STATISTICAL ANALYSIS PLAN

An Open-Label, Multicenter, Follow-up Study of ARGX-113-1904 to Evaluate the Safety, Tolerability, and Efficacy of Efgartigimod PH20 SC in Patients With Pemphigus (ADDRESS+)

Protocol:	ARGX-113-1905
SGS Internal Reference:	BE-80- 2000063
Development phase:	Phase 3
Sponsor:	argenx BV
Analysis purpose:	Final analysis
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SIGNATURE PAGE

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PROTOCOL HISTORY

Protocol: An Open-Label, Multicenter, Follow-up Study of ARGX-113-1904 to Evaluate the Safety, Tolerability, and Efficacy of Efgartigimod PH20 SC in Patients With Pemphigus (ADDRESS+)		
Version or ID	**Date** (ddMMMyyyy)	**Impact of the changes on the statistical analysis**
Final 1.0	12AUG2020	NAP
Final 2.0 (Amendment 1)	05FEB2021	1) New secondary objectives added: • Assess the health impact of glucocorticoid (GC) use in participants with PV or PF • Explore feasibility of (self-)administration of efgartigimod PH20 SC 2) Immunogenicity to rHuPH20 was made an exploratory objective/endpoint instead of a secondary endpoint (and is thus no longer in scope of this SAP) 3) Revised populations for analysis (Section 9.4 of protocol version 2.0)
Final 3.0 (Amendment 2)	05SEP2022	NAP

The considerations and methodologies described in this statistical analysis plan (SAP) apply only to the most recent version of the protocol/amendments listed above.

LIST OF ABBREVIATIONS

1904	ARGX-113-1904
1905	ARGX-113-1905
Ab	Antibody
ABQOL	Autoimmune Bullous Disease Quality of Life
ADA	anti-drug antibodies
ADaM	analysis data model
ADY	relative day in study
AE	adverse event
AESI	adverse events of special interest
AIS	aggregate improvement score
AP	alkaline phosphatase
ALQ	above the limit of quantification
ALT	alanine transaminase
AWADY	relative day in subperiod
AST	aspartate transaminase
ATC	Anatomical-Therapeutic-Chemical
BLA	biologics license application
BL(O)Q	below the limit of quantification
BMI	body mass index
bpm	beats per minute
BSA	body surface area
BUN	blood urea nitrogen
CBER	Centre for Biologics Evaluation and Research
C-GTI	Composite Glucocorticoid Toxicity Index
CI	confidence interval
CR	clinical remission
CRF	case report form
CRmin	complete remission on minimal therapy
CRoff	complete remission off therapy
CTCAE	Common Terminology Criteria for Adverse Events
CTP	clinical trial protocol
CWS	cumulative worsening score

DBP	diastolic blood pressure
DC	disease control
Dsg	desmoglein
DY	relative day
ECG	electrocardiogram
ED	early discontinuation
EFG	efgartigimod
eGFR	estimated glomerular filtration rate
EoC	end of consolidation
EoS	End of Study
EoT	End of Treatment
EQ-5D-5L	EuroQol Five-Dimension Five-Level Scale
GC	glucocorticoid
GGT	gamma-glutamyl transferase
GTI	Glucocorticoid Toxicity Index
GTI-SL	Glucocorticoid Toxicity Index – Specific List
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IgG	immunoglobulin G
IMP	investigational medicinal product
IRR	Injection-related reaction
ISR	Injection site reaction
IV	intravenous
IVIg	immunoglobulins given intravenously
LDH	lactate dehydrogenase
MAA	marketing authorization application
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
Nab	neutralizing antibody
NAP	not applicable
NCI	National Cancer Institute
NCPD	normalized cumulative prednisone dose

PD	pharmacodynamic
PDAI	Pemphigus Disease Area Index
PF	pemphigus foliaceus
PK	pharmacokinetic
PT	preferred term
PV	pemphigus vulgaris
PYFU	participant years of follow-up
QoL	quality of life
QTc	corrected QT interval
QTcB	Bazett's corrected QT interval
QTcF	Fridericia's corrected QT interval
rHuPH20	recombinant human hyaluronidase PH20
RBC	red blood cell
RO	roll-over
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	subcutaneous
SD	standard deviation
SE	standard error
SGS CR	SGS Clinical Research
SMQ	standardized MedDRA query
SOC	system organ class
SOP	standard operating procedure
STAT	statistics
TEAE	treatment-emergent adverse event
VS	vital signs
WBC	white blood cell
WHO-DD	World Health Organization Drug Dictionary
WI	work instruction

DEFINITION OF TERMS

Case report form (CRF)	A printed, optical, or electronic document designed to record protocol required information to be reported to the sponsor for each study participant.
Complete clinical remission (CR)	The absence of new lesions and complete healing of established lesions (except for post-inflammatory hyperpigmentation or erythema from resolving lesions).
Complete remission on minimal therapy (CRmin)	The absence of new and established lesions completely healed while the participant is receiving prednisone therapy at ≤10 mg/day for at least 2 months (8 weeks).
Complete remission off therapy (CRoff)	The absence of new and established lesions completely healed while the participant is receiving no prednisone therapy for at least 2 months (8 weeks).
Disease control (DC)	The absence of new lesions and the start of healing of established lesions.
Disease progression	Increase of ≥5 points in the PDAI activity score, observed at any post-baseline visit before DC.
Display	Analysis table, listing or figure
End of consolidation (EoC)	The time at which no new lesions have developed for a minimum of 2 weeks and approximately 80% of lesions have healed.
Flare	The appearance of 3 or more new lesions in a 4-week period that do not heal spontaneously within 1 week or the extension of established lesions, in a participant who had achieved DC.
Phase	Interval of time in the planned conduct of a study that is associated with a specific purpose: for example, screening, treatment, follow-up.

Significant digit	All digits of a number used to express it to the required degree of accuracy, starting from the first non-zero digit.
Standardized unit	unit populating –STRESU in the clinical database
Study drug or investigational medicinal product (IMP)	Pharmaceutical form of an active ingredient or placebo, being tested or used as a reference in a clinical study.
Treatment-emergent abnormality / toxicity	Any post-baseline abnormality/toxicity that was not present at baseline (e.g. hemoglobin normal or missing at baseline and grade 1 post-baseline; glucose low at baseline and high post-baseline; QTcF]450; 480] ms at baseline and >500 ms post-baseline)
Treatment failure	The absence of DC with oral prednisone 1.5 mg/kg/day for a minimum of 3 weeks, or absence of DC due to prednisone-related SAE, or flare before CRmin resulting in withdrawal of the participant.

1. INTRODUCTION

This SAP describes the final statistical analysis to be performed for ARGX-113-1905 (1905; BE-80- 2000063).

This SAP describes the safety, efficacy, pharmacokinetic (PK), pharmacodynamic (PD), and general characteristics parts of the statistical analyses to be performed for the final analysis of 1905. It specifies the manner in which the analyses will be presented, and describes the analytical methodology and procedures in greater detail than that of the statistical methods section of the 1905 protocol.

Analyses of exploratory endpoints are out of scope for this SAP; additionally, this SAP does not describe the methodology and procedures for the final analysis of 1905 data.

This SAP complies with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) standards, specifically the ICH-E3, ICH-E6, and ICH-E9 guidelines.

1.1 STUDY OBJECTIVES

The primary objective of study 1905 is to assess the safety of treatment, extended treatment, and retreatment with efgartigimod co-formulated with rHuPH20 for subcutaneous (SC) administration (EFG PH20 SC) in participants with pemphigus vulgaris (PV) or pemphigus foliaceus (PF).

According to the protocol, the secondary objectives of this study are:

- To evaluate the efficacy of EFG PH20 SC treatment in PV and PF
- To assess the health impact of glucocorticoid (GC) use in participants with PV or PF
- To evaluate the effects of EFG PH20 SC on quality of life (QoL) in participants with PV or PF.
- To evaluate the PK of EFG PH20 SC in participants with PV or PF
- To evaluate the PD of EFG PH20 SC in participants with PV or PF
- To evaluate the immunogenicity of EFG in participants with PV or PF
- To explore feasibility of (self-)administration of EFG PH20 SC

1.2 STUDY DESIGN

This is a prospective, multicenter, open-label extension (OLE) study on the efficacy, safety, participant outcome measures, tolerability, immunogenicity, PK, and PD of EFG PH20 SC in adult PV or PF participants, who participated in the antecedent study ARGX-113-1904 (1904).

Participants at the End of Study (EoS) visit or Early Discontinuation (ED) visit in 1904 will be given the option to enroll into 1905 after confirmation of eligibility while retaining the blinding of 1904. For each participant, the date of the baseline visit in 1905 will be the same as the date of the EoS/ED visit in 1904.

At baseline, participants will be treated according to their clinical status at EoS of 1904, as follows:

- Participants who have achieved CRmin or CRoff and are not currently in flare will be observed every 4 weeks through on-site visits without EFG PH20 SC treatment. In participants who have achieved CRmin (oral prednisone ≤10 mg per day for 2 months [8 weeks]), prednisone tapering may be pursued upon investigator's judgment until participants achieve CRoff.
- Participants in CR who have not achieved CRmin will receive weekly EFG PH20 SC administrations of 1000 mg while continuing the add-on therapy of oral prednisone until CRmin is achieved. Prednisone tapering may be pursued upon investigator's judgment until participants achieve CRoff. Participants will be treated through on-site visits or through home visits with an on-site visit once every 4 weeks.
- Participants who have achieved DC but not CR will receive weekly on-site administrations of 1000 mg EFG PH20 SC with an add-on therapy of oral prednisone until CR has been achieved, and then will continue to receive weekly EFG PH20 SC administrations of 1000 mg until CRmin is achieved either on-site or through home visits with an on-site visit once every 4 weeks.
- Participants under certain conditions of treatment failure as defined below, or participants with flare after having achieved CRmin, may roll over prematurely into 1905 and will be treated with EFG PH20 SC at a dose of [redacted], followed by weekly administrations of 1000 mg with an add-on therapy of oral prednisone until CRmin.

  The following types of treatment failure are considered here:
  - absence of DC with oral prednisone 1.5 mg/kg/day for a minimum of 3 weeks
  - participants who roll over due to prednisone-related SAE who have not achieved DC, or
  - flare between DC and achieving CRmin that is not controlled by 2 dose levels of OCS above the dose at which the flare is observed and that is at least 0.3 mg/kg/day

  In the absence of DC, participants will receive prednisone at the starting dose of 1.5 mg/kg/day. In case of uncontrolled flare before CRmin, participants will receive, as starting dose, the last dose from 1904. In case of flare after CRmin, participants will receive a prednisone dose in line with the severity of the flare.
- Participants who developed a prednisone-related SAE may prematurely roll over into 1905 and may be treated with EFG PH20 SC through on-site or home visits according to the clinical statuses as described above. Concomitant prednisone will be considered to fit the clinical statuses as far as compatible with the nature and severity of the SAE, with a lower dose to no concomitant prednisone being considered otherwise.

Details on the rules for prednisone dose adjustment can be found in the clinical trial protocol (CTP).

If DC is not attained after a minimum of 3 weeks of the participant receiving oral prednisone 1.5 mg/kg qd, then the participant will be considered a treatment failure and will be withdrawn from the study.

In case of flare in the period between DC and CRmin, the prednisone dose will be increased to achieve DC again. Participants who are not controlled by a dose that is 2 dose levels above the dose at which the flare is observed and that is at least 0.3 mg/kg/day, will be managed according to clinical judgment ie, either receive a further increased prednisone dose or be withdrawn from the study. Withdrawal of participants with a flare before CRmin will be defined as treatment failure.

In case of flare after having achieved CRmin (ie, while being off treatment with EFG PH20 SC), participants will be immediately treated/re-treated with EFG PH20 SC. The first day of new EFG PH20 SC treatment will define a new baseline for assessments of outcomes (DC, CR, etc.) and prednisone escalation or tapering schedule.

In the new treatment period, participants will be administered EFG PH20 SC at a weekly dose of [redacted], followed by weekly SC administrations of 1000 mg until CRmin. Oral prednisone will be administered at a dose chosen according to clinical judgment, with the recommendation of 0.3 mg/kg qd in the case of mild flare (PDAI activity score <15) and 0.5 mg/kg qd in the case of moderate to severe flare (PDAI activity score ≥15). The treatment goal of a new treatment period is to first achieve DC again and therefore these participants will be treated accordingly.

A new treatment period of EFG PH20 SC can be initiated in eligible participants until week 44. In participants requiring a new treatment period of EFG PH20 SC between weeks 45 and 49, the initiation will be optional and based on clinical judgment and participant consent. A new EFG PH20 SC treatment period will not be permitted after week 49 to ensure a minimum of 4 weeks of EFG PH20 SC treatment/period.

Except for oral prednisone, no other systemic therapies (eg, immunosuppressants, IVIg, immunoadsorption, anti-CD20 biologics) will be permitted during the study.

Participants or their caregivers (a person of legal age that the participant proposes to perform the administrations) may (self-)administer EFG PH20 SC after they have successfully completed (self-)administration training (in 1904 with at least one refresher training in 1905 or during 1905).

All participants and/or their caregivers will receive a home guide for transport, storage, preparation, and administration of the IMP.

The schedule of activities is in appendix 9.3.

1.3 EXPECTED SAMPLE SIZE

The maximum number of participants in 1905 will be the number of participants in 1904: up to approximately 213 participants.

1.4 RANDOMISATION AND BLINDING

Not applicable.

1.5 INTERIM ANALYSIS

Not applicable.

1.6 SOFTWARE

SAS version 9.4 or later (SAS Institute Inc., Cary, NC, USA) will be used for programming.

1.7 VALIDATION MODEL

SGS Clinical Research (SGS CR) statistics (STAT) standard operating procedures (SOPs) and work instructions (WIs) as effective at the project start will be followed throughout the project, provided the applicable regulatory requirements are still met.

Subject-level Analysis Dataset (ADSL), Analysis of Adverse Events Dataset (ADAE) and Analysis of Laboratory Test Results Dataset (ADLB) will be validated through independent programming (model C validation). The rest of the analysis will be reviewed by an independent person (model B validation).

2. GENERAL METHODOLOGY

2.1 ANALYSIS SETS

2.1.1 Analysis sets

The following analysis sets will be considered in the statistical analysis:

Roll-over set (ROLL):	all participants who rolled over from study 1904
Safety analysis set (SAF):	all participants who received at least 1 dose, or part of a dose, of IMP in study 1905

A participant is considered to have rolled over to 1905 once they have provided informed consent for the study (they have signed the informed consent form [ICF] for ARGX-113-1905), defined as having a complete informed consent signature date in the database.

2.1.2 As planned versus as actual analysis

Efficacy endpoints, C-GTI and GTI-SL will be analyzed according to the treatment to which participants were randomized in 1904. For other endpoints, the analysis will be conducted according to the actual treatment the participant received in both 1904 and 1905 (see section 2.4.2).

2.2 PHASES, PERIODS AND TIME POINTS

2.2.1 Phases and periods

All events and assessments will be allocated to phases, periods, and subperiods.

As explained in section 1.2, participants will be treated according to their clinical status at EoS of 1904. Also depending on their clinical status, the number of treatment periods needed in 1905 will be different. Therefore, not all participants will have all periods defined in below table.

Table 1: Phase, period and subperiod definition

Phase	Period	Subperiod	Start	End
Roll-over phase is only applicable for participants who achieved CRmin or CRoff in 1904 and who don't have an IMP administration at the roll-over visit.				
Roll-over		Off-treatment RO	Earliest of (date of signing the informed consent form (ICF) of study 1905 and date of roll-over), with 00:00 added as time part[a].	First IMP (1905) administration date/time – 1 minute for participants who received treatment. For participants who were not treated with IMP: Date of week 52/EoT/ET visit, with 23:59 added as time part. For participants who don't have a week 52/EoT/ET visit: date of last contact, with 23:59 added as time part.

	Treatment period 1 is only applicable for participants who did not achieve CRmin or CRoff in 1904			
Treatment	Treatment period 1[b,c]	On-treatment 1	Earliest of (date of signing the informed consent form (ICF) of study 1905 and date of roll-over), with 00:00 added as time part[a.]	For the participants with off-treatment 1 subperiod : last IMP administration date/time in treatment period 1. For other participants: Date of week 52/EoT/ET visit, with 23:59 added as time part. For participants who don't have a week 52/EoT/ET visit: date of last contact, with 23:59 added as time part.
		Off-treatment 1	Last IMP administration date/time in treatment period 1 + 1 minute	For the participants with a next treatment period: first IMP administration date/time in next treatment period – 1 minute. For other participants: Date of week 52/EoT/ET visit, with 23:59 added as time part. For participants who don't have a week 52/EoT/ET visit: date of last contact, with 23:59 added as time part.
	Treatment period 2 is applicable for participants with flare after CRmin in the roll-over phase or in treatment period 1 and who re-initiate IMP administration			
	Treatment period 2 [c]	On-treatment 2	First IMP administration date/time in treatment period 2	For the participants with off-treatment 2 subperiod : last IMP administration date/time in treatment period 2. For other participants: Date of week 52/EoT/ET visit, with 23:59 added as time part. For participants who don't have a week 52/EoT/ET visit: date of last contact, with 23:59 added as time part.

	Off-treatment 2	Last IMP administration date/time in treatment period 2 + 1 minute	For the participants with a next treatment period: first IMP administration date/time in next treatment period – 1 minute. For other participants: Date of week 52/EoT/ET visit, with 23:59 added as time part. For participants who don't have a week 52/EoT/ET visit: date of last contact, with 23:59 added as time part.
	Etc[c]		
Follow-up		End of treatment phase + 1 minute	Date of last contact, with 23:59 added as time part.

[a] In case no 1905 ICF date is available, participant data will not be considered in the analysis
[b] Not applicable for participants who enter 1905 on CRmin. They will start immediately in Treatment period 2 of the Treatment phase in case of flare
[c] A new treatment period is considered for participants with a flare after achieving CRmin (ie, while being off IMP treatment). A new treatment period is not considered after temporary IMP discontinuation for an adverse event. Repeat until the last on-treatment or off-treatment subperiod.

Participants who enter 1905 on CRmin, will not have a treatment period 1 in the treatment phase, but will start immediately with treatment period 2 at first IMP intake in 1905 (ie, after the first flare in 1905). Note: treatment period 2 is defined in 1905 as the treatment period starting after the first flare within 1905. Treatment given before a first flare in 1905 is considered belonging to treatment period 1.

Adverse events (AEs) and concomitant therapies will be allocated to phases and periods as described in sections 5.1.2 and 3.3.2 respectively. All other assessments will be allocated to phases (PDAI, PD, PK, albumin and LDL-C also to periods and subperiods) based on the assessment date(time).

In case of (partially) missing date(time) fields disabling allocation, information from the visit/timepoint label and protocol schedule of activities will be used to allocate to the correct phase, period and subperiod. If this is not possible (unscheduled visits or visits on a turning point between phases, periods or subperiods), assessments will be handled as follows:

- Treatment phase vs. roll-over phase: assessments will be allocated to the treatment phase unless the available parts of the assessments start or stop date/time provide evidence for allocating to the roll-over phase.
- Treatment phase vs. follow-up phase: assessments will be allocated to the treatment phase unless the available parts of the assessments start or stop date/time provide evidence for allocating to the follow-up phase.
- On-treatment vs. off-treatment subperiod within a treatment period: assessments will be allocated to the on-treatment subperiod unless the available parts of the assessments start or stop date/time provide evidence for allocating to the off-treatment subperiod.
- Multiple treatment periods: assessments will be allocated to the first period that is possible based on the available parts of the assessments start and stop date/time.

A set of subperiods will be derived over the combined treatment and follow-up phase, to support the analysis of treatment-emergent adverse events (TEAEs) versus post-TEAEs.

Table 2: Subperiod definition for AEs

Subperiod	Start	End
Treatment emergent 1	Treatment phase start date/time (see Table 1)	Date of first EFG where the next EFG is at least 61 days later + 60 days[a]
Post-treatment emergent 1	End date/time of previous subperiod + 1 minute	Start date/time of next subperiod - 1 minute
Treatment emergent 2	First EFG date/time following the start of previous post-treatment emergent subperiod	Date of first EFG where the next EFG is at least 61 days later + 60 days[a]
Post-treatment emergent 2	End date/time of previous subperiod + 1 minute	Start date/time of next subperiod - 1 minute
Etc.[b]		

EFG = efgartigimod (administration)
[a] With 23:59 added as time part
[b] Repeat until the last subperiod

The end date/time of the last subperiod will correspond with the end date/time of the last phase as defined in Table 1. AEs starting during the roll-over phase will also be considered as post-TEAEs.

2.2.2 Relative day

Relative day in the study (ADY) will be calculated according to the following rule:

- Concerned date < reference date: DY = concerned date – reference date
- Concerned date ≥ reference date: DY = concerned date – reference date + 1

The reference date is the date of the roll-over visit.

Additionally, relative day in the phase (ADYP) will be calculated using the first day of the phase as reference date.

Relative day in the treatment subperiods (AWADY) will be calculated in the same way, as needed, but using the first day of the subperiod as reference date.

2.2.3 Baseline and change from baseline

The baseline value for 1905 will be the value at the Roll-over visit (which corresponds with the last available value of the 1904 study (at the 1904 EoS visit/1905 Roll-over visit)).

Additionally, for PDAI and PD, changes from 1904 baseline will be presented, with 1904 baseline defined as the last available and non-missing value prior to first IMP administration in the 1904 study (detailed definition of 1904 baseline in 1904 SAP).

Change from baseline at time point t is defined as:

value at time point t – baseline value

Percentage change from baseline at time point t is defined as:

100*([value at time point t – baseline value] / baseline value)

Furthermore, for PDAI, PD, albumin and LDL-C a treatment period-specific baseline (TPnB) will be defined as the last available and non-missing value prior to the first administration of EFG PH20 SC in treatment period n, with n=1, 2, 3, etc….

Assessments on day 1 of a treatment period without time collection or with time information exactly equal to the time of first IMP administration and which are planned predose will be considered as predose.

Change from TPnB at time point t =

value at time point t – TPnB value.

Percent change from TPnB at time point t =

100*([actual value at time point t - TPnB value]/ TPnB value).

2.2.4 Analysis visits

All assessments (except safety assessments in the roll-over phase), including unscheduled assessments, will be allocated to analysis windows. Tables, listings and figures will present the analysis windows as defined below, not the CRF visits.

Allocation of assessments will be done using their relative day in the phase (ADYP) (see section 2.2.3) according to the following table:

Table 3: Analysis visits

Phase	Analysis window	Target ADYP	Lower limit ADYP	Upper limit ADYP
Roll-Over	Baseline [a]	-	-	-
	Week 4	29	1[c]	43
	Week 8	57	44	71
	Week (8 + x^b *4)	57 + (x^b*28)	44 + (x^b*28)	71 + (x^b*28)
	…	…	…	…
	Week 52	365	352	End day of phase
Treatment	Baseline [a]	-	-	-
	Week 1	8	1[c]	11
	Week 2	15	12	18
	Week 3	22	19	25
	Week (3+ x^b)	22 + (x^b*7 days)	19 + (x^b*7 days)	25 + (x^b*7 days)
	…	…	…	…

	Week 51	358	355	361
	Week 52	365	362	End day of phase
Follow-up	FU Week 4	28	1	42
	FU Week 8	56	43	End day of phase

[a] Baseline is the assessment at the roll-over visit, so no analysis visit windows are required for this time point. For participants with a roll-over phase, the baseline analysis visit will be assigned to the roll-over phase and will not be repeated in the treatment phase. For participants without a roll-over phase, the baseline analysis visit will be assigned to the treatment phase.
[b] x=1,…, 10 for roll-over phase, x=1,…,.47 for treatment phase
[c] An assessment at the roll-over visit will be attributed to Baseline in case it is before the first IMP administration, to Week 1 otherwise.

Baseline is defined in section 2.2.2.

For the analysis of ECG, a 12-weekly allocation will be used, as defined in Table 4.

Table 4: Analysis visits for ECG

Phase	Analysis window	Target ADYP	Lower limit ADYP	Upper limit ADYP
Treatment	Baseline [a]	-	-	-
	Week 12	85	1[a]	127
	Week 24	169	128	211
	Week 36	253	212	295
	Week 48	337	296	361
	Week 52	365	362	End day of phase
Follow-up	FU Week 4	28	1	42
	FU Week 8	56	43	End day of phase

[a] Baseline is the assessment at the roll-over visit, so no analysis visit windows are required for this time point.
[b] x=1 through the maximum number of 12-weeks periods on treatment for any participant minus 2

For GTI wider windows are used:

- Week 26 (wide range): from ADY=145 until ADY=221 with target on ADY=183
- Week 52 (wide range): from ADY=327 until ADY= end of treatment phase with target on ADY=365
- Other assessments will be allocated as in table 3 but will not be presented in the tables (only in listings).
- Additional visit window: Endpoint: last record post baseline.

Analysis of ABQOL and EQ-5D-5L will be done on following visits:

- Roll-over (per CRF visit)
- At CRmin (assessment done within 28 days after achieving CRmin)
- At start of new treatment period
- At EoT/ET (per CRF visit)

Additionally, assessments for PDAI, PD, albumin and LDL-C are also allocated to analysis visits based on AWADY using start of subperiod as reference day, as shown in Table 5. Assessments for PK will only be allocated to analysis visits based on Table 5.

Table 5: Additional analysis visits for PDAI, PD, PK, Albumin and LDL-C

Phase/ Period	Subperiod	Analysis window	Target AWADY	Lower limit AWADY	Upper limit AWADY
Roll-over	Off-treatment RO	Baseline [d]	-	-	-
		Week 4	29	1	43
		Week 8	57	44	71
		Week (8+ x^b *4)	57 + (x^b*28)	44 + (x^b*28)	71 + (x^b*28)
		…	…	…	…
		Week 52	365	352	End day of phase
Treatment /Treatment period n	On-treatment n	TPnB	1	-INF	1[a]
		Week 1	8	1[a]	11
		Week 2	15	12	18
		Week 3	22	19	25
		Week (3+ x^b)	22 + (x^b*7 days)	19 + (x^b*7 days)	25 + (x^b*7 days)
		…	…	…	…
		Week 52	365	362	End day of On-treatment n subperiod
	Off-treatment n	Week 1	8	1	11
		Week 2	15	12	18
		Week 3	22	19	25

	Week (3+ x^b)	22 + (x^b*7 days)	19 + (x^b*7 days)	25 + (x^b*7 days)
	…	…	…	…
	Week 52	365	362	End day of Off-treatment n subperiod

[a] An assessment on Day 1 will be attributed to TPnB in case it is before the first IMP administration, to Week 1 otherwise.
[b] x=1,…, 10 for roll-over phase, x=1,…,.48 for treatment phase
[c] Upper limit of last analysis window in roll-over phase cannot exceed first IMP administration date.
[d] Baseline is the assessment at the roll-over visit, so no analysis visit windows are required for this time point.

For those participants who will start a new treatment period, the last assessment in a period, prior to the administration of the new period, will be allocated to the appropriate visit within this previous period and will also be allocated as the treatment period baseline (TPnB) visit of the new period.

Per parameter and analysis window, the value closest to the target ADY/AWADY will be used in analysis tables and figures, other values will only be listed. If more than one value is located at the same distance from the target, then the latest in time will be selected. The value latest in time will be identified using, in order of preference, the assessment date/time, the visit label or the group identifier (if applicable). For immunogenicity assessments, values resulting in an unevaluable ADA/NAb status are given the lowest priority when the selection is made. For other assessments, missing values are removed before the selection is made.

Partially missing assessment dates disabling allocation to analysis windows will not be imputed and thus these assessments will not be considered in the per-timepoint analysis. Note that these assessments are included in analyses on worst-case.

2.2.5 Worst-case

A worst-case analysis visit will be created for the combined treatment and follow-up phase for parameters for which abnormalities and/or toxicity grades are defined to summarize values considered as the worst-case over time. For abnormalities, this visit is derived per parameter and in case both the lowest and the highest values are considered abnormal, a participant can have two worst-case analysis visits for a same parameter. For toxicity grades, the worst-case is the value associated to the highest toxicity grade and is derived per parameter and toxicity direction (hypo/hyper).

All non-missing post-baseline values in the treatment and follow-up phase, including unscheduled assessments, will be considered when deriving the worst-case analysis visit.

2.3 IMPUTATION AND ROUNDING RULES

2.3.1 Missing values

For imputation on missing values related to efficacy, see appropriate section of the applicable efficacy endpoint.

2.3.2 Handling partially or completely missing dates in calculations

Prednisone administration start dates with partially missing data will be imputed as follows:

- Missing day will be imputed with first day of the month or start date of the first phase, whichever comes latest.
- Missing day and month will be imputed with 1JAN or start date of the first phase, whichever comes latest.
- Completely missing date will be imputed with start date of the first phase.

Prednisone administration end dates with partially missing data will be imputed as follows:

- Missing day will be imputed with last day of the month or the date of last contact, whichever comes first.
- Missing day and month will be imputed with 31DEC or the date of last contact, whichever comes first.
- Completely missing end date will be considered as still ongoing at the end of the study.

2.3.3 Values below or above a threshold

Safety values expressed as below or above the detection limit will be imputed by the value of the detection limit itself. Listings will always show the non-imputed values.

Total IgG and IgG subtype values expressed as below or above the limit of quantification (BLQ or ALQ, respectively) will not be imputed. For anti-Dsg-1/Dsg-3 autoantibodies, BLQ and ALQ values will be imputed by the value of the detection limit itself. Listings will always show the non-imputed values.

PK concentrations below the limit of quantification (BLQ) will be flagged as such in the listings. For descriptive statistical analysis, all BLQ values will be set to zero. For ALQ values, all ALQ values will be set to the upper limit of quantification for descriptive analysis. Listings will always present the original value.

Anti-drug antibodies (ADA) against efgartigimod: titer of positive ADA samples reported as ‘negative titer’ will be imputed by 1.
Listings will always present ‘negative titer’.

2.3.4 *Rounding of derived variables*

Derived variables will be rounded to the appropriate number of decimals at display level:

- Estimated glomerular filtration rate (eGFR) will be rounded to 2 decimals.
- Normalized cumulative prednisone dose (NCPD) and prednisone dose at baseline will be rounded to 2 decimals.
- Cumulative prednisone dose will be rounded to 0 decimals.

2.3.5 *Outliers*

There will be no outlier detection. All measured values will be included in the analyses.

2.4 PRESENTATION OF RESULTS

Region/country specific outputs will be created to support region/country specific submissions. Specifically, all descriptive outputs described in this SAP will be repeated by region (Japanese / Non-Japanese as defined in the study protocol) to support the J-MAA submission. The definition of a Japanese participant in the protocol is a participant whose parents and 4 grandparents are Japanese, who has the Japanese nationality, was born in Japan, has not lived outside of Japan for a total of >10 years, and currently lives in Japan.

To support the Chinese submission, all outputs described in this SAP will be repeated for the following two subpopulations: Mainland Chinese and East Asian. Mainland Chinese is defined as any participant enrolled by an investigational site located in mainland China and with a race “Asian”. East Asian is defined as any participant enrolled by an investigational site located in East Asia (China, Japan), and with a race “Asian”. In addition, the Pharmacokinetic and Pharmacodynamics analyses described in sections 4.2 and 4.3 will be repeated for the complement of the Mainland Chinese and East Asian subgroups (i.e. Non-Mainland Chinese and Non-East Asian).

2.4.1 *Calculation of descriptive statistics and percentages*

For continuous parameters, full descriptive statistics will only be presented if there are at least 2 non-missing observations. Alternatively, only the number of non-missing data points and mean are shown.

Descriptive statistics will include the number of non-missing data points, the arithmetic mean, the standard deviation (SD), the standard error (SE), the median, minimum, first quartile (Q1), third quartile (Q3), and maximum.

Descriptive statistics for immunogenicity titer values will also include geometric mean (GM) and geometric standard deviation (GSD).

Mean, Q1, Q3, median, GM and GSD will be presented with 1 more decimal place than the measured values, with maximum 4 decimal places. SD and SE will be presented with 2 more decimal places than the measured values, with maximum 5 decimal places. Minimum and maximum will be presented with the same number of decimal places as the measured values, with maximum 3 decimal places.

Descriptive statistics of PK concentrations will include number of non-missing data points, arithmetic mean, SD, median, minimum and maximum, and the coefficient of variation (CV%). The descriptive statistics will be presented with 3 significant digits. If more than half of the values are BLQ, arithmetic mean will be set to BLQ and SD and CV% will not be calculated.

For event-type data, the denominator will be all participants in the analysis set per treatment and phase/period/subperiod (as applicable).

For frequency tabulations and cross-tabulations, the denominator will be all participants in the analysis set per treatment. For tables where results are shown by analysis visit, the denominator will be all participants in the analysis set per treatment and per analysis visit. Missing values will never be included in the denominator count when computing percentages. For cross-tabulations of post-baseline results versus baseline results, a 'missing' category will be shown for baseline results if applicable.

Percentages will be shown with one decimal place.

2.4.2 Presentation of treatments

The following treatment labels will be used in the tables and listings:

- EFG PH20 SC
- PBO PH20 SC - EFG PH20 SC
- Total EFG PH20 SC

2.4.3 Ordering in tables, listings and figures

All tables and figures will be presented per treatment and total, unless specified otherwise. In by visit displays, worst-case will be shown last, if present.

In listings for general characteristics, results will be ordered by treatment and participant, unless specified otherwise.

All other listings will be ordered by treatment, participant, analysis visit and time point, unless specified otherwise.

Safety assessments during the roll-over phase will not be tabulated, unless specified otherwise. These assessments will be included in listings, ordered by treatment, participant and time point.

In tables showing several parameters, each parameter will begin on a new page and parameters will be sorted alphabetically, within the parameter category if applicable.

Treatment columns will be ordered in the same order as mentioned in section 2.4.2.

2.5 SUBGROUPS

The disease status at the start of 1905 (at the roll-over visit) will be used as subgroup for several analyses.

Participants will be categorized in one of the following categories:

- CRmin
- CR
- DC - no CR
- Treatment failure
- Flare after CRmin

Notes:

1. Participants on CRoff are included in the category 'CRmin'.

2. Participants on EoC are included in the category ‘DC- no CR’.

3. Participants on CRmin who (inadvertently) receive IMP at the roll-over visit are included in the category 'DC - no CR'.

4. Participants with flare between DC and CRmin at the 1905 roll-over visit and who did not qualify as treatment failures in 1904, are included in the category ‘DC – no CR’.

5. Participants who are considered a treatment failure in 1904 due to a prednisone related serious adverse event (SAE) will be shown under their disease status at roll-over (reflecting the latest available disease status in 1904 before treatment failure). Participants with flare between DC and CRmin at the 1905 roll-over visit, are included in the category ‘Treatment failure’.

3. GENERAL CHARACTERISTICS ANALYSES

General characteristics data will be presented for the Roll-over set with the exception of treatment discontinuation data, concomitant therapy data and IMP administration data, which will be presented for the Safety analysis set.

3.1 PARTICIPANT DISPOSITION

The following participant data will be tabulated:

- The number of participants in each analysis set (for all participants (PV+PF) and for PV participants)
- The number of participants per disease status at roll-over from 1904: CRmin, CR, DC - no CR, treatment failure, flare after CRmin (for all participants (PV+PF) and for PV participants).
- The number and percentage of participants by country and site.
- The number and percentage of participants for each analysis visit within
  - The treatment and follow-up phase (as defined in Table 3)
  - Each phase/period/subperiod (as defined in Table 5)
- Descriptive statistics of the phase/period/subperiod duration, calculated as end date – start date + 1 day. The following will be presented:
  - Roll-over phase duration
  - Treatment phase duration
  - Follow-up phase duration
  - Each treatment period duration
  - Each subperiod duration within each treatment period
  - Total duration of all on-treatment subperiods (participants without any on-treatment subperiod have a total duration = 0)
- The number and percentage of participants who completed or discontinued the study as documented on the study termination page and the number and percentage of participants for each study discontinuation reason.
- The number and percentage of participants who completed or discontinued the treatment as documented on the end of treatment page and the number and percentage of participants for each treatment discontinuation reason (overall and by disease status at roll-over in 1905 for all participants (PV+PF) as well as for PV participants).
- The number and percentage of participants with minor and major protocol deviations.

All information collected in the CRF concerning study and treatment discontinuation and information on phases will be listed. All minor and major protocol deviations will be listed.

3.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

3.2.1 Available data

The following parameters will be available:

- Demographics: sex at birth, age at informed consent, race and ethnicity (if collection permitted), childbearing potential, height at baseline, weight at baseline, year of birth, date of signing ICF (listed only), country
- Baseline disease characteristics: pemphigus type (vulgaris/foliaceus) and subtype (mucosal-dominant / mucocutaneous / cutaneous) (from 1904), PDAI activity score and PDAI total score at baseline, ABQOL total score at baseline, anti-Dsg antibodies (aDsg1 only, aDsg3 only, both aDsg1 and aDsg3) and prednisone dose at baseline

3.2.2 Derivation rules

The following parameters will be derived:

- Region: country will be categorized into the following regions: North America (USA), Europe (Bulgaria, France, Hungary, Germany, Greece, Italy, Poland, Romania, Spain, UK), Asia (China, India, Japan), Rest of world (Australia, Georgia, Russian Federation, Serbia, Turkey, Ukraine)
- Disease severity: PDAI activity score will be categorized into the following disease severities: <15 (mild), 15-44 (moderate), ≥45 (severe)
- Prednisone equivalent dose at baseline (mg/kg/day) = normalized prednisone equivalent dose as detailed in section 3.4.2 of prednisone (actually) administered on the day of the roll-over visit.

  Results will be rounded as detailed in section 2.3.4

3.2.3 Presentation of results

Demographics will be presented using descriptive statistics for age, height, weight and BMI, and frequency tabulations for sex, childbearing potential, race, ethnicity, and region.

Baseline disease characteristics will be presented using descriptive statistics for PDAI activity and total score at baseline, ABQOL total score at baseline, prednisone equivalent dose per body weight at baseline (mg/kg/day) and prednisone equivalent dose at baseline (mg/day), and frequency tabulations for all other parameters.

Tables to be produced for the topline results (see list of outputs in section 8.1) will be presented overall and by disease status at roll-over in 1905. These tables will show data for PV+PF participants as well as for PV participants.

All demographic data and baseline disease characteristics will be listed.

3.3 PRIOR AND CONCOMITANT THERAPIES AND PROCEDURES

3.3.1 Available data

All therapies are coded using WHO-DD. Anatomical-Therapeutic-Chemical (ATC) selection is performed to select the most appropriate medication class. For the

selected class, ATC coding up to level 4 is available in the clinical database. For each therapy, a start date or prior flag and stop date or ongoing flag are collected.

Procedures are coded using the medical dictionary for regulatory activities (MedDRA) into preferred terms. For each finding, the indication and a start and stop date are collected.

Coding of therapies and procedures will be performed using the latest versions of the dictionaries available at the time of the 1904 study database lock.

3.3.2 Derivation rules

Based on their start and stop date, therapies and procedures will be allocated to each analysis phase and period during which they were administered. A therapy/procedure can therefore be reported in more than one analysis phase or period.

Analysis phases and periods are defined in section 2.2.1. Therapies/procedures with (partially) missing date(time)s will be allocated to each phase/period unless the available parts of the therapy/procedure start or stop date(time)s or prior and ongoing flags provide evidence the therapy/procedure was not taken during that period.

Based on their start and stop date(time), therapies and procedures will also be allocated into one or both of the following categories:

- Prior: any therapy/procedure that strictly started before the first IMP dose in 1905.
- Concomitant: any therapy/procedure that was taken on or after the first IMP dose in 1905.

A therapy/procedure that started before the date of first IMP dose in 1905 and continued during the study will be classified as both prior and concomitant.

Therapies/procedures with (partially) missing date(time)s will be allocated to each category unless the available parts of the therapy/procedure start or stop date(time) provide evidence not to do so.

3.3.3 Presentation of results

The number and percentage of participants with concomitant therapies and the number and percentage of participants with concomitant therapies by ATC class (level 1 and 3) and generic term will be tabulated using the Safety analysis set. Blank ATC levels, if any, will be shown as ‘not available’ in the tables. These tables will be provided overall, not by phase or period.

All prior and concomitant therapies data will be listed with detailed information about ATC classes.

All prior and concomitant procedures data will be listed.

3.4 IMP AND PREDNISONE ADMINISTRATION

3.4.1 Available data

For each study drug administration, the start and end date/time, the dose (in mg) and the actual volume are recorded.

For each continuous prednisone administration, the start and end date/time, and either the total daily dose (in mg) or the dose per administration (in mg) together with the frequency is recorded. This information is recorded for the prescribed dose as well as the actually administered dose. Only the actually administered dose information will be used for the analysis of exposure to prednisone.

Participants/caregivers may participate in (self-)administration training. Visits at which training took place and reasons for not following a training are recorded.

3.4.2 Derivation rules

The following parameters will be derived for EFG PH20 SC treatment periods and administrations:

- Number of re-treatment periods: number of treatment periods excluding treatment period 1, i.e.:
  - 0: for participants without any treatment period or only treatment period 1
  - 1: for participants with treatment period 2
  - 2: for participants with treatment period 2 and 3
  - Etc.
- Number of administrations: sum of all administrations of study drug. [redacted]
- Number of loading doses: i.e. daily doses of [redacted] of 1000 mg).

The following parameters will be derived for prednisone administration:

- NCPD (in mg/kg/day)
- Cumulative prednisone dose (in mg)

Result will be rounded as detailed in section 2.3.4

The NCPD will be calculated based on prednisone equivalent doses. The prednisone-equivalent dose is calculated as [dose of ATC]*[equivalence factor prednisone]/[equivalence factor ATC]. Following [equivalence factors] are used:

- Betamethasone [1.5]
- Cortisone [37.5]
- Deflazacort [15]
- Dexamethasone [1.5]
- Fluocortolone [10]
- Hydrocortisone [30]
- Methylprednisolone [8]
- Methylprednisolone acetate [8]
- Methylprednisolone sodium succinate [8]
- Paramethasone [4]
- Prednisolone [10]
- Prednisolone acetate [10]
- Prednisolone sodium succinate [10]
- Prednisone [10]
- Prednisone acetate [10]
- Prednylidene [12]
- Rimexolone [20]
- Triamcinolone [8]

Example: calculation of equivalent dosage of 12 mg methylprednisolone: 12*10/8= 15 mg prednisone.

Only systemic use of oral medication is included.

NCPD (mg/kg/day) is calculated for different periods (see section 3.4.3) as [the sum of (equivalent doses taking into account daily dose frequency)/(body weight in kg)]/(period duration in days) with body weight of visit closest before or at each start of prednisone equivalent medication record. If for a given day, no record exists in the CRF indicating prednisone use on that day, the dose will be assumed to be 0 mg.

Similarly, the cumulative prednisone dose (in mg) over these periods will be calculated based on the prednisone equivalent dose.

The following rules will be applied to allocate prednisone administrations to the correct period:

- Only start and stop dates (not times) will be considered
- Records with (partially) missing dates will be imputed as detailed in section 2.3.2.
- If administration date records overlap, then the doses reported in all the overlapping records will be combined.
- If an administration is reported as dose per administration with frequency, then the doses should be allocated to the correct dates, taking the start date and the frequency into account. Example:
  - Dose: 40 mg
  - Frequency: every other day
  - Start - Stop date: 01JAN2022 - 03JAN2022

  This will result in:
  - 40 mg be allocated to 01JAN2022
  - 0 mg allocated to 02JAN2022
  - 40 mg allocated to 03JAN2022
- Regardless of the time information, an administration on the day of the start of a new treatment period will only be allocated to that new treatment period, not to the period before.

The following parameters will be derived for IMP (self-)administration by participant and by caregiver:

- Number of participants/caregivers receiving the (self-)administration training.
- Number of training visits received by participant/caregiver.
- Number of participants/caregivers who were adequately trained and capable to (self-)administer EFG PH20 SC.
- Number of training visits before being considered capable to (self-)administer.

3.4.3 Presentation of results

Number of re-treatment periods will be summarized using descriptive statistics and a frequency tabulation based on Safety analysis set.

Number of EFG PH20 SC administrations and [redacted] will be summarized using descriptive statistics for following periods using Safety analysis set:

- Each treatment period separately
- Over the whole study

Cumulative prednisone dose and NCPD will be summarized using descriptive statistics for following phases/periods using Roll-over set:

- Over the roll-over phase
- Over the roll-over phase, until CRoff in the roll-over phase for participants who achieved CRoff in the roll-over phase
- Over the whole treatment phase
- Each treatment period separately
- Each treatment period separately, until CRmin within the applicable treatment period for participants who achieved CRmin within the applicable treatment period
- Each treatment period separately, until CRoff within the applicable treatment period for participants who achieved CRoff in the applicable treatment period
- Over the follow-up phase
- Over the whole study

All study drug administration data will be listed. Also, a detailed listing of prednisone administration and NCPD will be provided including prednisone equivalent doses with body weight at intake, CRmin, CRoff and end of treatment period.

Frequency tabulations with percentages will be produced for:

- Number of participants/caregivers receiving the (self-)administration training (denominator is all participants in SAF).
- Number of training visits received by participant/caregiver (denominator is number of participants/caregivers receiving training).
- Number of participants/caregivers who were adequately trained and capable to (self-)administer EFG PH20 SC (denominator is number of participants/caregivers receiving training).
- Number of training visits before being considered capable to (self-)administer EFG PH20 SC (denominator is number of participants/caregivers receiving training).
- Number of administrations by administrator and location (at home/on-site) per visit and overall.

Tables to be produced for the topline results (see list of output in section 8.1) will be presented overall and by disease status at roll-over in 1905 for all participants (PV+PF) as well as for PV participants.

4. EFFICACY, PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

4.1 EFFICACY

All efficacy endpoints are secondary endpoints in this roll-over study and will be evaluated descriptively. Efficacy endpoints will be presented for the Roll-over set.

4.1.1 Available data

Efficacy data are collected by assessments of PDAI, DC, EoC, CR, CRmin, CRoff, cumulative prednisone dose, flares and treatment failure. Quality of life will be measured using Autoimmune Bullous Disease Quality of life (ABQOL) Questionnaire and EuroQoL 5-Dimension 5-Levels- (EQ-5D-5L) Scale. The health impact of glucocorticoid (GC) use will be measured using the Glucocorticoid Toxicity Index (GTI).

4.1.2 Endpoints and derivation rules

For all references to visits, analysis visits are considered as described in section 2.2.4 unless specified otherwise. If multiple assessments fall within the same analysis window, only the assessment closest to the target date will be considered unless specified otherwise. Other assessments within this window will only be listed and not considered in the below analyses. Only the time to event endpoints will be derived using all possible measurements and not only the one closest to the target of the analysis visit.

4.1.2.1 PROPORTION OF PARTICIPANTS WHO ACHIEVE CRMIN AND CROFF

The proportion of participants who achieve CRmin in 1905 (as assessed by the investigator) will be derived within each treatment period, within the follow-up phase and over the entire study (ie, whether the participant achieves the status during at least one treatment period or during the follow-up phase).

Missing values for the below reasons , will be imputed as follows:

- all CR assessments missing: CRmin = non-response
- CRmin never ticked: CRmin = non-response
- CRmin is ticked but date of CRmin is missing: date for CRmin will be imputed by disease assessment visit date

Proportions will be calculated overall and by subgroup of disease status at roll-over.

Similar analyses as described above for CRmin will be performed for CRoff.

For the roll-over phase of participants who enter study 1905 on CRmin, only the proportion of participants achieving CRoff will be derived, as participants already achieved CRmin before the start of 1905. Participants entering 1905 on CRoff will be excluded from this calculation.

For the follow-up phase, participants who start the follow-up phase on CRmin (or CRoff) will be excluded from this calculation.

4.1.2.2 TIME TO DC, CR, CRMIN AND CROFF

Time to reaching DC, CR, CRmin and CRoff in each treatment period and in the follow-up phase will be derived as described below and will be analyzed overall and by subgroup of disease status at roll-over.

Time to attaining a disease status X within a treatment period, will be calculated as the difference between the first date that status X was achieved and the first IMP administration date in that treatment period.
Participants without any disease assessment in the treatment period are censored at day 1. Participants with disease assessment but not achieving status X during the treatment period are censored at the end of the treatment period.

Time to disease status X (days) =

> date (first date of achieving status X/end of treatment period) - first IMP administration date in the treatment period + 1

Time to status X for a specific treatment period will only be calculated in case the participant can still reach that status within the treatment period.
This means that for the roll-over phase of participants who enter study 1905 on CRmin, only the time to CRoff will be calculated. This will be done by replacing the first IMP administration date in the formula presented above with the date of the roll-over visit.

Time to attaining a disease status X within treatment period 1 or the follow-up phase will be calculated in case the participant can still reach that status in treatment period 1 or the follow-up phase respectively.

Time to disease status X (days) within the follow-up phase=

> date (first date of achieving status X/end of follow-up phase) – start date of follow-up phase + 1

4.1.2.3 NCPD

For calculation of NCPD, see section 3.4.2.

4.1.2.4 PROPORTION OF PARTICIPANTS WITH FLARE AFTER CRMIN

For participants who achieve CRmin (in 1904 or 1905), the proportion of participants who experience a flare in 1905 after CRmin (as assessed by the investigator) will be derived within the roll-over phase (flare after CRmin in 1904), within each treatment period (flare after CRmin within the treatment period), within the follow-up phase (flare after CRmin prior to follow-up phase) and over the entire study (ie, whether the participant achieves the status during the roll-over phase, during at least one treatment period or during the follow-up phase).

For the follow-up phase, participants who start the follow-up phase not on CRmin or CRoff will be excluded from this calculation.

Proportions will be calculated overall and by subgroup of disease status at roll-over.

4.1.2.5 TIME TO FLARE AFTER CRMIN

For participants who achieve CRmin (in 1904 or 1905) in a treatment period or in the follow-up phase, time to flare after CRmin will be calculated as:

(visit date of flare) - (date of CRmin) + 1.

Participants who do not experience a flare are censored at the end of the treatment period (or roll-over or follow-up phase as applicable).
For the roll-over phase of participants who enter study 1905 on CRmin, use date of roll-over visit instead of date of CRmin.

4.1.2.6 OTHER EFFICACY ENDPOINTS

Other efficacy endpoints are:

1. Number of flares: count number of flares as assessed by the investigator. A new flare only emerges after a new DC. Number of flares are counted over:

- the entire study (the whole roll-over, treatment + follow-up phase)
- within each treatment period
- within each treatment period between first DC and CRmin (or end of treatment period for participants without CRmin).
- within each treatment period after CRmin.

For participants who enter the study because of a flare in the 1904 study, the initial flare (at the roll-over visit) will not be counted. Flare counts will be presented overall and by subgroup of disease status at roll-over.

2. Proportion of treatment failures as assessed by the investigator over the treatment phase. Specific reasons for treatment failure can be derived as follows in following order:

- absence of DC: if participant did not achieve DC as assessed by the investigator
- flare: if previous reason is not applicable, the reason must be a flare between DC and CRmin that is not controlled by a prednisone dose that is 2 dose levels above the dose at which the flare is observed and that is a least 0.3mg/kg qd

3. PDAI at each visit: PDAI activity subscores (mucosal, skin and scalp), PDAI activity score and PDAI total score are assessed by the investigator at each visit.

4. QoL at each visit: ABQOL (17 items) and EQ-5D-5L (i.e., mobility, self-care, usual activities, pain/discomfort, anxiety/depression and VAS) are assessed by the investigator at baseline, start of re-treatment, CRmin and Week 52/EoT/ET. A total ABQOL score is calculated as the sum of all 17 items score 0 to 3 with higher score indicating worse condition. Missing items are imputed with the average score of the present items if at least half (9) of the items are present. The total score is rounded to the highest integer.

5. C-GTI at each visit: Composite Glucocorticoid Toxicity Index comprises the Aggregate Improvement Score (AIS) and the Cumulative Worsening Score (CWS) (health impact of GC) and is measured at baseline, Week 26 and Week 52/EoT/ET. AIS and CWS are calculated for the first 26 week period (W26), for the last 26 week

period (W52) and overall (Endpoint). The last post-baseline assessment (Endpoint) is considered as the overall CWS/AIS and is calculated as a cumulative score over all post-baseline timepoints. Details on calculation of CWS/AIS are provided in appendix 9.1. The complementary GTI specific list (GTI-SL) will only be listed.

4.1.3 Presentation of results

4.1.3.1 Proportion of participants who achieve CRmin and CRoff

Frequency tabulations will be provided of the percentage (with 95% exact confidence interval) of PV participants and all participants (PV+ PF) achieving CRmin within each treatment period, within the follow-up phase and over the entire study. The table will be repeated by disease status at roll-over.

Similar tables will be provided for the percentage of participants achieving CRoff.

4.1.3.2 Time to DC, CR, CRmin and CRoff

Time to DC, Time to CR, Time to CRmin and Time to CRoff will be descriptively presented with median times, quantiles and number and percentage of participants censored and with event, as obtained through Kaplan-Meier analysis.

The tables will be produced for PV participants and for all participants (PV+PF), also overall and by disease status at roll-over.

4.1.3.3 Cumulative Prednisone Dose and NCPD

Cumulative prednisone dose and NCPD will be summarized using descriptive statistics as descripted in section 3.4.3.

Tables will be provided for PV participants and all participants (PV+PF), overall and by disease status at roll-over.

4.1.3.4 Proportion of participants with Flare after CRmin

Frequency tabulations will be provided of the percentage (with 95% exact confidence interval) of PV participants and all participants (PV+ PF) experiencing a flare after CRmin within the roll-over phase, within each treatment period, within the follow-up phase and over the entire study. The table will be repeated by disease status at roll-over. The denominator of these tables is restricted to participants who achieved CRmin in the applicable treatment period.

4.1.3.5 Time to Flare after CRmin

Time to flare after CRmin will be descriptively presented with median times, quantiles and number and percentage of participants censored and with event, as obtained through Kaplan-Meier analysis.

The tables will be produced for PV participants and for all participants (PV+PF) who achieved CRmin, also overall and by disease status at roll-over.

4.1.3.6 Other efficacy endpoints

Descriptive statistics will be provided for the number of flares. Tables will be provided for PV participants and all participants (PV+PF), overall and by disease status at roll-over.

Frequency tabulations will be provided for the percentages of treatment failure (with 95% exact confidence interval) and its different reasons, overall and by disease status at roll-over.

PDAI activity subscores (mucosal, skin and scalp), PDAI activity score and PDAI total score will be summarized by means of descriptive statistics at each analysis visit. Actual values, changes from baseline and percent changes from baseline will be tabulated by analysis visits overall. Additionally, changes and percent changes versus 1904 baseline will be tabulated by analysis visits overall. Furthermore, actual values, changes from TPnB and percent changes from TPnB will be tabulated by analysis visits by period/subperiod. Tables to be provided for PV participants and for all participants (PV+PF).

Frequency tabulations will be provided for the percentages of participants within each outcome of QoL questionnaire items (ABQOL and EQ-5D-5L) at each analysis visit. Additionally, cumulative percentages (starting with the best outcome result) will be calculated. Descriptive statistics will be provided for the total ABQOL score and for the EQ-5D-5L VAS score.

Descriptive statistics will be provided for the C-GTI scores AIS and CWS. C-GTI will be analysed on complete cases: i.e. participants with C-GTI at baseline and at least one post-baseline visit. Participants where first post-baseline GTI improvements/worsening have not been obtained with respect to the baseline moment but with respect to a later moment (i.e. no GTI assessment at baseline visit) are excluded from analyses and are only listed.

4.1.3.7 OVERVIEW OF ANALYSES FOR EFFICACY ENDPOINTS

Following table summarizes the analyses to be done for efficacy using Roll-over set:

	Disease status at roll-over					
Endpoint	**CRmin**	**CR**	**DC - no CR**	**Treatment failure**	**Flare after CRmin**	**Overall**
Proportion CRmin[c]						
Overall[d]	X[a]	X	X	X	X	X
Period 1		X	X	X	X	X
Period 2, …, n	X	X	X	X	X	X
Follow-up	X	X	X	X	X	X
Proportion CRoff[c]						
Overall[d]	X[b]	X	X	X	X	X
Roll-over phase	X[b]					
Period 1		X	X	X	X	X
Period 2, …, n	X	X	X	X	X	X
Follow-up	X	X	X	X	X	X
Time to DC[c]						
Period 1				X	X	X

	Disease status at roll-over					
Endpoint	**CRmin**	**CR**	**DC - no CR**	**Treatment failure**	**Flare after CRmin**	**Overall**
Period2, …, n	X	X	X	X	X	X
Follow-up	X	X	X	X	X	X
Time to CR[c]						
Period 1			X	X	X	X
Period2, …, n	X	X	X	X	X	X
Follow-up	X	X	X	X	X	X
Time to CRmin[c]						
Period 1		X	X	X	X	X
Period2, …, n	X	X	X	X	X	X
Follow-up	X	X	X	X	X	X
Time to CRoff[c]						
Roll-over phase	X					
Period 1		X	X	X	X	X
Period 2, …, n	X	X	X	X	X	X
Follow-up	X	X	X	X	X	X
NCPD[c]	X	X	X	X	X	X
Proportion flare after CRmin[c]						
Overall[d]	X	X	X	X	X	X
Roll-over phase	X					
Period 1		X	X	X	X	X
Period 2, …, n	X	X	X	X	X	X
Follow-up	X	X	X	X	X	X
Time to flare after CRmin[c]						
Roll-over phase	X					
Period 1		X	X	X	X	X
Period 2, …, n	X	X	X	X	X	X
Follow-up	X	X	X	X	X	X
Number of flares[c]	X	X	X	X	X	X
Proportion treatment failure[c]	X	X	X	X	X	X
PDAI[c]						X
QoL, C-GTI						X

[a] Participants who enter 1905 on CRmin and do not have a flare in 1905 are excluded
[b] Participants who enter 1905 on CRoff and do not have a flare in 1905 are excluded

	Disease status at roll-over					
Endpoint	**CRmin**	**CR**	**DC - no CR**	**Treatment failure**	**Flare after CRmin**	**Overall**
[c] Analysis done for all participants (PV+PF) as well as for PV participants [d] Overall = during the roll-over phase (if applicable), during any treatment period or during the follow-up phase						

4.2 PHARMACOKINETICS

PK data will be presented for the Safety analysis set.

4.2.1 Available data

Blood samples will be collected for the determination of efgartigimod concentration at the time points indicated in the schedule of activities (see section 9.2). Sampling will be done predose on IMP administration visits (within 2 hours before IMP).

PK data obtained during off-treatment subperiods from participants who achieved CRmin (ie, no longer receiving weekly administrations of IMP) will not be included in the descriptive statistics.

In addition, following PK samples will be excluded from the descriptive statistics:

- When PK samples are taken outside the visit windows. The study visit windows are ±2 days, i.e. if PK sample is not within last IMP+7 days ± 2 days.
- When a predose sample is taken after IMP administration.
- When the IMP administration prior to the scheduled PK sample is missed (not applicable for Day 1 of a new treatment period).

A remark with reason for exclusion of the timepoint will be added in the appropriate listing.

4.2.2 Derivation rules

Not applicable.

4.2.3 Presentation of results

Individual concentration data and actual blood sampling times from dose administration for PK assessments will be listed.

Descriptive statistics per treatment period and time point on concentration data will be presented in tables.

PK concentrations will be reported in ng/mL by the lab and will be converted to ug/mL for analyses.

4.3 PHARMACODYNAMICS

PD data will be presented for the Roll-over set.

4.3.1 Available data

The following PD markers will be measured in serum: total immunoglobulin G (IgG), IgG subtypes (IgG1, IgG2, IgG3, and IgG4) and anti-Dsg-1/ Dsg-3 antibodies.

4.3.2 Derivation rules

Changes and percent changes (compared to baseline, 1904 baseline and TPnB) will be calculated at each analysis visit. See section 2.2.2 for calculation of change and percent change from baseline and TPnB, and section 2.2.4 for the definition of analysis visits overall and by period/subperiod.

Values of anti-Dsg-1/Dsg-3 autoantibodies above or below limit of quantification will be imputed by the upper or lower limit of quantification respectively. This will be explained by a footnote in the appropriate tables. Limits of quantification are provided by the lab. For total IgG and IgG subtypes, no imputation will be applied. Listings will always show the non-imputed values.

For participants with a baseline value below the limit of quantification (BLQ), the parameter will be excluded in presentation of actual values and when computing the change from baseline and the percent change from baseline. This will be explained by a footnote in the appropriate tables.

4.3.3 Presentation of results

All PD endpoints will be summarized by means of descriptive statistics at each analysis visit. Tables will present:

a) Actual values, changes from baseline and percent changes from baseline by analysis visits overall.

b) Changes and percent changes versus 1904 baseline by analysis visits overall.

c) Actual values, changes from TPnB and percent changes from TPnB by analysis visits by period/subperiod.

d) Changes and percent changes versus 1904 baseline by analysis visits by period/subperiod.

4.4 IMMUNOGENICITY

Immunogenicity data will be presented for the Safety analysis set.

4.4.1 Available data

Blood samples will be collected for the determination of anti-drug antibodies (ADA) to efgartigimod (in serum samples) and antibodies against rHuPH20 (in plasma samples, only analyzed in case of safety concerns and not in scope of this analysis) at the time points indicated in the schedule of activities (see section 9.2).

Immunogenicity samples are analyzed in a 3-tiered approach:

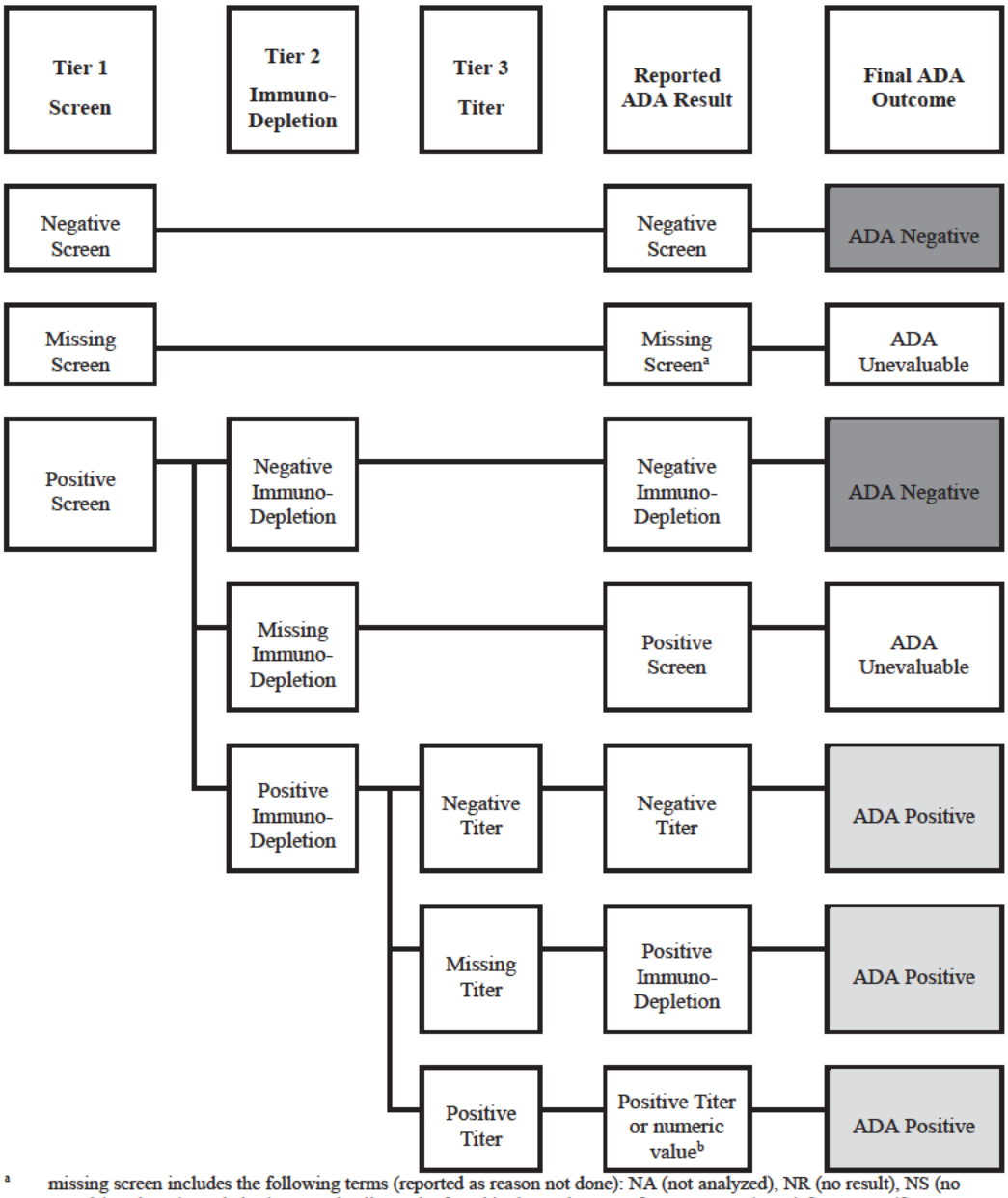
- All samples are evaluated in the ADA screening assay and are scored ADA screening positive or negative.
- If a sample scored positive in the ADA screening assay, it is further evaluated in the confirmatory assay and is scored confirmed positive (positive immunodepletion) or confirmed negative (negative immunodepletion).
- If a sample is scored as confirmed positive, the samples are further characterized in the ADA titration assay (to determine titer) and are also further analyzed in the NAb assay to confirm neutralizing activity. For NAb against efgartigimod, a screening assay is performed and results will be reported as negative or positive.

If available, a titer result will be reported for the ADA confirmed positive samples. However, a titer result is not always available:

- In case the ADA confirmed positive sample could not be run in the titration assay (e.g. due to insufficient sample volume/quality to perform the titer analysis), the result will be described as ‘positive immuno-depletion’ and the sample should be considered as ADA positive.
- If a sample is negative in the titration assay, it will be reported as ‘negative titer’ but it should be considered as ADA positive since it was confirmed positive in the second tier.
- If a sample could not be analyzed or reported as ‘positive screen’, the ADA sample status is ADA unevaluable

An overview of this 3-tiered approach and all possible ADA sample results that will be reported by the laboratory is presented in Figure 1. From these reported ADA sample results a final ADA sample status needs to be derived during the statistical analysis, as presented in the final column (‘Final ADA Outcome’):

Figure 1: ADA sample status



[a] missing screen includes the following terms (reported as reason not done): NA (not analyzed), NR (no result), NS (no sample) and SL (sample lost). More details can be found in the IS data transfer agreement (DTA) from LGC (for ADA against efgartigimod) with SGS SDO.

[b] 'positive titer' is reported in case it was not possible to retrieve a numeric value.

4.4.2 Derivation rules

4.4.2.1 Participant Classification for ADA against Efgartigimod– Overall

Table 6 below gives an overview of how the ADA participant classification will be derived, starting from the participant baseline ADA sample status.

Table 6: Participant classification for ADA against Efgartigimod

Participant ADA classification	**Highest[c] post-baseline[d] sample status**				
	ADA negative	**ADA positive (missing titer[a])**	**ADA positive (negative titer[b] or positive titer or numeric titer value)**		**ADA not evaluable**
Baseline ADA sample status					
ADA negative	ADA negative	Treatment-Induced ADA	Treatment-Induced ADA		*ADA unevaluable*
ADA positive (missing titer[a])	Treatment-Unaffected ADA	*ADA unevaluable*	*ADA unevaluable*		*ADA unevaluable*
ADA positive (negative titer[b] or positive titer or numeric titer value)	Treatment-Unaffected ADA	*ADA unevaluable*	**titer < 4 x baseline titer:** Treatment-Unaffected ADA	**titer ≥ 4x baseline titer:** Treatment-Boosted ADA	*ADA unevaluable*
ADA not evaluable	*ADA unevaluable*	*ADA unevaluable*	*ADA unevaluable*		*ADA unevaluable*

[a] Samples with missing titer have as reported ADA result 'positive immunodepletion'or 'positive titer';
[b] Results reported as 'negative titer', i.e. titer value <1 will be set to value of 1;
[c] Highest sample status, with order: (from low to high): ADA unevaluable, ADA negative, ADA positive (missing titer /positive immunodepletion), ADA positive with titer <= 1 ('negative titer' as reported ADA result, titer value set to 1), ADA positive with titer >1 (i.e. numeric titer and selecting the sample with highest titer)
[d] For the overall ADA participant classification, the highest post baseline sample status is used for comparison with the baseline ADA sample status.

ADA evaluable participant = participant classified as any of following categories: ADA negative, treatment-unaffected ADA, treatment-induced ADA, treatment-boosted ADA. The first 2 categories are classified as 'ADA negative', the latter 2 as 'ADA positive'.

ADA unevaluable participant = participant classified as ADA unevaluable or with missing baseline ADA sample or without post-baseline ADA samples.

Note: Fourfold difference in titer values is considered significant in case a twofold serial dilution is applied (= 2 times the dilution factor) (reference to Shankar et al., 2014).

ADA incidence = percentage of participants with treatment-induced or treatment-boosted ADAs (denominator: number of evaluable participants).

ADA prevalence = percentage of participants with treatment-unaffected ADA, treatment-induced ADA or treatment-boosted ADA (denominator: number of evaluable participants).

4.4.2.2 Participant Classification for NAb against Efgartigimod– Overall

All ADA confirmed positive samples will also be evaluated in the NAb assay. All samples that were not analyzed in the NAb assay (i.e. the ADA negatives) are per default NAb negative. Also, if a NAb sample is not reported, the NAb sample status is NAb unevaluable.

For NAb against efgartigimod, all samples evaluated in the NAb assay will be scored as NAb positive, NAb negative or NAb unevaluable by the laboratory. Based on these results, the participants will be categorized based on their baseline and post-baseline sample status as detailed in table 7.

Table 7: Participant classification for NAb against Efgartigimod

Participant NAb classification	**Highest[a] post-baseline NAb sample status**		
	NAb negative	**NAb positive**	**NAb not evaluable**
Baseline NAb sample status			
NAb negative	baseline neg – post-baseline neg	baseline neg – post-baseline pos	*NAb unevaluable*
NAb positive	baseline pos – post-baseline neg	baseline pos – post-baseline pos	*NAb unevaluable*
NAb not evaluable	*NAb unevaluable*	*NAb unevaluable*	*NAb unevaluable*

[a] Highest sample status in order: (from low to high): NAb unevaluable, NAb negative, NAb positive.
[b] For the overall NAb participant classification, the highest post baseline sample status is used for comparison with the baseline NAb sample status..

NAb unevaluable participant = participant classified as NAb unevaluable or with missing baseline NAb sample or without post-baseline NAb samples.

NAb incidence = percentage of participants with participant classification 'baseline neg – post-baseline pos' and 'baseline pos – post-baseline pos' (denominator: number of evaluable participants).

NAb prevalence = percentage of participants with participant classification 'baseline neg – post-baseline pos', 'baseline pos – post-baseline pos' or 'baseline pos – post-baseline neg' (denominator: number of evaluable participants).

4.4.3 Presentation of results

Frequency tabulations (number and percentages) will be provided with ADA negative/positive/unevaluable samples per analysis visit. In addition, these tables will be repeated by ADA participant category.

Frequency tabulations (number and percentages) will be provided overall on:

- participants per ADA participant category
- prevalence and incidence of ADA
- ADA unevaluable participants
- ADA baseline positive/negative samples

For details on the definitions, see the above section 4.4.2.1.

The above frequency tabulations will be repeated for NAb assay using the definitions as defined in section 4.4.2.2.

In addition, a cross-tabulation (number and percentages) will be provided of the overall NAb participant category (NAb positive participants and NAb not evaluable participants) versus the overall ADA participant category (treatment-unaffected ADA, Treatment-induced ADA, Treatment-boosted ADA, ADA Negative, ADA Unevaluable, Total).

ADA titer values against efgartigimod will be summarized by means of descriptive statistics by the ADA participant classification.

All available data on ADA and NAb against efgartigimod will be listed, showing also the sample status and participant classification.

5. SAFETY ANALYSES

All safety data will be presented for the Safety analysis set, unless mentioned otherwise.

5.1 ADVERSE EVENTS

5.1.1 Available data

Adverse events will be coded into system organ classes (SOC) and preferred terms (PT) using the latest version of the MedDRA dictionary available at the time of the 1904 study database lock.

For each AE, start and stop date/times will be collected as well as severity, a seriousness flag, relationship to IMP, prednisone and procedures, action taken towards IMP and prednisone, outcome, and AE of special interest (AESI) category (infection).

The grade (severity) of AEs will be assessed by the investigator according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

5.1.2 Derivation rules

Treatment-emergent adverse events (TEAE) are defined as AEs starting on or after any administration of IMP in 1905 up through 60 days after the last administration of IMP prior to the AE.

Post-treatment AEs are defined as AEs that start after the 60 days after the last IMP administration prior to the AE. AEs that start during the roll-over phase are also considered as post-treatment AEs

Based on their start date/time, AEs will be allocated to the phase in which they started. Each AE will therefore be reported in only one phase. Phases are defined in section 2.2.1. In case the AE start date/time is incomplete or missing, and the AE could consequently be allocated to more than one phase, a worst-case allocation will be done in following order:

- Treatment phase vs. roll-over phase: the AE will be allocated to the treatment phase unless the available parts of the AE start and stop date/time provide evidence for allocating to the roll-over phase.
- Treatment phase vs. follow-up phase: the AE will be allocated to the treatment phase unless the available parts of the AE start and stop date/time provide evidence for allocating to the follow-up phase.

A death case is defined as an AE with outcome ‘fatal’.

An AE for which the IMP was discontinued is defined as an AE with action taken ‘drug withdrawn’.

Treatment relatedness will be dichotomized as follows in tables:

- Treatment related: related, probably related, possibly related or missing
- Not treatment related: not related, unlikely related

Adverse events of special interest will be defined using MedDRA system organ class 'Infections and infestations'.

Injection-related reactions (IRRs) will be defined as all AEs with MedDRA preferred terms that are listed in either:

- Hypersensitivity standardized MedDRA query (SMQ) (broad selection)
- Anaphylactic reaction (SMQ) (broad selection)
- Extravasation events (injections, infusions and implants) (SMQ) (broad selection), excluding implants

AND occurring within 48 hours of an administration, or within 2 days in case no AE start time is available. In case of partially missing AE start date, the AE will be considered as an IRR, unless the available parts of the AE start date provide evidence it did not occur within 48 hours of an injection.

Injection site reactions (ISR) will be defined as all AEs with a MedDRA high level term of "Injection site reaction", regardless of the time of AE onset relative to an administration.

AE onset and duration will be calculated as follows when start and stop dates are fully known:

- AE onset day (vs. roll over visit date) =
  - AE start date ≥ date of first administration: AE start date – date of first IMP administration + 1 day
  - AE start date < date of first administration: AE start date – date of first IMP administration
- AE duration (days) =
  - AE end date – AE start date + 1 day
  - date of last contact – AE start date + 1 day (when the AE start date is fully known but the AE is not resolved at the end of the study)

    In this case the duration will be presented as ">x days".

Event rates per 100 participant years of follow-up (PYFU) will be calculated as 100*number of events/PYFU, with:

- PYFU overall (in years) calculated as [the sum over all participants of the study duration calculated as (last phase end date – first phase start date + 1 day)]/365.25.

  PYFU for TEAEs (in years) calculated as [the sum over all participants of all period durations during which an AE is considered to be treatment-emergent]/365.25.
- PYFU for post-TEAEs (in years) calculated as [the sum over all participants of all period durations during which an AE is considered to be post-treatment-emergent]/365.25.

Incidence rates per 100 participant years of follow-up (PYFU) will be calculated as 100*number of participants with events/PYFU.

5.1.3 Presentation of results

Unless mentioned otherwise tables will present TEAEs only.

The TEAE tables will be presented for the treatment and follow-up phase combined.

Tables to be produced for the topline results (see list of outputs in section 8.1) will be presented overall and by disease status at roll-over in 1905. These tables will show data for PV+PF participants as well as for PV participants.

An overview table will show the number and percentage of participants with at least one event, the incidence rate per 100 PYFU, the number of events and the event rate per 100 PYFU for the following:

- TEAEs
- Treatment related TEAEs
- Serious TEAEs
- Serious treatment related TEAEs
- Serious prednisone related TEAEs
- TEAEs of grade 3 or above
- Treatment-related TEAEs of grade 3 or above
- TEAEs related to prednisone
- TEAEs related to study procedures
- TEAEs for which the IMP was discontinued
- TEAEs for which the IMP was interrupted
- TEAEs of special interest
- Treatment related TEAEs of special interest
- TE IRR events
- Serious TE IRR events
- TE ISR events
- Fatal TEAEs

The overview table will be repeated specifically for ISR events, omitting the records related to TEAEs of special interest, prednisone-related TEAEs, IRR and ISR events.

A summary table by MedDRA system organ class and preferred term will show the number and percentage of participants with at least one event, the incidence rate per 100 PYFU, the number of events and the event rate per 100 PYFU. Each AE record in the clinical database is considered as a distinct adverse event and is counted as such.

The overview and summary tables mentioned above, will present:

- TEAEs
- post-TEAEs
- overall AEs (i.e., all AEs in the treatment + follow-up phase)

Separate tables will be prepared by MedDRA system organ class and preferred term showing the number and percentage of participants with at least one event, the incidence rate per 100 PYFU, the number of events and the event rate per 100 PYFU for the following:

- Most common TEAEs (>=5% in the Total group)
- Treatment related TEAEs
- Serious TEAEs
- Serious treatment related TEAEs
- Serious prednisone related TEAEs
- TEAEs of grade 3 or above
- Treatment-related TEAEs of grade 3 or above
- TEAEs related to prednisone
- TEAEs related to study procedures
- TEAEs for which the IMP was discontinued
- TEAEs of special interest
- Treatment related TEAEs of special interest
- TE IRR events
- Serious TE IRR events
- TE ISR events

All AEs, including pre-treatment events will be listed.

Separate listings will be prepared for serious AEs, AEs for which IMP was discontinued, fatal AEs and AESIs. A listing showing all coding information will be prepared as well.

5.2 CLINICAL LABORATORY EVALUATION

5.2.1 Available data

Per protocol, the following safety laboratory parameters are expected:

- Biochemistry: sodium, potassium, total calcium, HbA1c, creatinine, creatinine clearance (adjusted for BSA), blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, gamma-glutamyl transferase (GGT), low-density lipoprotein-cholesterol (LDL-C), C-reactive protein (CRP), alkaline phosphatase (AP), lactate dehydrogenase (LDH), uric acid, total protein, and albumin
- Hematology: hemoglobin, hematocrit, mean corpuscular volume (MCV), red blood cell (RBC) count, platelet count, white blood cell (WBC) count with differential
- Urinalysis: color, clarity/appearance, specific gravity, pH, protein, glucose, ketones, blood, bilirubin, urobilinogen, nitrite, leukocyte esterase, and microscopic examination of RBCs, WBCs, casts, crystals, and bacteria

Normal ranges are available as provided by the laboratory.

5.2.2 Derivation rules

Toxicity grades will be computed according to the NCI CTCAE toxicity grading list (version 5.0). The implementation of these toxicity grades for analysis is presented in appendix 9.2. Only the parameters described in appendix 9.2 will be computed, according to the declared limits for each grade.

The following abnormality categories will be defined for parameters with no toxicity grade available:

- Low: value < lower limit of normal range
- Normal: lower limit of normal range ≤ value ≤ upper limit of normal range
- High: value > upper limit of normal range

Notes:

- Classification will be done by using non-imputed values and limits as reported in standardized units in the clinical database: a value <X where X equals the lower limit of normal range will be classified as low. A value X with normal range <X will be classified as high.
- For the worst-case analysis visits as defined in section 2.2.5, an additional category low + high is defined in case there are both low and high post-baseline values.

The estimated glomerular filtration rate (eGFR) will be derived by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, if not already provided as such by the lab:

eGFR (mL/min/1.73m²) = 141 * minimum(creatinine (mg/dL)/ K; 1)α * maximum(creatinine (mg/dL)/ K; 1) -1.209 * 0.993age (years) * [1.018 if female] * [1.159 if race = black]

where K = 0.7 if female and K = 0.9 if male;

α = -0.329 if female and α = -0.411 if male

Note: in case results in mg/dL are not available, results in µmol/L will be used after conversion in mg/dL: 1 mg/dL = 88.4 µmol/L

5.2.3 Presentation of results

The statistical analysis will present results in standardized units, except for eGFR, which will be reported in mL/min/1.73m^2.

Continuous laboratory parameters will be summarized by means of descriptive statistics of the actual values and changes from baseline at each analysis visit. For albumin and LDL-C, also percent changes from baseline will be shown. Categorical parameters will be listed only.

Laboratory abnormalities will be presented as cross-tabulations of the abnormality at each post-baseline analysis visit and at the worst-case analysis visit versus the baseline abnormality. This table will also show numbers of participants with treatment-emergent abnormalities (see Definition of terms). The denominator for the percentage is the total number of participants per treatment and per analysis visit in

the Safety analysis set. Abnormalities will not be tabulated for those parameters for which toxicity grades are defined.

Laboratory toxicity grades will be presented as cross-tabulations of the toxicity at each post-baseline analysis visit and at the worst-case analysis visit versus the baseline toxicity. This table will also show numbers and cumulative numbers over decreasing toxicity grading of participants with treatment-emergent toxicities. The denominator for the percentage is the total number of participants per treatment and per analysis visit in the Safety analysis set. Parameters having toxicity grades defined in both directions (hypo and hyper) will be shown by direction.

Tables to be produced for the topline results (see list of outputs in section 8.1) will show data for PV+PF participants as well as for PV participants.

All laboratory data will be listed, but only for participants with any post-baseline abnormality/toxicity or clinically significant value.

5.3 VITAL SIGNS

5.3.1 Available data

The following vital signs parameters are collected: heart rate, systolic (SBP) and diastolic blood pressure (DBP) in supine position, body temperature, body weight.

5.3.2 Derivation rules

Abnormalities are defined in below table.

	Heart rate (bpm)	SBP (mmHg)	DBP (mmHg)	Temperature (°C)
Low	<40	<90	<45	<35.8
Normal	40-100	90-150	45-90	35.8-37.5
High	>100	>150	>90	>37.5

Note: For the worst-case analysis visit, as defined in section 2.2.5, an additional category low + high is defined in case there are both low and high post-baseline values.

BMI will only be used in the C-GTI derivations.

5.3.3 Presentation of results

Vital signs parameters (except BMI) will be summarized by means of descriptive statistics at each analysis visit. Actual values and changes from baseline will be shown in the same table.

Abnormalities will be presented as cross-tabulations of the abnormality at each post-baseline analysis visit and at the worst-case analysis visit versus the baseline abnormality. This table will also show numbers of participants with treatment-emergent abnormalities (see Definition of terms). The denominator for the percentage is the total number of participants per treatment and per analysis visit in the Safety analysis set.

Tables to be produced for the topline results (see list of outputs in section 8.1) will show data for PV+PF participants as well as for PV participants.

All vital signs data will be listed, but only for participants with any post-baseline abnormality or clinically significant value.

5.4 ELECTROCARDIOGRAMS

5.4.1 Available data

The following electrocardiogram (ECG) parameters will be collected: heart rate (HR), QRS interval, PR interval, RR interval, QT interval, QTcF and QTcB.

5.4.2 Derivation rules

Abnormalities for HR, QRS and PR interval are defined in below table.

	HR (bpm)	PR (ms)	QRS (ms)
Low	<40	<120	-
Normal	40-100	120-220	0-120
High	>100	>220	>120

Note: For the worst-case analysis visit, as defined in section 2.2.5, an additional category low + high is defined in case there are both low and high post-baseline values.

For QTc interval (ms), the following categories are defined:

- Actual values:
  - ≤ 450 (normal)
  -]450; 480]
  -]480; 500]
  - > 500
- Changes:
  - ≤ 30 (normal)
  -]30; 60]
  - > 60

Note: The worst-case, as defined in section 2.2.5, is the highest value and associated change.

5.4.3 Presentation of results

Uncorrected QT interval will only be listed, RR interval will not be displayed.

Continuous ECG parameters will be summarized by means of descriptive statistics at each analysis visit. Actual values and changes from baseline will be shown in the same table.

Abnormalities of the actual values will be presented as cross-tabulations of the abnormality at each post-baseline analysis visit, and at the worst-case analysis visit

versus the baseline abnormality. This table will also show numbers and cumulative numbers (QTcF and QTcB only) of participants with treatment-emergent abnormalities (see Definition of terms). The denominator for the percentage is the total number of participants per treatment and per analysis visit in the Safety analysis set.

Abnormalities of the QTcF and QTcB changes from baseline will be presented as a tabulation of the change from baseline abnormality at each post-baseline analysis visit and at the worst-case analysis visit. This table will also show cumulative numbers over decreasing change from baseline abnormalities of participants. The denominator for the percentage is the total number of participants per treatment and per analysis visit in the Safety analysis set.

Tables to be produced for the topline results (see list of outputs in section 8.1) will show data for PV+PF participants as well as for PV participants.

All ECG data will be listed, but only for participants with any post-baseline abnormality or clinically significant value or change.

5.5 PHYSICAL EXAMINATION

5.5.1 Available data

Physical examination results per body system will be available.

5.5.2 Presentation of results

Abnormal physical examination results will be listed.

6. CHANGES TO THE PLANNED ANALYSIS

6.1 CHANGES NOT COVERED BY PROTOCOL AMENDMENTS BEFORE DATABASE LOCK

Analysis visit labels deviate from the visit labels in the schedule of assessments of the protocol to accommodate the example in the ICH E3 guideline annex III.

The following extra endpoints will be derived, which are not covered in the CTP (see section 4.1.2.1 and 3.4.2):

- NCPD defined for different periods
- Proportion of participants achieving CRoff

6.2 CHANGES NOT COVERED BY PROTOCOL AMENDMENTS AFTER DATABASE LOCK

Not applicable.

6.3 CHANGES TO THE FINAL STATISTICAL ANALYSIS PLAN

Not applicable.

7. REFERENCES

ICH-E3 Structure and Content of Clinical Study Reports, July 1996.

ICH-E6(R2) Guideline for Good Clinical Practice – Step 5, December 2016

ICH Topic E9 Statistical Principles for Clinical Trials – Step 5 – Note for Guidance on Statistical Principles for Clinical Trials (CPMP/ICH/363/96), September 1998.

ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials – Step 5 (EMA/CHMP/ICH/436221/2017) February 2020

National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, November 2017.

G. Shankar, S. Arkin, L. Cocea et al. "Assessment and Reporting of the Clinical Immunogenicity of Therapeutic Proteins and Peptides—Harmonized Terminology and Tactical Recommendations." AAPS J. 2014:16(4):658-673.

Schimmer B.P., & Funder J.W. (2015). Acth, adrenal steroids, and pharmacology of the adrenal cortex. Brunton L.L., & Chabner B.A., & Knollmann B.C.(Eds.), Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12e. McGraw Hill.

Liu, D., Ahmet, A., Ward, L., Krishnamoorthy, P., Mandelcorn, E. D., Leigh, R., Brown, J. P., Cohen, A., & Kim, H. (2013). A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology, 9(1), 30.

8. LIST OF TABLES, LISTINGS AND FIGURES

8.1 TABLES

Note: tables to be produced for the topline results (TL) are indicated in last column

GENERAL CHARACTERISTICS			
14.1.1.1	Analysis Sets and Disease Status at Roll-over	ROLL	TL
14.1.1.2	Participant Disposition by Country and Site	ROLL	
14.1.1.3	Participant Disposition by Analysis Visits	ROLL	
14.1.1.4	Analysis Phase/Period Duration	ROLL	
14.1.1.5.1	Treatment Discontinuation	SAF	TL
14.1.1.5.2	Treatment Discontinuation by Disease Status at Roll-over	SAF	TL
14.1.1.6	Study Discontinuation	ROLL	
14.1.1.7	Major Protocol Deviations	ROLL	
14.1.1.8	Minor Protocol Deviations	ROLL	
14.1.2.1.1	Demographic Data	ROLL	TL
14.1.2.1.2	Demographic Data by Disease Status at Roll-over	ROLL	TL
14.1.2.2.1	Baseline Disease Characteristics	ROLL	TL
14.1.2.2.2	Baseline Disease Characteristics by Disease Status at Roll-over	ROLL	TL
14.1.2.3	Concomitant Therapies by ATC Class (Level 1 and 3) and Generic Term	SAF	
14.1.2.4.	Concomitant Prednisone Administration by ATC Class (Level 1 and 3) and Generic Term	SAF	TL
14.1.2.5.1	IMP Administration	SAF	TL
14.1.2.5.2	IMP Administration by Disease Status at Roll-over	SAF	TL
14.1.2.6	IMP (Self-)Administration Training of Participants	SAF	
14.1.2.7	IMP (Self-)Administration Training of Caregivers	SAF	
14.1.2.8	IMP Self-Administration	SAF	
EFFICACY			
14.2.1.1.1	Proportion of Participants Who Achieved CRmin	ROLL	TL
14.2.1.1.2	Proportion of Participants Who Achieved CRmin by Disease Status at Roll-over	ROLL	TL
14.2.1.1.3	Proportion of Participants Who Achieved CRoff	ROLL	TL
14.2.1.1.4	Proportion of Participants Who Achieved CRoff by Disease Status at Roll-over	ROLL	TL
14.2.1.2.1	Time to CRmin: Descriptive Statistics	ROLL	TL
14.2.1.2.2	Time to CRmin: Descriptive Statistics by Disease Status at Roll-over	ROLL	TL
14.2.1.2.3	Time to CRoff: Descriptive Statistics	ROLL	TL
14.2.1.2.4	Time to CRoff: Descriptive Statistics by Disease Status at Roll-over	ROLL	TL
14.2.1.2.5	Time to DC: Descriptive Statistics	ROLL	TL

14.2.1.2.6	Time to DC: Descriptive Statistics by Disease Status at Roll-over	ROLL	TL
14.2.1.2.7	Time to CR: Descriptive Statistics	ROLL	TL
14.2.1.2.8	Time to CR: Descriptive Statistics by Disease Status at Roll-over	ROLL	TL
14.2.1.3.1	NCPD: Descriptive Statistics	ROLL	TL
14.2.1.3.2	NCPD: Descriptive Statistics by Disease Status at Roll-over	ROLL	TL
14.2.1.3.3	Cumulative Prednisone Dose: Descriptive Statistics	ROLL	TL
14.2.1.3.4	Cumulative Prednisone Dose: Descriptive Statistics by Disease Status at Roll-over	ROLL	TL
14.2.1.4.1	Proportion of Participants Who Experienced Flare After CRmin	ROLL	TL
14.2.1.4.2	Proportion of Participants Who Experienced Flare After CRmin by Disease Status at Roll-over	ROLL	TL
14.2.1.4.3	Time to Flare After CRmin: Descriptive Statistics	ROLL	TL
14.2.1.4.4	Time to Flare After CRmin: Descriptive Statistics by Disease Status at Roll-over	ROLL	TL
14.2.1.5.1	Number of Flares – Descriptive Statistics	ROLL	TL
14.2.1.5.2	Number of Flares – Descriptive Statistics by Disease Status at Roll-over	ROLL	TL
14.2.1.6.1	Proportion of Treatment Failures	ROLL	TL
14.2.1.6.2	Proportion of Treatment Failures by Disease Status at Roll-over	ROLL	TL
14.2.1.7.1	PDAI in PV Participants: Descriptive Statistics of Actual Values, Changes from Baseline, Changes from 1904 Baseline and Changes from Treatment Period Baseline by Visit	ROLL	
14.2.1.7.2	PDAI in PV Participants: Descriptive Statistics of Actual Values, Percent Changes from Baseline, Percent Changes from 1904 Baseline and Percent Changes from Treatment Period Baseline by Visit	ROLL	
14.2.1.7.3	PDAI in PV+PF Participants: Descriptive Statistics of Actual Values, Changes from Baseline, Changes from 1904 Baseline and Changes from Treatment Period Baseline by Visit	ROLL	TL
14.2.1.7.4	PDAI in PV+PF Participants: Descriptive Statistics of Actual Values, Percent Changes from Baseline, Percent Changes from 1904 Baseline and Percent Changes from Treatment Period Baseline by Visit	ROLL	
14.2.1.8.1	C-GTI: Descriptive Statistics of CWS and AIS at Week 26, Week 52 and Overall	ROLL	
14.2.1.9.1	ABQOL: Frequency Tabulation of 17 Items by Visit	ROLL	
14.2.1.9.2	ABQOL: Descriptive Statistics of Actual Values and Changes from Baseline in ABQOL Total Score by Visit	ROLL	
14.2.1.10.1	EQ-5D-5L: Frequency Tabulation of 5 Dimensions by Visit	ROLL	
14.2.1.10.2	EQ-5D-5L: Descriptive Statistics of Actual Values and Changes from Baseline in VAS Score by Visit	ROLL	
PHARMACOKINETICS			
14.2.2.1	Descriptive Statistics of Efgartigimod Serum Concentration over time	SAF	

PHARMACODYNAMICS

14.2.3.1	Descriptive Statistics of Actual Values, Changes from Baseline, Changes from 1904 Baseline and Changes from Treatment Period Baseline in Total IgG Level and IgG Subtype Levels by Visit	ROLL	
14.2.3.2	Descriptive Statistics of Actual Values, Percent Changes from Baseline, Percent Changes from 1904 Baseline and Percent Changes from Treatment Period Baseline in Total IgG Level and IgG Subtype Levels by Visit	ROLL	
14.2.3.3	Descriptive Statistics of Actual Values, Changes from Baseline, Changes from 1904 Baseline and Changes from Treatment Period Baseline in anti-Dsg-1/-3 antibodies by Visit	ROLL	
14.2.3.4	Descriptive Statistics of Actual Values, Percent Changes from Baseline, Percent Changes from 1904 Baseline and Percent Changes from Treatment Period Baseline in anti-Dsg-1/-3 antibodies by Visit	ROLL	TL

IMMMUNOGENICITY

14.2.4.1	ADA: Anti-Drug Antibodies to Efgartigimod Sample Classification by Analysis Visit by Overall Anti-Drug Antibodies Participant Classification	SAF	
14.2.4.2	ADA: Anti-Drug Antibodies to Efgartigimod Participant Classification, Prevalence and Incidence	SAF	
14.2.4.3	NAb: Neutralizing Antibodies to Efgartigimod Sample Classification by Analysis Visit by Overall Neutralizing Antibodies Participant Classification	SAF	
14.2.4.4	NAb: Neutralizing Antibodies to Efgartigimod Participant Classification, Prevalence and Incidence	SAF	
14.2.4.5	NAb: Neutralizing Antibodies Positives to Efgartigimod Sample Classification by Overall Efgartigimod Anti-Drug Antibodies Participant Classification	SAF	
14.2.4.6	ADA: Descriptive Statistics of ADA Against Efgartigimod Titer Values by ADA Participant Classification Against Efgartigimod	SAF	

SAFETY

ADVERSE EVENTS

14.3.1.1.1	Adverse Events Overview	SAF - ROLL	TL
14.3.1.1.2	Adverse Events Overview by Disease Status at Roll-over	SAF - ROLL	TL
14.3.1.2.1	Treatment-Emergent and Post-Treatment Adverse Events by MedDRA System Organ Class and Preferred Term	SAF - ROLL	TL
14.3.1.2.2	Treatment-Emergent and Post-Treatment Adverse Events by MedDRA System Organ Class and Preferred Term by Disease Status at Roll-over	SAF - ROLL	TL
14.3.1.2.3	Most Common (>=5% in the Total Group) Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	SAF	TL
14.3.1.3	Treatment Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	SAF	

14.3.1.4.1	Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	SAF	TL
14.3.1.4.2	Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Disease Status at Roll-over	SAF	TL
14.3.1.5	Serious Treatment Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	SAF	
14.3.1.6	Serious Prednisone Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	SAF	
14.3.1.7.1	Grade 3 or More Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	SAF	TL
14.3.1.7.2	Grade 3 or More Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Disease Status at Roll-over	SAF	TL
14.3.1.8	Treatment Related Grade 3 or More Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	SAF	
14.3.1.9	Prednisone Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	SAF	
14.3.1.10	Procedures Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term	SAF	
14.3.1.11.1	Treatment-Emergent Adverse Events Leading to Discontinuation of IMP by MedDRA System Organ Class and Preferred Term	SAF	TL
14.3.1.11.2	Treatment-Emergent Adverse Events Leading to Discontinuation of IMP by MedDRA System Organ Class and Preferred Term by Disease Status at Roll-over	SAF	TL
14.3.1.12.1	Treatment-Emergent Adverse Events of Special Interest by MedDRA System Organ Class and Preferred Term	SAF	TL
14.3.1.12.2	Treatment-Emergent Adverse Events of Special Interest by MedDRA System Organ Class and Preferred Term by Disease Status at Roll-over	SAF	TL
14.3.1.13	Treatment Related Treatment-Emergent Adverse Events of Special Interest by MedDRA System Organ Class and Preferred Term	SAF	
14.3.1.14	Treatment-Emergent Injection-Related Reactions by MedDRA System Organ Class and Preferred Term	SAF	
14.3.1.15	Serious Treatment-Emergent Injection-Related Reactions by MedDRA System Organ Class and Preferred Term	SAF	
14.3.1.16.1	Treatment-Emergent Injection Site Reactions - Overview	SAF	TL
14.3.1.16.2	Treatment-Emergent Injection Site Reactions – Overview by Disease Status at Roll-over	SAF	TL
14.3.1.16.3	Treatment-Emergent Injection Site Reactions by MedDRA System Organ Class and Preferred Term	SAF	TL
14.3.1.16.4	Treatment-Emergent Injection Site Reactions by MedDRA System Organ Class and Preferred Term by Disease Status at Roll-over	SAF	TL
LABORATORY DATA			
14.3.2.1	Descriptive Statistics of Laboratory Test Actual Values and Changes from Baseline	SAF	

14.3.2.2	Descriptive Statistics of Albumin and Low-Density Lipoprotein-Cholesterol Actual Values and Changes from Baseline and Treatment Period Baseline	SAF	TL
14.3.2.3	Descriptive Statistics of Albumin and Low-Density Lipoprotein-Cholesterol Actual Values and Percent Changes from Baseline and Treatment Period Baseline	SAF	TL
14.3.2.4	Cross-Tabulation of Laboratory Abnormalities Versus Baseline	SAF	
14.3.2.5	Cross-Tabulation of Laboratory Toxicity Grades Versus Baseline	SAF	
VITAL SIGNS			
14.3.3.1	Descriptive Statistics of Vital Signs Actual Values and Changes from Baseline	SAF	
14.3.3.2	Cross-Tabulation of Vital Signs Abnormalities Versus Baseline	SAF	
ECG			
14.3.4.1	Descriptive Statistics of ECG Actual Values and Changes from Baseline	SAF	
14.3.4.2	Cross-Tabulation of ECG Abnormalities Versus Baseline	SAF	
14.3.4.3	Cross-Tabulation of QTCB/QTCF Abnormalities Versus Baseline	SAF	
14.3.4.4	Tabulation of QTc Change Abnormalities	SAF	

8.2 LISTINGS

GENERAL CHARACTERISTICS		
16.2.1.1	Analysis Sets and Disease Status at Roll-over	ROLL
16.2.1.2	Study Visits	ROLL
16.2.1.3	Study and Treatment Discontinuation	ROLL
16.2.2.1	Protocol Deviations	ROLL
16.2.2.2	Violations on Eligibility Criteria	ROLL
16.2.2.3	Covid-19 Related Comments	ROLL
16.2.4.1	Demographic Data	ROLL
16.2.4.2	Baseline Disease Characteristics	ROLL
16.2.4.3	Prior and Concomitant Therapies	ROLL
16.2.4.4	Prior and Concomitant Procedures	ROLL
16.2.5.1	IMP Administration	SAF
16.2.5.2	Prednisone Administration and cumulative dose	ROLL
16.2.5.3	NCPD and cumulative dose until endpoints	ROLL
16.2.5.4	IMP (Self-)Administration Training	SAF
PHARMACOKINETICS		
16.2.5.5	Individual Efgartigimod Serum Concentrations and Actual Blood Sampling Times	SAF
EFFICACY		
16.2.6.1	Disease Status and Flares	ROLL
16.2.6.2	Disease Status: Derived Parameters	ROLL

16.2.6.3	Lesion Assessment	ROLL
16.2.6.4	PDAI	ROLL
16.2.6.5	ABQOL	ROLL
16.2.6.6	EQ-5D-5L	ROLL
16.2.6.7	C-GTI	ROLL
16.2.6.8	GTI specific list	ROLL
PHARMACODYNAMICS		
16.2.6.9	Total IgG and IgG Subtypes	ROLL
16.2.6.10	Anti-Dsg-1/-3 antibodies	ROLL
IMMUNOGENICITY		
16.2.6.11	Efgartigimod Anti-drug Antibodies and Neutralizing Antibodies	SAF
SAFETY		
ADVERSE EVENTS		
16.2.7.1	Adverse Events	SAF
16.2.7.2	Serious Adverse Events	SAF
16.2.7.3	Fatal Adverse Events	SAF
16.2.7.4	Treatment-Emergent Adverse Events Leading to Discontinuation of IMP	SAF
16.2.7.5	Adverse Events of Special Interest	SAF
16.2.7.6	Adverse Events: Coding Information	ROLL
LABORATORY DATA		
16.2.8.1	Laboratory Test Results for Participants with Abnormal Values	SAF
VITAL SIGNS		
16.2.9.1	Vital Signs Results for Participants with Abnormal Values	SAF
ECG		
16.2.10.1	ECG Results for Participants with Abnormal Values	SAF
PHYSICAL EXAMINATION		
16.2.11.1	Physical Examination Abnormalities	SAF

9. APPENDICES

9.1 GTI: DERIVATION OF CWS AND AIS

9.1.1 Allocate weights

Weights per item are attributed as specified below. GTI at Wx is evaluated versus previous GTI assessment. The first time point is referred to as *start (or previous)* and the second time point within each comparison is referred to as *follow-up (or current)*.

Increase, decrease or no change in medication intake compared to previous assessment are checked in the GTI assessment. A missing evaluation, including for external data, will be considered as no change with weight=0.

External GTI data (i.e. LDL/HbA1c/BP and BMI) are allocated to a GTI assessment based on dates. The last available value of these external data since previous GTI assessment will be used.

Changes from severe to moderate do not have any impact on calculation of CWS/AIS. Severe outcome on an item however is captured on the specific list (SL).

9.1.1.1 BMI (COMPARED TO PREVIOUS ASSESSMENT)

- Moderate decrease in the direction of the normal range [<25 kg/ m2] by at least 5 BMI units -36
- Minor decrease in the direction of the normal range [<25 kg/ m2] by more than 2 but less than 5 BMI units -21
- No significant change (BMI remains within +/- 2 BMI units compared with start) OR BMI remains <25 kg/ m2 0
- Minor increase in BMI (increase by more than 2 but less than 5 BMI units, to above the upper limit of normal BMI [≥25kg/m2]) 21
- Moderate increase in BMI (increase by at least 5 BMI units above normal BMI [≥25kg/m2]) 36

9.1.1.2 GLUCOSE TOLERANCE (COMPARED TO PREVIOUS ASSESSMENT)

- Moderate improvement in glucose tolerance: -44
  - HbA1c declined >10% from start AND medication decrease
- Minor improvement in glucose tolerance: -32
  - HbA1c declined >10% from start AND no medication increase (unchanged or missing) AND start HbA1c ≥ 5.7
  - HbA1c within 10% of start AND decrease in diabetic medication
  - HbA1c < 5.7 AND decrease in diabetic medication AND HbA1c increased >10%
- No significant change in glucose tolerance: 0
  - HbA1c within 10% of start or (start and follow-up) HbA1c < 5.7 AND no change in medication (or missing)
  - HbA1c increased > 10% of start AND a decrease in medication AND follow-up HbA1c ≥ 5.7
  - HbA1c decreased by > 10% of start AND an increase in medication
- Minor worsening of glucose tolerance or medication status: 32
  - HbA1c increased >10% of start AND no change in medication (or missing) AND follow-up HbA1c ≥ 5.7%
  - HbA1c within 10% of start AND increase in diabetic medication
- Moderate worsening of glucose tolerance despite increased diabetic treatment: 44
  - HbA1c increased >10% of start AND an increase in diabetic medication AND follow-up HbA1c ≥ 5.7%

Note: changes in medication for glucose control, used in the above weight derivations, are assessed as a GTI specific question.

9.1.1.3 BLOOD PRESSURE (COMPARED TO PREVIOUS ASSESSMENT)

- Moderate improvement in BP: -44
  - Decrease in either systolic or diastolic BP of >10% of start AND medication decrease AND start systolic BP ≥120 mmHg or start diastolic BP ≥ 85 mmHg
- Minor improvement in BP: -19
  - Decrease in either systolic or diastolic BP of >10% of start AND no medication increase (unchanged or missing) AND start systolic BP ≥120 mmHg or start diastolic BP ≥ 85 mmHg
  - Systolic AND diastolic BP within 10% of start AND a decrease in medication
  - Systolic BP < 120 and diastolic BP < 85 (both start and end) AND a decrease in medication
- No significant change in BP: 0
  - Systolic AND diastolic BP within 10% of start or (start and follow-up) systolic / diastolic BP < 120/85 resp AND no change in medication (or missing)
  - Increase in systolic or diastolic BP >10% of start AND a decrease in medication AND follow-up systolic BP ≥120 mmHg or diastolic BP ≥ 85 mmHg
  - Decrease in systolic or diastolic BP of > 10% of start AND an increase in medication AND start systolic BP ≥120 mmHg or diastolic BP ≥ 85 mmHg
- Minor worsening of BP: 19
  - Increase in systolic or diastolic BP >10% of start AND no change in medication (or missing) AND follow-up systolic BP ≥120 mmHg or diastolic BP ≥ 85 mmHg
  - Systolic AND diastolic BP within 10% of start AND an increase in medication
  - Systolic BP < 120 and diastolic BP < 85 (both start and end) AND an increase in medication
- Moderate worsening of BP despite treatment 44
  - Increase in systolic or diastolic BP >10% of start AND an increase in medication AND follow-up systolic BP ≥120 mmHg or diastolic BP ≥ 85 mmHg

Notes:

1. changes in medication for BP control, used in the above weight derivations, are assessed as a GTI specific question.

2. check ≥ normal range and > 10% needs to be done separately for systolic and diastolic BP. In case of both an increase and decrease occurs, this is considered as no change in BP and the score will be based on the change in medication (score = +/-19 for increase/decrease, score = 0 for no change).

3. Hypertensive Emergency = Y or PRES = Y at current visit is provided a score 44 regardless of the value at previous visit

9.1.1.4 LIPID METABOLISM (LDL COMPARED TO PREVIOUS ASSESSMENT)

- Moderate improvement in lipids: -30
  - Decrease in LDL concentration >10% of start AND medication decrease
- Minor improvement in lipids: -10
  - Decrease in LDL concentration >10% of start AND no change in medication (or missing) AND start above target range
  - LDL within 10% of start AND decrease in medication
- No significant change in lipids: 0
  - LDL within 10% of start AND no change in medication (or missing)
  - Increase in LDL > 10% of start AND decrease in medication
  - Decrease in LDL > 10% of start AND no medication change (or missing) AND start LDL below or equal target range
  - Decrease in LDL > 10% of start AND increase in medication
- Minor worsening of LDL or medication status: 10
  - Increase in LDL >10% of start AND no change in medication (or missing)
  - LDL within 10% of start of start AND increase in medication
- Worsening of LDL despite treatment: 30
  - Increase in LDL >10% of start AND an increase in medication

Notes:

1. changes in medication for lipid control, used in the above weight derivations, are assessed as a GTI specific question.

2. target range for LDL is 1.81mmol/L

9.1.1.5 GLUCOCORTICOID-INDUCED MYOPATHY (COMPARED TO PREVIOUS ASSESSMENT)

- Moderate/severe weakness to none: -63
- Moderate/severe weakness to mild weakness: -54
- Mild weakness to none: -9
- No significant change: 0
- None to mild weakness: 9
- Mild to Moderate/severe weakness: 54
- None to Moderate/severe weakness: 63

9.1.1.6 SKIN TOXICITY (COMPARED TO PREVIOUS ASSESSMENT)

Allocate weights for each of the 5 subitems : acneiform rash, easy bruising, hirsutism, atrophy/striae, erosions/tears/ulcerations

- Moderate/severe to none: -26
- Moderate/severe to minor: -18
- Minor to none: -8
- No significant change: 0
- None to minor: 8
- minor to moderate/severe: 18
- None to moderate/severe: 26

Note: minor and mild or used fully interchangeable.

For the derivation from the grading to severe, moderate, minor (or mild): see table underneath:

Minor/Mild	Moderate	Severe (Specific Domain)
Acneiform rash (Grades 1-2)	Acneiform rash (Grade 3)	Acneiform rash (Grade 4)
Easy bruising (Grade 1)	Easy bruising (Grade 2)	
Hirsutism (Grade 1)	Hirsutism (Grade 2)	
Atrophy/Striae (Grade 1)	Atrophy/Striae (Grade 2)	Atrophy/Striae (Grade 3)
Erosions/Tears/Ulcerations (Grade 1)	Erosions/Tears/Ulcerations (Grade 2)	Erosions/Tears/Ulcerations (Grade 3)

9.1.1.8 NEUROPSYCHIATRIC EFFECTS (COMPARED TO PREVIOUS ASSESSMENT)

Allocate weights for each of the 4 subitems : insomnia, mania, cognitive impairment, depression

- Moderate/severe to none: -74
- Moderate/severe to minor: -63
- Minor to none: -11
- No significant change: 0
- None to minor: 11
- Minor to moderate/severe: 63
- None to moderate/severe: 74

Notes:

1. presence of psychosis or glucocorticoid-induced violence (as captured in the GTI specific list) always has weight=74. Disappearance of psychosis or glucocorticoid-induced violence has weight=-74.

2. minor and mild or used fully interchangeable

For the derivation from the grading to severe, moderate, minor (or mild): see table underneath:

Minor/Mild	Moderate	Severe (Specific Domain)
Insomnia – (Grade 1)	Insomnia – (Grade 2)	
Mania (Grade 1)	Mania (Grade 2)	Mania (Grade 3)
Cognitive impairment (Grade 1)	Cognitive impairment (Grade 2)	Cognitive impairment (Grade 3)
Depression (Grade 1)	Depression (Grade 2)	Depression (Grade 3)

9.1.1.9 INFECTION (COMPARED TO PREVIOUS ASSESSMENT)

- No significant infection: 0
- Specific infections < Grade 3 (oral or vaginal candidiasis, uncomplicated zoster): 19
- Grade 3, 4, or 5 or complicated herpes zoster: 93

Note:

Special case domain: each infection is a distinct event, so infections only have worsening. That means that a subject may have Infection grade 3 at W14 and again at W30 and the subjects may be assigned a score of 93 for the worsening from W14 to W30 if the investigator has collected 'Infection' at W30.

9.1.2 CWS and AIS calculation

9.1.2.1 CWS

The CWS is calculated as the sum of the worsening items: i.e. with weights >0. For the items with subitems, i.e. skin toxicity and neuropsychiatric effects, only the subitem with the highest positive weight is used. As an example, if neither insomnia nor depression were present at the start of the GTI interval but there is mild insomnia and moderate depression present at post-baseline, then only the moderate depression is used for the neuropsychiatric weight (+74 points).

In the CWS calculation, the most severe infection in every GTI interval is scored (so in case of 2 periods, the score for an infection is counted twice for the overall CWS at endpoint).

CWS is calculated at W26 and at W52 as the sum of the worsening items in all post-baseline timepoints up to that timepoint respectively. The overall CWS at endpoint is the sum of all worsening items over all post-baseline timepoints.

9.1.2.2 AIS

With the AIS, improvement as well as worsening is included in the calculations of the sum of the items. For the items with subitems, i.e. skin toxicity and neuropsychiatric effects, only the subitem with the highest positive weight is used as well as the subitem with the lowest negative weight is used. For example: if the highest positive skin subitem is +26 and the highest negative skin subitem is -18, then skin weight for AIS is +8.

AIS is calculated at W26 and at W52 as the sum of the items in all post-baseline timepoints up to that timepoint respectively. The overall AIS at endpoint is the sum over all post-baseline timepoints.

9.2 TOXICITY GRADES

Below table documents how the Common Terminology Criteria for Adverse Events CTCAE, v5.0: November 27, 2017 is implemented in the statistical analysis.

PARAMETER	Unit	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Amylase (pancreatic)		>1.0-1.5 *ULN	>1.5-2.0 *ULN	>2.0-5.0 *ULN	>5.0 *ULN
Alanine amino transferase		>1-3 *ULN	>3-5 *ULN	>5-20 *ULN	>20 *ULN
Albumin [1]	g/L	<LLN-30	<30-20	<20	-
	g/dL	<LLN-3	<3-2	<2	-
Alkaline phosphatase		>1.0-2.5 *ULN	>2.5-5.0 *ULN	>5.0-20.0 *ULN	>20.0 *ULN
Aspartate amino transferase		>1-3 *ULN	>3-5 *ULN	>5-20 *ULN	>20 *ULN
Bilirubin (total)		>1.0-1.5 *ULN	>1.5-3.0 *ULN	>3.0-10.0 *ULN	>10.0 *ULN
Calcium (ionized) low [1]	mmol/L	<LLN-1.0	<1.0-0.9	<0.9-0.8	<0.8
	mg/dL	<LLN-4.0	<4.0-3.6	<3.6-3.2	<3.2
Calcium (ionized) high [1]	mmol/L	>ULN-1.5	>1.5-1.6	>1.6-1.8	>1.8
	mg/dL	>ULN-6.0	>6.0-6.4	>6.4-7.2	>7.2
Calcium (corrected) low [1]	mmol/L	<LLN-2.00	<2.00-1.75	<1.75-1.50	<1.50
	mg/dL	<LLN-8	<8-7	<7-6	<6
Calcium (corrected) high [1]	mmol/L	>ULN-2.9	>2.9-3.1	>3.1-3.4	>3.4
	mg/dL	>ULN-11.5	>11.5-12.5	>12.5-13.5	>13.5
Cholesterol [1]	mmol/L	>ULN-7.75	>7.75-10.34	>10.34-12.92	>12.92
	mg/dL	>ULN-300	>300-400	>400-500	>500

Creatine kinase		>1.0-2.5 *ULN	>2.5-5.0 *ULN	>5.0-10.0 *ULN	>10.0 *ULN
Creatinine		>1.0-1.5 *ULN	>1.5-3.0 *ULN	>3.0-6.0 *ULN	>6.0 *ULN
Gamma-glutamyl transferase		>1.0-2.5 *ULN	>2.5-5.0 *ULN	>5.0-20.0 *ULN	>20.0 *ULN
Glucose low [1]	mmol/L	<LLN-3.0	<3.0-2.2	<2.2-1.7	<1.7
	mg/dL	<LLN-55	<55-40	<40-30	<30
Lipase		>1.0-1.5 *ULN	>1.5-2.0 *ULN	>2.0-5.0 *ULN	>5.0 *ULN
Magnesium low [1]	mmol/L	<LLN-0.5	<0.5-0.4	<0.4-0.3	<0.3
	mg/dL	<LLN-1.2	<1.2-0.9	<0.9-0.7	<0.7
Magnesium high [1]	mmol/L	>ULN-1.23	-	>1.23-3.30	>3.30
	mg/dL	>ULN-3.0	-	>3.0-8.0	>8.0
Potassium low [1]	mmol/L	-	<LLN-3.0	<3.0-2.5	<2.5
	mEq/L	-	<LLN-3.0	<3.0-2.5	<2.5
Potassium high [1]	mmol/L	>ULN-5.5	>5.5-6.0	>6.0-7.0	>7.0
	mEq/L	>ULN-5.5	>5.5-6.0	>6.0-7.0	>7.0
Sodium low [1]	mmol/L	<LLN-130	-	<130-120	<120
	mEq/L	<LLN-130	-	<130-120	<120
Sodium high [1]	mmol/L	>ULN-150	>150-155	>155-160	>160
	mEq/L	>ULN-150	>150-155	>155-160	>160
Triglycerides	mmol/L	1.71-3.42	>3.42-5.70	>5.70-11.4	>11.4
	mg/dL	150-300	>300-500	>500-1000	>1000
Partial thromboplastin time (activated or not specified		>1.0-1.5 *ULN	>1.5-2.5 *ULN	>2.5 *ULN	-

CD4 count [1]	giga/L	<LLN-0.50	<0.50-0.20	<0.20-0.05	<0.05
	counts/mm3	<LLN-500	<500-200	<200-50	<50
Fibrinogen		<1.00-0.75 *LLN	<0.75-0.50 *LLN	<0.50-0.25 *LLN	<0.25 *LLN
International normalized ratio		>1.2-1.5 *ULN	>1.5-2.5 *ULN	>2.5 *ULN	-
Lymphocytes (absolute count) low [1]	giga/L	<LLN-0.80	<0.80-0.50	<0.50-0.20	<0.20
	counts/mm^3	<LLN-800	<800-500	<500-200	<200
Lymphocytes (absolute count) high	giga/L	-	>4-20	>20	-
	counts/mm^3	-	>4000-20000	>20000	-
Neutrophils (absolute count) [1]	giga/L	<LLN-1.5	<1.5-1.0	<1.0-0.5	<0.5
	counts/mm^3	<LLN-1500	<1500-1000	<1000-500	<500
Platelets [1]	giga/L	<LLN-75	<75-50	<50-25	<25
	counts/mm^3	<LLN-75000	<75000-50000	<50000-25000	<25000
White blood cells [1]	giga/L	<LLN-3	<3-2	<2-1	<1
	counts/mm^3	<LLN-3000	<3000-2000	<2000-1000	<1000

[1] In case ULN/LLN is higher/lower than the upper/lower limit of grade 1 (or even higher grades), ULN/LLN will be ignored and only the fixed values of CTCAE will be considered. In case ULN/LLN is missing, a grade will only be derived if the value leaves no doubt on which grade is to be assigned.

9.3 SCHEDULE OF ACTIVITIES

9.3.1 Participants in CR, CR on minimal therapy, and CR off therapy at rollover from 1904

Trial period	**Open-label extension**														**UNS[b]**	**Follow-up**	
Visit number	**V1 Roll over[a]**	**V1 + 4 weeks**	**V1 + 8 weeks**	**V1 + 12 weeks**	**V1 + 16 weeks**	**V1 + 20 weeks**	**V1 +24 weeks**	**V1 + 28 weeks**	**V1 + 32 weeks**	**V1 + 36 weeks**	**V1 + 40 weeks**	**V1 + 44 weeks**	**V1 + 48 weeks**	**V1 +51weeks EoT/ET**		**Safety follow-up 1 EoT/ET + 4 weeks[c]**	**Safety follow-up 2 EoT/ET + 8 weeks EoS[c]**
Assessment/procedure	**±0 days**	**±2 days[d]**														**±3 days[d]**	**±3 days[d]**
Informed consent	X																
Inclusion/exclusion criteria	X																
Weight[e]	X						X[e]							X			
ECG[f,g]	X			X			X			X			X	X		X	X
Physical examination and vital signs[f,h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[f,i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X	X
Urine pregnancy test[f,j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X	X
Vaccination antibodies[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X	X
Blood sampling																	
• clinical chemistry and hematology[f,k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X	X
• anti-Dsg-1 and anti-Dsg-3 antibodies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X	X

Trial period	Open-label extension														UNS[b]	Follow-up	
Visit number	V1 Roll over[a]	V1 + 4 weeks	V1 + 8 weeks	V1 + 12 weeks	V1 + 16 weeks	V1 + 20 weeks	V1 +24 weeks	V1 + 28 weeks	V1 + 32 weeks	V1 + 36 weeks	V1 + 40 weeks	V1 + 44 weeks	V1 + 48 weeks	V1 +5l weeks EoT/ET		Safety follow-up 1 EoT/ET + 4 weeks[c]	Safety follow-up 2 EoT/ET + 8 weeks EoS[c]
Assessment/procedure	±0 days	±2 days[d]														±3 days[d]	±3 days[d]
• PK[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b,m]	X	X
• Total IgG and IgG subtypes[f,l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X	X
• immunogenicity[f,n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
• IgG autoantibody subtypes and specificity[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X	X
PDAI[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ABQOL[f,o]	X	at CRmin (or the next on-site visit)												X			
EQ-5D-5L[f,o]	X	at CRmin (or the next on-site visit)												X			
Disease assessment[f,p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lymphocyte populations (at selected sites)[q]	X			X			X				X			X		X	X
GTI	X						X[r]							X[r]			
IMP self-administration training[s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Efgartigimod PH20 SC[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Prednisone taper[u]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Trial period	Open-label extension														UNS[b]	Follow-up	
Visit number	V1 Roll over[a]	V1 + 4 weeks	V1 + 8 weeks	V1 + 12 weeks	V1 + 16 weeks	V1 + 20 weeks	V1 +24 weeks	V1 + 28 weeks	V1 + 32 weeks	V1 + 36 weeks	V1 + 40 weeks	V1 + 44 weeks	V1 + 48 weeks	V1 +51weeks EoT/ET		Safety follow-up 1 EoT/ET + 4 weeks[c]	Safety follow-up 2 EoT/ET + 8 weeks EoS[c]
Assessment/procedure	±0 days	±2 days[d]														±3 days[d]	±3 days[d]
Concomitant therapies/procedures	Continuous monitoring																
AE monitoring	Continuous monitoring																

ABQOL=Autoimmune Bullous Disease Quality of Life; AE=adverse events; ALT=alanine aminotransferase; ALP=alkaline phosphatase; AST=aspartate aminotransferase; BMI=body mass index; BUN=blood urea nitrogen; CR=complete clinical remission; CRmin=CR on minimal therapy; CRP=C-reactive protein; DC=disease control; Dsg=desmoglein; ECG=electrocardiogram; EoC=end of consolidation; EoS=end of study; EoT=end of treatment; EQ-5D-5L=EuroQol 5-dimension 5-level scale; ET=early termination; GGT=gamma-glutamyl transferase; GTI=Glucocorticoid Toxicity Index; IgG=immunoglobulin type G; IMP=investigational medicinal product; LDH=lactate dehydrogenase; LDL-C=low-density lipoprotein cholesterol; MCV=mean corpuscular volume; NAb=neutralizing antibody; PDAI=Pemphigus Disease Area Index; PD=pharmacodynamic; PK=pharmacokinetics; QTcF=Fridericia corrected QT interval; rHuPH20=recombinant human hyaluronidase PH20; RBC=red blood cells; SC=subcutaneous(ly); UNS=unscheduled visit; W=week; WBC=white blood cells; V=visit at site

[a] For participants who roll over from ARGX-113-1904 to ARGX-113-1905, the baseline visit will occur for these participants at the same visit as the EoS/ED visit in study ARGX-113-1904. All assessments will be performed before IMP administration.

[b] In case of suspected new lesions as reported by the participants, AEs, flare, or other safety reasons, participants should come to the clinic. This may require an unscheduled visit. Depending on the reason for the visit, different assessments need to be performed. Refer to Section 8 for more information. Participants with new lesions or flare after achieving CR should return to weekly on-site visits. Participants with flare who had achieved CRmin or CRoff should switch to the visit schedule outlined in Table 2.

[c] Follow-up 1 will be the EoS visit for participants who ended treatment before W49 or 4 weeks before ET. Both follow-up visits will be required only for participants who continue to receive efgartigimod PH20 SC for at least 1 visit between W49 and W52 or during the last 4 weeks before ET.

[d] Study visit windows are ±2 days during the treatment period and ±3 days for the follow-up visits.

[e] Weight will be measured and BMI will be calculated accordingly, at the rollover visit, at W26 (or the next on-site visit if W26 does not coincide with an on-site visit) and W52. Weight will also be measured if there has been an obvious change since the last measurement.

[f] Assessment or procedure will be completed predose at visits when IMP is administered.

[g] The ECG will be recorded at baseline, every 3 months while receiving efgartigimod PH20 SC treatment, at CRmin (or the next on-site visit if CRmin is achieved during a week without an on-site visit), and at EoS. The ECG (heart rate, PR, QT, and QRS interval) will be read centrally, and QTcF and QTcB will be calculated. The ECG will be recorded only at baseline and EoS in participants not receiving efgartigimod. Additional ECGs may be performed at the discretion of the investigator during unscheduled visits.

[h] A complete physical examination will be performed at each on-site visit. Vital sign measurements include systolic and diastolic blood pressure, heart rate, and body temperature.
[i] Urinalysis will be performed by dipstick method and will include specific gravity, pH, protein, glucose, ketones, blood, bilirubin, urobilinogen, nitrite, leukocyte esterase, and microscopic examination (if blood or protein is abnormal).
[j] A urine pregnancy test will be performed locally and at least once every 4 weeks.
[k] Clinical blood laboratory tests will include hematology and blood chemistry at all visits. The hematology profile includes hemoglobin, hematocrit, MCV, RBC count, platelet count, and WBC count with differential. The blood chemistry profile includes sodium, potassium, calcium, HbA1c, creatinine, creatinine clearance, BUN, ALT, AST, total bilirubin, GGT, CRP, ALP, LDH, LDL-C, uric acid, total protein, and albumin.
[l] PK and PD (total IgG and IgG subtypes) samples will be taken every 4 weeks as long as the participant is receiving efgartigimod PH20 SC treatment (until CRmin or the next on-site visit) and 4 weeks after CRmin (or the next on-site visit; this also applies if the participant achieved CRmin in ARGX-113-1904) or EoT. Blood samples will be taken predose (within 2 hours before the start of IMP administration during visits when IMP is administered).
[m] At unscheduled visits, blood samples for PK will only be taken if IMP is administered.
[n] Blood samples will be taken to test for immunogenicity to efgartigimod in serum and rHuPH20 in plasma every 4 weeks while the participant is receiving efgartigimod PH20 SC treatment (until CRmin or the next on-site visit) and 4 and 8 weeks after CRmin (or the next 2 on-site visits; this also applies if the participant achieved CRmin in ARGX-113-1904) or EoT. NAb will be tested for all confirmed positive immunogenicity samples.
[o] Questionnaires are to be completed before any other assessment.
[p] Disease assessment parameters include DC, EoC, CR, CRmin, CRoff, flare, and treatment failure. Participants who have achieved CR and have new lesions should come to the clinic for an unscheduled visit for disease assessment.
[q] Samples for lymphocyte populations will be taken at selected sites only: optionally at on-site visits at W13 (±2 weeks), W26 (±2 weeks), W39 (±2 weeks), W52 (±2 weeks) or EoT/ET and EoS, and mandatory at on-site visits at W52 (±2 weeks) or EoT/ET and EoS for participants in CRmin or CRoff.
[r] The GTI assessment will be performed at visit 1, W26 (or the next on-site visit), and W52.
[s] Participants and/or their caregivers will be invited to receive at least 1 refresher training for self-administration, or caregiver-supported administration of IMP. Training will continue until deemed successfully completed by authorized staff.
[t] Efgartigimod PH20 SC will be administered weekly at a dose of 1000 mg until CRmin. For IMP administrations between the scheduled site visits, the participant can choose between self-administration (if training successfully completed), home nurse visits, or return to the trial site for the SC injection only. Participants who have achieved CRmin or CRoff and are currently not in flare will be observed every 4 weeks without any further IMP administration until flare or EoS. Only for on-site visits and home nurse visits, participants should be followed up for safety monitoring for at least 1 hour after the first IMP administration, or followed by 15 minutes of observation for subsequent administrations and released according to their clinical status. The last planned IMP administration is at W52. If the participant withdraws from the study, efgartigimod PH20 SC will not be administered.
[u] Prednisone dose tapering will begin 2 weeks after achieving CR or 4 weeks after sustained EoC (thus, no new lesions have developed for a minimum of 6 weeks and approximately 80% or more of lesions have healed).

9.3.2 Participants not in CR at rollover from 1904, or participants experiencing flare in 1905

Trial period	Open-label extension					EoT/ET	UNS[d]	Follow-up	
	V1[a]	Observational visits	IMP admin only visit	Observational visits		EoT/ET		Follow-up	
Visit Number		Weekly on-site visits until CR[b]	Weekly home or on-site visits until CRmin[c]	On-site visits every 4 weeks until CRmin	On-site visits every 4 weeks until W52	W52		Safety follow-up 1	Safety follow-up 2
Trial Week	Rollover[a]	V1 + 7x	CR until CRmin	CR until CRmin	After CRmin until W52	W52		EoT/ET + 4 weeks[e]	EoT/ET + 8 weeks EoS[e]
Assessment/Procedure	±0 days	±2 days[f]				±2 days		±3 days[f]	
Informed consent	X								
Inclusion/exclusion criteria	X								
Weight[g]	X	X[g]		X[g]	X[g]	X			
ECG[h,i]	X	X		X	X	X		X	X
Physical examination and vital signs[i,j]	X	X		X	X	X	X	X	X
Urinalysis[i,k,l]	X	X		X	X	X	X[d]	X	X
Urine pregnancy test[i,m]	X	X		X	X	X	X[d]	X	X
Vaccination antibodies[i,l]	X	X		X	X	X	X[d]	X	X
Blood sampling									
• Clinical chemistry and hematology[i,l,n]	X	X		X	X	X	X[d]	X	X
• anti-Dsg-1 and anti-Dsg-3 antibodies[i,l]	X	X		X	X	X	X[d]	X	X

Trial period	Open-label extension					EoT/ET	UNS[d]	Follow-up	
	V1[a]	Observational visits	IMP admin only visit	Observational visits		EoT/ET		Follow-up	
Visit Number		Weekly on-site visits until CR[b]	Weekly home or on-site visits until CRmin[c]	On-site visits every 4 weeks until CRmin	On-site visits every 4 weeks until W52	W52		Safety follow-up 1	Safety follow-up 2
Trial Week	Rollover[a]	V1 + 7x	CR until CRmin	CR until CRmin	After CRmin until W52	W52		EoT/ET + 4 weeks[e]	EoT/ET + 8 weeks EoS[e]
Assessment/Procedure	±0 days	±2 days[f]				±2 days		±3 days[f]	
• PK[i,o]	X	X		X	X[o]	X	X[d,p]	X	X
• Total IgG and IgG subtypes[i,o]	X	X		X	X	X	X[d]	X	X
• immunogenicity[i,q]	X	X		X	X	X		X	X
• IgG autoantibody subtypes and specificity[i]	X	X[r]		X	X	X	X[d]	X	X
PDAI[i]	X	X		X	X	X	X	X	X
ABQOL[i,s,t]	X	X[s]		X[s]	X[s]	X			
EQ-5D-5L[i,s,t]	X	X[s]		X[s]	X[s]	X			
Disease assessment[i,u]	X	X		X	X	X	X	X	X
Photography (at selected sites)[v]	X	X[v]				X	X[d,v]		
Lymphocyte populations (at selected sites)[w]	X	X[w]		X[w]	X[w]	X[w]		X	X
GTI[x]	X	X[x]		X[x]	X[x]	X			
IMP self-administration training[y]	X	X	X	X	X	X			

Trial period	Open-label extension					EoT/ET	UNS[d]	Follow-up	
	V1[a]	Observational visits	IMP admin only visit	Observational visits					
Visit Number		Weekly on-site visits until CR[b]	Weekly home or on-site visits until CRmin[c]	On-site visits every 4 weeks until CRmin	On-site visits every 4 weeks until W52	W52		Safety follow-up 1	Safety follow-up 2
Trial Week	Rollover[a]	V1 + 7x	CR until CRmin	CR until CRmin	After CRmin until W52	W52		EoT/ET + 4 weeks[e]	EoT/ET + 8 weeks EoS[e]
Assessment/Procedure	±0 days	±2 days[f]				±2 days		±3 days[f]	
Efgartigimod PH20 SC[z]	X[z]	X[z]	X	X		X	X		
Prednisone taper[aa]	X	X		X	X	X	X		
Concomitant therapies/ procedures	Continuous monitoring								
AE monitoring	Continuous monitoring								

ABQOL=Autoimmune Bullous Disease Quality of Life; AE=adverse event; ALT=alanine aminotransferase; ALP=alkaline phosphatase; AST=aspartate aminotransferase; BMI=body mass index; BUN=blood urea nitrogen; CR=complete clinical remission; CRmin=CR on minimal therapy; CRP=C-reactive protein; DC=disease control; Dsg=desmoglein; ECG=electrocardiogram; EoC=end of consolidation; EoS=end of study; EoT=end of treatment; EQ-5D-5L=EuroQol 5-dimension 5-level scale; ET=early termination; GGT=gamma-glutamyl transferase; GTI=Glucocorticoid Toxicity Index; IgG=immunoglobulin type G; IMP=investigational medicinal product; LDH=lactate dehydrogenase; MCV=mean corpuscular volume; NAb=neutralizing antibody; PD=pharmacodynamic; PDAI=Pemphigus Disease Area Index; PK=pharmacokinetics; QTcF=Fridericia corrected QT interval; rHuPH20=recombinant human hyaluronidase PH20; RBC=red blood cells; SC=subcutaneous(ly); UNS=unscheduled visit; V=visit at site; V1 + 7x=visit 1 + 7 times x with 'x' being the weeks post V1 (eg, V1 + 7x3 is the visit at W3 [21 days post visit 1]); W=week; WBC=white blood cells

[a] For participants who roll over from ARGX-113-1904 to ARGX-113-1905, the baseline visit will occur at the EoS/ED visit of ARGX-113-1904. All assessments are performed before IMP administration.

[b] A minimum of 6 on-site visits (rollover (V1) to W6 or start of retreatment +5 weeks) is required before switching to home administrations, even if CR is reported earlier.

[c] Home visits are allowed once a participant achieves CR but not before W7 or not before the start of retreatment +6 weeks. The investigator should call the participant every 2 weeks until CRmin to confirm the participant is still in CR and to determine the prednisone tapering schedule.

[d] In case of suspected new lesions as reported by the participant, AEs, flare, or other safety reasons, the participant should come to the clinic. This may require an unscheduled visit. Depending on the reason for the visit, different assessments need to be performed. Refer to Section 8 for more information.

[e] Follow-up 1 will be the EoS visit for participants who ended treatment before W49, or 4 weeks before ET. Both follow-up visits will be required only for participants who continue to receive efgartigimod PH20 SC for at least 1 visit between W49 and W52, or during the last 4 weeks before ET.

[f] Study visit windows are ±2 days during the treatment period and ±3 days for the follow-up visits.

[g] Weight will be measured and BMI will be calculated accordingly, at the rollover visit, at W26 (or the next on-site visit if W26 does not coincide with an on-site visit) and W52. Weight will also be measured if there has been an obvious change since the last measurement.
[h] The ECG will be recorded at baseline, at the start of retreatment and every 3 months (or the next on-site visit) while receiving efgartigimod PH20 SC treatment, at CRmin (or the next on-site visit if CRmin is achieved during a week without an on-site visit), and EoS. The ECG (heart rate, PR, QT, and QRS interval) will be read centrally, and QTcF and QTcB will be calculated. Additional ECGs may be performed at the discretion of the investigator during unscheduled visits.
[i] Assessment or procedure will be completed predose at visits when IMP is administered.
[j] A complete physical examination will be performed at each on-site visit. Vital sign measurements include systolic and diastolic blood pressure, heart rate, and body temperature.
[k] Urinalysis will be performed by dipstick method and will include specific gravity, pH, protein, glucose, ketones, blood, bilirubin, urobilinogen, nitrite, leukocyte esterase, and microscopic examination (if blood or protein is abnormal).
[l] Samples will be taken every week from rollover (V1) to W9 or start of retreatment +8 weeks, and then every 4 weeks and at the visit when CR is observed. Once CR is achieved, samples will be taken every 4 weeks at on-site visits until EoS. For participants achieving CR between rollover (V1) and W6 or the start of retreatment +5 weeks, samples will be taken weekly from rollover (V1) to W6 or start of retreatment +5 weeks, and then every 4 weeks during on-site visits until EoS.
[m] A urine pregnancy test will be performed locally at least once every 4 weeks, at CR, and as of CR again every 4 weeks at on-site visits.
[n] Clinical blood laboratory tests will include hematology and blood chemistry at all visits. The hematology profile includes hemoglobin, hematocrit, MCV, RBC count, platelet count, WBC count with differential. The blood chemistry profile includes sodium, potassium, calcium, HbA1c, creatinine, creatinine clearance, BUN, ALT, AST, total bilirubin, GGT, CRP, ALP, LDH, low-density lipoprotein cholesterol (LDL-C), uric acid, total protein, and albumin.
[o] PK and PD (total IgG and IgG subtypes) samples will be taken every 4 weeks, at CR, and as of CR again every 4 weeks at on-site visits, as long as the participant is receiving efgartigimod PH20 SC treatment (until CRmin or the next on-site visit if CRmin is achieved during a week without an on-site visit), and 4 weeks after CRmin (or the next on-site visit) or EoT. Blood will be taken predose (within 2 hours before the start of IMP administration during visits when IMP is administered).
[p] Blood will be taken for PK assessment predose (within 2 hours before the start of IMP administration during visits when IMP is administered). At UNS visits, blood samples for PK analysis will be taken only if IMP is administered.
[q] Blood will be taken to test for immunogenicity to efgartigimod in serum and to rHuPH20 in plasma every 4 weeks, at CR, and as of CR every 4 weeks at on-site visits while the participant is receiving efgartigimod PH20 SC treatment (until CRmin or the next on-site visit if CRmin is achieved during a week without an on-site visit), and 4 and 8 weeks after CRmin (or the next 2 on-site visits) or EoT. NAb will be tested for all confirmed positive immunogenicity samples.
[r] Blood will be taken every 4 weeks and at the visit when CR is observed for IgG autoantibody subtypes and specificity. Once CR is achieved, samples will be taken every 4 weeks at on-site visits until EoS.
[s] The ABQOL and EQ-5D-5L will be administered at the start of retreatment, when achieving CRmin (or at the next on-site visit if CRmin is achieved during a week without an on-site visit), and at EoT/W52 only.
[t] Questionnaires are to be completed before any other assessment.
[u] Disease assessment parameters include DC, EoC, CR, CRmin, CRoff, flare, and treatment failure. Participants who have achieved CR and have new lesions should come to the clinic for a UNS visit for disease assessment.
[v] Pictures of different anatomical regions may be taken per judgment of the investigator. As a guidance, time points of baseline, DC, CR and flare are indicated. Pictures may also be taken at intermediate time points.
[w] Samples for lymphocyte populations will be taken at selected sites only: optionally at on-site visits at W13 (±2 weeks), W26 (±2 weeks), W39 (±2 weeks), W52 (±2 weeks) or EoT/ET and EoS, and mandatory at on-site visits at W52 (±2 weeks) or EoT/ET and EoS for participants in CRmin or CRoff.

[x] The GTI assessment will be performed at visit 1, W26 (or the next on-site visit) and W52.

[y] Participants and/or their caregivers will be invited to receive at least 1 refresher training for self-administration, or caregiver-supported administration of IMP. Training will continue until deemed successfully completed by authorized staff.

[z] Efgartigimod PH20 SC will be administered subcutaneously weekly at a dose of 1000 mg until CRmin. In case of treatment failure in ARGX-113-1904, or flare while not receiving efgartigimod therapy, efgartigimod PH20 SC will be administered on [redacted] followed by weekly SC administrations of 1000 mg until CRmin. For IMP administrations between the scheduled visits (after achieving CR), the participant can choose between self-administration (if training successfully completed), home nurse visits or return to the trial site for the SC injection only. Participants who have achieved CRmin or CRoff and are currently not in flare will be observed every 4 weeks without any further IMP administration until flare or EoS. Only for on-site visits and home nurse visits, participants should be followed up for safety monitoring for at least 1 hour after the first administration, or followed by 15 minutes of observation for subsequent administrations for safety monitoring and released according to their clinical status. The last planned IMP administration is at W52. If the participant withdraws from the study, efgartigimod PH20 SC will not be administered.

[aa] Prednisone dose tapering will begin 2 weeks after achieving CR or 4 weeks after sustained EoC (thus, no new lesions have developed for a minimum of 6 weeks and approximately 80% or more of lesions have healed).