the initial treatment period **or** Visit 14/Week 48 if during the maintenance period **and** a final/follow-up visit 12 weeks after the last study drug injection (for subjects not participating in the LTE study). Subjects who require rescue therapy (with or without study medication discontinuation) must continue with study visits until: Visit 6/Week 16 if during the initial treatment period **or** until Visit 10/Week 32 if during the maintenance period to be considered for LTE eligibility. (If during the maintenance period, rescue is needed after the Week 32 visit, no wait period is required.)

[e] The follow-up visit will be conducted for subjects who decline or are not eligible to enter the LTE study and should be conducted 12 weeks after the last study drug injection. (The follow-up visit is not required for subjects who will rollover to the LTE study.)

[f] The run-in period begins at least 2 weeks (i.e., 14 days) before Day 1/baseline. Subjects receiving rescue therapies during the run-in period are not eligible to participate in the study.

[g] Patient-reported outcome assessments and designated safety measurements should occur before investigator assessments, laboratory sample collections, and study drug administration.

CCI [redacted]

NRS CCI [redacted] to be recorded by subjects once daily in the evening (Visit 1/Screening through Visit 6/Week 16), beginning after the screening visit. Topical background therapy use (not including moisturizer) to be recorded by subjects once daily in the evening throughout the study, beginning after the screening visit. On designated visits, CCI [redacted]

CCI [redacted]

[j] Pruritus assessments (i.e., PP NRS, CCI [redacted] will be recorded the evening before the clinic visit. If a subject does not complete the CCI [redacted] in the evening before a scheduled visit, the subject will be allowed to complete the assessment the following day at the clinic visit before investigator assessments, laboratory sample collection, and study drug administration.

[k] Assessments to be completed by subjects for 7 consecutive days before the designated target visit dates during study treatment.

[l] Optional subject interviews will be conducted at the end of the initial treatment period between Week 16 and Week 18.

[m] Optional photographs of AD lesions will be performed only for consenting subjects at selected sites.

[n] Subjects with a history of asthma will complete the ACT (and PEF testing) at each scheduled visit. Subjects with de novo asthma will complete the ACT (and PEF testing) beginning from de novo diagnosis and at all subsequent scheduled visits.

[o] At screening, the investigator should specifically question all subjects about any medical history of asthma and their respiratory health (eg, wheezing, coughing, allergies, infections). A respiratory examination will be required for all subjects at all scheduled visits.

[p] PEF testing will be performed for all subjects at screening, baseline, Week 8, 16, 32, 48, and follow up visits. For subjects reporting a medical history of asthma, PEF testing (and ACT) will be performed at all visits during the clinical study. For subjects diagnosed with de novo asthma, PEF testing (and ACT) will be performed at all visits, starting with the visit in which the diagnosis was confirmed. 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.

[q] Complete PE should be performed at designated visits.

[r] Contraceptive counseling should occur at screening or at applicable visits when pre-pubertal subjects begin menses.

[s] Height collection will be performed for all subjects at screening. Height collection is only required for adolescents (ages 12-17) at designated post-screening visits.

[t] 12-lead ECGs should be performed in the supine position, before any scheduled vital sign measurements and blood draws.

[u] 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.

CCI [redacted]

[w] TB screening: QuantiFERON-TB Gold test for all subjects.

[x] Only for WOCBP. Pregnancy test results must be available prior to the administration of the study drug. Serum pregnancy test to be performed at the screening visit; UPT at all other visits. For prepubertal subjects, reconfirm pre-menses status at every visit and, in case of status change, collect information on contraceptive measures and perform a UPT according to the schedule for WOCBP.

[y] For postmenopausal subjects (i.e., no menses for 12 consecutive months), confirm status with a high FSH level in the postmenopausal range. Blood chemistry sample at the screening visit (V1) will also be used for an FSH test for the confirmation of postmenopausal status.

[z] See details on PK assessments. As a guideline, PK samples should be collected at approximately the same time of day throughout the study, to the extent possible, before study drug injection (pre-dose samples).

CCI [redacted]

[bb] Optional PGx sample collection is only for subjects who provide additional consent.

[cc] All nemolizumab (CD14152)-treated subjects who are clinical responders at Week 16 (defined as 1. IGA of 0 [clear] or 1 [almost clear]; OR 2. EASI-75) will be re-randomized (1:1:1) to receive nemolizumab (CD14152) Q4W, Q8W, or placebo Q4W.

[dd] Study drug reconstitution will be performed by the pharmacist (or other qualified personnel) throughout the study, and complete reconstitution confirmed, prior to delivery for injection. Study center staff will provide study drug injection training for subjects willing and able to self-inject (or have their caregiver inject) study medication. Subjects and/or caregivers will then be allowed to inject medication at subsequent visits. Based on the subject's preference, study center staff can also perform all injections.

[ee] 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. *In Germany only, subjects must undergo a 60 minute observation period after the first 3 injections and a 30 minute observation period after all subsequent doses.

[ff] Subjects will receive a loading dose on Day 1 (i.e., 2 injections of nemolizumab 30 mg or placebo).

[gg] Subjects will apply a moisturizer daily, and liberally as needed, to dry skin and AD lesions 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.

[hh] Authorized topical therapy use beginning ≥ 14 days before Day 1. The investigator should adjust background topical therapy use during the study, according to the disease activity and tolerability, including tapering when signs and symptoms improve, discontinuation when lesions clear, and restarting if signs and symptoms recur, based on investigator clinical judgment.

[ii] Appropriate amounts of TCS and/or TCI should be dispensed or prescribed at each visit, according to investigator judgement. Containers of previously dispensed/prescribed TCS and/or TCI should be collected at each visit. Collected containers with remaining medication may be re-dispensed back to the subject, when applicable.

[jj] *No dispensation of TCS and/or TCI should occur at the final study visit. Collection only.*

5. Endpoints

5.1. Co-Primary Efficacy Endpoints

- Proportion of subjects with an IGA success (defined as an IGA of 0 [clear] or 1 [almost clear] and a ≥ 2-point reduction from Baseline) at Week 16
- Proportion of subjects with EASI-75 (≥ 75% improvement in EASI from Baseline) at Week 16

5.2. Key Secondary Efficacy Endpoints

- Proportion of subjects with an improvement of PP NRS ≥ 4 at Week 16
- Proportion of subjects with PP NRS < 2 at Week 16

CCI

CCI

[redacted]

CCI

[redacted]

CCI

5.5. Safety Endpoints

- Incidence and severity of AEs, including AESIs, TEAEs, and SAEs
- Physical examination and Vital signs
- Clinical laboratory tests
- Electrocardiogram
- Peak expiratory flow
- Asthma Control Test (ACT)

CCI

6. Analysis Sets

For Initial Period and Maintenance Period, the following populations will be defined for analysis. Only subjects who are re-randomized after Initial Period will be included in the analysis population of Maintenance Period.

6.1. Intent-to-Treat Population

The intent-to-treat (ITT) population will consist of all randomized subjects. All primary and secondary efficacy endpoints will be analyzed based on the ITT population.

For maintenance Period, the ITT population will include subjects who are re-randomized after Initial Period.

The ITT population will be the primary population for all efficacy analyses. All analyses on the ITT population will be analyzed under the treatment group 'as randomized'. If a subject is stratified incorrectly, 'stratum at the randomization' will be used rather than 'actual stratum' for analysis or summary of efficacy data.

6.2. Enrolled Subjects in Maintenance Period Population

The enrolled subjects in maintenance period population will comprise all subjects in ITT Population who are re-randomized or continue on Placebo after initial period.

6.3. Safety Population

The safety population will comprise all subjects in ITT population who receive at least 1 dose of study drug. All safety data will be summarized based on the safety population under the treatment group 'as treated'.

For Maintenance Period, only subjects in ITT population who received at least one drug in the Maintenance Period will be included in the population.

Subject who are treated on error during the course of the study will be assigned to actual treatment as described below.

Initial Period:

- Subjects who are randomized to Placebo but treated at least once with Nemolizumab in error will be assigned to 'Nemolizumab Q4W'.
- Subjects who are randomized to Nemolizumab but treated at least once with Placebo in error will still be assigned to 'Nemolizumab Q4W'. If they always received Placebo in error during the period, then they will be assigned to 'Placebo'.

Maintenance Period:

- Subjects who are re-randomized to Nemolizumab Q4W but treated at least once with Placebo in error will be assigned to 'Nemolizumab Q4W to Q4W'.
- In case of subjects who re-randomized to Nemolizumab Q8W, they are supposed to receive Nemolizumab and Placebo alternately. If they are treated with Nemolizumab instead of Placebo at least once in error, they will be assigned to 'Nemolizumab Q4W to Q4W'. However if they are treated at least once with Placebo instead of Nemolizumab in error will be assigned to 'Nemolizumab Q4W to Q8W'.

- Subjects who are re-randomized to Placebo but treated with Nemolizumab at least once in error will assigned to 'Nemolizumab Q4W to Q4W'.
- Subjects who are randomized to Placebo for Initial Period and continue the Maintenance Period will be assigned to 'Placebo' even if treated with Nemolizumab at least once in error.

Overall Period:

- If subjects exited the study after Initial Period (i.e., not re-randomized nor continued with Placebo for Maintenance Period), overall period treatment group will be the same with Initial period treatment group assigned (i.e., can be either 'Nemolizumab Q4W' or 'Placebo').
- In case subjects who re-randomized for Maintenance Period,
    - Subjects who are re-randomized to Nemolizumab Q4W will be assigned to 'Nemolizumab Q4W' even if they treated by Placebo in error during the study.
    - Subjects who are re-randomized to Nemolizumab Q8W will be assigned to 'Nemolizumab Q4W to Q8W' if the error occurred during Initial Period. When the error is occurred during Maintenance Period, overall period treatment group will be 'Nemolizumab Q4W to Q8W' if receive Placebo instead of Nemolizumab or 'Nemolizumab Q4W' if receive Nemolizumab instead of Placebo during Maintenance Period.
    - Subjects who are re-randomized to Placebo will be assigned to 'Nemolizumab Q4W to Placebo' if the error is occurred in Initial Period. However if the error is occurred during Maintenance Period, the overall treatment group will be 'Nemolizumab Q4W'.
- Subjects who are randomized to Placebo for Initial Period and continue the Maintenance Period will be assigned to 'Placebo'.

6.4. Enrolled Safety Subjects in Maintenance Period Population

The enrolled safety subjects in maintenance period population will comprise only subjects in enrolled subjects in maintenance period population who received at least one drug in the maintenance period.

6.5. PK Analysis Population

The PK analysis population will include all subjects in the safety population who provide at least 1 post-Baseline evaluable drug concentration value and not include any biologically implausible value.

For Maintenance Period, only subjects in the safety population who provide at least 1 post-Week 16 evaluable drug concentration and not include any biologically implausible value in the Maintenance Period will be included in the population.

All PK and ADA endpoints will be analyzed using the PK analysis population under the treatment group 'as treated'.

6.6. Enrolled PK Subjects in Maintenance Period Population

The enrolled PK subjects in maintenance period population will comprise only subjects in enrolled Safety subject in maintenance period population who provide at least 1 post-week 16 evaluable drug concentration value and not include any biologically implausible value.

6.7. Per-Protocol Population

The per-protocol (PP) population will comprise all subjects in the ITT population who have no major protocol deviations that would have a significant effect on the efficacy of the study treatment. Only

primary and key secondary endpoints will be analyzed using the per-protocol population under the treatment group 'as randomized'.

6.8. PD Analysis Population

The PD analysis population(s) will be described in a separate pharmacodynamic plan by designated CRO.

6.9. Protocol Deviations

Protocol deviations will be recorded by the Clinical Research Associate (CRA) in the Clinical Trial Management System (CTMS). All protocol deviations will be categorized by deviation type which the deviation is associated with, and will be assessed individually on a regular basis on whether they are important (major) or non-important (minor). Details can be found in the Protocol Deviation and Non-compliance Management Plan.

Major protocol deviations would lead to an exclusion of the subject from the per-protocol population. A case by case decision regarding exclusions of subjects from the per-protocol population will be made in a blind data review meeting (BDRM) which will take place prior to unblinding the study.

Individual deviations (major and minor) will be presented in a data listing on the ITT population. A summary table for number and percentage of subjects with major protocol deviation will be summarized by type of deviation and treatment group for the Initial Period and the Maintenance Period for the ITT population.

Protocol deviations incurred as a direct result of the COVID-19 pandemic should be specifically recorded and presented as a COVID-19 deviation. The number and percentage of subjects with major COVID-19 deviation will be provided by type of deviation and treatment group for the Initial Period and the Maintenance Period for the ITT population.

Major protocol deviations will also be summarized by site for the ITT population.

7. Estimands

The co-primary and key secondary efficacy endpoints will be evaluated in the moderate-to-severe atopic dermatitis represented by the study inclusion/exclusion criteria and assigned to treatment during initial period. The estimand is defined to address the scientific question relevant to subjects who are able to complete treatment with a response assessment without further medication being required, other than the allowed background and rescue medication.

An intercurrent event is an event which occurs after start of treatment and thus complicates the description and interpretation of treatment effects. Table 7-1 below lists potential intercurrent events and the strategy to deal with them for the estimand. Estimands for the co-primary and key secondary endpoints are listed in Tables 7-2 and 7-3.

Table 7-1 List of Intercurrent Events

Intercurrent Event	Strategy to Deal With Intercurrent Event Within Analysis	Assessment of Subject
Treatment discontinuation	Treatment policy	Use observed response
CCI [redacted]		

Table 7-2: Estimands for Co-primary Endpoints (2 endpoints)

Endpoints	Estimands
Proportion of subjects with an IGA success (defined as an IGA of 0 [clear] or 1 [almost clear] and a ≥ 2-point reduction from Baseline) at Week 16	**Population:** ITT population (Full population; Baseline PP NRS ≥ 7)
	Endpoint: a binary response indicates if subjects have IGA of 0 [clear] or 1 [almost clear] and a ≥ 2-point reduction from Baseline at Week 16
	Intercurrent events: use of rescue therapies prior to Week 16 is considered as non-responder; the observed response at Week 16 after treatment discontinuation will be used in the analysis.
	Summary measure: treatment difference of nemolizumab and placebo in response rate
Proportion of subjects with EASI-75 (≥ 75% improvement in EASI from Baseline) at Week 16	**Population:** ITT population (Full population; Baseline PP NRS ≥ 7)
	Endpoint: a binary response indicates if subjects with at least 75% improvement in EASI from baseline at Week 16
	Intercurrent events: use of rescue therapies prior to Week 16 is considered as non-responder; the observed response at Week 16 after treatment discontinuation will be used in the analysis.
	Summary measure: treatment difference of nemolizumab and placebo in response rate

Table 7-3 Estimands for Key Secondary Endpoints (9 endpoints)

Endpoints	Estimands
Proportion of subjects with an improvement of PP NRS ≥ 4 at Week 16	**Population:** ITT population (Full population; Baseline PP NRS ≥ 7)
	Endpoint: a binary response indicates if subjects have IGA of 0 [clear] or 1 [almost clear] and a ≥ 2-point reduction from Baseline at Week 16
	Intercurrent events: use of rescue therapies prior to Week 16 is considered as non-responder; the observed response at Week 16 after treatment discontinuation will be used in the analysis.
	Summary measure: treatment difference of nemolizumab and placebo in response rate
Proportion of subjects with PP NRS < 2 at Week 16	**Population:** ITT population (Full population; Baseline PP NRS ≥ 7)
	Endpoint: a binary response indicates if subjects with PP NRS < 2 at Week 16
	Intercurrent events: use of rescue therapies prior to Week 16 is considered as non-responder; the observed response at Week 16 after treatment discontinuation will be used in the analysis.
	Summary measure: treatment difference of nemolizumab and placebo in response rate
	Population: ITT population (Full population; Baseline PP NRS ≥ 7)

CCI

[redacted]

CCI

8. General Aspects for Statistical Analysis

8.1. General Methods

All data will be listed, and summary tables will be provided. Summaries will be presented for each treatment and visit (if applicable).

Unless otherwise stated, continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum by treatment group and visit (if applicable). Categorical variables will be summarized using frequency and percentages of subjects for each category by treatment group and visit (if applicable).

Unless otherwise stated, all statistical tests will be 2-sided and conducted at the 5% level; all presented confidence intervals (CIs) will be 2-sided 95% CIs.

8.2. Key Definitions

Screening Period is a Period of approximately 2-4 weeks before Day 1/Baseline during which subject eligibility is evaluated and standardized background topical therapy is introduced over a run-in Period of at least 2 weeks before Day 1/Baseline.

The Initial Period is defined as Day 1/Baseline to Week 16 (before the Week 16 dose, with last dose at Week 12). If early discontinued during treatment period, it is defined as the period until 4 weeks after last dosing date or early termination date whichever is earlier.

The Maintenance Period is defined as Week 16 (Maintenance Baseline) to Week 48. If early discontinued during treatment period, it is defined as the period until 4 weeks after last dosing date or early termination date whichever is earlier.

Follow-up Period is defined as the post end of treatment period (i.e., 1 day after end of treatment period) to Follow-up visit in respective treatment period.

The Baseline value of the Initial Period will be taken as latest valid value prior to first injection of study drug. For subjects randomized but not treated, the Baseline value will be the latest value prior to the randomization. Week 16 measurements will serve as Baseline measurements for the Maintenance Period (i.e., Maintenance Baseline). If Week 16 measurements are missing for re-randomized subjects, the last valid non-missing measurement in the Initial Period (i.e., before the dosing for Maintenance Period at Week 16 visit) will be taken as the Baseline measurement for the Maintenance Period.

For diary data (e.g., Peak Pruritus (PP) NRS, Sleep disturbance (SD) NRS), the Baseline values will be the weekly prorated average of non-missing subject diary scores reported during the 7 days. A minimum of 4 daily scores out of the 7 days is required to calculate the weekly prorated average score. Refer the details for the analysis visit window for diary data in Section 8.4.

The date of first treatment is defined as the date of first injection of study drug. The date of fist treatment is the Baseline date.

The date of last treatment is defined as the date of last injection of study drug.

Study day is defined as the number of days from the date of first treatment and will be calculated as follows:

- If the event date≥date of first treatment, study day = event date–date of first treatment+1. Study Day 1 is therefore defined as the day of first treatment.
- If the event date<date of first treatment, study day = event date-date of first treatment.

A subject's date of last participation in the trial is the last date of contact.

8.3. Missing Data

The data after the receipt of rescue therapy will be handled before imputation as below:

Use of rescue therapy: Except OC, all efficacy data on or after the receipt of rescue therapy will be considered as 'not evaluable data' for analysis. For analysis purpose it will be replaced by the worst possible score for endpoint, and considered as 'treatment failure'. However, in OC analysis, all observed data even after the receipt of rescue treatment will be included for analysis, i.e. no imputation for missing data.

In case of diary data, if the date of rescue therapy use is within the analysis visit window, the subject at the analysis visit will be treated as treatment failure except for OC analysis, and the weekly average will be imputed using the worst case value.

Further details for the data handling for rescue therapy are in section 7.

The primary method to impute the missing values will be as follows:

Continuous Endpoints: For continuous endpoints during Initial Period, the MI under MAR assumption approach and the MMRM approach will be used to handle the missing data for the selected secondary endpoints.

CCI [redacted]

Binary Endpoints: All missing values will be treated as a non-responder for the binary endpoints for primary, key secondary and secondary endpoints during Initial Period. To assess the robustness of non-responder analysis for primary and key secondary endpoints, a tipping point analysis will be performed. The MI under MAR assumption, LOCF, and OC will be used as sensitivity analysis to impute the missing values for the primary and key secondary endpoints.

Adverse events and concomitant medications/procedures: Missing assessment times will have imputed times for the purposes of assessing treatment emergence for AEs or classifying medications/procedures into prior/concomitant. However, the assessment times (start date, stop date, and time if collected from CRF) without imputation will be presented in the listings.

For the start of a concomitant medication/procedure or AE:

- Only the year is reported: If the subject received the first study drug dose in the year reported, then the date of the first dose of study drug will be used as the start date; otherwise, January 1 of the year reported will be used as the start date.
- The month and year are reported: If the subject received the first study drug in the month and year reported, then the date of the first dose of study drug will be used as the start date; otherwise, the first day of the month and year will be used as the start date.

- The time is collected but missing: If the start date is the same as the date the subject started receiving study drug, then the time of the first dose of study drug will be used as the start time; otherwise, 00:00 will be used as the start time.

For the end of a concomitant medication/procedure or AE:

- Only the year is reported: The earlier between December 31 of the year reported and the date of the last study contact with the subject will be used as the stop date.
- The month and year are reported: The earlier between the last date of the month and year reported and the date of the final contact with the subject will be used as the stop date.
- The time is collected but missing: 23:59 (or 23:59:59 if collected up to seconds) will be used as the stop time.

If an AE has the start date completely missing and the stop date on/after the first dose date of study drug, this AE will be considered as treatment emergent (TEAE).

If a medication/procedure has the stop date completely missing, this medication/procedure will be considered as ongoing and concomitant. If the start date of a medication/procedure is completely missing and impossible to identify different by stop date, this medication will be considered as concomitant.

8.4. Analysis Visit Windows

Efficacy by-visit summaries will use the analysis visit. Unscheduled and early termination visits will be windowed based on the following analysis visit window which is based on study day. If multiple measurements are taken within the same window, the one taken closest to the target study day will be used for the analysis. If there are multiple measurements with same difference from target day, the later assessment should be used for the analysis.

Table 8-1: Analysis Visit Window

Analysis Visit	Target Study Day	Visit Window for EASI, IGA, CCI [redacted]
Baseline	1	<=1
Week 4	29	2 to 42
Week 8	57	43 to 70
Week 12	85	71 to 98
Week 15	106	NA
Week 16	113	99 to 126
Week 20	141	127 to 154
Week 24	169	155 to 182
Week 28	197	183 to 210
Week 32	225	211 to 238
Week 36	253	239 to 266
Week 40	281	267 to 294
Week 44	309	295 to 322

Week 48	337	>=323	CCI

CCI Visit window after Week 16 will not be applicable for PIQs.

CCI

For the diary data at post-baseline visit, only the diary data assessed within the timeframe below (+1 hour to end time in spec) will be considered for analysis. If >1 diary recorded on a day (within window), only one of them to take for analysis (i.e. latest one for evening diary, earliest one for morning diary).

- Evening assessment (PP/CC NRS, CCI recorded from 17:00:00 to 00:59:59

CCI

Consecutive daily assessment:

For the evening assessments (PP NRS, CCI) during Initial Period, the daily data collected up to Week 16 will be classified into analysis visits considering the data during the 7 days immediately preceding the target study day of analysis visit. Similarly, for the morning assessment (CCI CCI) during Initial Period, the 7 days data up to the target study day will be classified into analysis visit. Details of the analysis visit window are in the table below. Only the data belongs to Initial Period will be considered for classifying the analysis visit in Initial Period.

Table 8-2: Analysis Visit Window for Evening and Morning Assessments during Initial Period

Analysis Visit	Target Study Day of Analysis Visit	Visit Window for evening assessment (PP NRS, C CI	CCI
Baseline*	1	-7 to -1	
Week 1	8	1 to 7	
Week 2	15	8 to 14	
Week 3	22	15 to 21	
Week 4	29	22 to 28	
Week 5	36	29 to 35	
Week 6	43	36 to 42	
Week 7	50	43 to 49	
Week 8	57	50 to 56	
Week 9	64	57 to 63	
Week 10	71	64 to 70	
Week 11	78	71 to 77	
Week 12	85	78 to 84	
Week 13	92	85 to 91	
Week 14	99	92 to 98	
Week 15	106	99 to 105	
Week 16**	113	106 to 112 before dosing	

* if there are less than 4 days non-missing data available within window, the lower bound of interval will be extended up to 7 additional days to obtain 4 days non-missing data for Baseline weekly score calculation. The timeframe window will not be considered.
** if <4 days non-missing data within Week 16 window, the upper bound will be extended first up to +5 days to obtain 4 non-missing data. If still <4 non-missing data after extending the upper bound, the lower bound will be extended again up to +5 days to obtain 4 days non-missing data. For evening assessment, only the data before Week 16 dosing (or re-randomization if missing Week 16 dosing) will be considered for Initial Treatment Period analysis.

CCI
CCI The same window with evening assessment (PP NRS, CCI in Table 8-2 will be used for Initial Period. For Maintenance Period, the target study day of Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44 and Week 48 will be Day 141, Day 169, Day 197, Day 225, Day 253, Day 281, Day 309, and Day 337. If the data reported within analysis visit window but after week 16 dosing, it won't be part of initial period. The extended timeframe (+1 hour to end time) to be considered.

Intermittent daily assessment before the visit:
For the evening assessments (PP NRS and CCI the 7 days immediately preceding the actual subject visit date will be classified into the analysis visit. i.e., from 'actual subject visit date – 7 days' to 'actual subject visit date – 1 day'. Similarly, for the morning assessments (CCI the 7 days data from 'actual subject visit date – 6 days' to 'actual subject visit date' will be classified into the analysis visit. In maintenance period, the diary data will not be collected daily, so consider dosing date/time and include data for calculation only if it's done within analysis visit window/timeframe and before dosing.

In case of missing/skipped visit, unscheduled or early termination visit, the diary data will be windowed based on the study day (see Tables 8-3 and 8-4). If a subject missed/skipped a visit due to any reason (e.g., skipped a visit due to COVID-19), the diary data which have been reported during that time will be mapped to the analysis visit based on the study day and 7 days consecutive data will be classified into the analysis visit as in the tables below. For the unscheduled or early termination visit data, the same approach will be applied to window the data into analysis visit.

CCI

Table 8-3: Analysis Visit Window for Missing/Skipped Visit, Unscheduled or Early termination Visit for PP/CCI NRS and CCI

Analysis Visit	Target Study Day of Analysis Visit	Visit Window for evening assessment (PP NRS, CCI)*	CCI
Week 24	169	162 to168	
Week 32	225	218 to 224	
Week 40	281	274 to 280	
Week 48	337	330 to 336	

* for evening diary, only the data before dosing on the clinic visit date will be considered for analysis.

CCI

* if <4 days non-missing data within Week 16 window, the upper bound will be extended first up to +5 days to obtain 4 non-missing data. If still <4 non-missing data after extending the upper bound, the lower bound will be extended again up to +5 days to obtain 4 days non-missing data. Only the data before Week 16 dosing (or re-randomization if missing Week 16 dosing) will be considered for Initial Treatment Period analysis.

For efficacy, where two or more assessments (including both scheduled and unscheduled assessments) are available for the same visit interval, the one closest to the target visit date will be used for the summary and analyses. Safety and CCI data will not be windowed for by-visit summary. i.e., scheduled visit data will be used for analysis.

8.5. Pooling of Centers

Centers will not be pooled.

8.6. Subgroups

Descriptive summary and analysis for primary and selected key secondary endpoints will be produced for the following subgroups:

- Region (Europe, North America, Asia Pacific)
- Age groups (12-17, 18-65, and > 65)
- Sex
- Race
- Baseline IGA (3 or 4)
- Baseline PP NRS (≥ 7 and < 7)
- Previous use of any systemic therapy for AD (Yes, No)
- Previous use of any biologic therapy for AD (Yes, No)
- Previous use of any immunosuppressive or immunomodulatory drugs for AD (Yes, No)
- Previous use of Dupilumab for AD (Yes, No)
- Previous use of Cyclosporine for AD (Yes, No)
- Country

9. Demographic, Other Baseline Characteristics and Medication

Subject accounting, disposition, demographics, Baseline characteristics, previous therapies, and concomitant therapies by treatment will be summarized for the Initial Period and Maintenance Period.

9.1. Subject Disposition and Withdrawals

All subjects who provide informed consent will be accounted for in this study.

Subject accounting will summarize subjects screened, screen failed, randomized and randomized but not treated for the Initial Period for all subjects by overall and site. For the Maintenance Period subject randomized and subjects randomized but not treated will be summarized by overall and site, and all placebo-treated subjects will also be included for the summary.

Subject accounting by visit will be summarized by treatment group and overall for the Initial Period and the Maintenance Period at each visit (scheduled visits only).

Subject disposition will be summarized based on the ITT population by treatment group for the Initial Period and the Maintenance Period. Summaries will include subjects randomized, subjects randomized but not treated, subjects treated, subjects completed treatment, subjects discontinued treatment, primary reason for discontinuation of treatment (including summary of subjects who stopped treatment due to COVID-19), subjects completed the study, subjects discontinued from the study, primary reason for discontinuation from the study (including summary of subjects who discontinued due to COVID-19), subjects rolled over to long term extension (LTE), subjects completed Follow-up. Subjects who stopped treatment or discontinued study due to COVID-19 will be identified using “Other” specify field in CRF or “Comment as needed”.

Subject disposition will also be summarized by site on the ITT population.

Screen failure will be summarized for all screened subjects. Number of subjects screened and failed will be presented. Number and percentage of reason for screen failure will be summarized.

Subjects in each analysis population (ITT, Safety, PK, and PP population only for Initial Period) will be summarized by treatment group on the ITT population for each period.

In addition, time (days since the first dose of study drug) to permanent discontinuation of study drug by reason for discontinuation will be displayed graphically in subjects having permanently discontinued from the study drug.

Maintenance Period summary will include all subjects either who completed the Initial Period and re-randomized to the Maintenance Period or who received Placebo in both Initial and Maintenance Period.

Randomization, study completion, drug completion, visit dates will be listed for the ITT population. Screen failure reason will also be listed. Additional listings of discontinuation reason, missed visit and missed assessment for subjects who discontinued due to COVID-19 will be presented for the ITT population. An additional listing for Covid-19 relevant comments will be presented for the ITT population.

Analysis population will be summarized and listed on the ITT population.

9.2. Demographic and Baseline Characteristics

All variables will be summarized by treatment group at Baseline and Maintenance Baseline respectively. Summary statistics for demographic and other Baseline characteristics will be presented for the ITT, SAF, PP and PK population.

Age (years), height (cm), weight (kg), and BMI (kg/m^2) will be summarized using summary statistics for continuous variables. Age groups (12-17, 18-65, and > 65), sex, region (Europe, North America, Asia Pacific), country, race, ethnicity, and smoking status will be summarized using the summary statistics for categorical variables. Weight and BMI will additionally be presented for each age group. For the summary of height, weight and BMI in Maintenance Period, Maintenance Baseline will be used.

The Baseline disease characteristics, EASI, IGA, weekly average PP-NRS, PP-NRS (<7 and ≥7), weekly average AP-NRS, weekly SD-NRS, CCI [redacted] will be summarized. IGA will be summarized as a categorical variable. For Maintenance Period, Maintenance Baseline will be used to summarize.

A summary table for the stratification factors will be provided to show any discrepancies between what was reported through Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS) versus stratification using actual data at Baseline. Actual PP-NRS score will be derived using the diary data.

All demographic and baseline characteristics data will be listed on the ITT population.

9.3. Medical History

Medical history will be collected only at screening and will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 25.0, March 2022).

Medical history will be summarized by treatment group and period. The summary will include number and percentage of subjects reporting each system organ class (SOC) and preferred term (PT) and will be sorted alphabetically by SOC and descending frequency of PT within SOC in the Nemolizumab 30mg Q4W group. Summary tables will be presented for the ITT population.

Medical history data listings will be presented by subject number, period, start date, stop date, SOC, and PT for the ITT population.

9.4. Medical and Surgical Procedures

Medical and surgical procedures will be coded using MedDRA, Version 25.0, March 2022.

Prior medical and surgical procedures are defined as those which have been stopped before first treatment.

- Procedure before informed consent signed is defined as those stopped before the date of informed consent signed to the study.
- Procedure during screening period is defined as those stopped on or after the date of informed consent signed until before first treatment date.

Concomitant medical and surgical procedures will be defined as those started or stopped on or after the first treatment, or were ongoing during the study. If a procedure is started before the first treatment but ongoing or stopped on or after the first treatment, it will be considered concomitant.

- Procedures during treatment period are defined as those started, stopped, or ongoing during the period.
    - Procedure during Initial Period is defined if started or stopped or ongoing during Initial Period.
    - Procedure during Maintenance Period is defined if started or stopped or ongoing during Maintenance Period.
    - If early discontinued during Initial (or Maintenance) Period, the treatment period will be defined from start of treatment till 4 weeks after the last treatment or early discontinuation date whichever is earlier.
- Procedures during follow-up period are defined as those started, stopped, or ongoing during the period.
    - Follow-up Period is defined if used from post treatment period to follow-up visit date.
    - Procedure during Follow-up Period will be summarized in accordance with the respective period (Initial or Maintenance).
- If procedure is being used continuously during both periods (e.g., started in the Initial Period and ended or ongoing in the Maintenance Period), it will be counted for each period.

If the stop date and 'ongoing' are missing then the procedure will be considered concomitant. If stop date is partially missing, the procedure will be considered concomitant unless the non-missing part of date proves it ended prior to the first treatment date.

The following medical and surgical procedures (prior, concomitant and rescue procedures) will be summarized by treatment group and period using the number and percent of subjects reporting each SOC and PT and sorted alphabetically by SOC and descending frequency of PT within SOC in the Nemolizumab 30mg Q4W group. Summary tables will be presented for the ITT population.

- Prior procedure before screening (before informed consent date)
- Prior procedure before first dosing (from screening [informed consent date] before the first treatment)
- Concomitant procedure during treatment period (initial and maintenance)
- Concomitant procedure during follow-up period
- Rescue procedure during treatment period (initial and maintenance)
- Rescue procedure during follow-up period

Medical and surgical procedures listings and rescue procedure listing will be presented by treatment group for ITT population and sorted by subject number, start date, stop date, SOC, and PT.

9.5. Medication

Medications will be classified and summarized on the ITT population as follows:

- Prior medications are defined as those which stop before the first injection of study drug during the study.
    - Prior medication before informed consent signed is defined as those stopped before the date of informed consent signed to the study.
    - Prior medication during screening period is defined as those stopped during screening period (on or after the informed consent date until before the first treatment date).
- Concomitant medications are defined as those started or stopped on or after the first injection of study drug.

- Medication during treatment period are defined as those started, stopped, or ongoing during the period.
  - Medication during Initial Period is defined if started or ongoing or ended during Initial Period.
  - Medication during Maintenance Period is defined if started or ongoing or ended during Maintenance period.
  - If early discontinued during Initial (or Maintenance) Period, the treatment period will be defined from start of treatment till 4 weeks after the last treatment or early discontinuation date whichever is earlier.
- Medication during follow-up period are defined as those started, stopped, or ongoing during the period.
  - Follow-up Period is defined from post treatment period to follow-up visit date.
  - Medication during Follow-up Period will be summarized in accordance with the respective period (Initial or Maintenance).
- If medication is being used continuously during both periods (e.g., started in the Initial period and ended or ongoing in the Maintenance period), it will be counted for each period.

If the stop date and 'ongoing' are missing then the medication will be considered as concomitant medication. If stop date is partially missing, the medication will be considered as concomitant unless the non-missing part of date proves it ended prior to the first treatment date.

Medications (prior, concomitant and rescue medications) will be coded using Version B3 March 2022 of the World Health Organization's Drug Dictionary (WHO DD). Preferred Anatomical Therapeutic Chemical (ATC) coding will be performed.

The following summaries by ATC level 2, ATC level 4 and preferred term (PT) will be produced on the ITT population. Subjects with more than one medication in a given ATC level and preferred name will be counted only once in that category. It will be sorted ATC level alphabetically and descending frequency in PT within ATC level term.

- Prior medication before screening (before informed consent date)
- Prior medication before first dosing (from screening [informed consent date] before the first treatment)
- Concomitant medication during treatment period (initial and maintenance)
- Concomitant medication during follow-up period
- Rescue medication during treatment period (initial and maintenance)
- Rescue medication during follow-up period
- Background topical therapy (TCI/TCS) during treatment period (initial and maintenance)
- Background topical therapy (TCI/TCS) during follow-up period

All medications (prior and concomitant medications, rescue medications, background TCI/TCS will be listed for the ITT population. In addition background TCI/TCS dispensation and receipt will be listed for the ITT population.

9.6. Extent of Exposure

The extent of exposure will be summarized for the Initial Period and the Maintenance Period. Summary for Overall Treatment Period (from Initial to Maintenance Period) will be included in the Maintenance Period summary table.

The number of subjects exposed will be summarized for the Initial Period and Maintenance Period, and Overall Period (Initial + Maintenance).

- Treatment duration (in days) is calculated as follows, where date of first treatment is defined as the first day of the relevant study Period: [(date of last treatment – date of first treatment) + 1].
- Total number of doses administered will be calculated as the sum of all doses of study drug administered.
- Total number of doses planned will be calculated as the sum of all doses of study drug planned (dispensed) according to the treatment schedule of the treatment group. If a subject missed dosing due to skipped visit or completed a visit without dosing, this missed dose which is supposed to be dispensed will be accounted for the calculation.
- The number of subjects who missed at least one dose
- The number of subjects who missed at least one dose due to COVID-19*
- The number of doses missed
- The number of doses missed due to COVID-19*

**The reason for dose not administered reported in CRF is COVID-19 [This will be identified using Other specify field in CRF].*

9.7. 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).

Treatment compliance(%) will be calculated by Period as total number of actual injections/ total number of expected injections*100.

10. Efficacy

The ITT population will be the primary population for all efficacy analyses. Both primary and key secondary and secondary endpoints of the Initial Period will be analyzed for the following populations:

- Full population which includes all subjects in ITT population
- Baseline PP NRS ≥ 7

All efficacy variables will be summarized by treatment group at each analysis visit, separately for the Initial Period and Maintenance Period. The primary comparison of interest is nemolizumab 30 mg compared to placebo for the co-primary endpoints in both populations (Full population; Baseline PP NRS ≥ 7).

To control the type I error at 5% significance level, a serial gatekeeping approach will be implemented. The co-primary endpoints will be tested at 2.5% significance level for each population. If both co-primary endpoints are statistically significant at 2.5% significance level, the key secondary endpoints will be tested sequentially following hierarchical testing procedure using the pre-specified order of endpoints for each population. The comparisons for key secondary endpoints will be made sequentially, and the subsequent tests will be stop when no statistical difference is found.

If p < 2.5% for all endpoints (co-primary and key secondary) in at least one population, then 2.5% will be recycled to test other population at 5% level of significance.

Other secondary endpoint comparisons will not be adjusted for multiplicity.

10.1. Primary Efficacy Endpoints and Analysis

10.1.1. Primary Analysis of Primary Efficacy Endpoint

Primary efficacy endpoint consists of the two co-primary endpoints:

- Proportion of subjects with an IGA* success (defined as an IGA of 0 [clear] or 1 [almost clear] and a ≥ 2-point reduction from Baseline) at Week 16
- Proportion of subjects with EASI-75* (≥ 75% improvement in EASI from Baseline) at Week 16

  * Further details regarding IGA and EASI-75 can be found in Sections 10.3.1 and 10.3.2 respectively.

Assessment results after taking rescue medication will be considered as treatment failure i.e. non-responders. Missing values at Week 16 will be treated as non-responder.

Both co-primary endpoints will be analyzed using a Cochran-Mantel-Haenszel test adjusted for the randomized stratification variables (IGA severity [3=moderate, 4=severe] and PP NRS [≥7, <7] for full population; IGA severity only for Baseline PP NRS >=7 population) at 2.5% significance level (2-sided). In addition an unadjusted CMH test will be performed.

The proportion of subjects with IGA success and with EASI-75 at Week 16 will be summarized. The estimate of treatment unadjusted difference with the corresponding 2-sided 95% confidence interval and strata-adjusted difference with the corresponding 2-sided 97.5% confidence interval, and p-values will be presented.

Bar charts for the proportions of subjects with IGA success and subjects with EASI-75 at Week 16 will be presented.

In addition, the proportion of subjects with IGA success will be analyzed using non-responder imputation on the ITT population excluding subjects who used the different version of IGA.

Additional summary tables for primary endpoints will also be presented by visit but excluding subjects from the visit summarized if the visit was affected by pandemic.

10.1.2. Sensitivity Analyses of Primary Efficacy Endpoint

The following sensitivity analyses for both populations will be conducted for the robustness of the primary analyses.

- Same analysis on PP population
- Tipping point analysis (see Appendix 22.1)
- Multiple imputation (MI) methods (see Appendix 22.1)
- Last Observation Carried Forward (LOCF) imputation method for missing data Missing post-baseline values will be carried forward from the last non-missing post-baseline value. Baseline value will not be carried forward to post-baseline value.
- Observed Case (OC) - no data will be imputed. For this analysis, if any rescue medication is received, data post-rescue therapy will be analyzed as observed (i.e., not considered treatment failure).
- Same analysis on ITT using 'actual stratum' instead of 'stratum at the randomization'.

Tipping point analysis, multiple imputation methods, LOCF and OC analysis will be performed on the ITT population. Except OC analyses, assessments on or after rescue therapy used will be considered as treatment failure and will be considered as non-responders for analysis.

10.1.3. Subgroup Analyses of Primary and Key Secondary Efficacy Endpoints

In addition, the same analyses as described in Section 10.1.1 (with strata-adjusted 95% CI instead of strata-adjusted 97.5% CI) will be performed for the subgroups defined in Section 8.6.

The subgroup analyses will be performed on the ITT population (Full population; Baseline PP NRS ≥ 7) for primary and key secondary endpoints. Forest plot will be presented along with subgroup analysis results.

10.2. Key Secondary Efficacy Endpoints and Analysis

The same analyses as described in Sections 10.1.1, 10.1.2 and 10.1.3 will be performed for the key secondary endpoints on the ITT population (both Full population and population with baseline PP NRS≥7). Key secondary endpoints are defined as follows:

- Proportion of subjects with an improvement of PP NRS ≥ 4 at Week 16
- Proportion of subjects with PP NRS < 2 at Week 16

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Same with primary endpoints, additional summary tables for key secondary endpoints will be presented by visit but excluding subjects from the visit summarized if the visit was affected by pandemic.

As a sensitivity analysis, summary tables for key secondary endpoints will be presented by visit but using weekly average PP/SD NRS with at least 2 non-missing diary and also with at least 3 non-missing diary, respectively. No analysis visit window extension at Week 16 applies.

Further details regarding IGA, EASI-75, PP NRS and CCI [redacted] can be found in Sections 10.3.1, 10.3.2, 10.3.3 and 10.3.4.

In addition, forest plots will be presented for co-primary and key secondary endpoints on the ITT population.

10.3. Secondary Efficacy Endpoints and Analysis

Secondary efficacy endpoints during Initial Period:

Secondary endpoints during Initial Period will be analyzed for both populations (Full population; Baseline PP NRS ≥ 7) on the ITT population.

If a subject received any rescue therapy, the data on or after receipt of rescue therapy will be considered as treatment failure.

Hypothesis testing of between group treatment differences will only be applied to endpoint variables. All other variables, e.g. IGA, will be summarized descriptively.

Binary endpoints will be analyzed using a Cochran-Mantel-Haenszel test adjusted for the randomized stratification variables (IGA severity [3=moderate, 4=severe] and PP NRS [≥7, <7] for full population; IGA severity only for Baseline PP NRS >=7 population). Any subjects with missing data at respective Weeks will be regarded as a non-responder.

Analysis methods for continuous and QoL endpoints are listed in Table 10-1 below.

Continuous and QoL endpoints (change from Baseline to each visit) will be analyzed using an analysis of covariance (ANCOVA) including treatment group and randomization stratification variables as factors and appropriate Baseline values as a covariates, if applicable. Missing values will be imputed using MI under MAR assumption (see Appendix 22.1). The least squares means, estimated standard error, and 95% confidence interval (CI) for each endpoint will be presented for each treatment group and analysis visit. The estimated treatment difference for each endpoint at each analysis visit will be summarized by presenting the difference in least squares means between treatment groups, the two-sided 95% CI, and associated p-value. In addition, change from Baseline to each analysis visit in EASI, PP-NRS, CCI [redacted] CCI [redacted] and percent change from Baseline in PP-NRS and CCI [redacted] will be analyzed using a MMRM approach, including terms of treatment group, stratification variables, appropriate Baseline values, visit, and interactions between baseline score with visit and treatment group with visit. Kenward-Roger approximation will be used to estimate denominator degrees of freedom. An unstructured covariance will be used to model the within-patient errors in the analysis. If calculation within proc mixed for unstructured covariance not possible for "Type=UN" then use instead "Type=CS". A linear contrast will be used, within the MMRM framework, to estimate difference between nemolizumab and placebo. The least squares

means, estimated standard error, and 95% CI for each endpoint will be presented for each treatment group and scheduled analysis visit. The estimated treatment difference for each endpoint at each visit will be summarized by presenting the difference in least squares means between treatment groups, the two-sided 95% CI, and associated p-value. CCI [redacted]

Table 10-1 Analysis Methods

Continuous/QoL Endpoints in Initial Period	Analysis Method
EASI	ANCOVA using MI-MAR, MMRM
PP NRS	ANCOVA using MI-MAR, MMRM
CCI [redacted]	

All efficacy endpoints of the Initial Period will be summarized by treatment and analysis visit.

Secondary Endpoints During Maintenance Period:

All secondary endpoints of the Maintenance Period will be descriptively summarized by treatment group at each analysis visit for the ITT population.

10.3.1. Investigator's Global Assessment (IGA)

The IGA is a 5-point scale ranging from 0 (clear) to 4 (severe) used by the investigator or trained designee to evaluate the global severity of AD and the clinical response to a treatment (see Table 10-2).

Table 10-2: Investigator Global Assessment Scale

Status	Score	Definition
Clear	0	Minor, residual hypopigmentation/hyperpigmentation, no erythema or induration/papulation, no oozing/crusting.
Almost clear	1	Trace faint pink erythema, with barely perceptible induration/papulation and no oozing/crusting.
Mild	2	Faint pink erythema with mild induration/papulation and no oozing/crusting.
Moderate	3	Pink-red erythema with moderate induration/papulation with or without oozing/crusting.
Severe	4	Deep or bright red erythema with severe induration/papulation with oozing/crusting.

IGA success is defined as 0 (clear) or 1 (almost clear) on the IGA scale and a ≥ 2-point reduction from Baseline.

During Initial Period:
IGA will be collected at Screening, Baseline, Week 4, Week 8, Week 12, Week 16 and Early termination of the Initial Period.

IGA will be summarized as a categorical and continuous variable at each analysis visit. Absolute change from Baseline for the IGA score will also be presented in the summary for ITT and PP population.

IGA success will be calculated using Initial Period Baseline as the reference point for change on the IGA scale. The proportion of subjects with IGA success (OC, non-responder, LOCF) will be summarized.

Line plot for proportion of subject with IGA success using Non-responder imputation will be presented for Initial Period on the ITT population.

The number and percentage of subjects with IGA success and the number and percentage of subjects who achieved IGA success and an improvement of PP NRS >=4 from Baseline will be analyzed up to Week 12 for the ITT population using non-responder.

The estimate of treatment unadjusted and strata-adjusted differences with the corresponding 2-sided 95% confidence intervals, and p-values from the Cochran-Mantel-Haenszel test will be presented.

During Maintenance Period:
IGA will be collected at Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48 and Early termination of the Maintenance Period.

IGA will be summarized as a categorical and continuous variable at each analysis visit. Absolute change from Baseline and from Week 16 will be also presented in the summary for the ITT population.

IGA success will be calculated using Baseline and Maintenance Baseline (Week 16) as the reference point for change on the IGA scale. The proportion of subjects with IGA success will be summarized using OC, Non-responder and LOCF.

Line plot for proportion of subject with IGA success from Baseline using Non-responder imputation will be presented for Maintenance Period on the ITT population.

For the subset of subjects achieving IGA success at Week 16, the proportion of subjects maintaining IGA success at each visit throughout the Maintenance Period will be summarized. 'Maintaining IGA success'

is defined if achieved IGA success at every analysis visit until the analysis visit summarized. For example, if a subject achieved IGA success until Week 28 except Week 24, this subject will not be counted as 'Subjects maintained IGA success' at Week 28.

The number and percentage of subjects who achieved IGA success and an improvement of PP NRS >=4 from Week 16 will be summarized for the ITT population using OC and for the subset of subjects with such a response at Week 16.

No hypothesis testing will be performed for Maintenance Period.

10.3.2. Eczema Area and Severity Index (EASI)

The EASI is a validated measure commonly used in clinical trials and clinical practice to assess the severity and the extent of AD signs. The EASI score is a composite score ranging from 0 to 72 (see Table 6). The severity of erythema, induration/papulation, excoriation, and lichenification will be assessed by the investigator or trained designee on a scale of 0 (absent) to 3 (severe) for each of the 4 body areas: head/neck, trunk, upper limbs, and lower limbs, with half points allowed. In addition, the extent of AD involvement in each of the 4 body areas will be assessed as a percentage by body area of head, trunk, upper limbs, and lower limbs, and converted to a score of 0 to 6. The EASI score will be calculated (see Table 10-3).

Table 10-3: Eczema Area and Severity Index (EASI)

Body region	**EASI score**
Head/Neck (H)	(E + I + Ex + L) x Area x 0.1
Upper limbs (UL)	(E + I + Ex + L) x Area x 0.2
Trunk (T)	(E + I + Ex + L) x Area x 0.3
Lower limbs (LL)	(E + I + Ex + L) x Area x 0.4
EASI =	Sum of the above 4 body region scores

EASI-50, EASI-75 and EASI-90 are defined as a ≥50%, ≥75%, ≥90% improvement in EASI from Baseline, respectively.

<u>During Initial Period:</u>
EASI will be collected at Screening, Baseline, Week 4, Week 8, Week 12, Week 16 and Early termination of the Initial Period.

EASI will be summarized as a continuous variable at each analysis visit. Absolute change and percent change from Baseline for the EASI score will also be included in the summary for ITT and PP population.

Change from Baseline in EASI at each analysis visit up to Week 16 will be analyzed using ANCOVA, with missing values imputed using MI under MAR assumption, and MMRM. For the MI and MMRM analyses the least squares means (LSMeans), standard error of LSMeans, and 95% CI for change from Baseline, as well as the difference in LSMeans between the treatment groups, the two-sided 95% CI, and associated p-value will be presented. In addition, percent change from Baseline in EASI at each analysis visit up to Week 16 will be analyzed using MMRM.

EASI-50/75/90 will be calculated using Baseline as the reference point for change in EASI score. The proportion of subjects achieving EASI-50/75/90 (OC, non-responder, LOCF) will be summarized on ITT population. And the results using OC will be provided for PP population.

For the proportion of subjects with EASI-50/75/90 (non-responder) and subjects with EASI-75 and PP NRS improvement ≥ 4 (non-responder), the estimate of treatment unadjusted and strata-adjusted differences with the corresponding 2-sided 95% confidence intervals, and p-values from the Cochran-Mantel-Haenszel test will be presented.

Line plot for proportion of subject with EASI-50/75/90 from Baseline using Non-responder imputation will be presented for Initial Period on the ITT population.

Individual components of the EASI score (averaged across body regions) will be summarized as continuous variables. Change from Baseline in individual components of the EASI score will also be presented in the summary table.

Change from Baseline in individual components of the EASI (averaged across body regions) at each analysis visit up to Week 16 will be analyzed using MMRM. For the MMRM analyses the least squares means (LSMeans), standard error of LSMeans, and 95% CI for change from Baseline, as well as the difference in LSMeans between the treatment groups, the two-sided 95% CI, and associated p-value will be presented.

<u>During Maintenance Period:</u>
EASI will be collected at Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, and Week 48 of the Maintenance Period.

EASI will be summarized as a continuous variable at each analysis visit. Absolute change and percent change from Baseline and Maintenance Baseline (Week 16) in EASI at each analysis visit up from Week 16 to Week 48 will also be summarized.

EASI-50/75/90 will be calculated using Baseline and Maintenance Baseline (Week 16) for change in EASI score. The proportion of subjects with EASI-50/75/90 will be summarized using OC, non-responder and LOCF.

Line plot for proportion of subject with EASI-50/75/90 from Baseline using Non-responder imputation will be presented for Maintenance Period on the ITT population.

For the subset of patients achieving EASI-75 at Week 16, the proportion of subjects maintaining EASI-75 at each visit throughout the Maintenance Period will be summarized. ‘Maintaining EASI-75’ is defined if a subject achieved EASI-75 at every analysis visits until the analysis visit summarized. For example, if a subject achieved EASI-75 until Week 28 except Week 24 then this subject will not be considered as “Subject maintaining EASI-75” at Week 28.

The number and percentage of subjects who achieved EASI-75 and an improvement of PP NRS >=4 from Week 16 will be summarized for the ITT population using OC and for the subset of subjects with such a response at Week 16.

Individual components of the EASI score will be summarized as continuous variables. Change in individual components of the EASI score at each analysis visit from Week 16 to Week 48 will also be summarized.

No hypothesis testing will be performed.

10.3.3. Pruritus Numeric Rating Scale (NRS)

The Pruritus NRS is a scale to be used by the subjects to report the intensity of their pruritus (itch) during the last 24 hours. Peak pruritus (PP NRS) is an assessment of the maximum itch intensity in that Period while average pruritus (AP NRS) provides a measure of overall pruritus intensity.

Subjects will be asked the following question:

- For maximum itch intensity (PP NRS): "On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable', how would you rate your itch at the worst moment during the previous 24 hours?"
- For average itch intensity (AP NRS): "On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable', how would you rate your itch overall during the previous 24 hours?"

The screening PP/AP NRS will be determined by a single assessment using the PP/AP NRS (score ranging from 0 to 10) for the 24-hour Period immediately preceding the screening visit. The Baseline PP/AP NRS will be determined based on the average of daily PP/AP NRS (score ranging from 0 to 10) respectively during the 7 days immediately preceding Baseline (rounding to nearest whole number is not permitted). A minimum of 4 daily scores out of the 7 days immediately preceding Baseline is required for this calculation. PP/AP NRS at all follow-up visits will be determined in the same manner. Refer the details for the analysis visit window for diary data in Section 8.4. Subjects will receive instructions on how to record their PP/AP NRS scores and will complete the assessment once daily in the evening throughout the clinical study (including the run-in and the Follow-up Period).

In case of diary data, if the date of rescue therapy use is within the analysis visit window, the subject at the analysis visit will be treated as treatment failure except for OC analysis, and the weekly average will be imputed using the worst-case value for analysis

<u>During Initial Period:</u>
PP NRS will determined by an average as described above at every week from Baseline to Week 16 as a continuous variable for the Initial Period.

Descriptive summary of PP NRS will be provided for ITT and PP populations. Absolute change and percent change from Baseline for the PP NRS score will also be included in the summary.

AP NRS will determined by an average as described above at every week from Baseline to Week 16 as a continuous variable of the Initial Period. Descriptive summary of AP NRS will be provided for ITT population. Absolute change and percent change from Baseline for the AP NRS score will also be included in the summary.

Change from Baseline in PP NRS at each analysis visit up to Week 16 will be analyzed using ANCOVA, with missing values imputed using MI under MAR assumption, and MMRM. For the MI and MMRM analyses the least squares means (LSMeans), standard error of LSMeans, and 95% CI for change from Baseline, as well as the difference in LSMeans between the treatment groups, the two-sided 95% CI, and associated p-value will be presented. In addition, percent change from Baseline in PP NRS at each analysis visit up to Week 16 will be analyzed using MMRM.

Change from Baseline in percentage of itch-free days based on PP/AP NRS (score of 0 or 1) will also be summarized descriptively by visit.

Improvement in PP/AP NRS will be calculated using Baseline as the reference point for change in PP/AP NRS score. The proportion of subjects with PP NRS improvement ≥4 will be presented using OC, non-responder and LOCF. The proportion of subjects with an improvement of PP NRS ≥4 at Week 8 and Week 12, the proportion of subjects with a PP NRS <2 at Week 1, Week 2, Week 8 and Week 12, the proportion of subjects with AP NRS ≥4 at each visit up to Week 16, and the proportion of subjects with AP NRS < 2 at each analysis visit up to Week 16 will be analyzed using non-responder imputation. The estimate of treatment unadjusted and strata-adjusted differences with the corresponding 2-sided 95% confidence intervals, and p-values from the Cochran-Mantel-Haenszel test will be presented.

Line plot for proportion of subjects with PP NRS improvement ≥4 and for proportion of subjects with PP NRS <2 using Non-responder imputation will be presented for Initial Period on the ITT population.

"Itch-free days" will be defined if PP/AP NRS score is 0 or 1. The proportion of "itch-free days" will be calculated using 7 days diary data for the visit. A minimum of 4 daily scores out of the 7 days for the visit is required for the proportion calculation. The proportion of "itch-free days" will be calculated using number of days of PP/AP NRS score of 0 or 1 divided by number of days reported during the week. The summary of proportion of "itch-free days" based on PP NRS/AP NRS will be presented for Initial Period.

<u>During Maintenance Period:</u>
PP/AP NRS will determined by an average using 7 days data before the visit for Week 24, Week 32, Week 40, Week, Week 48 as a continuous variable for the Maintenance Period. Absolute change and percent change from Baseline and Maintenance Baseline (Week 16) for the PP/AP NRS score will also be included in the summary. No hypothesis testing will be performed.

Improvement in PP/AP NRS will be calculated using Baseline and Maintenance Baseline (Week 16) as the reference point for change in PP/AP NRS score. The proportion of subjects with an improvement of PP/AP NRS ≥4 and the proportion of subjects with a PP/AP NRS <2 will be summarized.

For the subset of patients achieving an improvement of PP/AP NRS ≥4 at Week 16, the proportion of subjects achieved such an improvement at each analysis visit during the Maintenance Period will be summarized. For the subset of patients achieving a PP/AP NRS <2 at Week 16, the proportion of subjects with PP/AP NRS <2 at each visit during the Maintenance Period will be summarized using OC.

Line plot for proportion of subjects with PP NRS improvement ≥4 and for proportion of subjects with PP NRS <2 using Non-responder imputation will be presented for Maintenance Period on the ITT population.

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CCI

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<u>During Initial Period:</u>
POEM will be collected at Baseline, Week 8, and Week 16 of the Initial Period. POEM total score will be summarized as a continuous variable using OC for ITT population. Absolute change from Baseline in POEM total score will also be summarized.

Change from Baseline in POEM total score at each visit up to Week 16 will be analyzed using ANCOVA, with missing values imputed using MI under MAR assumption. For the MI and MMRM analyses the least squares means (LSMeans), standard error of LSMeans, and 95% CI for change from Baseline, as well as the difference in LSMeans between the treatment groups, the two-sided 95% CI, and associated p-value will be presented.

<u>During Maintenance Period:</u>
POEM will be collected at Week 32, and Week 48 of the Maintenance Period. POEM total score will be summarized as a continuous variable using OC for ITT population. Absolute change from Baseline and Maintenance Baseline (Week 16) in POEM total score will also be summarized.

No hypothesis testing will be performed.

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[redacted]

During Initial Period:

The number and percentage of subjects who used rescue therapy during Initial Period will be summarized by medication group (topical, phototherapy, systemic), category (for topical, systemic), preferred term and analysis visit and overall during the Initial Period.

In addition, the time (in days) to first rescue therapy use will be calculated during the Initial Period using Kaplan-Meier methodology by presenting the point estimates of the quartiles estimates with the corresponding 95% CI. Subjects who do not use any rescue therapy during Initial Period will be censored for the analysis and date of last visit of Initial Period will be used as the censoring date. Subjects who discontinued during Initial Period without intake of rescue therapy will also be censored as described above. Kaplan-Meier curve will also be provided.

During Maintenance Period:

The number and percentage of subjects who used rescue therapy during Maintenance Period will be summarized by medication group (topical, phototherapy, systemic), category (for topical, systemic), preferred term and analysis visit and overall during maintenance period.

In addition, the time (in days) to first rescue therapy from Week 16 will be calculated during the Maintenance Period. Kaplan-Meier estimates of time to first rescue therapy will be summarized. Subjects without such an event during Maintenance Period will be censored for the analysis and date of last visit of Maintenance Period will be used as the censoring date. Subjects who discontinued during Maintenance Period without intake of rescue therapy will also be censored as described above. Kaplan-Meier curve will also be provided.

10.3.24. Relapse during Maintenance Period

Relapse is defined as worsening of AD requiring rescue therapy, if judged to be medically necessary by the investigator (i.e., clinically significant worsening of signs and/or symptoms of AD). Relapse will be determine using AE, PR and CM data.

The number and percentage of subjects with relapse (worsening of AD requiring rescue therapy) will be summarized for the Maintenance Period using OC.

In addition, the time to first relapse from Week 16 will be calculated during the Maintenance Period using Kaplan-Meier methodology by presenting the point estimates of the quartiles estimates with the corresponding 95% CI. Subjects without such an event during Maintenance Period will be censored for the analysis and date of last visit of Maintenance Period will be used as the censoring date. Subjects who discontinued during Maintenance Period without relapse will also be censored as described above. Kaplan-Meier curve will also be provided.

CCI

[redacted]

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[redacted]

13. Safety

All safety data will be summarized and listed on the Safety population.

Safety assessments will be conducted for all subjects at the screening visit (upon signing of the ICF) and at every subsequent visit. Safety will be assessed on the basis of AEs, unexpected adverse reactions, clinical laboratory data, vital signs, physical examination, respiratory examination, and ECG parameters. Summary of all safety endpoints will be presented by study Period (Initial Period, Maintenance Period, and Follow-up Period) for each treatment group.

13.1. Adverse Events

Adverse events (AEs) will be coded using MedDRA Version 25.0, March 2022.

Treatment-emergent AEs, defined as those AEs occurring after the first administration of study treatment until end of study, will be tabulated in frequency tables by System Organ Class (SOC) and Preferred Term (PT) based on the Medical Dictionary for Regulatory Activities for each study period (Initial Period, Maintenance Period, and Follow-up Period). Missing date information will be handled using the algorithm described in Section 8.3.

Additional summary tables by SOC and PT will be provided for SAEs, AEs related to the study drug(s), AEs related to the study procedure, adverse events of special interest (AESIs), and AEs leading to treatment discontinuation and study withdrawal.

AEs will be summarized using the number and percent of subjects reporting each SOC and PT and sorted alphabetically by SOC and by descending frequency of PT within SOC.

Subjects who experienced multiple events within the same SOC will be counted once in the SOC summary. When summarizing by causality or maximum severity, if a subject experiences more than 1 occurrence of the same AE, the occurrence with the greatest severity and the closest association with the study drug will be used in summary tables. For summary by maximum severity, subjects who experience multiple occurrence of an AE, the most severe category for each SOC and for each PT within each SOC will be considered in the summary.

TEAEs related to study drug/study procedure are those that are identified as reasonable possibility.

If relationship or severity is missing, the event will be considered as AE related to study drug/study procedure or severe AE.

An AESI is a noteworthy treatment-emergent event for the study drug that should be monitored closely and reported promptly. An AESI can be either serious or non-serious. Based on the potential risks of nemolizumab and the risks associated with biologics in general (i.e., class effects), the following AEs will be considered as AESIs: Injection-related reactions, Newly diagnosed asthma or worsening of asthma, Infections, Peripheral edema:limbs, bilateral, Facial edema and elevated ALT or AST (>3xULN) in combination with elevated Bilirubin (>2xULN).

The following summary tables for TEAEs will be presented for all TEAEs (i.e., TEAE, all causalities) and study drug related TEAEs separately and by period (treatment period which includes Initial Period and Maintenance Period) and Follow-up Period.

- Overall Summary of TEAEs
  Overall summary table includes summary of subjects reporting TEAEs, TEAE related to study drug, TEAE related to protocol procedure (including topical background therapy), Serious TEAE, Serious TEAE related to study drug, Severe TEAE, TEAE leading to temporary discontinuation of

study drug, TEAE leading to permanent discontinuation of study drug, TEAE leading to permanent discontinuation from study, TEAE of special interest, TEAE leading to death, TEAE related to study drug leading to death. For the summary of Follow-up period, the summaries of 'temporary discontinuation of drug' and 'permanent discontinuation of drug' will not be provided.

- TEAEs by System Organ Class and Preferred Term
- Serious TEAEs by System Organ Class and Preferred Term
- TEAEs by System Organ Class, Preferred Term and Maximum Severity
- Severe TEAEs by System Organ Class and Preferred Term
- TEAEs Leading to Permanent Discontinuation of Study Drug by System Organ Class and Preferred Term, which is only for Treatment period. No summary of Follow-up period.
- TEAEs occurred in >= 5% of subjects by System Organ Class and Preferred Term
- TEAEs occurred in >= 5% of subjects by Preferred Term

For overall study period which includes all periods (initial, maintenance and follow-up), the following summary tables will also be presented and repeated for all TEAEs (all causalities) and study drug related TEAEs.

- Overall Summary of TEAEs
- TEAEs by System Organ Class and Preferred Term

The overall study period summary will be presented by 4 treatment groups (Nemolizumab 30mg Q4W, Nemolizumab 30mg Q4W to Q8W, Nemolizumab 30mg Q4W to Placebo, and Placebo). Nemolizumab 30mg Q4W includes all subjects in the population who received Nemolizumab 30mg in Initial Period or who received Nemolizumab 30mg Q4W continuously during Initial and Maintenance Periods. Similarly, Placebo includes all subjects in the population who received Placebo in Initial Period or who received Placebo continuously during Initial and Maintenance Periods.

For the subset of subjects with COVID-19 infection, the following summary tables will be provided additionally and it will be repeated for all TEAEs and Study drug related TEAEs, separately.

- Overall summary of TEAEs
- TEAEs by System Organ Class and Preferred Term
- Serious TEAEs by System Organ Class and Preferred Term
- TEAEs of Special Interest by Category, System Organ Class and Preferred Term

A separate summary below for TEAEs of Special Interest will be provided by periods (initial, maintenance) and repeated for all TEAEs (all causalities) and Study drug related TEAEs.

- Overall Summary of TEAEs of Special Interest
- TEAEs of Special Interest by Category, System Organ Class and Preferred Term
- TEAEs of Special Interest by Category, System Organ Class, Preferred Term and Maximum Severity

Adjudicated events will also be summarized as below by periods (initial, maintenance) and repeated for all TEAEs (all causalities) and Study drug related TEAEs.

- Adjudicated TEAEs by System Organ Class and Preferred Term, which are confirmed by Independent Adjudication Committee (IAC).
- Confirmed Adjudicated TEAEs by System Organ Class, Preferred Term and Maximum Severity. Maximum severity will be based on the severity adjudicated by IAC.
- Asthma TEAEs and TEAE of Special Interest reported by Investigator with Adjudication by IAC, which include the data reported by Investigator and adjudications by IAC.

The subgroup summary by country and age group will also be provided for the following summaries. It will be repeated for all TEAEs and Study drug related TEAEs and for Treatment period, Follow-up period and Overall period, separately.

- Overall summary of TEAEs
- TEAEs by System Organ Class and Preferred Term

In addition, the exposure-adjusted incidence rate (i.e., number of subjects per 100 patient-years) will be summarized for all TEAEs (all causalities) and study drug related TEAEs during Treatment Period.

Exposure-adjusted incidence rates of TEAEs is defined as the number of subjects exposed to treatment and experiencing a certain event divided by the total time of all subjects who are at risk for the event. Specially, for subjects with no event the exposure time is the time from the first drug intake to the end of treatment period. Exposure years is calculated as last study drug exposure date minus first study drug exposure date plus one, divided by 365.25 which is the number of days count in a year. This exposure year calculated for each subject is then added cumulatively and is derived for each treatment arm. So each treatment arm will have one value for exposure years (aka. patient years). The exposure year calculation is different in case of subjects who have completed the study or discontinued from the study or having withdrawn from the study due to any reason. Only the event occurred during the treatment period will account for calculation.

Subject listings will be presented for all TEAEs, TEAEs of special interest, serious TEAEs, severe TEAEs, TEAE leading to permanent discontinuation of study drug, TEAEs leading to death and pre-treatment AEs. Subject listings of TEAEs for subjects with COVID-19 infection and adjudicated Asthma TEAEs will also be listed.

13.2. Laboratory Evaluations

13.2.1. Clinical Laboratory Evaluations

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

The following parameters will be reported for laboratory data.

- **Hematology:** Hemoglobin, hematocrit, white blood cell (WBC) count (with differential including eosinophils), red blood cell (RBC) count, platelet count, and mean cell volume (MCV).
- **Chemistry:** Creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyltransferase (GGT), alkaline phosphatase, lactate dehydrogenase (LDH), total bilirubin, direct bilirubin, creatinine phosphokinase ([CPK], CPK isoenzyme test will be performed only if CPK is

elevated to > 2.5 × ULN), albumin, total protein, uric acid, sodium, potassium, calcium, chloride, glucose, urea, total cholesterol, triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL). Follicle-stimulating hormone (FSH) will be collected for postmenopausal subjects.

- **Urinalysis:** pH, glucose, ketones, blood, protein, leukocytes, nitrites, bilirubin, urobilinogen, and specific gravity.

Laboratory assessments are performed at Screening, Baseline, Week 8, Week 16, Early Termination and Follow-up during the Initial Period.

Laboratory assessments are performed at Week 32, Week 48, Early Termination and Follow-Up during the Maintenance Period.

Hematology and chemistry laboratory data (absolute values and change from Baseline; and change from Week 16 for Maintenance Period) will be summarized as continuous variables (scheduled visits only) for the Initial Period and the Maintenance Period. Urinalysis laboratory data will be summarized by visit (scheduled visit only). Last post-baseline, worst post-baseline and maximum post-baseline results will also be included and will include unscheduled visits in the derivation. And worst post-baseline value will be defined as the highest or lowest value relative to the reference range during the respective treatment Period.

Shift tables will be generated using the reference ranges (Low, Normal, High and Missing) for hematology and chemistry laboratory data. The number and percentage of subjects shifting from reference ranges between Baseline and each visit (scheduled visits only) will be summarized for the Initial Period and the Maintenance Period. In addition, shift table from Week 16 will be provided for the Maintenance Period. Last, worst and maximum post baseline values will also be included in the shift tables and will include unscheduled visits in the derivation. Worst post baseline value will be defined as the highest or lowest value relative to the reference range.

Summary of the number and percentage of subjects who met criteria of potential clinically significant (CS) value will be summarized (scheduled visits only) for hematology and chemistry laboratory data. Last, worst and maximum post-baseline results will also be included in the summary. Potentially CS ranges for adult and adolescent are listed in sections 22.3 and 22.4.

For statistical and graphical summaries of the laboratory tests, values below or above the limit of detection (e.g. '< 3' or '>500') are substituted with the lower limit of detection minus 1% for values below the lower limit and are substituted with the upper limit of detection plus 1% for values above the upper limit (e.g. '< 3' is substituted by '2.97', '> 500' is substituted by '505'). In data listings, the values are shown including the < or > sign.

Distribution of Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP), Total bilirubin and Creatinine Phospokinease (CPK) will be displayed graphically as boxplot by treatment group for each scheduled visit and the maximum post-Baseline (including unscheduled visits in the derivation) values for the Initial Period and the Maintenance Period.

By-subject listing will be presented for all laboratory data. By-subject listing for subjects with at least one abnormal result (out of reference range) will be provided for hematology and clinical chemistry. By-subject listing for subjects with at least one potentially CS result will be provided for hematology and clinical chemistry.

All laboratory data will be listed for the Safety population.

13.2.2. Pregnancy Testing

All women of childbearing potential will have a serum pregnancy test at the screening visit and urine pregnancy tests (UPTs) at Baseline, Week 4, Week 8, Week 12 and Week 16, Early termination visit, and Follow-up of the Initial Period. UPTs will also be performed at Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, and Week 48, Early termination visit, and Follow-up of the Maintenance Period. Pregnancy test results must be available prior to the administration of the study drug.

All confirmed pregnancy test results, premenses status and childbearing potential assessment results will be listed on the Safety population.

13.2.3. Virology and TB Testing

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

All virology results will be listed on the Safety population.

Subjects will be assessed for TB infection with a QuantiFERON-TB Gold test at the screening visit.

All TB test results will be listed on the Safety population.

13.3. Vital Signs

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.

Vital signs will be collected at the Screening visit and at Baseline, Week 4, Week 8, Week 12 and Week 16, Early termination visit, and at Follow-up of the Initial Period. Vital signs will also be collected at Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Early termination visit, and at Follow-up of the Maintenance Period.

Height and weight will be measured at Screening for all subjects. Height assessments will be conducted for adolescent subjects (aged 12-17) at Week 8 and 16 of the Initial Period, as well as Week 24, Week 32, Week 40, and Week 48 of the Maintenance Period and at Follow-up. Weight assessments will be conducted for adolescent subjects at Baseline, and Week 16 of the Initial Period as well as at Week 32, and Week 48 of the Maintenance Period and at Follow-up.

All vital signs including height and weight (absolute values and change from Baseline; and change from Week 16 for Maintenance Period) will be summarized as continuous (scheduled visits only) for the Initial Period and the Maintenance Period. Last post-Baseline results (including unscheduled visits in the derivation) will also be included.

The number and percentage of subjects who met criteria of potential CS value for vital signs and weight will be summarized (scheduled visits only) for the Initial Period and the Maintenance Period. Last post-Baseline results (including unscheduled visits in the derivation) will also be included.

Distribution of pulse rate, systolic and diastolic blood pressure will be displayed graphically as boxplot by treatment group for each scheduled visit and maximum post-Baseline (including unscheduled visits in the derivation) values for the Initial Period and the Maintenance Period.

By-subject listing of subjects with potentially CS vital signs and weight will be provided.

Potentially CS ranges for adult and adolescent are in sections 22.3 and 22.4.

13.4. ECG

A 12-lead Electrocardiogram (ECG) will be performed and read centrally at Screening, Week 16, Week 48, Early termination visit, and at Follow-up.

The overall results of the ECGs recorded as 'Normal', 'Abnormal, NCS' or 'Abnormal, CS' will be summarized by treatment group and visit (scheduled visits only) for the Initial Period and the Maintenance Period. Clinical significance will be determined by the investigator.

13.5. 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, gastrointestinal system, musculoskeletal system, lymph nodes, nervous system, and extremities.

A physical examination will be performed at Screening, Baseline, Week 4, Week 8, and Week 16 of the Initial Period. Physical examination will also be performed at Week 24, Week 32, Week 40, and Week 48 of the Maintenance Period, as well as at Early termination visit, and at Follow-up.

The number and percentage of subjects with physical examination results classified as 'Normal', 'Abnormal, not Clinically Significant (NCS)' or 'Abnormal, CS' will be summarized (scheduled visits only), and body system for the Initial Period and the Maintenance Period.

Shift from Baseline of the physical examination category will also be summarized by body system for the Initial Treatment Period and shift from Baseline and from Week 16 will be summarized for the Maintenance Period.

By-subject listing will be provided for subjects who have at least one abnormal results from any body system or who missed the assessment due to any reason.

13.6. Respiratory Assessments

13.6.1. Respiratory Examination and PEF Testing

A respiratory examination consisting of questions regarding medical history of asthma, wheeze, dyspnea, and cough, will be performed for all subjects at Screening, Baseline, Week 4, Week 8, Week 12 and Week 16 of the Initial Period and at Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, and Week 48 of the Maintenance Period, as well as at Early termination visit, and at Follow-up.

Respiratory examination questionnaire results will be listed on the Safety population.

PEF testing will be performed for all subjects at Screening, Baseline, Week 4, Week 8, Week 12 and Week 16 of the Initial Period and at Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, and Week 48 of the Maintenance Period, as well as at Early termination visit, and at Follow-up.

PEF (absolute values and change from Baseline; and change from Week 16 for the Maintenance Period) will be summarized as a continuous variable (scheduled visits only) for the Initial Period and the Maintenance Period. PEF will be summarized separately for the subset of subjects with, and without, a history of asthma.

The number and percentage of subjects with PEF < 80% will be summarized by treatment group, visit (scheduled visits only), and medical history of asthma (with and without history of asthma) for the Initial Treatment Period and the Maintenance Period.

13.6.2. Asthma Control Test

Subjects with a medical history of asthma will take an Asthma Control Test (ACT) at Screening, Baseline, Week 4, Week 8, Week 12 and Week 16 of the Initial Period and at Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, and Week 48 of the Maintenance Period, as well as at Early termination visit, and Follow-up.

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.

Subjects with a new (de novo) diagnosis of asthma during the trial will take the ACT beginning at the visit the diagnosis was first confirmed and at all subsequent study visits thereafter.

ACT total score (absolute values and change from Baseline) will be summarized as a continuous variable (scheduled visits only) for the Initial Treatment Period and the Maintenance Period.

The number and percentage of subjects with an ACT score ≤ 19 will be summarized (scheduled visits only) for the Initial Period and the Maintenance Period.

CCI

14. Interim Analyses

No interim analysis is planned.

15. Changes from Analysis Planned in Protocol

In protocol Section 8.4.9 (Prior and Concomitant Therapies), concomitant medications/therapies are defined as any therapies taken during the study (i.e., from the screening visit to the end of study).

However, for the analysis purpose, concomitant medications/therapies are defined as medications/ therapies which start or stop or ongoing on or after the 1st injection of study drug.

16. Reference List

Not applicable.

17. Programming Considerations

All TFLs and statistical analyses will be generated using SAS® 9.4 or higher (SAS® Institute Inc., Cary, NC, USA). Computer-generated TFL output will adhere to the following specifications.

17.1. General Considerations

- A separate SAS program will be created for each output.
- Each output will be stored in a separate file.
- Output files will be provided in separate Word RTF and PDF format.
- Output files will be delivered in PDF format.
- The final TFLs will be provided in a combined PDF document including a table of contents which are hyperlinked to each output.
- Numbering of TFLs will follow International Conference on Harmonization (ICH) E3 guidance.

17.2. Table, Figure, and Listing Format

17.2.1. General

- All TFLs will be produced in landscape format, unless otherwise specified.
- All TFLs will be produced on paper size A4 using the Courier New font, size 8.
- The data displays for all TFLs will have a 0.8 inch (2cm) binding margin on top and bottom of a landscape oriented page and a minimum 0.3 inch (0.8cm) margin on the left and right sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TFLs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

17.2.2. Headers

- All output should have the following header at the top left of each page:
- Galderma Protocol RD.06.SPR.118169
- Dry-run on dummy treatment/Draft/Final
- All output should have Page n of N at the top corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date output was generated should appear along with the program name as a footer on each page.

17.2.3. Display Titles

- Each TFL are identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended, but sponsor preferences are obtained before final determination. A decimal system (x.y and x.y.z) are used to identify TFLs with related contents. The title is centered. The analysis population are identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the table.
- Column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
ITT Population

17.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in Initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the dose group column.
- For numeric variables, include "unit" in column or row heading when appropriate.
- Analysis population sizes will be presented for dose group in the column heading as (N=XX) (or in the row headings, if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis population.

17.2.5. Body of the Data Display

17.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left-justified;
- Whole numbers (e.g., counts) are right-justified; and
- Numbers containing fractional portions are decimal aligned.

17.2.5.2. *Table Conventions*

- Units will be included where available
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	n
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented are included.
- An Unknown or Missing category are added to each parameter for which information is not available for 1 or more subjects.

- Unless otherwise specified, the estimated mean, median, Q1 and Q3 for a set of values are printed out to 1 more significant digit than the original values, and standard deviations are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. Missing descriptive statistics or p-values which cannot be estimated are reported as "-".
  - Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Pre-determine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis population for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.
- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data are presented by the body system, treatment class, or SOC. The body system, drug class and SOC are displayed in alphabetically order. Within body system, drug class and SOC, preferred term will be display in descending frequency. If incidence for more than 1 preferred term is identical, they should then be sorted alphabetically.
  - P-values are presented with 4 decimal places. If the p-value is less than 0.0001, it will be presented as <0.0001. If the p-value is returned as >0.9999, it is presented as >0.9999.
  - The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis population presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.
  - For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note as needed if the subject are included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.
  - Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

17.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of subject number, visit/collection day, and visit/collection time.
- Missing data are represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates are printed in SAS DATE9.format ("DDMMMYYYY": 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available.

17.2.5.4. *Figure Conventions*

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

17.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Notes:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line, where possible.
- Subject specific footnotes are avoided, where possible.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z').

18. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health standard operating procedure (SOP) Developing Statistical Programs (3907).

Syneos Health SOPs Developing Statistical Programs (3907) and Conducting the Transfer of Biostatistical Deliverables (3908) describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

19. Index of Tables

Header	Table Number	Name	Analysis Set
14		TABLES	
14.1		Demographic Data Summary Tables	
14.1.1		Subject Disposition	
	14.1.1.1	Subject Accounting by Overall, Country and Site	Screened Subjects
	14.1.1.2	Subject Accounting by Visit	ITT Population
	14.1.1.3	Summary of Subject Disposition – Initial Period	ITT Population
	14.1.1.4	Summary of Subject Disposition – Maintenance Period	Enrolled Subjects in Maintenance Period Population
	14.1.1.5	Summary of Subject Disposition by Site – Initial Period	ITT Population
	14.1.1.6	Summary of Subject Disposition by Site – Maintenance Period	Enrolled Subjects in Maintenance Period Population
	14.1.1.7	Summary of Screen Failure	Screened Subjects
	14.1.1.8	Summary of Analysis Population	ITT Population
14.1.2		Protocol Deviations	
	14.1.2.1	Summary of Major Protocol Deviations	ITT Population
	14.1.2.2	Summary of Major Protocol Deviations by Site	ITT Population
14.1.3		Demographic and Baseline Characteristics	
14.1.3.1		Subject Demographic and Baseline Characteristics	
	14.1.3.1.1	Subject Demographic and Baseline Characteristics	ITT Population
	14.1.3.1.2	Subject Demographic and Baseline Characteristics	Safety Population
	14.1.3.1.3	Subject Demographic and Baseline Characteristics	PP Population
	14.1.3.1.4	Subject Demographic and Baseline Characteristics	PK Population
14.1.3.2		Baseline Disease Characteristics	
	14.1.3.2.1	Summary of Baseline Disease Characteristics	ITT Population
	14.1.3.2.2	Summary of Baseline Disease Characteristics	Safety Population
	14.1.3.2.3	Summary of Baseline Disease Characteristics	PP Population
	14.1.3.2.4	Summary of Baseline Disease Characteristics	PK Population
	14.1.3.2.5	Summary of Proportion of Subjects with Incorrect Randomization Stratification	ITT Population
14.1.3.3		Medical History, Medical and Surgical Procedures	
	14.1.3.3.1	Summary of Previous and Ongoing Medical History	ITT Population

Header	Table Number	Name	Analysis Set
	14.1.3.3.2	Summary of Prior Medical and Surgical Procedures before Informed Consent Signed	ITT Population
	14.1.3.3.3	Summary of Prior Medical and Surgical Procedures during Screening Period	ITT Population
	14.1.3.3.4	Summary of Concomitant Medical and Surgical Procedures during Treatment Period	ITT Population
	14.1.3.3.5	Summary of Concomitant Medical and Surgical Procedures during Follow-up Period	ITT Population
	14.1.3.3.6	Summary of Rescue Medical and Surgical Procedures during Treatment Period	ITT Population
	14.1.3.3.7	Summary of Rescue Medical and Surgical Procedures during Follow-up Period	ITT Population
14.1.4		Medications	
	14.1.4.1	Summary of Prior Medications before Informed Consent Signed by ATC level and Preferred Term	ITT Population
	14.1.4.2	Summary of Prior Medications during Screening Period by ATC level and Preferred Term	ITT Population
	14.1.4.3	Summary of Concomitant Medications during Treatment Period by ATC level and Preferred Term	ITT Population
	14.1.4.4	Summary of Concomitant Medications during Follow-up Period by ATC level and Preferred Term	ITT Population
	14.1.4.5	Summary of Rescue Medications during Treatment Period by ATC level and Preferred Term	ITT Population
	14.1.4.6	Summary of Rescue Medications during Follow-up Period by ATC level and Preferred Term	ITT Population
	14.1.4.7	Summary of Background Topical Therapy during Treatment Period by ATC level and Preferred Term	ITT Population
	14.1.4.8	Summary of Background Topical Therapy during Follow-up Period by ATC level and Preferred Term	ITT Population
14.2		Efficacy Data Summary Tables	
14.2.1		Primary Efficacy Parameters	
14.2.1.1		Primary Efficacy Parameter IGA Success	
	14.2.1.1.1	Analysis of Proportion of Subjects with an IGA Success at Week 16 - Missing as Non-Responder – Initial Period	ITT Population
	14.2.1.1.2	Sensitivity Analysis of Proportion of Subjects with an IGA Success at Week 16 - Missing as Non-Responder – Initial Period	PP Population

Header	Table Number	Name	Analysis Set
	14.2.1.1.4	Sensitivity Analysis of Proportion of Subjects with an IGA Success at Week 16 - Multiple Imputation (MI) Method – Initial Period	ITT Population
	14.2.1.1.5	Sensitivity Analysis of Proportion of Subjects with an IGA Success at Week 16 - Tipping Point Analysis – Initial Period	ITT Population
	14.2.1.1.7	Sensitivity Analysis of Proportion of Subjects with an IGA Success at Week 16 – LOCF – Initial Period	ITT Population
	14.2.1.1.8	Sensitivity Analysis of Proportion of Subjects with an IGA Success at Week 16 – OC - Initial Period	ITT Population
	14.2.1.1.9	Sensitivity Analysis of Proportion of Subjects with an IGA Success at Week 16 using Actual Stratifications - Missing as Non-Responder – Initial Period	ITT Population
	14.2.1.1.10	Subgroup Analysis of Proportion of Subjects with an IGA Success at Week 16 with Forest Plot – Missing as Non-Responder – Initial Period	ITT Population
	14.2.1.1.11	Analysis of Proportion of Subjects with an IGA Success at Week 16 - Missing as Non-Responder – Initial Period	ITT Population – Excluding Subjects using different version of IGA
	14.2.1.1.12	Analysis of Proportion of Subjects with an IGA Success by Visit - Missing as Non-Responder – Initial Period	ITT Population – Excluding Visits under Pandemic
14.2.1.2		Primary Efficacy Parameter EASI-75 Improvement	
	14.2.1.2.1	Analysis of Proportion of Subjects with EASI-75 at Week 16 - Missing as Non-Responder – Initial Period	ITT Population
	14.2.1.2.2	Sensitivity Analysis of Proportion of Subjects with EASI-75 at Week 16 - Missing as Non-Responder – Initial Period	PP Population
	14.2.1.2.4	Sensitivity Analysis of Proportion of Subjects with EASI-75 at Week 16 - Multiple Imputation (MI) Method – Initial Period	ITT Population
	14.2.1.2.5	Sensitivity Analysis of Proportion of Subjects with EASI-75 at Week 16 - Tipping Point Analysis – Initial Period	ITT Population
	14.2.1.2.7	Sensitivity Analysis of Proportion of Subjects with EASI-75 at Week 16 – LOCF – Initial Period	ITT Population
	14.2.1.2.8	Sensitivity Analysis of Proportion of Subjects with EASI-75 at Week 16 – OC – Initial Period	ITT Population

Header	Table Number	Name	Analysis Set
	14.2.1.2.9	Sensitivity Analysis of Proportion of Subjects with EASI-75 at Week 16 using Actual Stratifications - Missing as Non-Responder – Initial Period	ITT Population
	14.2.1.2.10	Subgroup Analysis of Proportion of Subjects with EASI-75 at Week 16 with Forest Plot – Missing as Non-Responder – Initial Period	ITT Population
	14.2.1.2.11	Analysis of Proportion of Subjects with EASI-75 by Visit - Missing as Non-Responder – Initial Period	ITT Population – Excluding Visits under Pandemic
14.2.2		Key Secondary Efficacy Parameters	
14.2.2.1		Key Secondary Efficacy Parameter PP NRS Improvement ≥ 4	
	14.2.2.1.1	Analysis of Proportion of Subjects with Weekly Average PP NRS Improvement ≥ 4 at Weeks 1, 2, 4 and 16 - Missing as Non-Responder – Initial Period	ITT Population
	14.2.2.1.2	Sensitivity Analysis of Proportion of Subjects with Weekly Average PP NRS Improvement ≥ 4 at Weeks 1, 2, 4 and 16 - Missing as Non-Responder – Initial Period	PP Population
	14.2.2.1.3	Sensitivity Analysis of Proportion of Subjects with Weekly Average PP NRS Improvement ≥ 4 at Weeks 1, 2, 4 and 16 - Multiple Imputation (MI) Method – Initial Period	ITT Population
	14.2.2.1.4	Sensitivity Analysis of Proportion of Subjects with Weekly Average PP NRS Improvement ≥ 4 at Weeks 1, 2, 4 and 16 - Tipping Point Analysis – Initial Period	ITT Population
	14.2.2.1.6	Sensitivity Analysis of Proportion of Subjects with Weekly Average PP NRS Improvement ≥ 4 at Weeks 1, 2, 4 and 16 – LOCF – Initial Period	ITT Population
	14.2.2.1.7	Sensitivity Analysis of Proportion of Subjects with Weekly Average PP NRS Improvement ≥ 4 at Weeks 1, 2, 4 and 16 – OC – Initial Period	ITT Population
	14.2.2.1.8	Sensitivity Analysis of Proportion of Subjects with Weekly Average PP NRS Improvement ≥ 4 at Weeks 1, 2, 4 and 16 using Actual Stratifications - Missing as Non-Responder – Initial Period	ITT Population
	14.2.2.1.9	Subgroup Analysis of Proportion of Subjects with Weekly Average PP NRS Improvement ≥ 4 at Weeks 1, 2, 4 and 16 with Forest Plot – Missing as Non-Responder – Initial Period	ITT Population

Header	Table Number	Name	Analysis Set
	14.2.2.1.10	Analysis of Proportion of Subjects with Weekly Average PP NRS Improvement ≥ 4 by Visit - Missing as Non-Responder – Initial Period	ITT Population – Excluding Visits under Pandemic
14.2.2.2		Key Secondary Efficacy Parameters: PP NRS < 2	
	14.2.2.2.1	Analysis of Proportion of Subjects with Weekly Average PP NRS < 2 at Weeks 4 and 16 - Missing as Non-Responder – Initial Period	ITT Population
	14.2.2.2.2	Sensitivity Analysis of Proportion of Subjects with Weekly Average PP NRS < 2 at Weeks 4 and 16 - Missing as Non-Responder – Initial Period	PP Population
	14.2.2.2.3	Sensitivity Analysis of Proportion of Subjects with Weekly Average PP NRS < 2 at Weeks 4 and 16 - Multiple Imputation (MI) Method – Initial Period	ITT Population
	14.2.2.2.4	Sensitivity Analysis of Proportion of Subjects with Weekly Average PP NRS < 2 at Weeks 4 and 16 - Tipping Point Analysis – Initial Period	ITT Population
	14.2.2.2.6	Sensitivity Analysis of Proportion of Subjects with Weekly Average PP NRS < 2 at Weeks 4 and 16 – LOCF – Initial Period	ITT Population
	14.2.2.2.7	Sensitivity Analysis of Proportion of Subjects with Weekly Average PP NRS < 2 at Weeks 4 and 16 – OC – Initial Period	ITT Population
	14.2.2.2.8	Sensitivity Analysis of Proportion of Subjects with Weekly Average PP NRS < 2 at Weeks 4 and 16 using Actual Stratifications - Missing as Non-Responder – Initial Period	ITT Population
	14.2.2.2.9	Subgroup Analysis of Proportion of Subjects with Weekly Average PP NRS Improvement < 2 at Weeks 4 and 16 with Forest Plot – Missing as Non-Responder – Initial Period	ITT Population
	14.2.2.2.10	Analysis of Proportion of Subjects with Weekly Average PP NRS < 2 by Visit - Missing as Non-Responder – Initial Period	ITT Population – Excluding Visits under Pandemic
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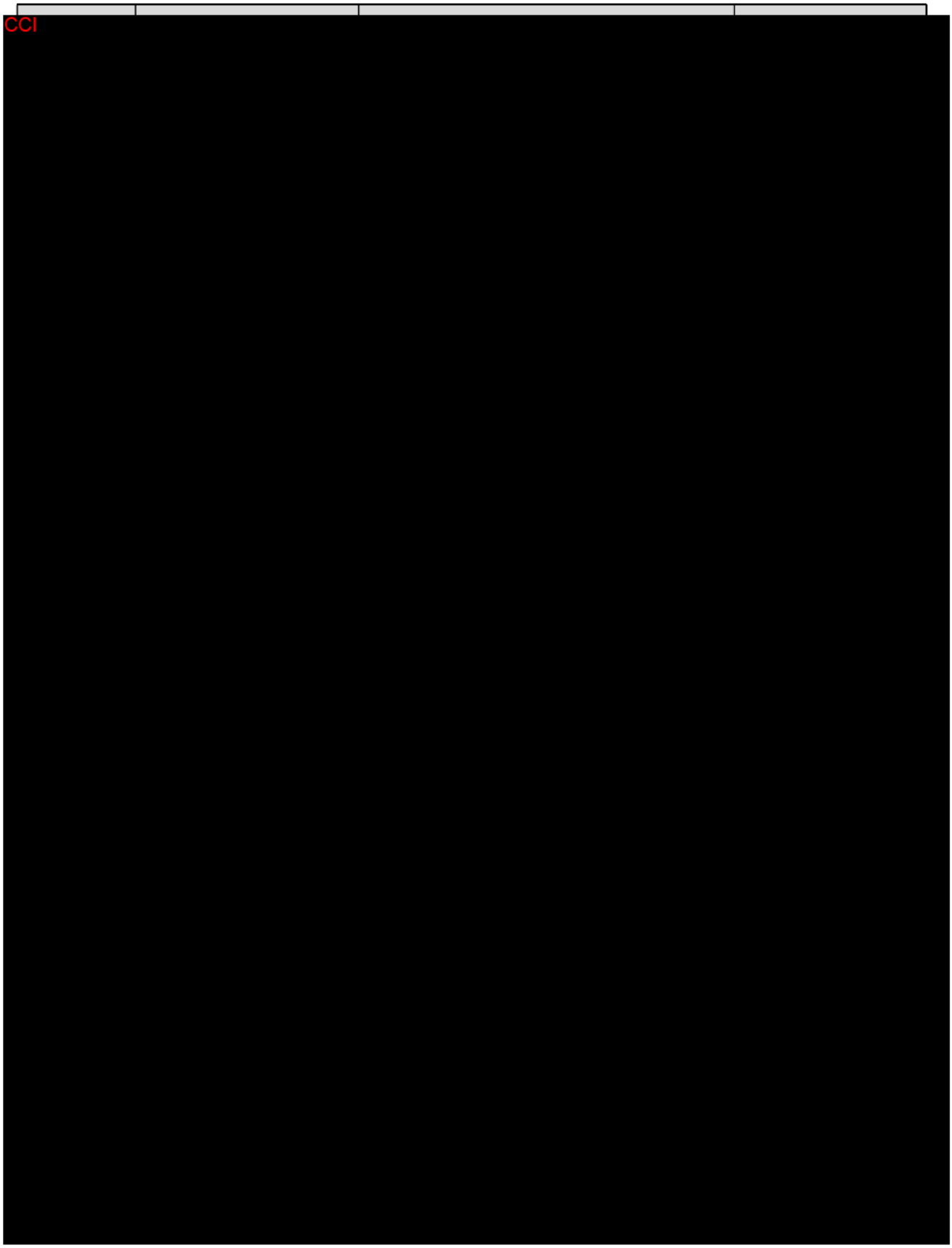

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Header	Table Number	Name	Analysis Set
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14.3		Safety Data Summary Tables	
14.3.1		Adverse Events	
	14.3.1.1.1	Overall Summary of Treatment Emergent Adverse Events (TEAEs) during Treatment Period, All Causalities	Safety Population
	14.3.1.1.2	Overall Summary of Treatment Emergent Adverse Events (TEAEs) during Follow-up Period, All Causalities	Safety Population

Header	Table Number	Name	Analysis Set
	14.3.1.1.3	Overall Summary of Treatment Emergent Adverse Events (TEAEs) during Overall Study Period, All Causalities	Safety Population
	14.3.1.1.4	Overall Summary of Treatment Emergent Adverse Events (TEAEs) during Treatment Period, Study Drug Related	Safety Population
	14.3.1.1.5	Overall Summary of Treatment Emergent Adverse Events (TEAEs) during Follow-up Period, Study Drug Related	Safety Population
	14.3.1.1.6	Overall Summary of Treatment Emergent Adverse Events (TEAEs) during Overall Study Period, Study Drug Related	Safety Population
	14.3.1.1.7	Overall Summary of Treatment Emergent Adverse Events (TEAEs) during Treatment Period, All Causalities	Safety Population – Subjects with COVID-19 Infection
	14.3.1.1.8	Overall Summary of Treatment Emergent Adverse Events (TEAEs) during Follow-up Period, All Causalities	Safety Population – Subjects with COVID-19 Infection
	14.3.1.1.9	Overall Summary of Treatment Emergent Adverse Events (TEAEs) during Treatment Period, Study Drug Related	Safety Population – Subjects with COVID-19 Infection
	14.3.1.1.10	Overall Summary of Treatment Emergent Adverse Events (TEAEs) during Follow-up Period, Study Drug Related	Safety Population – Subjects with COVID-19 Infection
	14.3.1.1.11	Overall Summary of Treatment Emergent Adverse Events (TEAEs) during Treatment Period by Country, All Causalities	Safety Population
	14.3.1.1.12	Overall Summary of Treatment Emergent Adverse Events (TEAEs) during Follow-up Period by Country, All Causalities	Safety Population
	14.3.1.1.13	Overall Summary of Treatment Emergent Adverse Events (TEAEs) during Overall Study Period by Country, All Causalities	Safety Population
	14.3.1.1.14	Overall Summary of Treatment Emergent Adverse Events (TEAEs) during Treatment Period by Country, Study Drug Related	Safety Population
	14.3.1.1.15	Overall Summary of Treatment Emergent Adverse Events (TEAEs) during Follow-up Period by Country, Study Drug Related	Safety Population

Header	Table Number	Name	Analysis Set
	14.3.1.1.16	Overall Summary of Treatment Emergent Adverse Events (TEAEs) during Overall Study Period by Country, Study Drug Related	Safety Population
	14.3.1.1.17	Overall Summary of Treatment Emergent Adverse Events (TEAEs) during Treatment Period by Age Group, All Causalities	Safety Population
	14.3.1.1.18	Overall Summary of Treatment Emergent Adverse Events (TEAEs) during Follow-up Period by Age Group, All Causalities	Safety Population
	14.3.1.1.19	Overall Summary of Treatment Emergent Adverse Events (TEAEs) during Overall Study Period by Age Group, All Causalities	Safety Population
	14.3.1.1.20	Overall Summary of Treatment Emergent Adverse Events (TEAEs) during Treatment Period by Age Group, Study Drug Related	Safety Population
	14.3.1.1.21	Overall Summary of Treatment Emergent Adverse Events (TEAEs) during Follow-up Period by Age Group, Study Drug Related	Safety Population
	14.3.1.1.22	Overall Summary of Treatment Emergent Adverse Events (TEAEs) during Overall Study Period by Age Group, Study Drug Related	Safety Population
	14.3.1.1.23	Overall Summary of Treatment Emergent Adverse Events (TEAEs) of Special Interest during Treatment Period, All Causalities	Safety Population
	14.3.1.1.24	Overall Summary of Treatment Emergent Adverse Events (TEAEs) of Special Interest during Follow-up Period, All Causalities	Safety Population
	14.3.1.1.25	Overall Summary of Treatment Emergent Adverse Events (TEAEs) of Special Interest during Treatment Period, Study Drug Related	Safety Population
	14.3.1.1.26	Overall Summary of Treatment Emergent Adverse Events (TEAEs) of Special Interest during Follow-up Period, Study Drug Related	Safety Population
	14.3.1.2.1	Treatment Emergent Adverse Events (TEAEs) during Treatment Period by SOC and PT, All Causalities	Safety Population
	14.3.1.2.2	Treatment Emergent Adverse Events (TEAEs) during Follow-up Period by SOC and PT, All Causalities	Safety Population
	14.3.1.2.3	Treatment Emergent Adverse Events (TEAEs) during Overall Study Period by SOC and PT, All Causalities	Safety Population

Header	Table Number	Name	Analysis Set
	14.3.1.2.4	Treatment Emergent Adverse Events (TEAEs) during Treatment Period by SOC and PT, All Causalities	Safety Population – Subjects with COVID-19 Infection
	14.3.1.2.5	Treatment Emergent Adverse Events (TEAEs) during Follow-up Period by SOC and PT, All Causalities	Safety Population – Subjects with COVID-19 Infection
	14.3.1.2.6	Treatment Emergent Adverse Events (TEAEs) during Treatment Period by Country, SOC and PT, All Causalities	Safety Population
	14.3.1.2.7	Treatment Emergent Adverse Events (TEAEs) during Follow-up Period by Country, SOC and PT, All Causalities	Safety Population
	14.3.1.2.8	Treatment Emergent Adverse Events (TEAEs) during Overall Study Period by Country, SOC and PT, All Causalities	Safety Population
	14.3.1.2.9	Treatment Emergent Adverse Events (TEAEs) during Treatment Period by Age Group, SOC and PT, All Causalities	Safety Population
	14.3.1.2.10	Treatment Emergent Adverse Events (TEAEs) during Follow-up Period by Age Group, SOC and PT, All Causalities	Safety Population
	14.3.1.2.11	Treatment Emergent Adverse Events (TEAEs) during Overall Study Period by Age Group, SOC and PT, All Causalities	Safety Population
	14.3.1.3.1	Treatment Emergent Adverse Events (TEAEs) during Treatment Period by SOC and PT, Study Drug Related	Safety Population
	14.3.1.3.2	Treatment Emergent Adverse Events (TEAEs) during Follow-up Period by SOC and PT, Study Drug Related	Safety Population
	14.3.1.3.3	Treatment Emergent Adverse Events (TEAEs) during Overall Study Period by SOC and PT, Study Drug Related	Safety Population
	14.3.1.3.4	Treatment Emergent Adverse Events (TEAEs) during Treatment Period by SOC and PT, Study Drug Related	Safety Population – Subjects with COVID-19 Infection
	14.3.1.3.5	Treatment Emergent Adverse Events (TEAEs) during Follow-up Period by SOC and PT, Study Drug Related	Safety Population – Subjects with COVID-19 Infection
	14.3.1.3.6	Treatment Emergent Adverse Events (TEAEs) during Treatment Period by Country, SOC and PT, Study Drug Related	Safety Population
	14.3.1.3.7	Treatment Emergent Adverse Events (TEAEs) during Follow-up Period by Country, SOC and PT, Study Drug Related	Safety Population
	14.3.1.3.8	Treatment Emergent Adverse Events (TEAEs) during Overall Study Period by Country, SOC and PT, Study Drug Related	Safety Population

Header	Table Number	Name	Analysis Set
	14.3.1.3.9	Treatment Emergent Adverse Events (TEAEs) during Treatment Period by Age Group, SOC and PT, Study Drug Related	Safety Population
	14.3.1.3.10	Treatment Emergent Adverse Events (TEAEs) during Follow-up Period by Age Group, SOC and PT, Study Drug Related	Safety Population
	14.3.1.3.11	Treatment Emergent Adverse Events (TEAEs) during Overall Study Period by Age Group, SOC and PT, Study Drug Related	Safety Population
	14.3.1.4.1	Exposure-Adjusted Incidence Rate for Treatment Emergent Adverse Events (TEAEs) during Treatment Period by SOC and PT, All Causalities	Safety Population
	14.3.1.5.1	Exposure-Adjusted Incidence Rate of Treatment Emergent Adverse Events (TEAEs) during Treatment Period by SOC and PT, Study Drug Related	Safety Population
	14.3.1.6.1	Serious Treatment Emergent Adverse Events (TEAEs) during Treatment Period by SOC and PT, All Causalities	Safety Population
	14.3.1.6.2	Serious Treatment Emergent Adverse Events (TEAEs) during Follow-up Period by SOC and PT, All Causalities	Safety Population
	14.3.1.6.3	Serious Treatment Emergent Adverse Events (TEAEs) during Treatment Period by SOC and PT, All Causalities	Safety Population – Subjects with COVID-19 Infection
	14.3.1.6.4	Serious Treatment Emergent Adverse Events (TEAEs) during Follow-up Period by SOC and PT, All Causalities	Safety Population – Subjects with COVID-19 Infection
	14.3.1.7.1	Serious Treatment Emergent Adverse Events (TEAEs) during Treatment Period by SOC and PT, Study Drug Related	Safety Population
	14.3.1.7.2	Serious Treatment Emergent Adverse Events (TEAEs) during Follow-up Period by SOC and PT, Study Drug Related	Safety Population
	14.3.1.7.3	Serious Treatment Emergent Adverse Events (TEAEs) during Treatment Period by SOC and PT, Study Drug Related	Safety Population – Subjects with COVID-19 Infection
	14.3.1.7.4	Serious Treatment Emergent Adverse Events (TEAEs) during Follow-up Period by SOC and PT, Study Drug Related	Safety Population – Subjects with COVID-19 Infection
	14.3.1.8.1	Treatment Emergent Adverse Events (TEAEs) during Treatment Period by SOC, PT and Maximum Severity, All Causalities	Safety Population
	14.3.1.8.2	Treatment Emergent Adverse Events (TEAEs) during Follow-up Period by SOC, PT and Maximum Severity, All Causalities	Safety Population

Header	Table Number	Name	Analysis Set
	14.3.1.9.1	Treatment Emergent Adverse Events (TEAEs) during Treatment Period by SOC, PT and Maximum Severity, Study Drug Related	Safety Population
	14.3.1.9.2	Treatment Emergent Adverse Events (TEAEs) during Follow-up Period by SOC, PT and Maximum Severity, Study Drug Related	Safety Population
	14.3.1.10.1	Severe Treatment Emergent Adverse Events (TEAEs) during Treatment Period by SOC and PT, All Causalities	Safety Population
	14.3.1.10.2	Severe Treatment Emergent Adverse Events (TEAEs) during Follow-up Period by SOC and PT, All Causalities	Safety Population
	14.3.1.11.1	Severe Treatment Emergent Adverse Events (TEAEs) during Treatment Period by SOC and PT, Study Drug Related	Safety Population
	14.3.1.11.2	Severe Treatment Emergent Adverse Events (TEAEs) during Follow-up Period by SOC and PT, Study Drug Related	Safety Population
	14.3.1.12.1	Treatment Emergent Adverse Events (TEAEs) Leading to Permanent Discontinuation of Study Drug during Treatment Period by SOC and PT, All Causalities	Safety Population
	14.3.1.13.1	Treatment Emergent Adverse Events (TEAEs) Leading to Permanent Discontinuation of Study Drug during Treatment Period by SOC and PT, Study Drug Related	Safety Population
	14.3.1.14.1	Treatment Emergent Adverse Events (TEAEs) of Special Interest during Treatment Period by Category, SOC and PT, All Causalities	Safety Population
	14.3.1.14.2	Treatment Emergent Adverse Events (TEAEs) of Special Interest during Follow-up Period by Category, SOC and PT, All Causalities	Safety Population
	14.3.1.14.3	Treatment Emergent Adverse Events (TEAEs) of Special Interest during Treatment Period by Category, SOC and PT, All Causalities	Safety Population – Subjects with COVID-19 Infection
	14.3.1.14.4	Treatment Emergent Adverse Events (TEAEs) of Special Interest during Follow-up Period by Category, SOC and PT, All Causalities	Safety Population – Subjects with COVID-19 Infection
	14.3.1.15.1	Treatment Emergent Adverse Events (TEAEs) of Special Interest during Treatment Period by Category, SOC and PT, Study Drug Related	Safety Population

Header	Table Number	Name	Analysis Set
	14.3.1.15.2	Treatment Emergent Adverse Events (TEAEs) of Special Interest during Follow-up Period by Category, SOC and PT, Study Drug Related	Safety Population
	14.3.1.15.3	Treatment Emergent Adverse Events (TEAEs) of Special Interest during Treatment Period by Category, SOC and PT, Study Drug Related	Safety Population – Subjects with COVID-19 Infection
	14.3.1.15.4	Treatment Emergent Adverse Events (TEAEs) of Special Interest during Follow-up Period by Category, SOC and PT, Study Drug Related	Safety Population – Subjects with COVID-19 Infection
	14.3.1.16.1	Treatment Emergent Adverse Events (TEAEs) Occurred in PT >= 5% of Subjects during Treatment Period by SOC and PT, All Causalities	Safety Population
	14.3.1.16.2	Treatment Emergent Adverse Events (TEAEs) Occurred in PT >= 5% of Subjects during Follow-up Period by SOC and PT, All Causalities	Safety Population
	14.3.1.16.3	Treatment Emergent Adverse Events (TEAEs) Occurred in PT >= 5% of Subjects during Treatment Period by PT, All Causalities	Safety Population
	14.3.1.16.4	Treatment Emergent Adverse Events (TEAEs) Occurred in PT >= 5% of Subjects during Follow-up Period by PT, All Causalities	Safety Population
	14.3.1.17.1	Treatment Emergent Adverse Events (TEAEs) Occurred in PT >= 5% of Subjects during Treatment Period by SOC and PT, Study Drug Related	Safety Population
	14.3.1.17.2	Treatment Emergent Adverse Events (TEAEs) Occurred in PT >= 5% of Subjects during Follow-up Period by SOC and PT, Study Drug Related	Safety Population
	14.3.1.17.3	Treatment Emergent Adverse Events (TEAEs) Occurred in PT >= 5% of Subjects during Treatment Period by PT, Study Drug Related	Safety Population
	14.3.1.17.4	Treatment Emergent Adverse Events (TEAEs) Occurred in PT >= 5% of Subjects during Follow-up Period by PT, Study Drug Related	Safety Population
	14.3.1.18.1	Adjudicated Treatment Emergent Adverse Events (TEAEs) during Treatment Period by SOC and PT, All Causalities	Safety Population
	14.3.1.18.2	Adjudicated Treatment Emergent Adverse Events (TEAEs) during Follow-up Period by SOC and PT, All Causalities	Safety Population

Header	Table Number	Name	Analysis Set
	14.3.1.19.1	Adjudicated Treatment Emergent Adverse Events (TEAEs) during Treatment Period by SOC and PT, Study Drug Related	Safety Population
	14.3.1.19.2	Adjudicated Treatment Emergent Adverse Events (TEAEs) during Follow-up Period by SOC and PT, Study Drug Related	Safety Population
	14.3.1.20.1	Treatment Emergent Adverse Events (TEAEs) of Asthma and AESI reported by Investigator during Treatment Period with Adjudication Outcome by IAC – All Causalities	Safety Population
	14.3.1.20.2	Treatment Emergent Adverse Events (TEAEs) of Asthma and AESI reported by Investigator during Follow-up with Adjudication Outcome by IAC – All Causalities	Safety Population
	14.3.1.20.3	Treatment Emergent Adverse Events (TEAEs) of Asthma and AESI reported by Investigator during Treatment Period with Adjudication Outcome by IAC – Study Drug Related	Safety Population
	14.3.1.20.4	Treatment Emergent Adverse Events (TEAEs) of Asthma and AESI reported by Investigator during Follow-up with Adjudication Outcome by IAC – Study Drug Related	Safety Population
	14.3.1.21.1	Treatment Emergent Adverse Events (TEAEs) of Special Interest during Treatment Period by Category, SOC, PT and Maximum Severity – All Causalities	Safety Population
	14.3.1.21.2	Treatment Emergent Adverse Events (TEAEs) of Special Interest during Follow-up by Category, SOC, PT and Maximum Severity – All Causalities	Safety Population
	14.3.1.21.3	Treatment Emergent Adverse Events (TEAEs) of Special Interest during Treatment Period by Category, SOC, PT and Maximum Severity – Study Drug Related	Safety Population
	14.3.1.21.4	Treatment Emergent Adverse Events (TEAEs) of Special Interest during Follow-up by Category, SOC, PT and Maximum Severity – Study Drug Related	Safety Population
	14.3.1.22.1	Confirmed Adjudicated Treatment Emergent Adverse Events (TEAEs) during Treatment Period by SOC, PT and Maximum Severity – All Causalities	Safety Population
	14.3.1.22.2	Confirmed Adjudicated Treatment Emergent Adverse Events (TEAEs) during Follow-up by SOC, PT and Maximum Severity – All Causalities	Safety Population

Header	Table Number	Name	Analysis Set
	14.3.1.22.3	Confirmed Adjudicated Treatment Emergent Adverse Events (TEAEs) during Treatment Period by SOC, PT and Maximum Severity – Study Drug Related	Safety Population
	14.3.1.22.4	Confirmed Adjudicated Treatment Emergent Adverse Events (TEAEs) during Follow-up by SOC, PT and Maximum Severity – Study Drug Related	Safety Population
14.3.2		Listings of Deaths, Other Serious and Significant Adverse Events	
	14.3.2.1	Listing of Serious Treatment Emergent Adverse Events (TEAEs)	Safety Population
	14.3.2.2	Listing of Severe Treatment Emergent Adverse Events (TEAEs)	Safety Population
	14.3.2.3	Listing of Treatment Emergent Adverse Events (TEAEs) Leading to Permanent Discontinuation of Study Drug	Safety Population
	14.3.2.4	Listing of Treatment Emergent Adverse Events (TEAEs) of Special Interest	Safety Population
	14.3.2.5	Listing of Treatment Emergent Adverse Events (TEAEs) Leading to Death	Safety Population
14.3.3		Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events	
14.3.4		Laboratory Value	
14.3.4.1		Clinical Laboratory Data	
14.3.4.1.1		Hematology Data	
	14.3.4.1.1.1	Summary of Laboratory Data for Hematology – Initial Period	Safety Population
	14.3.4.1.1.2	Summary of Laboratory Data for Hematology – Maintenance Period	Enrolled Safety Subjects in Maintenance Period Population
	14.3.4.1.1.3	Shift from Baseline for Hematology by Reference Ranges – Initial Period	Safety Population
	14.3.4.1.1.4	Shift from Baseline for Hematology by Reference Range – Maintenance Period	Enrolled Safety Subjects in Maintenance Period Population
	14.3.4.1.1.5	Shift from Maintenance Baseline for Hematology by Reference Range – Maintenance Period	Enrolled Safety Subjects in Maintenance Period Population
	14.3.4.1.1.6	Summary of Potentially Clinically Significant Hematology – Initial Period	Safety Population
	14.3.4.1.1.7	Summary of Potentially Clinically Significant Hematology – Maintenance Period	Enrolled Safety Subjects in Maintenance Period Population
	14.3.4.1.1.8	Listing of Subjects with Abnormal Hematology Results	Safety Population
	14.3.4.1.1.9	Listing of Subjects with Potentially Clinically Significant Hematology Results	Safety Population

Header	Table Number	Name	Analysis Set
14.3.4.1.2		Blood Chemistry Data	
	14.3.4.1.2.1	Summary of Laboratory Data for Clinical Chemistry – Initial Period	Safety Population
	14.3.4.1.2.2	Summary of Laboratory Data for Clinical Chemistry – Maintenance Period	Enrolled Safety Subjects in Maintenance Period Population
	14.3.4.1.2.3	Shift from Baseline for Clinical Chemistry by Reference Range – Initial Period	Safety Population
	14.3.4.1.2.4	Shift from Baseline for Clinical Chemistry by Reference Range – Maintenance Period	Enrolled Safety Subjects in Maintenance Period Population
	14.3.4.1.2.5	Shift from Maintenance Baseline for Clinical Chemistry by Reference Range – Maintenance Period	Enrolled Safety Subjects in Maintenance Period Population
	14.3.4.1.2.6	Summary of Potentially Clinically Significant Clinical Chemistry - Initial Period	Safety Population
	14.3.4.1.2.7	Summary of Potentially Clinically Significant Clinical Chemistry - Maintenance Period	Enrolled Safety Subjects in Maintenance Period Population
	14.3.4.1.2.8	Listing of Subjects with Abnormal Clinical Chemistry Results	Safety Population
	14.3.4.1.2.9	Listing of Subjects with Potentially Clinically Significant Clinical Chemistry Results	Safety Population
14.3.4.1.3		Urinalysis Data	
	14.3.4.1.3.1	Summary of Laboratory Data for Urinalysis – Initial Period	Safety Population
	14.3.4.1.3.2	Summary of Laboratory Data for Urinalysis – Maintenance Period	Enrolled Safety Subjects in Maintenance Period Population
14.3.4.2		Vital Signs	
	14.3.4.2.1	Summary of Vital Signs, Height and Weight – Initial Period	Safety Population
	14.3.4.2.2	Summary of Vital Signs, Height and Weight – Maintenance Period	Enrolled Safety Subjects in Maintenance Period Population
	14.3.4.2.3	Summary of Potentially Clinically Significant Vital Signs and Weight - Initial Period	Safety Population
	14.3.4.2.4	Summary of Potentially Clinically Significant Vital Signs and Weight - Maintenance Period	Enrolled Safety Subjects in Maintenance Period Population
	14.3.4.2.5	Listing of Subjects with Potentially Clinically Significant Vital Signs, Weight and Height	Safety Population

Header	Table Number	Name	Analysis Set
14.3.4.3		Electrocardiogram (ECG) Data	
	14.3.4.3.1	Summary of Electrocardiogram (ECG) Interpretation - Initial Period	Safety Population
	14.3.4.3.2	Summary of Electrocardiogram (ECG) Interpretation - Maintenance Period	Safety Population
14.3.4.4		Other Safety	
	14.3.4.4.1	Summary of Physical Examination - Initial Period	Safety Population
	14.3.4.4.2	Summary of Physical Examination - Maintenance Period	Enrolled Safety Subjects in Maintenance Period Population
	14.3.4.4.3	Shift from Baseline in Physical Examination - Initial Period	Safety Population
	14.3.4.4.4	Shift from Initial Baseline in Physical Examination - Maintenance Period	Enrolled Safety Subjects in Maintenance Period Population
	14.3.4.4.5	Shift from Maintenance Baseline in Physical Examination - Maintenance Period	Enrolled Safety Subjects in Maintenance Period Population
	14.3.4.4.6	Summary of Respiratory Assessments – Peak Expiratory Flow (PEF) – Initial Period	Safety Population
	14.3.4.4.7	Summary of Respiratory Assessments – Peak Expiratory Flow (PEF) – Maintenance Period	Enrolled Safety Subjects in Maintenance Period Population
	14.3.4.4.8	Summary of Respiratory Assessments – Peak Expiratory Flow (PEF) for Subjects with Asthma History – Initial Period	Safety Population
	14.3.4.4.9	Summary of Respiratory Assessments – Peak Expiratory Flow (PEF) for Subjects with Asthma History – Maintenance Period	Enrolled Safety Subjects in Maintenance Period Population
	14.3.4.4.10	Summary of Respiratory Assessments – Peak Expiratory Flow (PEF) for Subjects without Asthma History – Initial Period	Safety Population
	14.3.4.4.11	Summary of Respiratory Assessments – Peak Expiratory Flow (PEF) for Subjects without Asthma History – Maintenance Period	Enrolled Safety Subjects in Maintenance Period Population
	14.3.4.4.12	Summary of Peak Expiratory Flow (PEF) < 80% of Predicted Value – Initial Period	Safety Population
	14.3.4.4.13	Summary of Peak Expiratory Flow (PEF) < 80% of Predicted Value - Maintenance Period	Enrolled Safety Subjects in Maintenance Period Population
	14.3.4.4.14	Summary of Asthma Control Test (ACT) and Proportion of ACT <= 19 – Initial Period	Safety Population

Header	Table Number	Name	Analysis Set
	14.3.4.4.15	Summary of Asthma Control Test (ACT) and Proportion of ACT <= 19 – Maintenance Period	Enrolled Safety Subjects in Maintenance Period Population
	14.3.4.4.16	Summary of Immunogenicity - Anti-drug Antibody (ADA) and Neutralizing Antibody - Initial Period	PK Population
	14.3.4.4.17	Summary of Immunogenicity - Anti-drug Antibody (ADA) and Neutralizing Antibody - Maintenance Period	Enrolled PK Subjects in Maintenance Period Population
14.3.4.5		Extent of Exposure and Treatment Compliance	
	14.3.4.5.1	Summary of Exposure to Study Drug - Initial Period	Safety Population
	14.3.4.5.2	Summary of Exposure to Study Drug - Maintenance Period	Enrolled Safety Subjects in Maintenance Period Population

20. Index of Figures

Header	Figure Number	Name	Analysis Set
14		Figures	
14.1		Demographic Data Summary Tables	
14.1.1		Subject Disposition	
	14.1.1.9	Time (days) to Permanent Discontinuation of Study Drug by Reason for Discontinuation – Initial Period	ITT Population
	14.1.1.10	Time (days) to Permanent Discontinuation of Study Drug by Reason for Discontinuation – Maintenance Period	Enrolled Subjects in Maintenance Period Population
14.2.1		Primary Efficacy Parameters	
14.2.1.1		Primary Efficacy Parameter: IGA Success	
	14.2.1.1.3	Bar Chart of Proportion of Subjects with an IGA Success at Week 16 - Missing as Non-Responder – Initial Period	ITT Population
	14.2.1.1.6	Sensitivity Analysis of Proportion of Subjects with an IGA Success at Week 16 - Tipping Point Analysis – Initial Period	ITT Population
14.2.1.2		Primary Efficacy Parameter: EASI-75 Improvement	
	14.2.1.2.3	Bar Chart of Proportion of Subjects with EASI-75 at Week 16 - Missing as Non-Responder – Initial Period	ITT Population
	14.2.1.2.6	Sensitivity Analysis of Proportion of Subjects with EASI-75 at Week 16 - Tipping Point Analysis – Initial Period	ITT Population
14.2.2		Key Secondary Efficacy Parameters	
14.2.2.1		Key Secondary Efficacy Parameters: PP NRS Improvement ≥ 4	
	14.2.2.1.5	Sensitivity Analysis of Proportion of Subjects with Weekly Average PP NRS Improvement ≥ 4 at Weeks 1, 2, 4 and 16 - Tipping Point Analysis – Initial Period	ITT Population
14.2.2.2		Key Secondary Efficacy Parameters: PP NRS < 2	
	14.2.2.2.5	Sensitivity Analysis of Proportion of Subjects with Weekly Average PP NRS < 2 at Weeks 4 and 16 - Tipping Point Analysis – Initial Period	ITT Population
14.2.2.3		Key Secondary Efficacy Parameters: SD NRS Improvement ≥ 4	
	14.2.2.3.5	Sensitivity Analysis of Proportion of Subjects with Weekly Average SD NRS Improvement ≥ 4 at Week 16 - Tipping Point Analysis – Initial Period	ITT Population
14.2.2.4		Key Secondary Efficacy Parameter: EASI-75 and PP NRS Improvement ≥ 4 at Week 16	

Header	Figure Number	Name	Analysis Set
	14.2.2.4.5	Sensitivity Analysis of Proportion of Subjects with EASI-75 and Weekly Average PP NRS Improvement ≥ 4 at Week 16 - Tipping Point Analysis – Initial Period	ITT Population
14.2.2.5		Key Secondary Efficacy Parameter: IGA Success and Weekly Average PP NRS Improvement ≥ 4 at Week 16	
	14.2.2.5.5	Sensitivity Analysis of Proportion of Subjects with an IGA Success and Weekly Average PP NRS Improvement ≥ 4 at Week 16 - Tipping Point Analysis – Initial Period	ITT Population
14.2.3		Secondary Efficacy Parameters	
14.2.3.1		Secondary Efficacy Parameter: IGA	
14.2.3.1.1		Secondary Efficacy Parameter: IGA – Initial Period	
	14.2.3.1.1.5	Line Plot of Proportion of Subjects with IGA Success – Missing as Non-Responder – Initial Period	ITT Population
14.2.3.1.2		Secondary Efficacy Parameter: IGA – Maintenance Period	
	14.2.3.1.2.3	Line Plot of Proportion of Subjects with IGA Success from Initial Baseline – Missing as Non-responder – Maintenance Period	Enrolled Subjects in Maintenance Period Population
14.2.3.2		Secondary Efficacy Parameter: EASI	
14.2.3.2.1		Secondary Efficacy Parameter: EASI –Initial Period	
	14.2.3.2.1.6	Line Plot of Proportion of Subjects with EASI-50, EASI-75, or EASI-90 - Missing as Non-Responder – Initial Period	ITT Population
14.2.3.2.2		Secondary Efficacy Parameter: EASI – Maintenance Period	
	14.2.3.2.2.4	Line Plot of Proportion of Subjects with EASI-50, EASI-75, and EASI-90 from Initial Baseline – Missing as Non-Responder - Maintenance Period	Enrolled Subjects in Maintenance Period Population
14.2.3.3		Secondary Efficacy Parameter: PP NRS	
14.2.3.3.1		Secondary Efficacy Parameter: PP NRS – Initial Period	
	14.2.3.3.1.5	Line Plot of Proportion of Subjects with Weekly Average PP NRS Improvement ≥ 4 - Missing as Non-Responder – Initial Period	ITT Population
	14.2.3.3.1.7	Line Plot of Proportion of Subjects with Weekly Average PP NRS < 2 - Missing as Non-Responder – Initial Period	ITT Population
14.2.3.3.2		Secondary Efficacy Parameter: PP NRS – Maintenance Period	
	14.2.3.3.2.3	Line Plot of Proportion of Subjects with Weekly Average PP NRS Improvement ≥ 4 from Initial Baseline – Missing as Non-Responder - Maintenance Period	Enrolled Subjects in Maintenance Period Population

Header	Figure Number	Name	Analysis Set
	14.2.3.3.2.6	Line Plot of Proportion of Subjects with Weekly Average PP NRS < 2 – Missing as Non-Responder - Maintenance Period	Enrolled Subjects in Maintenance Period Population
14.2.3.7		Secondary Efficacy Parameter: SD NRS	
14.2.3.7.1		Secondary Efficacy Parameter: SD NRS – Initial Period	
	14.2.3.7.1.3	Line Plot of Subjects with Weekly Average SD NRS Improvement ≥ 4 - Missing as Non-Responder – Initial Period	ITT Population
14.2.3.7.2		Secondary Efficacy Parameter: SD NRS – Maintenance Period	
	14.2.3.7.2.3	Line Plot of Proportion of Subjects with Weekly Average SD NRS Improvement ≥ 4 from Initial Baseline – Missing as Non-Responder - Maintenance Period	Enrolled Subjects in Maintenance Period Population
14.2.3.22		Rescue Therapy Used	
14.2.3.22.1		Rescue Therapy Used – Initial Period	
	14.2.3.22.1.3	Kaplan Meier Curve for Time to First Rescue Therapy Used - OC - Initial Period	ITT Population
14.2.3.22.2		Rescue Therapy Used – Maintenance Period	
	14.2.3.22.2.3	Kaplan Meier Curve for Time to First Rescue Therapy Used - OC - Maintenance Period	Enrolled Subjects in Maintenance Period Population
14.2.3.23		Relapse – Maintenance Period	
	14.2.3.23.2	Kaplan Meier Curve for Time to First Relapse- OC - Maintenance Period	Enrolled Subjects in Maintenance Period Population
14.2.4		Pharmacokinetics	
	14.2.4.3	Mean Nemolizumab Time-Concentration Profiles - Initial Period	PK Population
	14.2.4.4	Mean Time-Concentration Profiles - Maintenance Period	Enrolled PK Subjects in Maintenance Period Population
14.3.4		Laboratory Value	
14.3.4.1		Clinical Laboratory Data	
14.3.4.1.2		Blood Chemistry Data	
	14.3.4.1.2.10	Distribution of Aspartate Aminotransferase (AST) by Visit with Maximum Post- Baseline Values – Initial Period	Safety Population
	14.3.4.1.2.11	Distribution of Aspartate Aminotransferase (AST) by Visit with Maximum Post-Maintenance Baseline Values – Maintenance Period	Enrolled Safety Subjects in Maintenance Period Population
	14.3.4.1.2.12	Distribution of Alanine Aminotransferase (ALT) by Visit with Maximum Post-Baseline Values – Initial Period	Safety Population
	14.3.4.1.2.13	Distribution of Alanine Aminotransferase (ALT) by Visit with Maximum Post-Maintenance Baseline Values – Maintenance Period	Enrolled Safety Subjects in Maintenance Period Population

Header	Figure Number	Name	Analysis Set
	14.3.4.1.2.14	Distribution of Alkaline Phosphatase (ALP) by Visit with Maximum Post-Baseline Values – Initial Period	Safety Population
	14.3.4.1.2.15	Distribution of Alkaline Phosphatase (ALP) by Visit with Maximum Post-Maintenance Baseline Values – Maintenance Period	Enrolled Safety Subjects in Maintenance Period Population
	14.3.4.1.2.16	Distribution of Total Bilirubin by Visit with Maximum Post-Baseline Values – Initial Period	Safety Population
	14.3.4.1.2.17	Distribution of Total Bilirubin by Visit with Maximum Post-Maintenance Baseline Values – Maintenance Period	Enrolled Safety Subjects in Maintenance Period Population
	14.3.4.1.2.18	Distribution of Creatinine Phosphokinase by Visit with Maximum Post-Baseline Values – Initial Period	Safety Population
	14.3.4.1.2.19	Distribution of Creatinine Phosphokinase by Visit with Maximum Post-Maintenance Baseline Values – Maintenance Period	Enrolled Safety Subjects in Maintenance Period Population
14.3.4.2		Vital Signs	
	14.3.4.2.6	Distribution of Vital Signs by Visit with Maximum Post-Baseline Values – Initial Period	Safety Population
	14.3.4.2.7	Distribution of Vital Signs by Visit with Maximum Post-Maintenance Baseline Values – Maintenance Period after Initial Period	Enrolled Safety Subjects in Maintenance Period Population

21. Index of Listings

Header	Listing Number	Name	Analysis Set
16.2		Subject Data Listings	
16.2.1		Discontinued Subjects	
	16.2.1.1	Randomization	ITT Population
	16.2.1.2	Study Completion Status	ITT Population
	16.2.1.3	Screen Failures	Screened Subjects
	16.2.1.4	Study Drug Completion Status	ITT Population
	16.2.1.5	Visit Dates	ITT Population
	16.2.1.6	Missing Visits Due to COVID-19	ITT Population
	16.2.1.7	Missing Assessment due to COVID-19	ITT Population
	16.2.1.8	Covid-19 relevant comments	ITT Population
16.2.2		Protocol Deviations	
	16.2.2.1	Protocol Deviations	ITT Population
	16.2.2.2	Protocol Deviations Related to COVID-19	ITT Population
16.2.3		Subjects Excluded from Analysis Sets	
	16.2.3.1	Subjects in Analysis Populations	ITT Population
	16.2.3.2	Inclusion and Exclusion Criteria Not Met	Screened Subjects
16.2.4		Demographic Data	
	16.2.4.1	Demographics and Baseline Characteristics	ITT Population
	16.2.4.2	Baseline Disease Characteristics	ITT Population
	16.2.4.3	Medical History	ITT Population
	16.2.4.4	Medical and Surgical Procedures	ITT Population
	16.2.4.5	Rescue Medical and Surgical Procedures	ITT Population
	16.2.4.6	Prior and Concomitant Medications	ITT Population
	16.2.4.7	Rescue Medications	ITT Population
	16.2.4.8	Background Therapy Medications	ITT Population
	16.2.4.9	Background TCI/TCS Dispensation and Recipient	ITT Population
	16.2.4.10	Subjects with Difference between Randomization Stratification and Actual Stratification	ITT Population
16.2.5		Compliance and Exposure Information	
	16.2.5.1	Study Drug Dispensation	Safety Population
	16.2.5.2	Study Drug Administration	Safety Population
	16.2.5.3	Study Drug Compliance	Safety Population
	16.2.5.4	Nemolizumab Serum Concentrations	PK Population
16.2.6		Individual Efficacy Response Data	
	16.2.6.1	Investigator's Global Assessment (IGA)	ITT Population
	16.2.6.2	Eczema Area and Severity Index (EASI)	ITT Population
	16.2.6.3	Weekly Average Pruritus and CCI CCI Numeric Rating Scale	ITT Population
	CCI [redacted]		

Header	Listing Number	Name	Analysis Set
		CCI	
16.2.7		Adverse Event Listings	
	16.2.7.1	Treatment Emergent Adverse Events (TEAE)	Safety Population
	16.2.7.2	Pre-Treatment Adverse Events	Safety Population
	16.2.7.3	Treatment Emergent Adverse Events (TEAE)	Safety Population – Subjects with COVID-19 Infection
	16.2.7.4	Treatment Emergent Adverse Events (TEAE) comments	Safety Population
	16.2.7.5	Adjudicated Asthma Treatment Emergent Adverse Events (TEAE)	Safety Population
	16.2.7.6	Adjudicated Asthma Treatment Emergent Adverse Events (TEAE) Comments by Independent Adjudication Committee	Safety Population
16.2.8		Listing of Individual Laboratory Measurements by Subject	
16.2.8.1		Clinical Laboratory Data	
	16.2.8.1.1	Laboratory Data - Hematology	Safety Population
	16.2.8.1.2	Laboratory Data – Clinical Chemistry	Safety Population
	16.2.8.1.3	Laboratory Data - Urinalysis	Safety Population
	16.2.8.1.4	Childbearing Potential and Premenses Status	Safety Population
	16.2.8.1.5	Pregnancy Test Results	Safety Population
	16.2.8.1.6	Tuberculosis Test Results	Safety Population
	16.2.8.1.7	Virology	Safety Population
16.2.8.2		Other Safety Data	
	16.2.8.2.1	Vital Signs, Height and Weight	Safety Population
	16.2.8.2.2	Electrocardiogram (ECG)	Safety Population
	16.2.8.2.3	Physical Examination	Safety Population
	16.2.8.2.4	Respiratory Assessment – Medical Interview	Safety Population

Header	Listing Number	Name	Analysis Set
	16.2.8.2.5	Respiratory Assessment – Peak Expiratory Flow (PEF)	Safety Population
	16.2.8.2.6	Known Asthma, Wheeze, Dyspnea and Cough Triggers	Safety Population
	16.2.8.2.7	Asthma Control Test (ACT)	Safety Population
	16.2.8.2.8	Subjects with a drop by >= 15% from Baseline for either PEF or ACT	Safety Population
	CCI [redacted]		

22. Appendices

22.1. Tipping point analysis and Multiple imputation (MI) methods

Prior to conducting tipping point analysis and MI imputation, subjects with data after the receipt of rescue therapy will be considered treatment failure i.e., non-responder for analysis. Tipping point analysis and MI imputation will be performed for subjects with real missing data which is not induced by the receipt of rescue therapy.

Tipping point analysis will be performed by converting non-responders due to missing data to responders in successive increments (Δ) for both treatment groups to assess the robustness of analysis. The value of Δ that overturns (i.e. non-significant) the primary results will represent the tipping point. A graphic display of all possible combination of the number of responders among both treatment groups will be presented.

Multiple imputation (MI) methods for missing data. The MI imputation will be carried out as follows.

1. Imputation Phase

a. A 50 imputed datasets with a monotone missing pattern will be created using SAS MI procedure based on the observed data (Markov-Chain-Monte-Carlo method, MCMC). The seed to be used is 118169 (the Protocol number). Pattern of missing data will be evaluated and it is expected that the pattern of missing data will be monotonic. For non-monotone missing data patterns, MCMC method of MI procedure will be used to impute enough data so that the remaining missing data is monotone.

b. Each of the imputed datasets will be used to generate 50 complete datasets, using following approaches:

   i. Ordinal data (e.g., IGA score): A logistic regression method to impute the ordinal missing data, including treatment, randomization strata, and assessments from earlier time points as covariates. Potential auxiliary variables (e.g., the number of injections) may be explored and added into the imputation model. Response or total score of the subjects will be derived using these imputed data.

   ii. Continuous data (e.g., EASI score): A linear regression model including treatment, randomization strata, and assessments from earlier time points as covariates will be used to impute the score. Potential auxiliary variables (e.g., the number of injections) may be explored and added into the imputation model. Response or total score of the subjects will be derived using these imputed data.

2. Analysis Phase: The analysis will be conducted using the complete datasets.

a. Binary endpoint: The complete datasets will be modelled for the endpoint using CMH method. Proportion of responders in each treatment arm, difference and standard error will be calculated.

b. Continuous endpoint: The complete datasets will be analyzed using ANCOVA including treatment group and randomization stratification factors as factors and appropriate Baseline values as a covariate, if applicable. LSMeans in each treatment arm, difference and standard errors will be calculated.

3. Pooling Phase: The results from the analysis phase will be combined as follows.

a. Binary endpoint: The results from the CMH analysis of the multiple imputed datasets will be combined using the Rubin (1987) and Li et al (1991) approach to produce pooled CMH statistics

and p-value. Proportion of responders in each treatment arm, difference and standard error will be combined using the MIANALYZE procedure in SAS.

b. Continuous endpoint: The LSMeans in each treatment arm, difference and standard errors from the ANCOVA of the multiple imputed datasets will be combined using the MIANALYZE procedure in SAS.

22.2. Example SAS Code

1. The example SAS code for CMH model is listed as below:

```
Proc freq data=analysis_data;

    Tables stratum*trt*resp/ cmh alpha=0.1;
Run;
```

2. The example SAS code for MMRM model is listed as below:

```
Proc mixed data = analysis_data;

   class stratum trtp avisit subjid;
  model chg = base stratum trtp avisit trtp*avisit base*avisit / ddfm=kr;
  repeated avisit / subject=subjid(trtp) type=un;
  lsmeans trtp/ cl diff;
  lsmeans trtp*avisit/ slice=avisit cl diff;
run;
```

3. The example SAS code for ANCOVA model is listed as below:

```
Proc mixed data = analysis_data;
  class stratum trtp;
  model chg = base stratum trtp;
  lsmeans trtp/ cl diff;
run;
```

4. The example SAS code for imputation phase by PROC MI:

```
proc mi data=analysis_data seed=118169 minimum=0 maximum=xx nimpute=50 out=out_data;
  mcmc impute=monotone nbiter=200 niter=100;
  var base stratum y4 y8 y12 y16;
run;

Proc mi data = analysis_data seed=118169  minimum=0 maximum=xx nimpute=number_of_imputations
out=out_data;
  class trtp stratum;
  monotone reg (/details);
  var base stratum y4 y8 y12 y16;
run;
```

For IGA,

```
Proc mi data = analysis_data seed=118169  minimum=0 maximum=xx nimpute=number_of_imputations
out=out_data;
  class trtp stratum;
  monotone logistic (/details);
  var base stratum y4 y8 y12 y16;
run;
```

5. The example SAS code for pooling phase for ANCOVA model by PROC MIANALYZE:

```
proc sort data=diff; by avisitn trtp; run;
proc sort data=lsm; by avisitn trtp; run;
proc mianalyze data=diff; by avisitn trtp;
modeleffects estimate;
stderr stderr;
ods output ParameterEstimates=estdiff; run;

proc mianalyze data=lsm; by avisitn trtp;
modeleffects estimate;
stderr stderr;
ods output ParameterEstimates=estlsm; run;
```

22.3. Potentially clinically significant ranges – Adults

Test Parameter	Reference range (as per Lab Manual) LLN	Reference range (as per Lab Manual) ULN	Potentially Clinically Significant Ranges (min and/or max limits)	SI Units
SERUM				
White Blood Cell Count (WBC)	4.00	10.70	<3.0 at post-baseline and ≥3.0 at baseline >15.0 at post-baseline and ≤15 at baseline	x10E9/L
Neutrophils (absolute)	1.60	7.40	<1.5 at post-baseline and ≥1.5 at baseline >9 at post-baseline and ≤9 at baseline	x10E9/L
Eosinophils (absolute)	0.00	0.70	>0.7 at post-baseline and ≤0.7 at baseline	x10E9/L
Basophils (absolute)	0.00	0.20	>0.2 at post-baseline and ≤0.2 at baseline	x10E9/L
Monocytes (absolute)	0.10	0.90	>0,9 at post-baseline and ≤0,9 at baseline	x10E9/L
Lymphocytes (absolute)	1.00	4.00	<0.8 at post-baseline and ≥ 0.8 at baseline >4.0 at post-baseline and ≤ 4.0 at baseline	x10E9/L
Hemoglobin ***Male**	* 135.00	* 175.00	* <100 g/L at post-baseline and ≥ 100 g/L at baseline * ≥200 g/L at post-baseline and < 200 g/L at baseline	g/L
****Female**	** 120.00	** 160.00	** <90 g/L at post-baseline and ≥ 90 g/L at baseline ** ≥180 g/L at post-baseline and < 180 g/L at baseline	
Hematocrit ***Male**	* 0.40	* 0.52	<0.30 at post-baseline and ≥ 0.30 at baseline >0.6 at post-baseline and ≤ 0.6 at baseline	L/L
****Female**	** 0.36	** 0.46		
Platelets	150.00	350.00	<100 at post-baseline and ≥ 100 at baseline >700 at post-baseline and ≤ 700 at baseline	x10E9/L
Sodium	135.00	148.00	<129 at post-baseline and ≥ 129 at baseline >150 at post-baseline and ≤ 150 at baseline	mmol/L
Potassium	3.50	5.30	<3.5 at post-baseline and ≥ 3.5 at baseline >5.5 at post-baseline and ≤ 5.5 at baseline	mmol/L
Calcium - total	2.14	2.62	<2 at post-baseline and ≥ 2 at baseline	mmol/L
Chloride	98.00	110.00	<95 at post-baseline and ≥ 95 at baseline >115 at post-baseline and ≤ 115 at baseline	mmol/L
Glucose	3.90	6.90	<3 at post-baseline and ≥ 3 at baseline >13.9 at post-baseline and ≤ 13.9 at baseline	mmol/L
Creatinine ***Male**	* 62	* 106	>1.5 x ULN at post-baseline and ≤1.5 x ULN at baseline	µmol/L
****Female**	** 44	** 80		
Blood urea nitrogen (BUN)	2.1	8.9	>8.9 at post-baseline and ≤8.9 at baseline	mmol/L
AST	0.00	41.00	>3 x ULN at post-baseline and ≤3 x ULN at baseline	U/L
ALT	0.00	45.00	>3 x ULN at post-baseline and ≤3 x ULN at baseline	U/L
Alkaline phosphatase ***Male**	* 40	* 129	>2.5 x ULN at post-baseline and ≤2.5 x ULN at baseline	U/L
****Female**	** 35	** 104		
Bilirubin total	0.00	21.00	>1.5 x ULN at post-baseline and ≤1.5 x ULN at baseline	µmol/L

CPK ***Male** ****Female**	20.00	* 200 ** 180	>2.5 x ULN at post-baseline and ≤2.5 x ULN at baseline >2.5 x ULN at post-baseline and ≤2.5 x ULN at baseline	U/L
GGT	0.00	65.00	>2.5 x ULN at post-baseline and ≤2.5 x ULN at baseline	U/L
Protein total	60.00	85.00	<50 at post-baseline and ≥50 at baseline >95 at post-baseline and ≤95 at baseline	g/L
Albumin	32.00	55.00	<30 at post-baseline and ≥30 at baseline	g/L
Uric acid ***Male** ****Female**	* 0.24 ** 0.15	* 0.51 ** 0.45	* >0.51 at post-baseline and ≤0.51 at baseline ** >0.45 at post-baseline and ≤0.45 at baseline	mmol/L
Cholesterol total	0.00	5.17	>7.75 at post-baseline and ≤7.75 at baseline	mmol/L
Triglycerides	0.00	2.25	>3.42 at post-baseline and ≤3.42 at baseline	mmol/L
VITAL SIGNS and WEIGHT				
Pulse rate	N/A	N/A	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	beats/min
Diastolic blood pressure	N/A	N/A	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	mmHg
Systolic blood pressure	N/A	N/A	≤95 mmHg and decrease from baseline ≥20 mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	mmHg
Weight	N/A	N/A	≥5% increase from baseline ≥5% decrease from baseline	

22.4. Potentially clinically significant ranges – Adolescents

Test Parameter	Reference range (as per Lab Manual)		Potentially Clinically Significant Ranges (min and/or max limits)	SI Units
	LLN	ULN		
SERUM				
White Blood Cell Count (WBC)	4.00	10.70	<3 at post-baseline and ≥3 at baseline >15.0 at post-baseline and ≤15 at baseline	x10E9/L
Neutrophils (absolute)	1.60	7.40	<1.5 at post-baseline and ≥1.5 at baseline >9 at post-baseline and ≤9 at baseline	x10E9/L
Eosinophils (absolute)	0.00	0.70	>0.7 at post-baseline and ≤0.7 at baseline	x10E9/L
Basophils (absolute)	0.00	0.20	>0.2 at post-baseline and ≤0.2 at baseline	x10E9/L
Monocytes (absolute)	0.10	0.90	>0.9 at post-baseline and ≤0.9 at baseline	x10E9/L
Lymphocytes (absolute)	1.00	4.00	<0.8 at post-baseline and ≥0.8 at baseline >4.0 at post-baseline and ≤4.0 at baseline	x10E9/L
Hemoglobin ***Male** ****Female**	114.00	* 175.00 ** 160.00	<100 g/L at post-baseline and ≥100 g/L at baseline >200 g/L at post-baseline and ≤200 g/L at baseline	g/L
Hematocrit ***Male** ****Female**	0.36	* 0.52 ** 0.46	<0.30 at post-baseline and ≥0.30 at baseline >0.6 at post-baseline and ≤0.6 at baseline	L/L
Platelets	150.00	420.00	<100 at post-baseline and ≥100 at baseline	x10E9/L

			>700 at post-baseline and ≤700 at baseline	
Sodium	135.00	148.00	<129 at post-baseline and ≥129 at baseline >150 at post-baseline and ≤150 at baseline	mmol/L
Potassium	3.50	5.30	<3.5 at post-baseline and ≥3.5 at baseline >5.5 at post-baseline and ≤5.5 at baseline	mmol/L
Calcium - total	2.14	2.62	<2 at post-baseline and ≥2 at baseline	mmol/L
Chloride	98.00	110.00	<95 at post-baseline and ≥95 at baseline >115 at post-baseline and ≤115 at baseline	mmol/L
Glucose	3.90	6.90	<3 at post-baseline and ≥3 at baseline >13.9 at post-baseline and ≤13.9 at baseline	mmol/L
Creatinine	31.00	106.00	> 1.5 x ULN 1st IMP dose and ≤ 1.5 x ULN 1st IMP dose	µmol/L
Blood urea nitrogen (BUN)	1.80	7.14	>7.14 at post-baseline and ≤7.14 at baseline	mmol/L
AST	0.00	41.00	>3 x ULN at post-baseline and ≤3 x ULN at baseline	U/L
ALT ***Male**	5.00	* 30.00	>3 x ULN at post-baseline and ≤3 x ULN at baseline	U/L
****Female**		** 20.00		U/L
Alkaline phosphatase ***Male**	0.00	* 389.00	>2.5 x ULN at post-baseline and ≤2.5 x ULN at baseline	U/L
****Female**		** 186.00		
Bilirubin total	0.00	21,00	>1,5 x ULN at post-baseline and ≤1,5 x ULN at baseline	µmol/L
CPK ***Male**	2.00	* 251.00	>2.5 x ULN at post-baseline and ≤2.5 x ULN at baseline	U/L
****Female**		** 147.00	>2.5 x ULN at post-baseline and ≤2.5 x ULN at baseline	
GGT ***Male**	0.00	* 42.00	>2.5 x ULN at post-baseline and ≤2.5 x ULN at baseline	U/L
****Female**		** 24.00	>2.5 x ULN at post-baseline and ≤2.5 x ULN at baseline	
Protein total	60.00	85.00	<50 at post-baseline and ≥50 at baseline >95 at post-baseline and ≤95 at baseline	g/L
Albumin	32.00	55.00	<30 at post-baseline and ≥30 at baseline	g/L
Uric acid ***Male**	* 0.18	* 0.51	>0.51 at post-baseline and ≤0.51 at baseline	mmol/L
****Female**	** 0.13	** 0.45	>0.45 at post-baseline and ≤0.45 at baseline	
Cholesterol total	0.00	5.17	>7.75 at post-baseline and ≤7,75 at baseline	mmol/L
Triglycerides	0.00	2.25	>3.42 at post-baseline and ≤3,42 at baseline	mmol/L
VITAL SIGNS and WEIGHT				
Pulse rate	N/A	N/A	≤50 bpm and decrease from baseline ≥20 bpm ≥110 bpm and increase from baseline ≥20 bpm	beats/min
Diastolic blood pressure	N/A	N/A	≤50 mmHg and decrease from baseline ≥10 mmHg ≥90 mmHg and increase from baseline ≥10 mmHg	mmHg
Systolic blood pressure	N/A	N/A	≤90 mmHg and decrease from baseline ≥20 mmHg ≥135 mmHg and increase from baseline ≥20 mmHg	mmHg
Weight	N/A	N/A	≥5% increase from baseline ≥5% decrease from baseline	kg

118169_Galderma_SAP_Final_1.0_Version_09 NOV2022

Final Audit Report 2022-11-10

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"118169_Galderma_SAP_Final_1.0_Version_09NOV2022" History

PPD

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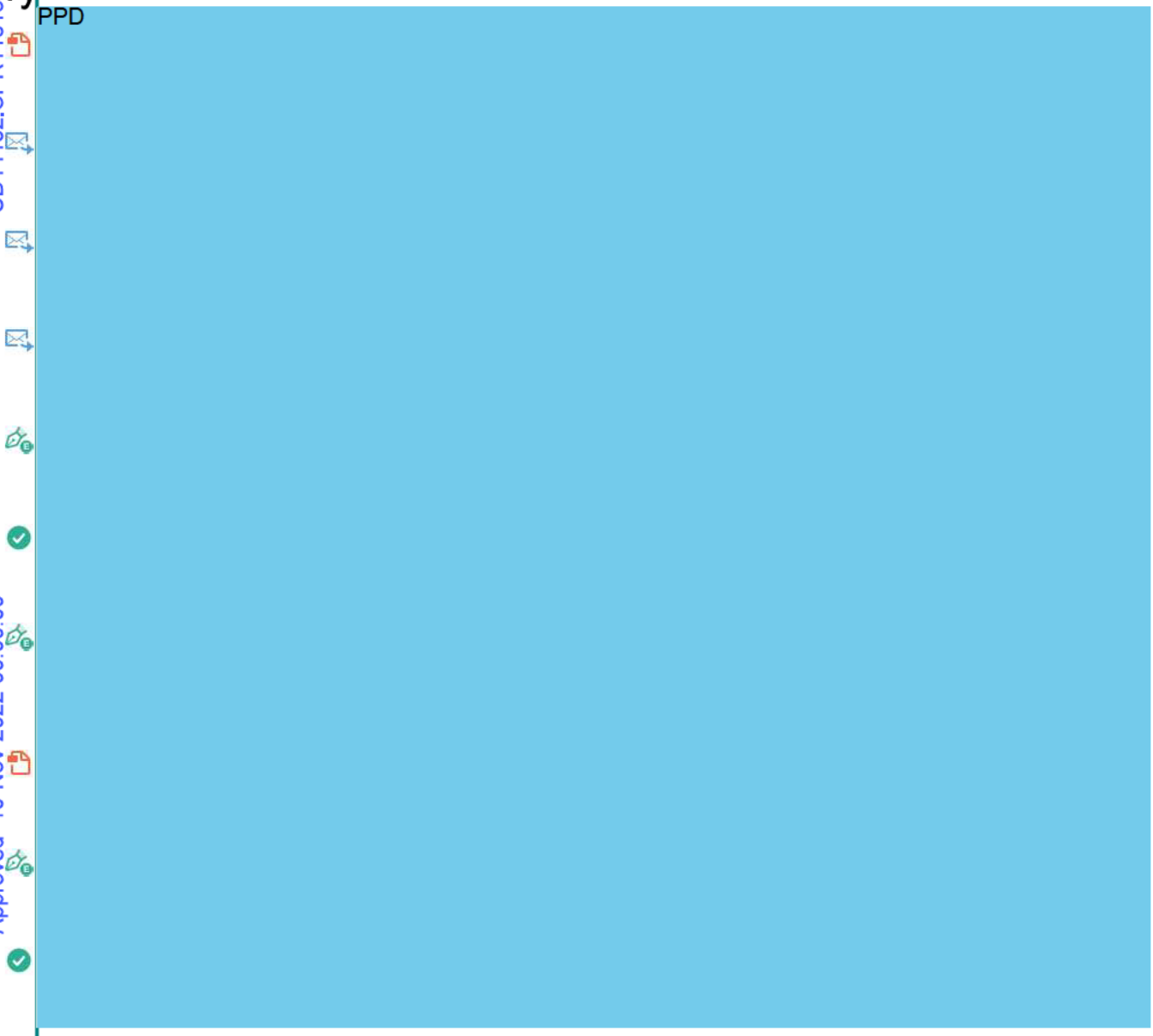

PPD

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CD14152.SPR118169.SAP.V01

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