STATISTICAL ANALYSIS PLAN

ARGX-113-1904

Protocol:	ARGX-113-1904
SGS CR number:	BE-80-2000062
Development phase:	Phase 3
Sponsor:	argenx BV
Analysis purpose:	Final analysis
SAP version number:	Final 2.0
SAP version date:	22NOV2023

SIGNATURE PAGE

Name and function	Signature and date (ddMMMyyyy)
SGS Clinical Research author and reviewer:	
[redacted] Biostatistician	[redacted]
[redacted] Biostatistical Coordinator	[redacted]
Sponsor's approval: The approver agrees the statistical analysis will be performed according to this statistical analysis plan.	
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PROTOCOL HISTORY

ARGX-113-1904

Protocol:		
Version or ID	**Date (ddMMMyyyy)**	**Impact of the changes on the statistical analysis**
Final 1.0	22JUL2020	NAP
Final 2.0 (Amendment 1)	10FEB2021	NAP
Final 3.0 (Amendment 2)	18MAY2021	NAP
Final 4.0 (Amendment 3)	09JUN2022	NAP

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
AE	adverse event
AESI	adverse events of special interest
AIS	aggregate improvement score
ALQ	above the limit of quantification
ANCOVA	Analysis of covariance
ATC	Anatomical-Therapeutic-Chemical
BMI	body mass index
Bpm	beats per minute
BLQ	below the limit of quantification
C-GTI	Composite Glucocorticoid Toxicity Index
CMH	Cochran-Mantel-Haenszel
CR	clinical remission
CRF	case report form
CRmin	complete remission on minimal therapy
CRoff	complete remission off prednisone therapy
CSP	Clinical study protocol
CTCAE	Common Terminology Criteria for Adverse Events
CWS	cumulative worsening score
DBP	diastolic blood pressure
DC	disease control
Dsg	desmoglein
DY	relative day
ECG	Electrocardiogram
ED	early discontinuation
EoC	end of consolidation

EoS	end of study
EQ-5D-5L	EuroQol 5-Dimension 5-Level Scale
FU	Follow-up
GM	Geometric mean
GSD	Geometric standard deviation
GTI	Glucocorticoid Toxicity Index
GTI-SL	Glucocorticoid Toxicity Index – Specific List
HR	heart rate
ICE	Intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG	immunoglobin G
IMP	investigational medicinal product
IRR	Injection-related reaction
ISR	Injection site reaction
IV	intravenous
IVIg	immunoglobulins given intravenously
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measurements
NCI	National Cancer Institute
NCPD	normalized cumulative prednisone dose
NAb	neutralizing antibody
OLE	open-label extension
PD	Pharmacodynamics
PDAI	Pemphigus Disease Area Index
PK	Pharmacokinetics
PF	pemphigus foliaceus
PT	preferred term
PV	pemphigus vulgaris
rHuPH20	recombinant human hyaluronidase PH20
QoL	quality of life

QTc	corrected QT interval
QTcB	Bazett's corrected QT interval
QTcF	Fridericia's corrected QT interval
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	subcutaneous
SCR	all screened participants analysis set
SD	standard deviation
SE	standard error
SGS CR	SGS Clinical Research
SOC	system organ class
SOP	standard operating procedure
STAT	statistics
TEAE	treatment-emergent adverse event
WHO-DD	World Health Organization Drug Dictionary

DEFINITION OF TERMS

case report form (CRF)	A printed, optical, or electronic document in which protocol required information is recorded for each study participant.
Display	Analysis table, figure or listing.
Phase	Interval of time in the planned conduct of a study that is associated with a specific purpose: for example, screening, treatment, follow-up.
IMP	Pharmaceutical form of an active ingredient or placebo, being tested or used as a reference in a clinical study.
treatment-emergent abnormality	Any post-baseline abnormality that was not present at baseline (e.g. hemoglobin normal 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).
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 prednisone therapy (CRoff)	The absence of new and established lesions completely healed while the participant is receiving no prednisone therapy (or the equivalent) 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.

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	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.
Treatment failure	Absence of DC with oral prednisone 1.5 mg/kg/day for a minimum of 3 weeks, or flare between DC and CRmin that is not controlled by a dose that is 2 dose levels above the dose at which the flare is observed and that is of at least 0.3 mg/kg qd, or the occurrence of an SAE considered related to prednisone by the investigator.

TABLE OF CONTENTS

1. INTRODUCTION

This statistical analysis plan (SAP) describes the final statistical analyses to be performed for study ARGX-113-1904 (BE-80-2000062).

This SAP covers the efficacy, safety, pharmacokinetic (PK), pharmacodynamic (PD), immunogenicity and general characteristics of the statistical analysis. It specifies the analysis displays to be presented and describes the methods and procedures in a more elaborated way than in the statistical methods section of the protocol. Analyses of exploratory endpoints are not in scope of this SAP.

The statistical analysis will process and present the results following the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) standards, in particular the ICH-E3, ICH-E6, and ICH-E9 guidelines.

1.1 STUDY OBJECTIVES

According to the ARGX-113-1904 protocol, the primary objective of this study is to demonstrate the efficacy of efgartigimod PH20 SC compared to placebo in the treatment of participants with pemphigus vulgaris (PV).

The secondary objectives of study are:

- To demonstrate the efficacy of efgartigimod PH20 SC in the treatment of participants with PV or pemphigus foliaceus (PF).
- To assess the safety of efgartigimod PH20 SC in participants with PV or PF.
- To assess the health impact of glucocorticoid (GC) use in participants with PV or PF.
- To evaluate the effects of efgartigimod PH20 SC on quality of life (QoL) in participants with PV or PF.
- To evaluate the PK of efgartigimod PH20 SC in participants with PV or PF.
- To evaluate the PD of efgartigimod PH20 SC in participants with PV or PF.
- To evaluate the immunogenicity of efgartigimod PH20 SC in participants with PV or PF.
- To evaluate the competency of participants or caregivers to self-administer efgartigimod PH20 SC.

The exploratory objectives include the following but are out of scope of this SAP:

- To evaluate the disease-specific genetic background and effects of efgartigimod PH20 SC on the serological and immunological profiles of participants with PV or PF.
- To evaluate the effects of efgartigimod PH20 SC on markers of pemphigus pathology in skin of participants with PV or PF.

1.2 STUDY DESIGN

This study is a prospective, multicenter, randomized, double-blinded, placebo-controlled study to investigate the efficacy, safety, participant outcome measures, tolerability, immunogenicity, PK, and PD of efgartigimod PH20 SC in adult participants with PV or PF.

The study comprises a screening period of up to 3 weeks, a treatment period of up to 30 weeks, and an 8-week follow-up period for participants who do not enrol into the open-label extension (OLE) study ARGX-113-1905.

After confirmation of eligibility, participants will be randomized in a 2:1 ratio to receive efgartigimod PH20 SC or placebo, as follows:

- Efgartigimod PH20 SC will be administered on day 1 and day 8 at a dose of [redacted] mg, followed by weekly administrations of 1000 mg until CRmin is observed. Efgartigimod PH20 SC will be administered at on-site visits until CR, with a minimum of 6 weekly on-site visits. After achieving CR, efgartigimod PH20 SC will be administered at on-site visits or at home by a nurse until CR on minimal therapy is achieved.
- Placebo (vehicle with 2000 U/mL of rHuPH20) SC will be administered using the same regimen.

CR is defined as the absence of new lesions and complete healing of established lesions (except for post-inflammatory hyperpigmentation or erythema from resolving lesions). CRmin is defined as the absence of new lesions and complete healing of established lesions while the participant is receiving minimal prednisone therapy of ≤10 mg/day for at least 2 months (8 weeks).

Randomization will be stratified by disease status (relapsing and newly diagnosed), disease severity (PDAI activity score <30 and PDAI activity score ≥30), and body weight (<77.5 kg and ≥77.5 kg) at baseline. Participants with severe PV or PF (PDAI activity score ≥45) will comprise a maximum of 30% of the overall study population.

All participants, regardless of treatment assignment, will concomitantly receive oral prednisone (or equivalent such as prednisolone) at 0.5 mg/kg qd starting dose. Except for oral prednisone (or equivalent), no other systemic therapies (eg, immunosuppressants, IVIg, immunoadsorption, anti-CD20 biologics) will be permitted during the study.

Participants who experience treatment failure, or flare after achieving CRmin, will be allowed to roll over into the OLE study ARGX-113-1905 earlier than week 30. Participants who do not roll over into study ARGX-113-1905 will complete an 8-week treatment-free follow-up period. Participants experiencing an SAE related to prednisone in ARGX-113-1904 are considered treatment failures and may also benefit from an early roll over to the OLE, according to clinical judgment of the investigators.

1.3 EXPECTED SAMPLE SIZE

Approximately 213 participants with PV or PF will be randomized as follows for 1904 study:

- Approximately 183 participants with PV will be randomized in a 2:1 ratio to receive efgartigimod PH20 SC or placebo, respectively
- Up to approximately 30 participants with PF may be randomized in a 2:1 ratio to receive efgartigimod PH20 SC or placebo, respectively

All participants who were randomized into ARGX-113-1904 will be eligible to roll over to study 1905.

1.4 SOFTWARE

SAS version 9.4 or later will be used for programming.

1.5 VALIDATION MODEL

SGS Clinical Research (SGS CR) statistics (STAT) and pharmacokinetics (PK) 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.

Analysis Data Model (ADaM) datasets (except subject-level analysis dataset [ADSL]), analysis tables and listings will be reviewed by an independent person (model B validation). ADaM dataset ADSL and the primary endpoint will be reviewed through independent programming (model C validation).

2. GENERAL METHODOLOGY

2.1 ANALYSIS SETS

2.1.1 Analysis sets

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

All screened participants set (SCR):	participants who *signed an informed consent* to participate in the study
Modified Intent-to-treat analysis set (mITT):	all participants who were *randomized* into the study and received at least one dose, or part of a dose, of IMP
Per Protocol set (PP):	all participants in the mITT population for whom no major protocol deviations affecting the efficacy and data validity were reported
Safety analysis set (SAF):	all participants who were *randomized* into the study and received at least one dose, or part of a dose, of IMP
PK analysis set (PK)	all participants in the safety analysis set for whom at least one post-baseline serum PK concentration is available
PD analysis set (PD)	all participants in the safety analysis set for whom at least one post-baseline serum PD concentration is available

Note: Having signed an informed consent is defined as having a complete informed consent signature date in the database.

The efficacy analyses will be done on the mITT analysis set. The analyses of primary and key secondary efficacy endpoints will be repeated on the PP analysis set. The general characteristics and safety analyses will be done on the safety analysis set. PK analysis will be performed on the PK analysis set. PD analysis will be done on the PD analysis set. Immunogenicity will be analyzed on the safety analysis set.

2.1.2 As planned versus as actual analysis

All analyses on the mITT and PP analysis set will be performed according to the planned randomization group. All other analyses will be performed according to the actual received IMP.

2.2 PHASES AND TIME POINTS

2.2.1 Analysis Phases and Periods

All events and assessments will be allocated to phases and periods as defined below.

Table 1: Phase definition

Phase	Period	Start	End
Screening		Date of signing the informed consent form (ICF), with 00:00 added as time part [a]	First IMP administration date/time – 1 minute
Treatment	On Treatment	First IMP administration date/time	Last IMP administration date with 23:59 added as time part.
	Off Treatment	End of on treatment period + 1 minute	For participants who roll over to study 1905, date of study termination (of study 1904), with 23:59 added as time part.
			For participants who do not roll over to study 1905, date of end of study/early discontinuation visit [b], with 23:59 added as time part.
			For participants who do not roll over to study 1905 and have no end of study/early discontinuation visit, date of treatment discontinuation (of study 1904), with 23:59 added as time part.
Following phase is only applicable for participants in the treatment phase who do not roll over to study 1905.			
Follow-up		End of treatment phase + 1 minute	Date of study termination (of study 1904), with 23:59 added as time part.

[a] For rescreened participants without new IC signed the rescreening visit date is used as start of screening phase
[b] Treatment phase lasts until EoS/ED also if a participant may be off treatment after CRmin

Per definition and for each participant, the first phase starts on the date of the earliest available ICF signature, and the last available phase ends on the date of study termination with 23:59 added as time part.

Adverse events and concomitant medications will be allocated to phases (AE's also to periods) as described in sections 5.1.2 and 3.4.2 respectively. All other assessments will be allocated to phases based on the assessment date/time.

A set of subperiods will be derived within the treatment phase, to support the analysis of treatment-emergent adverse events (TEAEs) versus post-TEAEs, as defined in Table 2 below.

Table 2: Subperiod definition for AE

Subperiod	Start	End
Treatment emergent 1	Treatment period 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 within a period will be the end date/time of the period as defined in Table 1.

In case of (partially) missing date/time fields disabling allocation, the visit label will be used to allocate to the correct phase. If this is not possible (unscheduled visits or visits on a turning point between phases), 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 a non-treatment phase.

2.2.2 Baseline and change from baseline

The baseline value will be the last available and non-missing value prior to the first dose of study medication. Assessments on day 1 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 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)

2.2.3 Relative day

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

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

Unless stated otherwise, the reference date is the date of first administration of IMP.

Additionally relative days in the phase/period (ADYP) will be calculated using the first day of the phase/period as reference date (date of first IMP for screening phase). Per definition ADY=ADYP for the screening.

2.2.4 Analysis visits

All assessments, including unscheduled assessments, will be allocated to analysis windows as defined below. Tables and listings will present the analysis windows, not the case report form (CRF) visits. Allocation of assessments will be done using their relative day (ADYP, see section 2.2.3). Visit windows are the mid-point between the scheduled study days for each visit.

Table 3: Analysis visits

Following analysis visits are allocated based on ADYP using start of phase as reference day.

Phase	Analysis window	Target ADYP	Lower limit ADYP	Upper limit ADYP
Screening	Screening	-21	-INF	1
Treatment	Baseline	1	-INF	1[1]
	Week 1	8	1[1]	11
	Week 2	15	12	18
	Week 3	22	19	25
	Week (3+ x[2])	22 + (x[2]*7 days)	19 + (x[2]*7 days)	25 + (x[2]*7 days)
	…	…	…	…
	Week 29	204	201	207
	Week 30	211	208	End day of treatment phase
Follow-up	FU Week 3	21	1	35
	FU Week 7	49	36	End of follow-up phase

[1] An assessment on Day 1 will be attributed to Baseline in case it is before the first IMP administration, to Week 1 otherwise.
[2] x=1,…,.25

Table 4: Additional analysis visits for PD, Albumin, LDL-C and PDAI

Additionally following analysis visits are allocated based on ADYP using start of period as reference day.

Phase	Period	Analysis window	Target ADYP	Lower limit ADYP	Upper limit ADYP
Treatment	On treatment	Baseline	1	-INF	1[1]
		Week 1	8	1[1]	11
		Week 2	15	12	18
		Week 3	22	19	25
		Week (3+ x[2])	22 + (x[2]*7 days)	19 + (x[2]*7 days)	25 + (x[2]*7 days)
		…	…	…	…
		Week 30	211	208	Last IMP administration date
	Off treatment	Week 1	8	1	11
		Week 2	15	12	18
		Week 3	22	19	25
		Week (3+ x[2])	22 + (x[2]*7 days)	19 + (x[2]*7 days)	25 + (x[2]*7 days)
		…	…	…	…
		Week 30	211	208	End day of treatment phase

[1] An assessment on Day 1 will be attributed to Baseline in case it is before the first IMP administration, to Week 1 otherwise.
[2] x=1,…,.26

Per parameter and analysis window, the value closest to the target ADYP will be used in analysis tables, 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 time, the visit label or the group identifier (if applicable). For immunogenicity assessments, missing values resulting in an unavailable 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.

As the schedule of assessments is dependent of CR and consequently varies between participants, data might get spread over time for the 4-weekly visits after CR. Therefore some visit windows will be changed for some parameters:

1. For ABQOL and EQ-5D-5L
    - Week 14 (wide range): from ADYP=96 until ADYP=123
    - Week 30 (wide range): from ADYP= 124 until ADYP=end of treatment phase
    - Additional visit window: Endpoint: last record post baseline.
2. For GTI
    - Week 14 (wide range): from ADYP=61 until ADYP=137 with target on ADYP=99
    - Week 30 (wide range): from ADYP=173 until ADYP= end of treatment phase with target on ADYP=211
    - Other assessments will be allocated as in table 3 but will not be presented in the tables (only in listings).
    - Additional visit window: Overall: last record post baseline.
3. For ECG
    - Week 11 (wide range): from ADYP=75 until ADYP=102

The same rules for record selection as for the regular visit windows will be applied in case of more records occur in the same window.

2.2.5 Worst-case

A worst-case analysis visit will be created for parameters for which abnormalities and/or toxicity grades are defined to summarize values considered as the worst-case. For abnormalities it is derived per parameter and in case both the lowest and the highest values are considered abnormal, a participant can have 2 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, including unscheduled assessments and follow-up visits, 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

Partially missing date of diagnosis and of disease onset will be imputed as follows:

- Missing day will be imputed with first day of the month
- Missing day and month will be imputed with 1JAN

If the imputed date of diagnosis is before the date of disease onset, date of diagnosis will be imputed with date of disease onset.

If the imputed date of disease onset is after the date of diagnosis, date of disease onset will be imputed with date of diagnosis.

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, 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 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.
Antibodies (Ab) against rHuPH20: titer of positive rHuPH20 Ab samples reported as 'negative titer' will be imputed by 5.

Neutralizing antibodies (NAb) against rHuPH20: titer of positive rHuPH20 NAb samples reported as 'negative titer' will be imputed by 100.

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:

- Cumulative prednisone dose will be rounded to 0 decimals.
- BMI and time since diagnosis will be rounded to 1 decimal.
- eGFR and NCPD will be rounded to 2 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 Pharmacokinetics and Pharmacodynamics analyses described in sections 4.2 and 4.3 (except the Japanese-specific analysis) will be repeated for the complement of the Mainland Chinese and East Asian subgroups (i.e. Non-Mainland Chinese and Non-East Asian).

To support the EU submission, all outputs described in this SAP will be repeated for the participants with a history of relapsing disease. This subgroup includes participants that met the following inclusion criteria in the protocol of study ARGX-113-1904:

> 4 iii. Experiencing flare with PDAI activity score ≥15, a maximum of 4 years since disease onset, and off prednisone therapy ± a conventional immunosuppressant (eg, azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil) or dapsone.
>
> 4 iiii. Experiencing flare with PDAI activity score ≥15, a maximum of 4 years since disease onset, and receiving a tapered dose of oral prednisone (or equivalent), provided that prednisone has been given at stable dose ± a conventional immunosuppressant (eg, azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil) or dapsone for at least 2 weeks and participants are fit to start prednisone treatment at 0.5 mg/kg qd at baseline.

2.4.1 Calculation of descriptive statistics and percentages

For continuous variables, 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, Q1, Q3 and maximum.

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

Mean, median, Q1 and Q3, geometric mean (GM) and geometric standard deviation (GSD) will be presented with one more decimal place than the individual values, with maximum 4 decimal places. SD and SE will be presented with 2 more decimal places than the individual values, with maximum 5 decimal places. Minimum and maximum will be presented with the same number of decimal places than the individual values, with maximum 3 decimal places. GM and GSD of percent changes from baseline are presented with one decimal.

Descriptive statistics for PK concentrations will include n (number of observed values), arithmetic mean, SD, median, minimum and maximum, and the coefficient of variation (CV%). Serum concentrations will be presented with 3 significant digits in the original concentration units, except values ≥1000, which will be presented without the decimals. The descriptive statistics should be rounded to the same number of significant digits as the individual values. 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 safety data, the number and percentage of participants with an event, and the number of events will be shown. The denominator will be all participants in the analysis set per treatment and phase (and period in case of AE's).

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.

2.4.2 Presentation of treatments

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

- EFG PH20 SC
- PBO PH20 SC

In the general characteristics analysis, a grand total will be added to summarize all participants over treatments. Grand totals will be shown last.

2.4.3 Order in tables and listings

All tables and figures will be presented per treatment, 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.

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.

The Efgartigimod treatment group will always be shown first, then the Placebo treatment group.

3. GENERAL CHARACTERISTICS ANALYSES

3.1 PARTICIPANT DISPOSITION

3.1.1 Available data

The following participant data will be tabulated:

- The number of participants in each analysis set.
- The number and percentage of participants for each phase and analysis visit.
- Descriptive statistics of the phase duration, calculated as phase end date – phase start date + 1 day. Duration of 'on treatment' phase will also be presented for participants with/without treatment failure.
- 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.
- The number and percentage of participants who roll over to study ARGX-113-1905 and the number and percentage of participants by reason not rolling over (i.e. 'not eligible', 'not willing to' and 'other').

All information collected in the CRF concerning treatment allocation and study and treatment discontinuation will be listed.

3.1.2 Presentation of results

Tables to be produced for the topline results (see list of output in 8.1) will be presented for all participants (PV+PF) as well as for PV participants and PF participants separately.

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), region, childbearing potential, height, weight and BMI at screening, year of birth, date of signing ICF (listed only).

- Baseline disease characteristics: date of pemphigus onset (listed only), date of pemphigus diagnosis, pemphigus type (vulgaris/foliaceus) and subtype (mucosal-dominant / mucocutaneous / cutaneous), type of procedure used for confirmation of diagnosis (cutaneous histology / direct immunofluorescence / indirect immunofluorescence / ELISA), relapsing (yes / no), newly diagnosed (yes / no), number of relapses (if applicable), prior use of immunosuppressants (yes / no), prior use of rituximab (yes / no), PDAI activity score and PDAI total score at baseline, baseline severity [PDAI activity <30/≥30 as well as PDAI activity score 15-44 (moderate), ≥45 (severe)], ABQOL total score at baseline, Karnofsky performance score, positive (≥ 20 RU/ml) anti-Dsg antibodies (aDsg1 only, aDsg3 only, both aDsg1 and aDsg3, neither aDsg1 nor aDsg3), prednisone equivalent dose per body weight at baseline (mg/kg/day), prednisone equivalent dose at baseline (mg/day) and stratification factors (as randomized).

3.2.2 Derivation rules

The following parameters will be derived:

- Time since pemphigus diagnosis (months): (date of first IMP – date of diagnosis)*12/365.25

Notes:

- Partially missing dates will be imputed as detailed in section 2.3.2.
- Result will be rounded as detailed in section 2.3.4 .

- Prior use of immunosuppressants is defined as use of medications with ATC level 2 = 'IMMUNOSUPPRESSANTS' and start date prior to first IMP administration
- Prior use of rituximab is defined as use of medication with CMDECOD = 'RITUXIMAB' and start date prior to first IMP administration
- Derivation of prednisone equivalent dose is detailed in section 3.5.2. Since day 1 can be considered as a transition day, prednisone equivalent dose on day 2 will be used as baseline.
- Region: 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)

3.2.3 Presentation of results

Demographics will be presented using descriptive statistics for age, height, weight and BMI at screening and frequency tabulations for sex, childbearing potential, weight at baseline (<77.5 kg, ≥77.5 kg), geographical region, race and ethnicity.

Baseline disease characteristics will be presented using descriptive statistics for time since diagnosis (overall and for newly diagnosed subjects and subjects relapsing), number of relapses, PDAI activity score and PDAI total score at baseline, ABQOL

total score at baseline, Karnofsky performance score and prednisone dose; frequency tabulations for all other parameters.

Descriptive analyses will be presented for all participants (PV+PF) as well as for PV participants and PF participants separately.

All demographic data and baseline disease characteristics will be listed.

3.3 MEDICAL HISTORY AND CONCOMITANT DISEASES

3.3.1 Available data

Medical history findings are coded using the medical dictionary for regulatory activities (MedDRA) into system organ classes and preferred terms. For each finding, a start and stop date or ongoing flag is collected. The MedDRA version will be updated to the latest one until the database lock of 1904.

3.3.2 Derivation rules

Medical history finding: not ongoing at screening, ended before date of signing informed consent.

Concomitant disease: medical history condition still ongoing at screening.

3.3.3 Presentation of results

Medical history and concomitant diseases will be tabulated separately. Both tables will show:

- The number and percentage of participants with findings
- The number and percentage of participants with findings by system organ class (SOC) and preferred term (PT)

All medical history (not ongoing at screening) and concomitant disease (still ongoing at screening) data will be listed.

3.4 PRIOR AND CONCOMITANT THERAPIES AND PROCEDURES

3.4.1 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.

3.4.2 Derivation rules

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

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

A medication that started before the first dose date 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.

Intercurrent events of unallowed therapies that may influence efficacy are defined as:

- Immunosuppressants at therapeutic doses for at least 4 weeks in total
- IVIg/SCIg at immunomodulating dose (≥1 g/kg/month)
- Immunoadsorption or plasma exchange, at least 1 procedure
- Rituximab or other anti-CD20 biologics, at least 1 infusion
- IV or IM corticosteroids
- Tetracyclines at least 100 mg/day for at least 2 weeks in total
- Any interventional study drug under development for pemphigus

Note: if dose is missing and/or period of intake cannot be derived, it is still considered an intercurrent event.

Details on the derivation of intercurrent events are provided in Appendix 9.1. More information how these intercurrent events are handled can be found in the efficacy section 4.1.

3.4.3 Presentation of results

Prior and concomitant therapies will be tabulated (separately), by ATC class (level 1 and 3) and generic term. Concomitant therapies will exclude oral Prednisone and equivalent medications administered for pemphigus; these will be presented separately.

Tables to be produced for the topline results (see list of output in 8.1) will be presented for all participants (PV+PF) as well as for PV participants.

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

3.5 IMP AND PREDNISONE ADMINISTRATION

3.5.1 Available data

For each IMP administration and for prednisone administration, the start and end date/times, doses (per administration), dose units and volume with units (for IMP only) will be recorded.

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

3.5.2 Derivation rules

The following parameters will be derived for IMP administration:

- Number of administrations: sum of all administrations of study drug. [redacted] administrations are expected on day 1 and day 8.
- Number of [redacted] doses: i.e. daily doses of [redacted] mg [redacted] administrations of 1000 mg).

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 efgartigimod.
- Number of training visits before being considered capable to self-administer.

Normalised cumulative Prednisone dose (NCPD) will be calculated based on prednisone equivalent doses (Schimmer e.a., 2015, and Liu e.a., 2013). 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 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 of analysis period, no record exists in the CRF indicating prednisone use that day, the dose will be assumed to be 0 mg. NCPD will be calculated with and without considering main intercurrent events (see efficacy section 4.1.2.2). Additionally the cumulative prednisone dose (in mg) over these periods will be calculated. Following periods are considered (including start and end of the period):

- Whole planned treatment phase, defined as the period from Day 1 to Day 218 (regardless of whether the assessment is on treatment or follow up phase)
- Start of treatment phase until CR in participants who achieved CR (up to Day 218)
- Start of treatment phase until CRmin in participants who achieved CRmin (up to Day 218)

Days with prednisone equivalent dose <=10 mg and <=20 mg will be flagged in the analysis dataset. The number of days with prednisone equivalent dose <= 10 mg in

the treatment phase will be calculated as well as the proportion of days <= 10 mg in the treatment phase (=100 * number of days <=10 mg /duration of treatment phase).

3.5.3 Presentation of results

Number of administrations and number of [redacted] doses will be summarized using descriptive statistics. Analysis on NCPD is described in the efficacy section 4.1.2.2.

Number of days and proportion of days with prednisone equivalent dose <= 10 mg are analysed in the same way as NCPD, except for the subgroup analyses where only results will be presented for the disease type subgroup.

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, dates of ICE, CR, CRmin and EoS.

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 (denominator is number of participants/caregivers receiving training)
- Number of participants/caregivers who were adequately trained and capable to self-administer efgartigimod (denominator is number of participants/caregivers receiving training)
- Number of training visits before being considered capable to self-administer (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 8.1) will be presented for all participants (PV+PF) as well as for PV participants. Tables on IMP administration will also be presented for PF participants separately.

Line plots for the mean daily prednisone dose (mg) and mean cumulative prednisone dose (g) over time will be produced for all participants (PV+PF) as well as for PV participants. These plots will be produced under the following approaches for handling missing data:

a) complete case analysis;

b) last observation carried forward;

c) baseline observation carried forward.

4. EFFICACY, PHARMACOKINETIC, PHARMACODYNAMIC AND IMMUNOGENICITY ANALYSES

4.1 EFFICACY AND QUALITY OF LIFE

4.1.1 Available data

Efficacy will be evaluated by assessments of PDAI, DC, EoC, CR, CRmin, complete remission off prednisone therapy (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) (see section 9.3).

4.1.2 Endpoints and derivation rules

The analysis of primary and key secondary endpoints will be repeated on the PP set. In addition, these analyses will also be repeated on the mITT population excluding data impacted by the conflict in Ukraine, i.e. excluding participants from Ukraine that have not completed the study by the onset of conflict (24Feb2022). All the above repetitions will be performed on the primary estimand only.

For all references to weeks, 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 response endpoint (see section 4.1.2.2) will be derived using all possible measurements and not only the one closest to the target of the analysis visit. Visits during the treatment and FU phase will be considered defining the different responses, unless mentioned otherwise.

4.1.2.1 PRIMARY ENDPOINT

The primary endpoint is the proportion of PV participants having achieved CRmin (as assessed by the investigator) within 30 weeks. A stratified Cochran-Mantel-Haenszel (CMH) test will be calculated with the stratification factors of disease status, disease severity, and body weight at randomization.

Disease activity relative day will be calculated as specified in Section 2.2.3. Any CRmin achieved with a relative day up to day 218 is counted as a primary endpoint response. CRmin cases achieved for the first time after day 218 will not be considered.

The main analysis on the primary endpoint will use the ‘composite strategy’ approach in case of main intercurrent events. This strategy implies that when a main intercurrent event (ICE) occurs, a participant is considered a non-responder. This happens in the following situations:

- Intercurrent medications (see section 3.4.2) before CRmin
  - Immunosuppressants or dapsone at therapeutic doses for at least 4 weeks in total in the last 12 weeks before achieving CRmin
  - IVIg/SCIg at immunomodulating dose (≥1 g/kg/month) before achieving CRmin
  - Immunoadsorption or plasma exchange (at least 1 procedure) before achieving CRmin
  - Rituximab or other anti-CD20 biologics (at least 1 infusion) before achieving CRmin
  - IV or IM corticosteroids administered (at least 1 administration, any dose) once the participant has achieved minimal prednisone (or prednisone equivalent) dose of <= 10 mg/day (i.e., during the 8 week period required in the protocol to confirm the CRmin status) or administered at any moment before achieving CRmin in any of the three following situations:

    a) more than 60 mg for 3 consecutive days

    b) more than 40 mg for 4 consecutive days

    c) more than 7 days in total
  - Tetracyclines administered at least 100 mg/day for at least 2 weeks in total in the last 10 weeks before achieving CRmin
  - Any interventional study drug under development for pemphigus given before achieving CRmin
- Discontinuation of IMP before CRmin due to lack of efficacy
- Death

The conditions on intercurrent medications above are tailored for the primary endpoint (CRmin). Conditions on intercurrent medications based on medication type, minimal dosing and minimal duration apply to the secondary endpoints below with composite strategy or hypothetical strategy. However, conditions on intercurrent medications like “in the last x weeks before achieving CRmin” are specific for CRmin only. Details on the derivation of intercurrent events are provided in Appendix 9.1.

Missing values for reasons other than the main intercurrent events, 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

A supplementary analysis for this primary analysis on mITT will use the ‘treatment policy strategy’ where the occurrence of the intercurrent event is considered irrelevant: CRmin as assessed by the investigator is used regardless of whether or not the intercurrent event occurs. Missing values for reasons other than the main intercurrent events will be handled as stated above for the primary estimand.

A landmark analysis will be performed as a supplementary analysis, i.e. proportion of PV participants having achieved CRmin (as assessed by the investigator) at 30 weeks (weeks 22-30 CR on minimal therapy). This implies that a responder is defined as a participant that is still in CR and on ≤10mg/day for at least 2 months (8 weeks), at week 30. Disease activity relative day will be calculated as specified in Section 2.2.3. If the disease status at week 30 analysis visit (see Section 2.2.4) is not missing, then that disease status will be used. If the disease status at week 30 analysis visit is missing but disease status at any analysis visits from week 26 to week 29 is not missing the last non-missing analysis visit assessment from week 26 will be used. If all disease status assessments at the analysis windows for week 26 to week 30 are missing, then CRmin at week 30 is No.

A 'composite strategy' approach for dealing with the ICEs will be applied. Accordingly, use of intercurrent medication or permanent IMP discontinuation due to lack of efficacy before or at week 30 will be considered as a non-responder regardless the outcome of the algorithm above.

Additionally, a sensitivity analysis on this landmark analysis will be performed as above without using the week 26 to week 29 data to impute any potential missing disease status at week 30.

4.1.2.2 KEY SECONDARY ENDPOINTS (ALPHA CONTROLLED)

The following key secondary endpoints, which will be tested in the mITT population in hierarchical order (see section 4.1.4), are defined as:

1) The proportion of PV+PF participants that have achieved CRmin within 30 weeks using the same stratified CMH as for the primary endpoint. As this first key secondary endpoint is similar to the primary endpoint, the same approach for handling the main ICEs (both composite strategy and treatment policy strategy), as suggested for the primary analysis, will be applied.

2) Normalised cumulative Prednisone dose (NCPD, mg/kg/day) over the whole planned treatment phase in PV participants, will be analyzed by an analysis of covariance (ANCOVA) model to compare both treatment groups. Only actual administrations of prednisone are considered (not as scheduled). The model will include treatment and the stratification variables will be considered as factors.

Main intercurrent events are handled using the hypothetical strategy, that is, as follows:

- Intercurrent medications (see section 3.4.2): stop calculating cumulative dose after ICE. In case 'immunosuppressants for at least 4 weeks in total' is the ICE, use end of the 4 weeks IC medication as stop for cumulative dose calculation. In case 'tetracyclines for at least 2 weeks in total' is the ICE, use end of the 2 weeks IC medication as stop for cumulative dose calculation. In case 'IV or IM corticosteroids ' is the ICE, use the first day of this IC medication as stop for cumulative dose calculation.
- Discontinuation of IMP before CRmin due to lack of efficacy: stop calculating cumulative dose after this ICE.

Details on the derivation of intercurrent events are provided in Appendix 9.1.

A non-parametric stratified Mann-Whitney test will be performed as sensitivity analysis.

A supplementary analysis for this secondary endpoint will use the 'treatment policy strategy' where the occurrence of the intercurrent event is considered irrelevant: NCPD is calculated regardless of whether or not the intercurrent event occurs.

3) Time to CR in PV participants, calculated as the difference between the first date CR was achieved and the first IMP administration date.
Time to CR (days) = date (first CR) - first IMP date + 1

Main intercurrent events are handled as follows (composite strategy):

- Intercurrent medications (see section 3.4.2) before CR: participant is assumed to not reach CR until the theoretical end of the study and is censored at day 218.
- Discontinuation of IMP before CR due to lack of efficacy: participant is assumed to not reach CR until the theoretical end of the study and is censored at day 218.

Participants without any disease assessment are censored at day 1. Participants with disease assessment but not achieving CR in the period from Day 1 to Day 218 and without intercurrent event in that period are censored at the earliest of day 218 and the end of treatment + FU phase.

A supplementary analysis for this secondary endpoint will use the 'treatment policy strategy' where the occurrence of the intercurrent event is considered irrelevant: Time to CR is calculated regardless of whether or not the intercurrent event occurs.

4) Time to DC in PV participants, calculated as the difference between the first date DC was achieved and the first IMP administration date. Similar calculations, ICE handling and censoring rules are applied as for 'time to CR' (composite strategy).

A supplementary analysis for this secondary endpoint will use the 'treatment policy strategy' where the occurrence of the intercurrent event is considered irrelevant: time to DC is calculated regardless of whether or not the intercurrent event occurs.

Both time to event endpoints will be statistically evaluated using the stratified Fleming-Harrington weighted logrank statistic FH (1,0), with the stratification factors disease status, disease severity, and body weight at randomization. For both, Kaplan-Meier survival plots by treatment arm will be produced (as in-text figures only).

5) NCPD over the whole planned treatment phase in all participants: same derivation as second key secondary endpoint (composite strategy and treatment policy strategy) but for all participants.

6) Time to DC in all participants: same derivation as fourth key secondary endpoint (composite strategy) but for all participants.

7) Time to CR in all participants: same derivation as third key secondary endpoint (composite strategy) but for all participants.

4.1.2.3 OTHER SECONDARY ENDPOINTS (NOT ALPHA CONTROLLED)

All other secondary endpoints will be analyzed using the mITT population. Analyses related to data in the period after an event (CRmin, DC) can only be performed in participants with that event.

1. Proportion of PF participants who achieve CRmin within 30 weeks: same derivation as for the primary endpoint (composite strategy) but then for PF participants.
2. Time to CRmin in PV, PF and all participants: same derivation as third key secondary endpoint (composite strategy) but using date of achieving CRmin. Time to CRmin is defined as the time to the moment that the participant achieves CRmin status defined as complete remission while receiving prednisone therapy at 10 mg/day or less for at least 8 weeks, based on the assessment of the investigator. The 8-week period with minimal prednisone necessary to confirm CRmin is included as part of this time period. For example, a participant that achieves complete remission with prednisone <= 10 mg/day at week 15 for the first time and maintains this status for 8 weeks will have a time to CRmin of 15 + 8 = 23 weeks.
3. Proportion of participants achieving DC in PV, PF and all participants (composite strategy)
4. Proportion of participants achieving CR in PV, PF and all participants (composite strategy)

For all subsequent secondary endpoints a treatment policy strategy is applied ignoring ICEs.

5. Proportion of treatment failures as assessed by the investigator in PV and in all participants. Specific reasons for treatment failure can be derived as follows in following order:
    - absence of DC: if participant didn't achieve DC as assessed by the investigator
    - prednisone related SAE: occurrence of an SAE after DC considered related to prednisone by the investigator
    - flare: if previous 2 reasons are 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

    Failure is defined for the whole treatment phase.
6. Number of flares in PV and in all participants: 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 whole treatment + follow-up phase, between first DC and CRmin (or end of treatment period for participants without CRmin) and after CRmin. The initial flare at baseline (if applicable) is not counted.
7. Time to first flare from first DC in PV and in all participants is calculated as (visit date of flare)-(date of first DC)+1. Similarly time to first flare from first CR and time to first flare from CRmin will be calculated as (visit date of flare)-(date of first CR and date of CRmin respectively)+1.

8. Proportion of PV and all participants with at least one flare after DC. The same periods are considered as for number of flares: i.e. whole treatment + follow-up phase, between first DC and CRmin (or end of treatment period for participants without CRmin) and after CRmin.
9. Duration of CRmin in PV, PF and in all participants: count the number of weeks CRmin is maintained. I.e. participant remains without a lesion after CRmin and with prednisone equivalent dose ≤ 10 mg/day maintained and with PDAI activity score=0 maintained. The 8-week period with minimal prednisone necessary to confirm CRmin is included as part of this duration. Participant is censored at EoS if still on CRmin at end of treatment phase (or follow-up phase if applicable).
10. PDAI at each visit in PV and in all participants: PDAI activity subscores (mucosal, skin and scalp), PDAI activity score and PDAI total score are assessed by the investigator at each visit. Data after the first occurrence of an intercurrent event will also be used (treatment policy strategy). Missing data (intermittent as a result of the scattered way of data collection and non-intermittent as a result of study discontinuation), will be imputed using last observation carried forward (LOCF).
11. QoL in PV and in all participants: 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, Week 4, Week 14 and at EoS. 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.
12. C-GTI in PV and in all participants: 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 14 and EoS/ED. AIS and CWS are calculated for the first 14 week period (W14), for the last 16 week period (W30) and for the treatment phase overall (Overall). The last post-baseline assessment (Overall) is considered as the overall CWS/AIS and is calculated as a cumulative score over all post-baseline timepoints. The complementary GTI specific list (GTI-SL) will only be listed.

4.1.3 Presentation of results and statistical analysis

Wherever the stratification factors will be used in the efficacy analyses, the eCRF values of these will be used and not the ones coming from the randomization. Also for participants randomized without disease status, disease severity and body weight stratification, i.e. Japanese and PF participants, these factors will be derived from the eCRF in order to include these participants in the statistical models.

For the analysis of the PF only population, all stratified models/tests for binary and survival endpoints will only be stratified by the following 2 strata: relapsing vs. newly-diagnosed.

Examples of SAS code for the statistical analysis procedures are provided in Appendix 9.1.5.

Frequency tabulations will be provided of the percentage of PV participants having achieved CRmin within 30 weeks (primary endpoint). The table will be repeated for subgroups including treatment differences in proportions with 95% Wald CI, and overall (PV+PF participants).

A stratified CMH test will be calculated with the stratification factors of disease status, disease severity, and body weight at randomization; the strata-adjusted difference in proportions with the Klingenberg midpoint and 95% confidence interval and 2-sided CMH test p-value will be provided as well as an adjusted common OR with its 95% confidence interval. Homogeneity of the odds ratios will be tested by means of a Breslow Day test with Tarone's adjustment.

A supplementary analysis using the treatment policy strategy will be done for PV participants and overall.

The supplementary landmark analysis at week 30 will be performed on the mITT population for PV participants and overall using the stratified CMH test.

Summary statistics on NCPD, cumulative prednisone dose, number of days and proportion of days with prednisone equivalent dose <= 10 mg will be provided for PV participants and an ANCOVA model with factors for treatment and the stratification variables will be applied on NCPD over the whole treatment phase only. Least square (LS) means and standard error (SE) with 95% 2-sided CI for placebo and efgartigimod will be reported, along with the difference in LS means of IMP vs placebo (with SE), 95% 2-sided CI, and 2-sided p-value. A non-parametric stratified Mann-Whitney test will be performed as sensitivity for PV participants. The 2-sided p-value resulting from this hypothesis test will signify whether the null hypothesis that the distributions of the NCPD for both treatment arms are identical can be rejected. The test will be conducted at a significance level of α=0.05. A supplementary analysis using the treatment policy strategy applying the same ANOVA model will be done.
The table with summary statistics on NCPD will be repeated by subgroups, for PF participants and overall.

Time to CR and Time to DC will be descriptively presented with median times, quantiles and number and percentage of participants censored and with event. In addition, Kaplan-Meier survival plots by treatment arm will be produced (as in-text figures only). Both treatment groups will be compared using the stratified Fleming-Harrington weighted logrank statistic FH (1,0). Also the Cox proportional hazard model will be used: the model will include treatment as fixed effects and stratification factors as covariates. The HR for efgartigimod vs. placebo will be provided, along with the associated 95% 2-sided Wald-type CI and 2-sided p-value. The table will be produced for PV participants and overall. The descriptive statistics will also be presented by subgroups.

Duration of CRmin and other 'time to event' parameters of the 'other secondary endpoints' in section 4.1.2.3 will be descriptively presented and treatment groups will be compared using the logrank statistic.

Frequency tabulations will be provided for the percentages of treatment failure and its different reasons. Failure rates will be compared using the same CMH-test as for the primary endpoint analysis.

Proportion of participants achieving DC and CR and proportion of participants with flare will be tabulated and treatment groups will be compared using the same CMH-test as for the primary endpoint analysis.

Descriptive statistics for PDAI on absolute values, changes from baseline and percent changes from baseline will be calculated per timepoint. Results will be presented separately for observed data and LOCF imputed data. Changes from baseline on LOCF imputed data will be compared between treatment arms at each analysis visit using an ANCOVA model with factors for treatment, baseline value and the stratification variables. Least square (LS) means and standard error (SE) with 95% 2-sided CI for placebo and efgartigimod will be reported, along with the difference in LS means of IMP vs placebo (with SE), 95% 2-sided CI, and 2-sided p-value.

The number of flares will be descriptively presented and analyzed by the same ANCOVA model as for the NCPD analysis. Time to the first flare will be presented and analyzed in the same way as time to CR or time to DC, however using the logrank statistic.

Frequency tabulations will be provided for the percentages of participants within each outcome of QoL questionnaire items (ABQOL and EQ-5D-5L). 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. Changes from baseline will be analyzed by means of a mixed model for repeated measurements (MMRM). The model will include treatment, visit and treatment by visit interaction terms as fixed effects, with baseline value, interaction of baseline value with visit, and stratification factors as covariates. Within-subject correlation will be modeled by assuming an unstructured covariance matrix (UN) for the error terms and Kenward-Roger degrees of freedom method will be used. Least square means and SE with 95% 2-sided CI for placebo and efgartigimod will be reported, along with the difference in LS means of IMP vs placebo (with SE), 95% 2-sided CI, and 2-sided p-value.

If the default Newton–Raphson algorithm used by SAS PROC MIXED fails to converge, the following will be tried to avoid lack of convergence while maintaining an unstructured variance:

A. The Fisher scoring algorithm (via the SCORING = 5 option of the PROC MIXED statement) will be used to obtain the initial values of covariance parameters.

B. If the above fails, the no-diagonal factor analytic structure will be used which effectively performs the Cholesky decomposition via the TYPE=FA0(V) option of the REPEATED statement, where V is the total number of distinct visits in the response vector (counting only rows where all model components are non-missing).

C. If all the above fails, the variance-and-correlations parameterization will be attempted using TYPE =UNR.

In the rare case where all the above fails, the following covariance structures will be tested for convergence (in order): toeph, arh(1), csh, toep, ar(1) and cs. However, if one of these simpler covariance structures is used, this needs to be implemented in combination with sandwich variance estimator (EMPIRICAL option).

Descriptive statistics will be provided for the C-GTI scores AIS and CWS; treatment groups will be compared using the same ANCOVA model and stratified Mann-Whitney test as for the NCPD analysis. C-GTI will be analysed on complete cases: i.e. participants with C-GTI at least at baseline and post-baseline. 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.

4.1.4 Fixed-Sequence testing procedure

To control the type I error for the primary and secondary endpoints (alpha controlled), the primary efficacy endpoint will be tested at the 5% 2-sided alpha level and will act as gatekeeper for the testing of secondary endpoints. The primary endpoint and secondary endpoints will be tested in a strict hierarchical order as listed below to control the type I error (for definitions see section 4.1.2.1 and 4.1.2.2). If a certain endpoint turns out to be non-significant at the 5% significance level, subsequent endpoints will no longer be evaluated.

1. Primary endpoint: the proportion of PV participants who achieve CRmin within 30 weeks using composite strategy approach
2. Proportion of PV+PF participants that have achieved CRmin within 30 weeks using composite strategy approach
3. NCPD in PV participants using hypothetical strategy approach
4. Time to CR in PV participants using composite strategy approach
5. Time to DC in PV participants using composite strategy approach
6. NCPD in PV+PF participants using hypothetical strategy approach
7. Time to CR in PV+PF participants using composite strategy approach
8. Time to DC in PV+PF participants using composite strategy approach

The individual per-endpoint tables will only show unadjusted p-values. A fixed-sequence testing procedure table will be produced. This table will show both unadjusted p-values and p-values adjusted for multiplicity. For a given endpoint, the adjusted-for-multiplicity p-value is calculated as the maximum between its unadjusted p-value and the highest of all unadjusted p-values tested before.

4.1.5 Subgroup analyses for efficacy

Subgroups are defined based on the following categorizing factors:

- Gender (Male, Female)
- Age (18 -< 65, 65 -<75, >=75 years)
- Weight at screening (<50, 50-<75, 75 -< 100, 100 -<125, >= 125 kg)
- BMI at screening (Underweight: < 18.5 kg/m^2, Normal weight: 18.5 -< 25 kg/m^2, Overweight: 25 -< 30 kg/m^2, Obese: >= 30 kg/m^2)
- Race (Asian, Black or African American, White, Other)
- Baseline eGFR (Normal: >= 90 mL/min/1.73m^2, Mildly impaired: 60 -<90 mL/min/1.73m^2, Moderately impaired: 30 -< 60 mL/min/1.73m^2, Severely impaired: <30 mL/min/1.73m^2)
- Disease type (PV/PF) and PV subtype (mucosal-dominant vs (muco-)cutaneous)
- Disease status (relapsing vs newly diagnosed)
- Disease severity (PDAI activity score <30 and PDAI activity score ≥30); moderate (15<=PDAI <=44) vs severe (PDAI ≥45)
- Region (North America; Europe; Asia; Rest of World)

Subgroup analyses will be performed on the primary and key secondary efficacy endpoints on the mITT population.

Following table summarizes the analyses:

Table 5: Summary of analyses

Endpoint	PV	PF[f]	All (PV+PF)	Strategy
Proportion CRmin	X[1,c,p]	X	X[2,c,p,s]	C+T
NCPD	X[2,c,p]	X	X[2,s]	H+T
Time to CR	X[2,c,p]	X	X[2,s]	C+T
Time to DC	X[2, c,p]	X	X[2,s]	C+T
Time to CRmin	X	X	X	C
Proportion DC / CR	X	X	X	C
Proportion treatment failure	X		X	T
Number of flares (incidence rate)	X		X	T
Proportion of participants with flare	X		X	T
Time to first flare	X		X	T
Duration of CRmin	X	X	X	T
PDAI, QoL, C-GTI	X		X	T

[1] Primary endpoint
[2] Key secondary endpoint
[c] Besides main analysis also supplementary analysis will be performed.
[f] PF as part of subgroup analysis or as separate analysis.
[p] Also analysis on PP analysis set and mITT excluding data impacted by the conflict in Ukraine will be performed.
[s] Also subgroup analyses will be performed.

C=composite strategy (taking into account ICEs)

H=hypothetical strategy (taking into account ICEs)

T=treatment policy strategy (ignoring ICEs)

4.2 PHARMACOKINETICS

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 assessments (see section 9.5). Sampling will be done predose on IMP administration visits (within 2 hours before IMP).

An additional PK sample will be taken on day 3 and on day 11 (±1 day) until samples from 24 participants are obtained.

PK data obtained during off treatment period 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 based on time since previous IMP:

- 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. On Day 3 and Day 11 the visit window is ±1 day (ie, ±24h).
- 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).

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

4.2.2 Derivation rules

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

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 time point on concentration data will be presented in tables.

4.3 PHARMACODYNAMICS

4.3.1 Available data

The following pharmacodynamic 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 vs baseline will be calculated. Participants with a baseline value below the limit of quantification (BLQ) will be excluded when computing the change from baseline and the percent change from baseline. Values of anti-Dsg-1/Dsg-3 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.

In addition, for all pharmacodynamic endpoints, descriptive statistics of the actual vales will also include GM and GSD. GM and GSD are not applicable for descriptive statistics of the absolute changes from baseline. For these selected endpoints, descriptive statistics of percent changes from baseline will also include GM and GSD. GM and GSD of percent changes from baseline are calculated as $100x\{\exp(\theta)-1\}$

where θ is respectively the arithmetic mean and arithmetic SD of a variable calculated as log(aval)-log(base).

4.3.3 Presentation of results

All pharmacodynamic endpoints 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. Also, the same subgroup analyses will be performed as for efficacy.

4.4 IMMUNOGENICITY

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) at the time points indicated in the schedule of assessments (see section 9.5).

Immunogenicity samples are analyzed in a 3-tiered approach:

- All samples are evaluated in the ADA screening assay and are scored as 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. For Nab against rHuPH20, the screening Nab assay is followed by a titer Nab assay in case the sample screened positive.

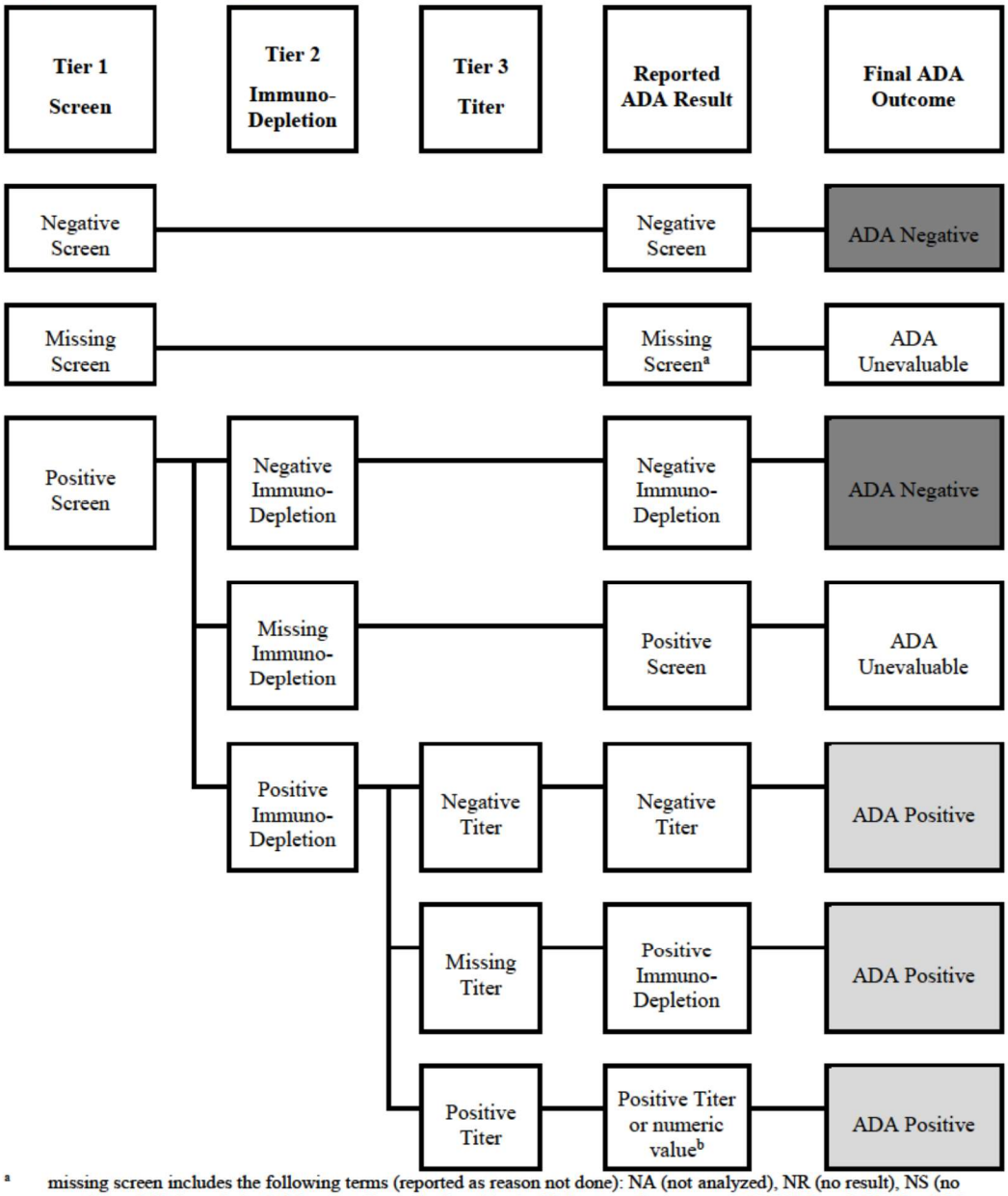
If available, a titer result will be reported for the ADA confirmed positive samples. However, a titer result is not always available:

- 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 given below. 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) and the DTA from Covance Indianapolis (for antibodies against rHuPH20) 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

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 sample status				
	ADA negative	**ADA positive (missing titer[a])**	**ADA positive (negative titer[b] 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 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. positive titer and selecting the sample with highest titer)

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 ANTIBODIES AGAINST RHUPH20

Table 7 below gives an overview of how the anti-rHuPH20 antibody (rHuPH20 Ab) participant classification will be derived, starting from the participant baseline rHuPH20 Ab sample status.

Table 7: Participant classification for antibodies against rHuPH20

Participant anti-rHuPH20 Ab classification	**Highest[c] post-baseline sample status**				
	rHuPH20 Ab **negative**	rHuPH20 Ab **positive (missing titer[a])**	rHuPH20 Ab **positive (negative titer[b] or numeric titer value)**		rHuPH20 Ab **not evaluable**
Baseline rHuPH20 Ab sample status					
rHuPH20 Ab negative	rHuPH20 Ab negative	Treatment-Induced rHuPH20 Ab	Treatment-Induced rHuPH20 Ab		rHuPH20 Ab *unevaluable*
rHuPH20 Ab positive (missing titer[a])	Treatment-Unaffected rHuPH20 Ab	rHuPH20 Ab *unevaluable*	rHuPH20 Ab *unevaluable*		rHuPH20 Ab *unevaluable*
rHuPH20 Ab positive (negative titer[b] or numeric titer value)	Treatment-Unaffected rHuPH20 Ab	rHuPH20 Ab *unevaluable*	**titer < 4 x baseline titer:** Treatment-Unaffected rHuPH20 Ab	**titer ≥ 4x baseline titer:** Treatment-Boosted rHuPH20 Ab	rHuPH20 Ab *unevaluable*
rHuPH20 Ab not evaluable	rHuPH20 Ab *unevaluable*	rHuPH20 Ab *unevaluable*	rHuPH20 Ab *unevaluable*		rHuPH20 Ab *unevaluable*

[a] Samples with missing titer have as reported rHuPH20 Ab result 'positive immunodepletion' or 'positive titer';
[b] Results reported as 'negative titer', i.e. titer value <5 will be set to value of 5;
[c] Highest sample status, with order: (from low to high): rHuPH20 Ab unevaluable, rHuPH20 Ab negative, rHuPH20 Ab positive (missing titer/positive immunodepletion), rHuPH20 Ab positive with titer <= 5 ('negative titer' as reported rHuPH20 Ab result, titer value set to 5), rHuPH20 Ab positive with titer >5 (i.e. positive titer and selecting the sample with highest titer)

rHuPH20 Ab evaluable participant = participant classified as any of following categories: rHuPH20 Ab negative, treatment-unaffected rHuPH20 Ab, treatment-induced rHuPH20 Ab, treatment-boosted rHuPH20 Ab. The first 2 categories are classified as 'rHuPH20 Ab negative', the latter 2 as 'rHuPH20 Ab positive'.

rHuPH20 Ab unevaluable participant = participant classified as rHuPH20 Ab unevaluable or with missing baseline rHuPH20 Ab sample or without post-baseline rHuPH20 Ab samples

Anti-rHuPH20 Ab incidence = percentage of participants with treatment-induced or treatment-boosted rHuPH20 Ab s (denominator: number of evaluable participants).

Anti-rHuPH20 Ab prevalence = percentage of participants with treatment-unaffected rHuPH20 Ab, treatment-induced rHuPH20 Ab or treatment-boosted rHuPH20 Ab (denominator: number of evaluable participants).

4.4.2.3 PARTICIPANT CLASSIFICATION FOR NAB AGAINST EFGARTIGIMOD

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 8.

Table 8: 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

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).

4.4.2.4 PARTICIPANT CLASSIFICATION FOR NAB AGAINST RHUPH20

All rHuPH20 Ab confirmed positive samples will also be evaluated in the NAb assay against rHuPH20. All samples that were not analyzed in the NAb assay (i.e. the rHuPH20 Ab negatives) are per default NAb negative. Also, if a NAb sample is not reported, the NAb sample status is NAb unevaluable. NAb against rHuPH20 will be evaluated using a screening assay followed by titer analysis (ie, a 2-tiered approach). For NAb against rHuPH20, all samples evaluated in this NAb screening assay will be scored as NAb negative or NAb positive by the laboratory. In case the sample is NAb positive, a titration assay will occur and the sample will be reported as 'negative titer',

'positive titer' or by an actual titer value. Based on these results, the participants will be categorized based on their baseline and post-baseline sample status as detailed in following Table 9.

A 3-tiered approach, including an additional NAb confirmatory assay to determine the specificity of the response, will be implemented as a post-hoc analysis. This analysis will be described in an addendum to this SAP or the ISI (Integrated Summary of Immunogenicity) SAP.

Table 9: Participant classification for NAb against rHuPH20

Participant rHuPH20 NAb classification	**Highest[c] post baseline sample status**				
	rHuPH20 NAb negative	**rHuPH20 NAb positive (missing titer[a])**	**rHuPH20 NAb positive (negative titer[b] or numeric titer value)**		**rHuPH20 NAb not evaluable**
Baseline rHuPH20 NAb sample status					
rHuPH20 NAb negative	rHuPH20 NAb negative	Treatment Induced rHuPH20 NAb	Treatment Induced rHuPH20 NAb		*rHuPH20 NAb unevaluable*
rHuPH20 NAb positive (missing titer[a])	Treatment Unaffected rHuPH20 NAb	*rHuPH20 NAb unevaluable*	*rHuPH20 NAb unevaluable*		*rHuPH20 NAb unevaluable*
rHuPH20 NAb positive (negative titer[b] or numeric titer value)	Treatment Unaffected rHuPH20 NAb	*rHuPH20 NAb unevaluable*	**titer < 4 x baseline titer:** Treatment Unaffected rHuPH20 NAb	**titer ≥ 4x baseline titer:** Treatment Boosted rHuPH20 NAb	*rHuPH20 NAb unevaluable*
rHuPH20 NAb not evaluable	*rHuPH20 NAb unevaluable*	*rHuPH20 NAb unevaluable*	*rHuPH20 NAb unevaluable*		*rHuPH20 NAb unevaluable*

[a] Samples with missing titer have as reported rHuPH20 NAb result 'positive screen' or 'positive titer';
[b] Results reported as 'negative titer', i.e. titer value <100 will be set to value of 100;
[c] Highest sample status, with order: (from low to high): rHuPH20 NAb unevaluable, rHuPH20 NAb negative, rHuPH20 NAb positive (missing titer), rHuPH20 NAb positive with title <100 ('negative titer' as reported NAb result, titer value set to 100), rHuPH20 NAb positive (i.e. actual titer value and selecting the sample with highest titer) .

rHuPH20 NAb evaluable participant = participant classified as any of following categories: rHuPH20 NAb negative, treatment-unaffected rHuPH20 NAb, treatment-induced rHuPH20 NAb, treatment-boosted rHuPH20 NAb. The first 2 categories are classified as 'rHuPH20 NAb negative', the latter 2 as 'rHuPH20 NAb positive'.

rHuPH20 NAb unevaluable participant = participant classified as rHuPH20 NAb unevaluable or with missing baseline rHuPH20 NAb sample or without post-baseline rHuPH20 NAb samples

NAb incidence = percentage of participants with participant classification 'treatment-induced rHuPH20 NAb' or treatment-boosted rHuPH20 NAb' (denominator: number of evaluable participants).

NAb prevalence = percentage of participants with participant classification 'treatment-unaffected rHuPH20 NAb', 'treatment-induced rHuPH20 NAb' or 'treatment-boosted rHuPH20 NAb' (denominator: number of evaluable participants).

4.4.3 Presentation of results

Analyses will be done for ADA against efgartigimod and antibodies against rHuPH20.

Frequency tabulations (number and percentages) will be provided with ADA or rHuPH20 Ab negative/positive/unevaluable samples per analysis visit. These tables will be presented by ADA or rHuPH20 Ab participant category.

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

- Participants per ADA or rHuPH20 Ab participant classification
- Prevalence and incidence of ADA or rHuPH20 Ab
- ADA or rHuPH20 Ab unevaluable participants
- ADA or rHuPH20 Ab baseline positive/negative samples

For details on the definitions, see the above section 4.4.2.1. and 4.4.2.2.

The above frequency tabulations will be repeated for NAb assay using the definitions as defined in section 4.4.2.3. and 4.4.2.4.

In addition, a frequency tabulation (number and percentages) will be provided for:

- NAb against efgartigimod positive participants within the ADA participant classification (Treatment-unaffected ADA, Treatment-induced ADA, Treatment-boosted ADA, ADA Negative, ADA Unevaluable)
- NAb against rHuPH20 Ab positive participants within the rHuPH20 Ab participant classification
- rHuPH20 Ab positive participants within efgartigimod ADA participant classification

Correlation tables by ADA and NAb participant classification against efgartigimod and by rHuPH20 Ab will be provided for the following parameters for PV and PF participants combined:

- Mean (SD) drug concentration over time
- Mean (SE) percent change from baseline in total IgG
- Overall Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Overall Anti-Drug Antibodies Participant Classification
- Overall Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Overall Anti-Drug Antibodies Participant Classification
- Overall Injection-related reactions by Overall Anti-Drug Antibodies Participant Classification
- Overall Injection site reactions by Overall Anti-Drug Antibodies Participant Classification
- Proportion of participants with CRmin within 30 weeks*

* Difference in proportion responders between each of the 4 categories versus ADA Negative, NAb baseline neg – post-baseline neg and rHuPH20 Ab Negative, including 95% exact confidence interval will be calculated.

ADA titer values against efgartigimod and rHuPH20 Ab titer values will be summarized by means of descriptive statistics by ADA participant classification or rHuPH20 Ab participant classification respectively.

All available data on ADA and NAb against efgartigimod, rHuPH20 Ab and rHuPH20 NAb will be listed, showing also the sample status and participant classification.

5. SAFETY ANALYSES

5.1 ADVERSE EVENTS

5.1.1 Available data

Adverse events (AEs) are coded into SOC and PT using the latest version of the MedDRA available at the moment of the database lock. For each AE, start and stop date/times are collected as well as severity (NCI CTCAE v5.0), a seriousness flag, treatment relatedness, relatedness to procedures, action taken towards the IMP, outcome, and AE of special interest (AESI) category (infection).

5.1.2 Derivation rules

Treatment-emergent adverse events (TEAE) are defined as AEs starting on or after first administration of any IMP up through 60 days after the last administration of the IMP prior to the AE. Post-TEAEs are AEs starting after first administration of IMP that are not TEAEs.

Based on their start date/time, AEs will be allocated to the phase during which they started. Each AE will therefore be reported in only one phase. 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 as detailed below:

- Treatment phase vs. non-treatment phase: the AE will be allocated to the treatment phase unless the available parts of the AE start or stop date/time provide evidence for allocating to the non-treatment 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. first administration) =
  - 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
  - Study completion date or Study discontinuation date – 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) will be calculated as [the sum over all participants of the study duration calculated as (last phase end date – first IMP date + 1 day)]/365.25.
- PYFU for TEAEs (in years) will be 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) will be 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.

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

- TEAEs
- Treatment related TEAEs
- Serious TEAEs
- Serious treatment related TEAEs
- Serious prednisone related TEAEs
- Grade ≥ 3 TEAEs
- Treatment related Grade ≥ 3 TEAEs
- 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 events 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 participant years of follow-up and the number of events and the event rate per 100 participant years of follow-up.

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 for the following:

- Most common (>=5% in any group) TEAEs
- Treatment related TEAEs
- Serious TEAEs
- Serious treatment related TEAEs
- Serious prednisone related TEAEs
- Grade ≥ 3 TEAEs
- Treatment related Grade ≥ 3 TEAEs
- 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.

5.2 CLINICAL LABORATORY EVALUATION

5.2.1 Available data

Per protocol, the following laboratory parameters are expected:

- Biochemistry: sodium, potassium, calcium (total), 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), high-density lipoprotein-cholesterol (HDL-C), total cholesterol, triglycerides, 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 RBC, WBC, casts, crystals, and bacteria.
- Specialty laboratory parameters: apolipoprotein B (apoB), lipoprotein A, fibrinogen, von Willebrand factor, D-dimer, proprotein convertase subtilisin/kexin type 9 serine protease (PCSK9).

Normal ranges are available as provided by the laboratory.

5.2.2 Derivation rules

Toxicity grades will be computed according to the National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) toxicity grading list (version 5.0). The implementation of these toxicity grades for analysis is presented in appendix 9.4. Only the parameters described in appendix 9.4 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.

5.2.3 Presentation of results

The statistical analysis will present results in standardized units, except creatinine clearance which is presented in original units (ml/min/1.73m2).

Continuous laboratory 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. For albumin and low-density lipoprotein-cholesterol (LDL-C) also percent changes vs baseline will be shown.

Laboratory abnormalities will be presented as a cross-tabulation 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.

Laboratory toxicity grades will be presented as a cross-tabulation (shift table) of the toxicity (NCI CTCAE grades) 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.

All laboratory data will be listed, but only for participants with any post-baseline abnormality.

5.3 VITAL SIGNS

5.3.1 Available data

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

5.3.2 Derivation rules

Abnormalities are defined in below table.

	SBP (mmHg)	DBP (mmHg)	Temperature (°C)
Low	<90	<45	<35.8
Normal	90-150	45-90	35.8-37.5
High	>150	>90	>37.5

Note: 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.

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

5.3.3 Presentation of results

VS parameters (without 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 a cross-tabulation 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).

All vital signs data will be listed, but only for participants with any post-baseline abnormality or any reading determined as clinically significant by the investigator.

5.4 ELECTROCARDIOGRAMS

5.4.1 Available data

The following electrocardiogram (ECG) parameters will be collected: heart rate (HR), QRS interval, PR 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 QTcB and QTcF 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 post-baseline value and associated change.

5.4.3 Presentation of results

Uncorrected QT interval will only be listed.

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 a cross-tabulation 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 over decreasing abnormalities (QTcF and QTcB only) of participants with treatment-emergent abnormalities. 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.

All ECG data will be listed, but only for participants with any post-baseline abnormality.

5.5 PHYSICAL EXAMINATIONS

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.

NCPD, time to CR and time to DC for PV+PF participants are added to the fixed-sequence testing procedure.

NCPD (mg/kg/day) is calculated for different periods 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 instead of using weight at baseline.

The following extra analyses will be conducted, which are not covered in the clinical study protocol (CSP):

- Cox proportional hazard model on time to event endpoints
- Stratified Mann-Whitney test on NCPD and GTI endpoints
- Selected endpoints on the subset of PF participants

The following extra endpoints will be derived, which are not covered in the CSP (see section 4.1.2.3 and 3.5.2):

- Time to CRmin
- NCPD defined for different periods
- Cumulative prednisone dose (mg) over different periods
- Time to first flare for different periods
- Proportions of participants with DC/CR
- Duration of CRmin

The CSP pre-specified a list of medications whose use is to be considered an intercurrent event to be handled using the composite strategy. These medications were: immunosuppressants or dapsone, IVIg at immunomodulating doses, immunoadsorption or plasma exchange, rituximab or anti-CD20 biologics and IV corticosteroids. In this SAP, the following therapies, not mentioned in the CSP, have also been added as intercurrent events to be handled with the composite strategy: tetracyclines and any interventional study drug under development for pemphigus.

The following analysis, covered in the CSP, will not be performed since no comparable historical data are available for the control arm in the PF literature:

- The magnitude of the effect of efgartigimod PH20 SC compared to placebo in the PF subpopulation will be evaluated using the posterior distribution of the treatment effect (difference between efgartigimod PH20 SC and placebo) obtained in a Bayesian analysis. This Bayesian analysis will incorporate historical data for the placebo in an informative maximum a posteriori probability estimate prior with robustness modifier.

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, 01 July 1996.

ICH Topic E6(R1) Guideline for Good Clinical Practice – Step 4, 10 June 1996.

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) 17 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.

Lu K, Mehrotra D. Specification of covariance structure in longitudinal data analysis for randomized clinical trials. Statistics in Medicine. 2010; 29: 474-488. DOI: 10.1002/sim.3820.

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 AND LISTINGS

8.1 TABLES

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

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IMMUNOGENICITY

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9. APPENDICES

9.1 MAIN INTERCURRENT EVENTS (ICE)

The conditions below are tailored for the primary endpoint (CRmin). Conditions based on medication type, minimal dosing and minimal duration apply to the other endpoints with composite strategy or hypothetical strategy. However, conditions like "in the last 12 weeks before achieving CRmin" are specific for CRmin only. For these strategies, NCPD is calculated until and excluding the first day of ICE unless specified otherwise.

9.1.1 Immunosuppressants or dapsone at therapeutic doses for at least 4 weeks in total in the last 12 weeks before achieving CRmin

- Azathioprine, at least 1 mg/kg/day
- Mycophenolate mofetil, at least 2 g/day
- Mycophenolic acid, at least 1000 mg/day
- Mycophenolate mofetil hydrochloride, at least 2 g/day
- Cyclophosphamide, at least 1 mg/kg/day, or IV pulse 500 mg/month
- Methotrexate (sodium), at least 5 mg/week (in Japan), whereas 10 mg/week in Europe
- Ciclosporin, at least 3 mg/kg/day
- Dapsone, at least 1 mg/kg/day
- Hydroxychloroquine sulfate, at least 400mg/day
- Thalidomide, at least 50mg/day

For CRmin and time to CRmin these events should occur in the last 12 weeks before CRmin to be considered as an ICE. NCPD is calculated until and including the last day of the applicable 4 weeks intake.

9.1.2 IVIg/SCIg at immunomodulating dose (≥1 g/kg/month) before achieving CRmin

- 'Immunoglobulins NOS' or 'Immunoglobulin G Human' or 'Immunoglobulins' or 'Immunoglobulin Human Normal' or 'Anti-D Immunoglobulin

  and cmroute='INTRAVENOUS' or 'SUBCUTANEOUS'.

9.1.3 Immunoadsorption or plasma exchange (at least 1 procedure) before achieving CRmin

- 'Plasmapheresis' or 'Immunoadsorption therapy' as PRDECOD, at least one cycle

9.1.4 Rituximab or other anti-CD20 biologics (at least 1 infusion) before achieving CRmin

- Rituximab, at least one cycle of 1 g or 375 mg/m^2
- Obinutuzumab
- Ofatumumab
- Ocrelizumab
- Ibritumomab tiuxetan
- Veltuzumab
- Tocilizumab

9.1.5 IV or IM corticosteroids

- administered (at least 1 administration, any dose) once the participant has achieved minimal prednisone (or prednisone equivalent) dose of <= 10 mg/day (i.e., during the 8 week period required in the protocol to confirm the CRmin status) or administered at any moment before achieving CRmin in any of the three following situations:

  a) more than 60 mg of prednisone equivalent for 3 consecutive days

  b) more than 40 mg of prednisone equivalent for 4 consecutive days

  c) more than 7 days in total
- medications with ATC level2 ='H02 CORTICOSTEROIDS FOR SYSTEMIC USE' and cmroute='INTRAVENOUS' or 'INTRAMUSCULAR'

For endpoints other than CRmin and time to CRmin, any administration of this type of medication is to be considered as an ICE.

9.1.6 Tetracyclines administered at least 100 mg/day for at least 2 weeks in total

- medications with ATC level4 = 'TETRACYCLINES'

For CRmin and time to CRmin these events should occur in the last 10 weeks before CRmin to be considered as an ICE. NCPD is calculated until and including the last day of the applicable 2 weeks intake.

9.1.7 Any interventional study drug under development for pemphigus given before achieving CRmin

- medications under development for pemphigus will be evaluated during the course of the study

9.2 SAS CODE

9.2.1 MMRM model

Calculate &meanbase. as mean of base of all unique participants in FAS.

[redacted]

9.2.2 ANCOVA model

[redacted]

Note: this is the script for NCPD. For other variables this code needs to be adapted according the model specifications in section 4.1. For example, for PDAI, the dependent variable is CHG and the baseline value needs to be added to the set of covariables.

9.2.3 Time to event analysis: stratified Fleming-Harrington weighted logrank test

[redacted]

9.2.4 Time to event analysis: logrank test

[redacted]

9.2.5 Cochran-Mantel-Haenszel test with Klingenberg midpoint and CI

[redacted]

[redacted]

9.2.6 Cox Proportional Hazard regression model

[redacted]

9.2.7 Stratified Mann-Whitney test

[redacted]

9.3 GTI: DERIVATION OF CWS AND AIS

9.3.1 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).

9.3.1.1 BMI (COMPARED TO PREVIOUS ASSESSMENT)

- Moderate decrease in the direction of the normal range [<25 kg/ m^2] by at least 5 BMI units -36
- Minor decrease in the direction of the normal range [<25 kg/ m^2] 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/ m^2 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/m^2]) 21
- Moderate increase in BMI (increase by at least 5 BMI units above normal BMI [≥25kg/m^2]) 36

9.3.1.2 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.

9.3.1.3 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

9.3.1.4 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

9.3.1.5 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

9.3.1.6 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)

9.3.1.8 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)

9.3.1.9 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.

9.3.2 CWS and AIS calculation

9.3.2.1 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).

CWS is calculated at W14 and at W30 as the sum of the worsening items in all post-baseline timepoints up to that timepoint respectively. The overall CWS is the sum of all worsening items over all post-baseline timepoints.

9.3.2.2 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 W14 and at W30 as the sum of the items in all post-baseline timepoints up to that timepoint respectively. The overall AIS is the sum over all post-baseline timepoints.

9.4 TOXICITY GRADES (CTCAE, V5.0)

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

CTCAE, v5.0: November 27, 2017

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	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	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	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	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	mmol/L	>ULN-2.9	>2.9-3.1	>3.1-3.4	>3.4

PARAMETER	Unit	GRADE 1	GRADE 2	GRADE 3	GRADE 4
	mg/dL	>ULN-11.5	>11.5-12.5	>12.5-13.5	>13.5
Cholesterol	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 (fasting) 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	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	mmol/L	>ULN-1.23	-	>1.23-3.30	>3.30
	mg/dL	>ULN-3.0	-	>3.0-8.0	>8.0
Potassium low	mmol/L	-	<LLN-3.0	<3.0-2.5	<2.5
	mEq/L	-	<LLN-3.0	<3.0-2.5	<2.5
Potassium high	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	mmol/L	<LLN-130	-	<130-120	<120

PARAMETER	Unit	GRADE 1	GRADE 2	GRADE 3	GRADE 4
	mEq/L	<LLN-130	-	<130-120	<120
Sodium high	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	giga/L	<LLN-0.50	<0.50-0.20	<0.20-0.05	<0.05
	counts/mm^3	<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	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)	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	giga/L	<LLN-75	<75-50	<50-25	<25
	counts/mm^3	<LLN-75000	<75000-50000	<50000-25000	<25000

PARAMETER	Unit	GRADE 1	GRADE 2	GRADE 3	GRADE 4
White blood cells	giga/L	<LLN-3	<3-2	<2-1	<1
	counts/mm^3	<LLN-3000	<3000-2000	<2000-1000	<1000

[1] Grade definition will also be applied when the fasting conditions into which the sample was drawn have not been declared (e.g. unscheduled samples, unknown), when only (a) sporadic result(s) for the parameter was (were) non-fasting (usually unscheduled samples), and in case of scheduled post-meal samples on a same day (e.g. 4 hours after dose and after a meal).

Note: 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.

9.5 SCHEDULE OF ASSESSMENTS

Trial Period	Screening	Treatment						EoS/ ED[a]	UNS[b]	Follow-up	
		V1 (BL)	V2	Observational visits	IMP admin only visit	Observational visits					
Visit Number				Weekly on-site visits until CR[c]	Weekly home or on-site visits until CRmin[d]	On-site visits every 4 weeks until CRmin	On-site visits every 4 weeks after CRmin until W31	W31		Follow-up W34	Follow-up W38[e]
Trial Day/Week	D-21 to D-1	D1 (W1)	D8 (W2)	D15 (W3) until CR	CR until CRmin	CR until CRmin	CRmin until W31	W31		EoS/ED +3W	EoS/ED +7W
Visit Window		±0 days	±2 days[f]	V1 + 7× ±2 days[f]				±2 days[f]		±3 days[f]	
Assessment/ Procedure											
Informed consent[g]	X										
Inclusion/exclusion criteria	X	X									
DIF/histopathology[h]	X										
Concomitant therapies/procedures	X	Continuous monitoring									
Karnofsky performance score	X										
Demography	X										
Height and weight[i]	X			X[i]		X[i]	X[i]	X			

Trial Period	Screening	Treatment						EoS/ ED[a]	UNS[b]	Follow-up	
		V1 (BL)	V2	Observational visits	IMP admin only visit	Observational visits					
Visit Number				Weekly on-site visits until CR[c]	Weekly home or on-site visits until CRmin[d]	On-site visits every 4 weeks until CRmin	On-site visits every 4 weeks after CRmin until W31	W31		Follow-up W34	Follow-up W38[e]
Trial Day/Week	D-21 to D-1	D1 (W1)	D8 (W2)	D15 (W3) until CR	CR until CRmin	CR until CRmin	CRmin until W31	W31		EoS/ED +3W	EoS/ED +7W
Visit Window		±0 days	±2 days[f]	V1 + 7× ±2 days[f]				±2 days[f]		±3 days[f]	
Physical examination and vital signs[j,k]	X	X	X	X		X	X	X	X	X	X
ECG[j]	X			X[l]		X[l]		X			
Medical and surgical history	X										
Randomization[m]		X									
Urinalysis[j,n,o]	X	X	X	X		X	X	X	X[b]	X	X
Urine pregnancy test[j,p]		X		X[p]		X	X	X	X[b]	X	X
Blood sampling:											
Active viral infection test[q]	X										
Serum pregnancy test[r]	X										
Clinical chemistry & hematology[j,o,s]	X	X	X	X		X	X	X	X[b]	X	X

Trial Period	Screening	Treatment						EoS/ ED[a]	UNS[b]	Follow-up	
		V1 (BL)	V2	Observational visits	IMP admin only visit	Observational visits					
Visit Number				Weekly on-site visits until CR[c]	Weekly home or on-site visits until CRmin[d]	On-site visits every 4 weeks until CRmin	On-site visits every 4 weeks after CRmin until W31	W31		Follow-up W34	Follow-up W38[e]
Trial Day/Week	D-21 to D-1	D1 (W1)	D8 (W2)	D15 (W3) until CR	CR until CRmin	CR until CRmin	CRmin until W31	W31		EoS/ED +3W	EoS/ED +7W
Visit Window		±0 days	±2 days[f]	V1 + 7× ±2 days[f]				±2 days[f]		±3 days[f]	
Anti-Dsg-1 and anti-Dsg-3 antibodies[j,o]	X	X	X	X		X	X	X	X[b]	X	X
PK[j,o,t]		X	X[t]	X		X	X	X	X[b,t]	X	X
Total IgG and IgG subtypes[j,o,u]	X	X	X	X		X	X	X	X[b]	X	X
Vaccination antibodies[j,o,v]	X	X	X	X		X	X	X	X[b]	X	X
Anti-drug antibodies[j,w]		X		X (every 2 weeks)		X	X	X		X	X
IgG autoantibody subtypes/specificity and cytokines[j,x]		X		X[x]		X	X	X	X[b]	X	X
B- and T-cell populations[j]		X		X[y]				X			
RNA transcriptional profile[j]		X		X[y]				X			

Trial Period	Screening	Treatment						EoS/ ED[a]	UNS[b]	Follow-up	
		V1 (BL)	V2	Observational visits	IMP admin only visit	Observational visits					
Visit Number				Weekly on-site visits until CR[c]	Weekly home or on-site visits until CRmin[d]	On-site visits every 4 weeks until CRmin	On-site visits every 4 weeks after CRmin until W31	W31		Follow-up W34	Follow-up W38[e]
Trial Day/Week	D-21 to D-1	D1 (W1)	D8 (W2)	D15 (W3) until CR	CR until CRmin	CR until CRmin	CRmin until W31	W31		EoS/ED +3W	EoS/ED +7W
Visit Window		±0 days	±2 days[f]	V1 + 7× ±2 days[f]				±2 days[f]		±3 days[f]	
HLA/non-HLA genotyping[j]		X		X[z]							
Substudies:											
Skin biopsies (at selected sites)[j,aa]		X		X[aa]				X[aa]			
Photography (at selected sites)[j,bb]		X	X[bb]	X[bb]					X[b,bb]		
QoL Assessments:											
EQ-5D-5L[j,cc]		X		X[dd]		X[dd]	X[dd]	X			
ABQOL[j,cc]		X		X[dd]		X[dd]	X[dd]	X			
GTI[j]		X		X[ee]		X[ee]	X[ee]	X			
IMP self-administration training[ff]				X		X					
IMP administration[gg]		[redacted]		X	X	X			X[b]		
PDAI[j]	X	X	X	X		X	X	X	X	X	X

Trial Period	Screening	Treatment						EoS/ ED[a]	UNS[b]	Follow-up	
		V1 (BL)	V2	Observational visits	IMP admin only visit	Observational visits					
Visit Number				Weekly on-site visits until CR[c]	Weekly home or on-site visits until CRmin[d]	On-site visits every 4 weeks until CRmin	On-site visits every 4 weeks after CRmin until W31	W31		Follow-up W34	Follow-up W38[e]
Trial Day/Week	D-21 to D-1	D1 (W1)	D8 (W2)	D15 (W3) until CR	CR until CRmin	CR until CRmin	CRmin until W31	W31		EoS/ED +3W	EoS/ED +7W
Visit Window		±0 days	±2 days[f]	V1 + 7× ±2 days[f]				±2 days[f]		±3 days[f]	
Disease assessment[hh]			X	X		X	X	X	X	X	X
Prednisone taper[ii]				X	X	X	X	X	X	X	X
AE monitoring	Continuous monitoring										

ABQOL=Autoimmune Bullous Disease Quality of Life; admin=administration; BL=baseline; BMI=body mass index; CR=complete clinical remission; CRmin=CR on minimal therapy; D=day; DC=disease control; DIF=direct immunofluorescence; Dsg=desmoglein; ECG=electrocardiogram; ED=early discontinuation; EoC=end of consolidation; EoS=end of study; FSH=follicle-stimulating hormone; GTI=Glucocorticoid Toxicity Index; HLA=human leukocyte antigen; IgG=immunoglobulin G; ICF=informed consent form; IMP=investigational medicinal product; OLE=open-label extension; PDAI=Pemphigus Disease Area Index; PK=pharmacokinetics; RBC=red blood cells; UNS=unscheduled visit; WBC=white blood cells; W=week; V=visit

[a] All participants will complete EoS/ED, which will be the end of the trial for participants who enroll in the OLE trial ARGX-113-1905. Participants who do not enroll in the OLE trial ARGX 113 1905 will complete the follow-up visits at W34 and W38.

[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. See Section Section 8 for more information. Participants with new lesions or flare after achieving CR should return to weekly on-site visits until CR is achieved again.

[c] A minimum of 6 on-site visits, V1(BL)/W1 to W6, are required before switching to home administrations, even if CR is achieved earlier than W6. The W7 visit is the first eligible "IMP administration only" visit (refer to column "Weekly home or on-site visits until CRmin"), at home or on-site, if CR is achieved between W1 and W6.

[d] Home visits are allowed once participants achieve CR, but not before W7. The investigator should call the participant every 2 weeks until CRmin is achieved to confirm the participant is still in CR. On-site visits may continue at the investigator's discretion.

[e] W38 (follow-up visit 2) is the end of the trial for participants who do not enroll in the OLE trial ARGX-113-1905. The W38 follow-up visit will only be required for those participants who were still receiving IMP at least once from W27 onward. For participants who ended treatment prior to W27, W34 will be the end of the trial.

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

[g] No trial-related assessments can be initiated before the participant has provided a signed ICF.
[h] Only required if not available from medical history.
[i] Height and weight will be measured (and BMI will be calculated accordingly) at screening, at week W15 (or the next on-site visit if W15 does not coincide with an on-site visit), and EoS/ED. Weight will also be measured if there has been an obvious change since the last measurement.
[j] At visits in which IMP is administered, the assessment or procedure should be completed before dosing.
[k] A complete physical examination will be completed at each on-site visit. Vital sign measurements include systolic and diastolic blood pressure, heart rate, and body temperature. Supine blood pressure and heart rate will be measured using standard equipment after at least 10 minutes rest.
[l] ECG to be taken at W12. If the W12 visit does not coincide with an on-site visit, then the assessment should be performed at the next on-site visit. ECG (heart rate, PR, QT, and QRS interval) will be read centrally. QTcF and QTcB will be calculated.
[m] Randomization will take place on day 1 after all eligibility checks are confirmed (eg, PDAI) and before other baseline assessments are run, and prior to dosing.
[n] 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 test results are abnormal).
[o] Samples will be taken every week from V1(BL)/W1 to W9 and then every 4 weeks and at the visit where CR is observed. Once CR is achieved, samples will be taken every 4 weeks at on-site visits until EoS/ED. For participants achieving CR between V1(BL)/W1 and W6, samples will be taken weekly from W1 to W6 and then every 4 weeks at on-site visits until EoS/ED.
[p] A urine pregnancy test will be conducted and analyzed locally during on-site visits at least once every 4 weeks (before and after CR) and at the time of CR.
[q] Viral testing for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc), hepatitis B virus (HBV) DNA, hepatitis C virus (HCV) antibodies, HCV messenger RNA (mRNA), and human immunodeficiency virus (HIV) antibodies.
[r] At screening, a serum pregnancy test must be performed in women of childbearing potential or FSH test to confirm postmenopausal status.
[s] Clinical blood laboratory tests will include hematology and blood chemistry at all visits and international normalized ratio (INR) or activated partial thromboplastin time (aPTT) at screening only. The hematology profile includes hemoglobin, hematocrit, mean corpuscular volume (MCV), RBC count, platelet count, WBC count with differential. The blood chemistry profile includes sodium, potassium, calcium, hemoglobin A1c (HbA1c), creatinine, creatinine clearance, blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, gamma-glutamyl transferase (GGT), C-reactive protein (CRP), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol, triglycerides, uric acid, total protein, and albumin.
[t] For PK assessment, blood samples will be taken predose (within 2 hours before the start of IMP administration at visits where IMP is administered). An additional PK sample will be taken on D3 and on D11 (±1 day) until samples from 24 participants are obtained. At unscheduled visits blood samples for PK will only be taken if IMP is administered.
[u] At screening, total IgG will be measured as part of inclusion and exclusion criteria. The pharmacodynamic (PD) biomarkers total IgG and its subtypes (IgG1, IgG2, IgG3, and IgG4) will be measured centrally from a blood sample taken predose.
[v] An extra sample(s) will be taken for additional research (including vaccination antibodies and other additional research). The actual testing of vaccination antibodies depends on (a) whether a vaccination was given to the participant; (b) whether a test is available for the vaccination given to the participant; and (c) whether the sample requirements (serum, volume, frozen sample, storage duration) match the serum samples taken and reserved for this. Timepoints for analysis will be decided upon occurrence of vaccination during the study.
[w] Anti-drug antibodies to efgartigimod (in serum samples) and antibodies against rHuPH20 (in plasma samples) will be tested predose every 2 weeks from V1(BL)/W1 to W9 and then every 4 weeks at on-site visits and at the visit where CR is observed. Once CR is achieved, samples will be taken every 4 weeks at on-site visits until EoS/ED. For participants achieving CR between V1(BL)/W1 and W6, samples will be taken predose at V1(BL)/W1, W3, W5, the visit

where CR is observed, W10, and then every 4 weeks at on-site visits until EoS/ED. Neutralizing antibodies (Nab) will be tested for all confirmed positive ADA samples.

[x] Blood sampling for IgG autoantibody subtypes and specificity will be taken every 4 weeks (V1[BL]/W1, W5, W9, etc) and at the visit where CR is observed. Once CR is achieved, samples will be taken every 4 weeks at on-site visits until EoS/ED. For participants achieving CR between V1(BL)/W1 and W6, samples will be taken at V1(BL)/W1, W5, the visit where CR is observed, W10, and then every 4 weeks at on-site visits until EoS/ED. Serum aliquots from all time points will be used for IgG subtype and specificity analyses. For cytokines and complementary specificity analyses, aliquots from baseline, after 4 weeks (W5), W13 (or the visit at which CR is observed if before W13), and EoS/ED will be used.

[y] Samples for B- and T-cell populations and RNA transcriptional profiles will be performed at baseline, after 4 weeks (W5) and at W13 (or the visit at which CR is observed if before W13) and at EoS/ED.

[z] HLA/non-HLA genotyping will be performed at baseline and D15.

[aa] Two 4 mm skin biopsies, 1 peri-lesional and 1 non-lesional, will be collected solely based on voluntary participation at baseline and after healing of 80% of blisters (EoC) or at EoS/ED (in case EoC has not been achieved) for scientific purposes.

[bb] 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 timepoints.

[cc] Questionnaires are to be completed prior to any other activity.

[dd] Assessments will be performed at baseline, after 4 weeks (W5), W15, and EoS/ED visits. If the W15 visit does not coincide with an on-site visit, then the assessment should be performed at the next on-site visit.

[ee] The GTI assessment will be performed only at baseline, W15 and EoS/ED. If W15 does not coincide with an on-site visit, then the assessment should be performed at the next on-site visit.

[ff] Participants will be trained to self-administer IMP (foreseen in the OLE trial; not in the ARGX-113-1904 trial) during the first 4 visits as of V3 when IMP is administered; thereafter, training for self-administration is optional (only if needed).

[gg] IMP will be administered until CRmin. To ensure proper safety monitoring, participants should remain at the site for at least 1 hour after the first administration and for 15 minutes after subsequent administrations. Participants will be released according to their clinical status. For Germany-specific monitoring instructions, refer to Section 10.16.2.1. Participants who experience treatment failure, or flare after achieving CRmin, will be allowed to roll over into the OLE trial ARGX-113-1905 earlier than W31. Participants who do not roll over into trial ARGX-113-1905 will complete the treatment-free follow-up period.

[hh] Disease assessment parameters include disease control (DC), end of consolidation (EoC), complete clinical remission (CR), complete remission on minimal therapy (CRmin), complete remission off therapy (CRoff), flare, and treatment failure. Participants who have achieved CR and have new lesions should come to the clinic for a UNS for disease assessment.

[ii] 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).