STATISTICAL ANALYSIS PLAN

A Phase 3, Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Efficacy and the Safety of Efgartigimod (ARGX-113) PH20 Subcutaneous in Adult Patients With Primary Immune Thrombocytopenia

Protocol:	ARGX-113-2004
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Development phase:	Phase 3
Sponsor:	argenx
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SIGNATURE PAGE

Name and function	**Date (ddMMMyyyy) and Signature**
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PROTOCOL HISTORY

Protocol:		
Version or ID	**Date (ddMMMyyyy)**	**Impact of the changes on the statistical analysis**
Final 1.0	12SEP2020	NAP
Final 2.0	12JAN2021	NAP
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Final 4.0	15JUL2022	Change in key secondary endpoints hierarchical order and analysis (no impact on DSMB analysis) Removing additional safety laboratory tests
Final 5.0	17FEB2023	Change in allowed time window for collection of PK, PD and immunogenicity samples Additional other secondary endpoint not alpha controlled
Final 6.0	06APR2023	NAP

Japan specific protocol:		
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Final 2.1	21JAN2021	No
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Final 4.1	09AUG2022	No
Final 6.1	18APR2023	No

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Final 2.2	24MAR2021	No
Final 2.3	27APR2021	No
Final 3.1	09SEP2021	No
Final 4.1	12AUG2022	No
Final 4.2	16NOV2022	No
Final 6.1	27APR2023	No

Serum Pregnancy Test protocol:		
Version or ID	**Date (ddMMMyyyy)**	**Impact of the amendment on the statistical analysis**
Final 2.1	19APR2021	Serum Pregnancy-specific

LIST OF ABBREVIATIONS

ADA	anti-drug antibody
ADaM	analysis data model
ADSL	subject-level analysis dataset
ADY	relative day
AE	adverse event
AESI	adverse event of special interest
ALQ	Above the upper limit of quantification
anti-D	anti-RhD
ASH	American Society of Hematology
ATC	anatomical therapeutic chemical
BLQ	Below the lower limit of quantification
BMI	Body Mass Index
bpm	beats per minute
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum observed serum concentration
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CTCAE	common terminology criteria for adverse events
CTP	clinical trial protocol
C_{trough}	Serum concentration observed at pre-dose
CV%	coefficient of variation
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EoS	end of study
FACIT	Functional Assessment of Chronic Illness Therapy
FACT-Th6	Functional Assessment of Cancer Therapy questionnaire-Th6
FAS	Full analysis set
HR	heart rate/hazard ratio
ICF	informed consent form

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IgG	immunoglobulin G
IgGx	immunoglobulin G subtype
IMP	investigational medicinal product
[redacted]	[redacted]
[redacted]	[redacted]
IRR	injection-related reaction
IRT	interactive response technology
ISR	injection site reaction
ITP	immune thrombocytopenia
ITP-PAQ	ITP-Patient Assessment Questionnaire
IV	intravenous
IVD	in vitro diagnostic
IVIg	intravenous immunoglobulin
IWG	International Working Group
KM	Kaplan-Meier
LS	least square
M-CS	mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measurements
NAb	neutralizing antibodies
NAP	not applicable
NCI	National Cancer Institute
OD	optical density
OR	odds ratio
P-CS	physical component summary
PD	Pharmacodynamic(s); PD analysis set
PK	Pharmacokinetic(s); PK analysis set
PP	per protocol
PRO	patient reported outcome
PT	preferred term
PYFU	patient years of follow-up

qw	weekly
q2w	every other week
QoL	quality of life
QTc	corrected QT interval
QTcB	Bazett's corrected QT interval
QTcF	Fridericia's corrected QT interval
RhD	Rhesus D antigen
rHuPH20	recombinant human hyaluronidase PH20 enzyme
SAP	statistical analysis plan
SAE	serious adverse event
SAF	safety analysis set
SBP	systolic blood pressure
SC	subcutaneous
SCR	all screened participants analysis set
SD	standard deviation
SE	standard error
SGS CR	SGS Clinical Research
SMQ	Standardised MedDRA Queries
SoA	schedule of assessments
SOC	system organ class
SOP	standard operating procedure
STAT	statistics
TEAE	treatment-emergent adverse event
TPO-RA	thrombopoietin receptor agonist
VS	vital signs
WHO	World Health Organization
WI	work instruction

DEFINITION OF TERMS

(electronic) case report form ([e]CRF)	A printed, optical, or electronic document designed to record CTP required information to be reported to the sponsor for each study participant.
display	Analysis table, figure or listing.
equivalent name	Regrouping of generic terms which are considered equivalent, done by medical review by the sponsor. Equivalent names will be used in the analysis related to ITP therapies.
phase	Interval of time in the planned conduct of a study associated with a specific purpose: for example, screening, treatment, follow-up.
study drug	Pharmaceutical form of an active ingredient or placebo, being tested or used as a reference in a clinical study.
treatment-emergent abnormality /toxicity	Any postbaseline abnormality/toxicity that was not present at baseline (e.g. hemoglobin normal at baseline and grade 1 postbaseline; glucose low at baseline and high postbaseline; QTcFri]450; 480] ms at baseline and >500 ms postbaseline)

TABLE OF CONTENTS

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the final statistical analysis to be performed for the ARGX-113-2004 study.

This SAP covers the efficacy, safety, pharmacokinetic (PK), pharmacodynamics (PD), immunogenic and general characteristics parts 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 clinical trial protocol (CTP).

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[1], ICH-E6[2], and ICH-E9[3,4] guidelines.

1.1 STUDY OBJECTIVES

According to the CTP, the primary objective of this study is:

- To evaluate the efficacy of efgartigimod PH20 SC compared to placebo PH20 SC in achieving a sustained platelet count response in patients with chronic primary immune thrombocytopenia (ITP), with a sustained platelet count response defined as platelet counts of at least 50×10^9/L for at least 4 of the 6 visits between week 19 and 24 of the trial.

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

- To evaluate the efficacy of efgartigimod PH20 SC compared to placebo PH20 SC in overall platelet count response.
- To evaluate the incidence and severity of bleeding events while receiving treatment with efgartigimod PH20 SC compared to placebo PH20 SC.
- To evaluate the efficacy of efgartigimod PH20 SC compared to placebo PH20 SC in International Working Group (IWG) response
- To evaluate the safety and tolerability of efgartigimod PH20 SC administered weekly (qw) or every other week (q2w) compared to placebo PH20 SC.
- To evaluate the use of rescue treatment and changes in concurrent ITP therapy while receiving treatment with efgartigimod PH20 SC compared to placebo PH20 SC.
- To evaluate the effects of efgartigimod PH20 SC treatment on Quality of Life (QoL - Short Form-36 [SF-36]) measures and Patient Reported Outcomes (PRO) compared to placebo PH20 SC.
- To assess the immunogenicity of efgartigimod and rHuPH20.
- To assess the PK of efgartigimod PH20 SC.
- To assess the PD effects of efgartigimod PH20 SC.

According to the CTP, the exploratory objectives are:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

1.2 STUDY ENDPOINTS

1.2.1 Primary endpoint

The primary endpoint is the proportion of patients with chronic ITP with a sustained platelet count response defined as achieving platelet counts of at least 50×10^9/L for at least 4 of the 6 visits between week 19 and 24 of the study.

Participants who discontinue treatment prior to visit 24 due to lack of efficacy (e.g. more than 3 occurrences of rescue therapy) or due to an AE, and who have not achieved sustained platelet count response between week 19 and 24, are considered non-responders. Participants who receive rescue therapy at week 12 or later, or for whom dose and/or frequency of concurrent ITP therapies have increased at week 12 or later, are also considered non-responders.

1.2.2 Secondary endpoints

Key Secondary Efficacy Endpoints Subject to Alpha Control:

- Extent of disease control defined as the number of cumulative weeks over the planned 24-week treatment period with platelet counts of $\geq50\times10^9$/L in the chronic ITP population.
- Proportion of patients in the overall population (chronic and persistent ITP) with a sustained platelet count response defined as achieving platelet counts of at least 50×10^9/L for at least 4 of the 6 visits between week 19 and 24 of the study.
- Proportion of patients in the overall population achieving platelet counts of at least 50×109/L for at least 6 of the 8 visits between week 17 and 24 of the study.
- Incidence and severity of the WHO-classified bleeding events in the overall population.

Other Secondary Endpoints Not Subject to Alpha Control (overall population):

- Proportion of patients with overall platelet response defined as achieving a platelet count of $\geq50\times10^9$/L on at least 4 occasions at any time during the 24-week treatment period.
- Extent of disease control defined as the number of cumulative weeks until week 12, with platelet counts of $\geq50\times10^9$/L.

- Proportion of patients with overall platelet response defined as achieving a platelet count of $\geq 50 \times 10^9$/L on at least 4 occasions at any time until week 12.
- Mean change from baseline in platelet count at each visit.
- Time to response defined as the time to achieve 2 consecutive platelet counts of $\geq 50 \times 10^9$/L.
- The number of cumulative weeks over the planned 24-week treatment period with platelet counts ≥30×109/L and at least 20×109/L above baseline.
- In patients with baseline platelet count of <15×109/L, the number of cumulative weeks over the planned 24-week treatment period with platelet counts of ≥30×109/L and at least 20×109/L above baseline.
- Proportion of patients with an IWG response
- Proportion of patients with and IWG complete response
- Proportion of patients with an initial response
- Rate of receipt of rescue therapy (rescue per patient per month).
- Proportion of patients for whom dose and/or frequency of concurrent ITP therapies have increased at week 12 or later.
- Change from baseline in PRO (Functional Assessment of Chronic Illness Therapy [FACIT-Fatigue], Functional Assessment of Cancer Therapy questionnaire-Th6 [FACT-Th6]) and QoL (SF-36) at planned visits.
- Incidence and prevalence of antibodies to efgartigimod and rHuPH20.
- Titers of antibodies to efgartigimod and rHuPH20.
- Presence of neutralizing antibodies (NAb) against efgartigimod and rHuPH20, and titers of NAb against rHuPH20.
- Pharmacokinetic parameters of efgartigimod: serum efgartigimod concentration observed predose (C_{trough}).
- Pharmacodynamics markers: Total IgG and antiplatelet antibody levels.

Safety Evaluation:

- Incidence and severity of treatment-emergent adverse events (AEs), adverse events of special interest (AESIs), and serious adverse events (SAEs).
- Vital signs (VS), electrocardiogram (ECG), and laboratory assessments.

Exploratory Endpoints:

- [redacted].
- [redacted]
- [redacted].
- [redacted].

- [redacted].
- [redacted]

1.3 STUDY DESIGN

This is a phase 3, multicenter, randomized, double-blinded, placebo-controlled, parallel-group trial to evaluate the efficacy, safety, and effect on QoL/PRO of efgartigimod PH20 SC treatment in adult patients with primary ITP.

The total maximum trial duration per patient is up to 35 weeks:

- a screening period of up to 2 weeks
- a treatment period of 24 weeks
- an End-of-Treatment visit 1 week after visit 24
- a follow-up period of 8 weeks

The target population is adult patients with persistent or chronic primary ITP, having an average platelet count of $<30\times10^9$/L, and, at the start of the trial taking concurrent ITP treatment(s) and having received at least 1 prior therapy for ITP in the past, or not taking treatment for ITP but having received at least 2 prior treatments for ITP. If participants are receiving concurrent ITP therapies at baseline, these therapies should have been maintained at a stable dose and dosing frequency for 4 weeks before randomization.

As of week 12, the start or an increase in the dose and/or schedule of permitted concurrent ITP therapy is allowed for participants who have an "insufficient response" (ie, no platelet count of $\geq30\times10^9$/L in any of the visits during the last 4 weeks). These participants will be considered as "non-responders" for the primary endpoint analysis.

After confirmation of eligibility, the participants enter a 24-week treatment period and will be randomized to receive efgartigimod PH20 SC or placebo PH20 SC, qw from visits 1 to 4, and then from visits 5 to 16 either qw or q2w, adjusted according to their platelet counts. From visits 17 to 24, participants will be fixed on the dose schedule they were receiving at visit 16 or at the last visit at which IMP was administered before visit 16 (ie, either qw or q2w). Refer to CTP section 6.7 (dose regimen modification) and section 6.6.1 (permitted concomitant ITP therapies) for more details.

"Rescue therapy" is defined as an occurrence where the participant needs treatment with 1 or more rescue treatments. An "occurrence" is defined as a period of maximum 5 days where 1 or more rescue treatments are administered simultaneously or consecutively to the trial participant. The start date/time of the occurrence is the start of the administration of the first rescue treatment.

Rescue therapy is allowed postbaseline during the 24-week treatment period for participants with a platelet count of $<30\times10^9$/L and 1 of the following:

- an immediate risk of bleeding or a clinically significant bleeding, or wet purpura
- requirement for urgent or emergent surgery (elective surgeries must be postponed until trial completion)

The following rescue therapies are permitted:

- IV methylprednisolone up to 1 g/day×1-3 days, or oral dexamethasone up to 40 mg/day×1-3 days, or oral prednisone up to 1 mg/kg/day×1-2 days
- Intravenous immunoglobulin (IVIg): up to 1 g/kg/day×1-2 days
- IV anti-D: up to 50-75 mcg/kg/day×1-2 days
- platelet transfusions

Participants completing the 24-week randomized trial period will perform the end-of-treatment visit and can enter the open-label extension trial (OLE - ARGX-113-2005). If a participant has had an SAE during the ARGX-113-2004 trial, his/her eligibility for the ARGX-113-2005 trial should be evaluated by the investigator and the sponsor's trial physician. The decision to enroll the participant will be made case by case. The platelet counts from the ARGX-113-2004 trial will be taken into account to assess the dosing frequency in ARGX-113-2005.

Participants who complete the 24-week trial period but who do not enter the open-label extension trial, or participants who discontinue the trial early, with the exception of participants who withdraw their consent, will be followed for 8 weeks for ongoing safety and efficacy monitoring.

For participants who discontinue the trial early, all the assessments listed for the Early Discontinuation visit as specified in the schedule of assessments (SoA, see appendix 9.5), will be performed.

End-of-Study is defined as last participant last visit in the ARGX-113-2004 trial.

1.4 EXPECTED SAMPLE SIZE

Approximately 180 participants with chronic ITP and up to 39 participants with persistent ITP were planned to be randomized in a 2:1 ratio to receive efgartigimod PH20 SC or placebo PH20 SC, respectively.

Non-Japanese participants were stratified according to the following factors:

- History of splenectomy (yes versus no)
- Receiving concurrent ITP therapies at baseline (yes versus no)

For Japanese patients enrolled in sites in Japan, there was no stratification, ie, randomization was performed within the full set of Japanese patients.

The null and alternative hypotheses are defined as H_0: $\pi_1 = \pi_2$ versus H_A: $\pi_1 \neq \pi_2$, where π_1 and π_2 are the population probabilities to achieve a sustained platelet count response (primary efficacy endpoint) for participants with chronic ITP receiving placebo PH20 SC and for participants with chronic ITP receiving efgartigimod PH20 SC, respectively.

In the placebo PH20 SC group, the response rate of participants with chronic ITP who reach the primary endpoint is expected to be ≤5%, while the response rate of participants with chronic ITP in the efgartigimod PH20 SC group is expected to be 21.8% (i.e. $\pi_1 = 0.05$ and $\pi_2 = 0.218$), based on the observed response rates in trial ARGX-113-1801. Given these assumptions, a total of N = 180 randomized participants with chronic ITP will ensure a power of at least 80% to reject the null hypothesis at a 1-sided significance level α of 0.025, based on Fisher's exact test.

For the first key secondary endpoint "extent of disease control" assuming distribution for cumulative number of weeks of disease control over the planned 24-week treatment period with platelet counts of $\geq 50 \times 10^9$/L in the chronic ITP population similar to those observed in ARGX-113-1801, a total of N=180 participants will ensure a power of >99% (2-sided α of 0.05), conditionally on reaching the primary endpoint, to detect a significant difference between both treatment groups. For ensuring a power of at least 90%, a total number of N=75 participants would be needed, given these assumptions. Calculations are based on the Wilcoxon-Mann-Whitney test, where the O'Brien-Castelloe approach[5] was taken to compute the power, taking into account a 2:1 allocation ratio to receive efgartigimod PH20 SC versus placebo PH20 SC.

1.5 RANDOMIZATION AND BLINDING

Approximately 180 participants with chronic ITP and up to 39 participants with persistent ITP will be randomized in a 2:1 ratio to receive efgartigimod PH20 SC or placebo PH20 SC, respectively. The results of all screening procedures have to be available prior to randomization (visit 1) to determine the eligibility for randomization into the study. Randomization should be performed as soon as possible after screening with a maximum of 2 weeks, however only after confirmation of eligibility of the patient. If a patient meets all the eligibility criteria and after approval from the sponsor, he/she will be randomized via interactive response technology (IRT). If a patient is not eligible, the patient should be recorded as a screen failure in the IRT system.

ARGX-113-2004 is a randomized, double-blinded, placebo-controlled study with limited access to the IMP treatment assigned.

1.6 INTERIM ANALYSIS

Not applicable.

1.7 SOFTWARE

SAS version 9.4 or higher will be used for programming.

1.8 VALIDATION MODEL

SGS Clinical Research (SGS CR) statistics (STAT) and pharmacokinetics (PK) standard operating procedures (SOPs) and work instructions (WIs) as effective at the time of the activity 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 validated according to model B: review by an independent person. The ADaM dataset ADSL, the primary endpoint, and following key secondary endpoints: extent of disease control and bleeding events will be validated according to model C: independent programming (see SOP.STAT.020 and SOP.PK.020).

2. GENERAL METHODOLOGY

2.1 ANALYSIS SETS

2.1.1 Analysis sets

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

Table 1: Analysis sets

All screened participants set (SCR):	Participants who *signed an informed consent* to participate in this study
Full analysis set (FAS):	All randomized participants
FAS-chronic	Participants from the full analysis set including only participants with chronic ITP
Per-Protocol (PP):	Participants from the full analysis set, excluding the participants having any major protocol deviations
PP-chronic	Participants from the PP analysis set including only participants with chronic ITP
Safety analysis set (SAF):	All participants who received at least 1 dose or part of a dose
PK analysis set (PK):	Safety analysis set excluding placebo participants and including participants with at least one serum post dose PK measurement
PD analysis set (PD):	Safety analysis set including participants with at least one serum post dose PD measurement

Notes:

- Having signed an informed consent is defined as having a complete informed consent signature date in the database.
- Randomized is defined as having a complete randomization date in the database or any information to confirm randomization.

The efficacy analyses will be performed on the FAS or FAS-chronic where applicable. Sensitivity analyses of primary and key secondary efficacy endpoints will be performed on the PP or PP-chronic where applicable. General characteristics, safety and immunogenicity analyses (ADA, Antibodies, NAb) will be performed on the SAF. PK analysis will be performed on the PK. PD analysis will be performed on the PD.

2.1.2 As planned versus as actual analysis

For analyses performed on the SAF, PK and PD the actual treatment of the participant received will be considered. For analyses on the FAS, and PP, the planned treatment of the participant will be considered.

Only complete misallocation to a different treatment will lead to differences between planned and actual treatment in the analysis. Other occasional misdosings will not lead to a difference between planned treatment and actual treatment in the analysis.

2.2 PHASES AND TIME POINTS

2.2.1 Phases and periods

All events and assessments will be allocated to phases (see Table 2). The treatment phase consists of 24 weeks where all participants will receive injections of efgartigimod PH20 SC or placebo PH20 SC, including the End-of-Treatment visit, 1 week after visit 24. Only for participants who discontinue from the study or do not roll-over to ARGX-113-2005 a follow-up phase of 8 weeks is foreseen.

Table 2: Phase definition

Phase	Start	End[a]
Screening	Date of signing the informed consent form (ICF), with 00:00 added as time part.	First administration of the investigational medicinal product (IMP) date/time - 1 minute or End-of-Study date, with 23:59 added as time part (for participants not treated)
Treatment	First administration of the IMP date/time	End-of-Treatment visit end date, with 23:59 added as time part (for participants completing the treatment phase and not rolling over to 2005), or End-of-Study date, with 23:59 added as time part (for participants completing the treatment phase rolling over to 2005) or Early Discontinuation visit date[b], with 23:59 added as time part (for participants early discontinuing from trial during the treatment phase).
Follow-up	Early Discontinuation visit date + 1 day, with 00:00 added as time part or End-of-Treatment visit date + 1 day, with 00:00 added as time part (for participants completing the treatment phase but not rolling over to study ARGX-113-2005).	End-of-Study date, with 23:59 added as time part

[a] The last phase of a participant ends with the End-of-Study date, with 23:59 added as time part
[b] If no Early Discontinuation visit was performed, use the End-of-Treatment date.

Table 3: Phase and period definition for the analysis of injection site reactions

Phase	Period	Start	End[a]
Treatment + Follow-up	Week 1-12	First efgartigimod administration date/time	First efgartigimod administration date + 83 days, with 23:59 added as time part
	Week 13-24	First efgartigimod administration date + 84 days, with 00:00 added as time part	First efgartigimod administration date + 167 days, with 23:59 added as time part

Week 24–36	First efgartigimod administration date + 168 days, with 00:00 added as time part	First efgartigimod administration date + 251 days, with 23:59 added as time part

[a] The last period ends on the date of End-of-Treatment visit date for participants completing the study and rolling over to study ARGX-113-2005, on the End-of-Study date with 23:59 added as time part for participants early discontinuing and for participants completing the study but not rolling over to study ARGX-113-2005

Adverse events (AEs) and concomitant medications will be allocated to phases as described in sections 5.1.2 and 3.5.2 respectively. All other assessments will be allocated to phases based on the assessment date/time.

In case of (partially) missing date(time) fields disabling allocation or date(time) equal to dosing date(time), information from visit label and protocol SoA will be used to allocate to the correct phase and period. If this is not possible, assessments will be handled as follows:

- Treatment phase versus screening phase: assessments will be allocated to the treatment phase unless the available parts of the assessments start or stop date(time) provide evidence for allocating to the screening phase.
- Follow-up phase versus treatment phase: assessments will be allocated to the treatment phase unless the available parts of the assessments start or stop date(time) provide evidence for allocating to the follow-up phase.

2.2.2 Baseline and change from baseline

The baseline value is defined as the last available non-missing value prior to first administration of the IMP. For total IgG, only results from the IVD assay will be considered, excluding screening samples.

Vital signs (VS) assessments on day 1 are considered pre-dose (no assessment time collected, pre-dose per protocol).

For parameters related to questionnaires, the baseline is the last value before or at the day of first administration of the IMP, independent of the time of administration.

Change from baseline at time point t = value at time point t – baseline value.

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

- When baseline value is not zero: 100*((value at time point t – baseline value) / baseline value)
- When both baseline value and value at time point t are zero: 0
- When baseline value is zero and value at time point t is not zero: not calculated

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 as follows:

- For assessments in screening and treatment phase: the date of first administration of study drug.
- For assessment in follow-up phase: the start date of the follow-up phase.

2.2.4 Analysis visits

All assessments, including unscheduled assessments, will be allocated to analysis windows. Tables and listings will present the analysis windows as defined below, not the CRF visits. Assessments will be allocated using their relative day in the phase (see section 2.2.3).

Table 4: Analysis visits

Phase	Analysis window	Target ADY	Lower limit ADY	Upper limit ADY
Screening	Screening[d]	-14	-INF	1
Treatment	Baseline[d]	1	-INF	1[e]
	Week 1	8	1[e]	11
	Week 2	15	12	18
	Week 3	22	19	25
	Week 4	29	26	32
	Week (4 + x[a])	29 + (x[a]*7 days)	26 + (x[a]*7 days)	32 + (x[a]*7 days)
	…	…	…	…
	Week 23	162	159	165
	Week 24	169	166	n[b]
Follow-up				
	SEFU Week 4	28	1	42
	SEFU Week 8	56	43	n[c]

[a] x=1,…,18; [b]Relative day of End-of-Treatment phase; [c]Relative day of end of follow-up phase
[d] As the interval of screening and baseline are overlapping, the same assessment can be attributed to both timepoints.
[e] An assessment on day 1 will be attributed to baseline in case it is before the injection, to Week 1 otherwise, unless the assessment is related to questionnaires for which time will not be considered and therefore be allocated to baseline.

Table 5: Analysis visits for total IgG and PK

Phase	Analysis window	Target ADY	Lower limit ADY	Upper limit ADY
Treatment	Baseline	1	-INF	1[a]
	Week 1	8	1[a]	11
	Week 2	15	12	18
	Week 3	22	19	29
	Week (3 + x[b] *2)	22 + (x[b] *14)	16 + (x[b]*14)	29 + (x[b]*14)
	Week 23	162	156	165
	Week 24	169	166	n[c]
Follow-up				
	SEFU Week 4	28	1	42
	SEFU Week 8	56	43	n[d]

[a] An assessment on day 1 will be attributed to baseline in case it is before the injection to Week 1 otherwise. In addition, baseline pre and post dose PK assessments will be attributed to the baseline.
[b] x ranges from 1 to 9.
[c] relative day of end of treatment phase
[d] relative day of end of FU phase

Table 6: Analysis visits for anti-platelet antibodies

Phase	Analysis window	Target ADY	Lower limit ADY	Upper limit ADY
Treatment	Baseline	1	-INF	1[a]
	Week 7	50	1[a]	78
	Week 15	106	79	134
	Week 23	162	135	165
	Week 24	169	166	n[b]

[a] An assessment on day 1 will be attributed to baseline in case it is before the injection to Week 7 otherwise.
[b] relative day of end of treatment phase

Table 7: Analysis visits for immunogenicity

Phase	Analysis window	Target ADY	Lower limit ADY	Upper limit ADY
Screening	Screening[a]	-14	-INF	1
Treatment	Baseline	1	-INF	1[b]
	Week 3	22	1	36
	Week (3 + x[c] *4)	22 + (x[c] *28)	9 + (x[c]*28)	36 + (x[c]*28)
	Week 23	162	149	165
	Week 24	169	166	n[d]
Follow-up				
	SEFU Week 4	28	1	42
	SEFU Week 8	56	43	n[e]

[a] As the interval of screening and baseline are overlapping, it may be that the same assessment will be attributed to both timepoints.
[b] An assessment on day 1 will be attributed to baseline in case it is before the injection to Week 3 otherwise.
[c] x ranges from 1 to 4.
[d] relative day of end of treatment phase
[e] relative day of end of FU phase

Baseline is defined in section 2.2.2.

Per parameter and analysis window, the value closest to the target ADY will be used in analysis tables, other values will only be listed. If more than 1 value is located at the same distance from the target, then the value 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. Missing values are removed before the selection is made.

For efficacy only: In case of (partially) missing date/time fields, the CRF visit label will be used to allocate to the correct analysis visit (VISIT2 becomes Week 1, VISIT3 becomes Week 2 etc.). For VISIT = END_OF_STUDY_EARLY_DISCONTINUATION the corresponding analysis visit from ADSV should be used.

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 postbaseline values, including unscheduled assessments will be considered when deriving the worst-case analysis visit.

2.3 IMPUTATION AND ROUNDING RULES

2.3.1 Missing values

Missing values for safety will not be imputed (ie, observed cases analysis). For imputation on missing values related to efficacy, see appropriate section of the applicable efficacy endpoint.

2.3.2 Values below or above a threshold

Anti-drug antibodies (ADA) against efgartigimod: titer of positive ADA samples reported as 'negative titer' (see section 4.4.2.1) will be imputed by 1. Antibodies (Ab) against rHuPH20: positive rHuPH20 Ab samples reported as 'negative titer' (see section 4.4.2.2) will be imputed by 5. NAb against rHuPH20: positive rHuPH20 NAb samples reported as 'negative titer' (see section 4.4.2.4) will be imputed by 100. Listings will always present 'negative titer'.

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.

PK concentrations below the detection limit will be flagged as Below the lower Limit of Quantification (BLQ) in the listings. For descriptive statistics by scheduled timepoint, BLQ values will be set to zero. For Above the upper Limit of Quantification (ALQ) values, all ALQ values will be set to the upper limit of quantification for the descriptive statistics by scheduled timepoint. Listings will always present the original value.

Total IgG values expressed as below or above the limit of quantification (BLQ or ALQ, respectively) will be imputed by the value of the detection limit itself. For participants with a baseline total IgG value below/above the quantification limit, total IgG will be excluded from the statistical analyses involving change and percent change from baseline. Listings will always show the non-imputed values.

2.3.3 Rounding

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

- Time since diagnosis and BMI will be rounded to 1 decimal.
- Ratios will be rounded to the number of decimals of the parameter with the least number of decimals.
- PD and safety laboratory results will be rounded to a maximum of 3 decimals.

2.3.4 Outliers

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

2.4 PRESENTATION OF RESULTS

All descriptive outputs described in this SAP will be repeated by origin (Japanese / Non-Japanese / overall as defined in the study protocol) to support the summary document of 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. Note that these additional outputs will not be included in the submissions to other health authorities.

To support the marketing authorization application in China, all descriptive outputs in this SAP, except PK and PD, will be repeated on the Mainland Chinese and East Asian subpopulations. PK and PD analyses will be repeated by origin (Mainland Chinese / Non-Mainland Chinese and East Asian / Non-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 and with a race “Asian”.

These additional descriptive outputs will not be included in the submissions to other health authorities.

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 median, minimum, Q1, Q3, and maximum. In addition, for PD, the standard error (SE) will be provided. For efficacy and descriptive tables by analysis visit, the standard error (SE) and 95% CI will be provided in addition.

Descriptive statistics for PK concentrations will include n (number of observed values), arithmetic mean, SD, median, minimum and maximum, coefficient of variation (CV%), geometric mean and geometric CV%.

Serum concentrations will be reported as received by the bioanalytical laboratory. Descriptive statistics will be presented with 3 significant digits in µg/mL (where appropriate), except values ≥ 1000 which will be presented without the decimals and rounded to the nearest integer. If at least one BLQ value is reported at a specific time point, the GM and geometric CV% for that time point will not be calculated. In addition, if more than half of the values per time point are BLQ, the arithmetic mean will be reported as BLQ and SD, CV%, GM, and geometric CV% will not be calculated.

For event-type safety data, the number and percentage of participants with an event will be shown. The denominator will be the number of all participants in the analysis set per treatment and phase.

For frequency tabulations and cross-tabulations, the denominator will be the number of all participants in the analysis set per treatment. For tables where results are shown by analysis visit, the denominator will be the number of 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 postbaseline 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:

- efgartigimod PH20 SC
- placebo 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 Ordering in tables and listings

All tables 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 PH20 SC treatment group will always be shown first, then the placebo PH20 SC treatment group.

3. GENERAL CHARACTERISTICS ANALYSES

3.1 PARTICIPANT DISPOSITION

The following participant data will be tabulated:

- The number of participants in each analysis set
- The number and percentage of participants by country and site
- The number and percentage of participants for each analysis visit.
- Descriptive statistics of the phase duration (see section 2.2.1), calculated as phase end date – phase start date + 1 day
- The number and percentage of screen failures, of participants randomized but not treated and of participants who completed or discontinued the trial as documented on the study termination page and the number and percentage of participants for each trial discontinuation reason (including reasons for screen failures).
- 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-113-2005.

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

3.2 PROTOCOL DEVIATIONS AND ELIGIBILITY

The number and percentage of participants with major and minor protocol deviations will be tabulated overall and by class of deviation.

All available information concerning major and minor protocol deviations, violations on eligibility criteria, participants not treated and participants excluded from the efficacy analysis will be listed.

3.3 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

3.3.1 Available data

The following parameters will be available:

- Demographics: sex at birth, age at informed consent, race, ethnicity, height, weight at baseline, year of birth, date of signing ICF.
- Baseline disease characteristics: date of diagnosis, history of splenectomy (yes versus no), receiving concurrent ITP therapies at baseline (yes vs. no), history of gastrointestinal bleeding (yes versus no + number of times), history of intracranial hemorrhage (yes versus no + number of times), history of hemorrhage for coagulation disorder (yes versus no + number of times), participant with chronic or persistent ITP, received prior ITP therapy (yes versus no), baseline platelet level, baseline SF-36 (v2), baseline PRO: FACT Th6 questionnaire (Total FACT Th6 score) and FACIT fatigue Scale (Total FACIT Fatigue score), WHO-classified bleeding events.

3.3.2 Derivation rules

The following parameters will be derived:

- Body mass index (BMI) at baseline (kg/m²) = (body weight at baseline (kg)) / (height at screening (m))²
  Note: The BMI will be recalculated and rounded as detailed in section 2.3.3, even when already available in the database.
- Age category at baseline: 18-<65 years; 65-<75 years; ≥75 years
- Weight category at baseline: <50 kg, 50-<75 kg, 75 – <100 kg, 100 – <125 kg, ≥ 125 kg
- Baseline platelet level category: ($<15\times10^9$/L versus $\geq15\times10^9$/L)
- Ethnicity category: Japanese versus non-Japanese (including Hispanic or Latino, Not Hispanic or Latino, and Not allowed to ask per local regulations)
- Region:
  - East Asia: China, Japan, Korea, Taiwan
  - Europe: EU and EEA countries, EFTA countries (Norway, Iceland, Liechtenstein and Switzerland) and UK
  - Latin America (LATAM): Mexico, Argentina, Chile
  - Middle East and Africa (MEA): Israel, Jordan, Tunisia, Turkey, South Africa
  - non-EU Central and Eastern Europe (non-EU CEE): Russia, Georgia, Serbia, Ukraine
  - North America: United States, Canada
  - Rest of the world: any countries not mentioned above
- Time since diagnosis (years): (date of ICF – date of initial diagnosis)/365.25. Partially missing dates of diagnosis will be imputed as follows:
  - Missing start day will be imputed with 1
  - Missing start day and month will be imputed with 1JAN

  Note: Result will be rounded as detailed in section 2.3.3.
- Baseline WHO bleeding score category: No bleeding, Grade 1, ≥ Grade 2, calculated as the maximum bleeding scale over the different body systems available at baseline.
- See section 3.5.2 for categories of type of ITP therapy.
- Number of prior ITP therapies: derived as the distinct number of equivalent ITP therapies (equivalent name, see also section 3.5.2) that stopped before first IMP dose date
- See section 4.1.2.3 for the definitions of ITP-PAQ, FACT Th6, FACIT and the WHO-classified bleeding events.
- Recruitment cohort: wave 1 (signed ICF before the protocol amendment 4 of 15Jul2022) / wave 2 (signed ICF after 15Jul2022)

3.3.3 Presentation of results

Demographics will be presented using descriptive statistics for age, height, weight and BMI at baseline, and frequency tabulations for age category, weight category at baseline, sex at birth, race, ethnicity, ethnicity category, region and recruitment cohort.

Baseline disease characteristics will be presented using descriptive statistics for:

- time since diagnosis
- platelet level
- SF-36 (v2): norm-based P-CS and M-CS scores
- total FACT-Th6 score
- total FACIT-Fatigue score
- number of prior ITP therapies
- number of types of prior ITP therapies

Baseline disease characteristics will be presented using frequency tabulations for:

- baseline platelet level category
- history of splenectomy
- receiving concurrent ITP therapies at baseline
- history of gastrointestinal bleeding
- number of events of gastrointestinal bleeding
- history of intracranial hemorrhage
- number of events of intracranial hemorrhage
- history of hemorrhage from coagulation disorder
- number of events of hemorrhage from coagulation disorder
- participant with chronic or persistent ITP
- received prior ITP therapy (yes/no), number of prior ITP therapies, number of prior ITP therapies received category (<3, ≥3)
- number of types of prior ITP therapies
- WHO bleeding score
- WHO bleeding score category

All demographic data and baseline disease characteristics will be listed. History of splenectomy, history of gastrointestinal bleeding, history of intracranial hemorrhage and history of hemorrhage of coagulation disorder will be shown on a separate listing specific for ITP history.

3.4 MEDICAL HISTORY AND CONCOMITANT DISEASES

3.4.1 Available data

Medical history findings are coded into system organ classes (SOC) and preferred terms (PTs) using the medical dictionary for regulatory activities (MedDRA), version 26.0. For each finding, a start and stop date or ongoing flag is collected.

For primary ITP history the following data are collected:

- Date of initial diagnosis
- Date of confirmation per American Society of Hematology (ASH) criteria
- Persistent/chronic ITP

In-patient hospitalization for the management of ITP during the study, for at least an overnight stay, is recorded separately. The hospitalization date and time of admission and discharge is collected.

3.4.2 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

Duration of hospitalization (days):

- Date of discharge - date of admission + 1 day
- Study discontinuation date – date of admission + 1 day (when no date of discharge is available)

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

3.4.3 Presentation of results

Prior splenectomy events had to be captured as ITP therapy in the clinical database and will therefore not be shown in the medical history displays.

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 gastrointestinal bleeding, intracranial hemorrhage and coagulation disorder hemorrhage
- The number and percentage of participants with findings by SOC and PT

For hospitalizations for ITP management the following data will be shown:

- Incidence of hospitalizations
- Summary statistics of the duration of hospitalizations

All medical history, prior vaccinations, primary ITP history, concomitant disease data and hospitalizations will be listed.

3.5 PRIOR AND CONCOMITANT THERAPIES

3.5.1 Available data

All therapies are coded using the WHO-DRUG Dictionary version MAR2023 (Global) Format B3. Anatomical therapeutic chemical (ATC) selection is performed. The 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.

3.5.2 Derivation rules

Based on their start and stop date, therapies will be allocated into 1 or both of the following categories:

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

A medication that started before the first IMP dose date and continued during the study will be classified as both prior and concomitant.

The ITP-specific therapies will be allocated to the following categories:

- Prior ITP therapy: stopped prior to first IMP dose date
- Continued concurrent ITP therapy: started prior to first IMP dose date and continued on or after first IMP dose date
- New concurrent ITP therapy: started on or after first IMP dose date or therapy of which the mean daily dose has increased compared to baseline

ITP therapy records with the same equivalent name will be combined to do the allocation in case the end and start date overlap or are subsequent, the start date of the next record being one day after the end date of the current record. For the combination of records, records with (partially) missing dates will be excluded. Therapies with (partially) missing dates will be allocated to each category unless the available parts of the therapy start or stop date or the started prior to trial/ongoing at end of trial flag provide evidence not to do so.

The type of ITP therapy will be allocated to the following categories according to the medical review performed by the sponsor: corticosteroids / IVIG, anti-D / fostamatinib / splenectomy / TPO-RA/ dapsone / danazol / anti-CD20 / other immunosuppressants. Therapies that cannot be assigned to any of these 9 categories will be categorized to type 'Other'.

Rescue ITP therapy will be allocated to the following categories:

- methylprednisolone, dexamethasone, prednisolone, prednisone: selection based on ATC4 = “H02AB”
- immunoglobulins given IV (IVIg): selection based on ATC4 = “J06BA”
- IV anti-D: selection based on CMDECOD = ‘ANTI-D IMMUNOGLOBULIN’, ‘SPECIFIC IMMUNOGLOBULINS’
- platelet transfusions: selection based on CMDECOD = ‘PLATELETS, CONCENTRATED’
- other: rescue medications that are not in any of the 4 previous categories

Occurrence of rescue therapy: a period of maximum 5 days where 1 or more rescue treatments are administered simultaneously or consecutively to the study participant. The start date/time of the occurrence is the start of the administration of the first rescue treatment. If this period exceeds the maximum of 5 days, a new occurrence will be assigned, with start date/time of the occurrence being the start date 5 days after the initial occurrence start date.

More information on the use of rescue therapy can be found in the CTP section 6.6.4.

3.5.3 Presentation of results

Non-ITP prior and concomitant therapies, including vaccines, will be tabulated (separately), by ATC class (level 1 and 3) and generic term.

Prior and concurrent ITP therapy will be tabulated by ATC class (level 1 and 3) and equivalent name (or generic term if 'other'). Rescue ITP therapies will be tabulated by category and generic term.

Prior ITP therapy and concurrent ITP therapy will also be tabulated (separately) by type of ITP therapy and equivalent name (or generic term if 'other').

All prior and concomitant therapies data will be listed with detailed information about ATC classes. Similarly, prior ITP therapy, concurrent ITP therapy, vaccines, and rescue ITP therapy will be listed separately.

3.6 STUDY DRUG ADMINISTRATION

3.6.1 Available data

For each study drug administration, the start and end date/times, and the volumes will be recorded.

Data on self-administration by participant or their caregiver will also be collected.

3.6.2 Derivation rules

The following parameters will be derived:

- Number of administrations: sum of all administrations of study drug.
- Compliance (%): 100*(number of doses received/number of doses expected); Compliance will be calculated over the 24-week treatment period and will take into account the weekly or every other week administration.

  Notes:
  - Dosing is expected at a visit except if the reason not done is due to biweekly administration, due to platelet count > 150 or platelet count > 400 or rescue therapy. As some of these reasons are entered as free text in the eCRF, the list of reasons not done will be reviewed by the sponsor and text to be considered as a valid reason will be flagged.
  - For participants who discontinued early, visits on or after treatment discontinuation are not considered in the compliance calculation.
- Number and percentage of participants who ever switched to every other week dosing

- The dosing regimen is derived for each analysis visit until treatment discontinuation as follows:
  - The first 4 weeks (ie, baseline to week 3) are always considered as weekly.
  - Every other week dosing starts at the administration not done due to biweekly administration or at the performed visit subsequent to the one not done due to platelet count > 150 or platelet count > 400
  - Every other week dosing ends at the date of an administration not done due to rescue medication or at the date of the second of at least two consecutive administrations of a dose
  - All other administrations done in between every other week periods are considered as weekly.

  Note: reasons for not dosing can contain free text and will therefore be categorized by the sponsor. This categorization will be used for the derivation of the dosing regimen.
- Fixed dosing regimen (weekly, every other week): derived for participants still being dosed at or after CRF visit 17:
  - Weekly: if participant received rescue therapy during the period of 28 days prior to visit 16
  - Else, the dosing regimen will equal the dosing regimen at analysis week 16
- Cumulative duration of every other week dosing: number of weeks for which the participant was on the every other week dosing regimen
- Percentage of time of every other week dosing: 100*(cumulative duration of every other week dosing/number of weeks up to and including week 24. Weeks after treatment discontinuation will not be considered.
- completing training: the final outcome for a participant/caregiver is considered completed if the participant/caregiver had passed at least 4 trainings in the last 10 weeks between analysis week 14 and 23 and is being considered capable at least once after 4 or more trainings

3.6.3 Presentation of results

Overall number of administrations, compliance, number of participants who ever switched to every other week dosing, cumulative duration of every other week dosing and dosing regimen between week 17 and 24 will be summarized using descriptive statistics.

A frequency table will be created showing IMP training information, for participants and caregivers separately:

- The number and percentage of participants/caregivers receiving training (using as denominator the total number of participants per treatment group in the safety analysis set)
- Total number of training visits received per participant/caregiver. Express as number and percentage of participants/caregivers receiving 1, 2, 3, etc. trainings (using as denominator the total number of participants/caregivers that received training per treatment group in the safety analysis set)
- Number and percentage of participants/caregivers considered capable to perform self-administration during at least one training visit (using as denominator the total number of participants/caregivers that received training per treatment group in the safety analysis set)
- Minimum number of training visits required by participant/caregiver to be considered capable for first time to perform self-administration. Express as number and percentage of participants/caregivers requiring 1, 2, 3, etc. trainings (using as denominator the total number of participants/caregivers that received training per treatment group in the safety analysis set).
- Number and percentage of participants/caregivers completing training. The denominator is the total number of participants per treatment group in the safety analysis set.

All study drug administration data and self-administration training data (by participant and caregiver) will be listed.

4. EFFICACY, PHARMACOKINETIC, PHARMACODYNAMIC AND IMMUNOGENICITY ANALYSES

4.1 EFFICACY

4.1.1 Available data

Efficacy will be assessed using platelet count, WHO-classified bleeding events, PROs (FACIT-Fatigue, FACT-Th6), QoL (SF-36, ITP-PAQ), [redacted]

4.1.2 Endpoints and derivation rules

All efficacy endpoints will be analyzed on the overall FAS population or a subset of participants in the FAS with chronic ITP. 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 4.1.2.3) will be derived using all possible measurements and not only the one closest to the target of the analysis visit. Only visits during the treatment phase will be considered for defining the different responses and time to response parameters.

4.1.2.1 PRIMARY ENDPOINT

The primary endpoint is the proportion of participants with a sustained platelet count response (week 19 – 24) within the adult population with chronic ITP.

A participant is considered a responder, ie, has a sustained platelet count response, if he/she shows platelet counts of at least 50×10^9/L for at least 4 of the 6 analysis visits between weeks 19 and 24 of the study. ($\geq50\times10^9$/L prim resp).

The main analysis on the primary endpoint will use the 'composite variable strategy' in case of main intercurrent events using the Cochran-Mantel-Haenszel test (see also section 4.1.3.2). This strategy implies that when a main intercurrent event occurs, a participant is considered a non-responder, if the participant has not achieved sustained platelet count response before the occurrence of the main intercurrent event. This happens in the following situations:

- early discontinuation of treatment (prior to week 24) due to lack of efficacy (DSDECOD = "Lack of efficacy") or due to an AE
- initiation of rescue therapy at week 12 or later: relative day of start date of rescue medication ≥ lower limit ADY of analysis visit corresponding to Week 12

- increase of dose and/or frequency of concurrent ITP therapies or start of a new concurrent ITP therapy at week 12 or later:
  - (if start date concurrent ITP therapy ≥ lower limit ADY of analysis visit corresponding to Week 12) and (dose > previous dose of the specific ITP therapy OR frequency > previous frequency of the specific ITP therapy)

    AND
  - (if start date concurrent ITP therapy ≥ lower limit ADY of analysis visit corresponding to Week 12) and (dose > dose of the specific ITP therapy at baseline OR frequency > frequency of the specific ITP therapy at baseline)

    OR
  - new ITP therapy

  Note: if for frequency a change is detected, but it is not clear whether a real increase has taken place, it will be considered worst-case and analysed as increase (e.g.: Baseline value 'QD' changed to e.g. 'at will', 'as needed'; Baseline value 'As needed' changed to e.g. 'QD, ', 'continuous'). Dose and frequency will always be considered in combination (ie, mean daily doses will be compared).

Missing values for reasons other than the main intercurrent events, will be imputed as described in section 4.1.2.5 (approach 1).

A complementary analysis for this primary analysis will use the 'treatment policy strategy' where these main intercurrent events are handled differently.

The occurrence of the intercurrent event is irrelevant: the values for the platelet counts are used regardless of whether or not the intercurrent event occurs. For this strategy the data will be used as is, without taking into account intercurrent events. Missing values for reasons other than the main intercurrent events, will be imputed as described in section 4.1.2.5 (approach 1).

4.1.2.2 KEY SECONDARY ENDPOINTS (ALPHA CONTROLLED)

The following key secondary endpoints, which will be tested in hierarchical order (see section 4.1.3.1), are defined:

1) Extent of disease control defined as the number of cumulative weeks over the planned 24-week treatment period with platelet counts of $\geq 50 \times 10^9$/L in the chronic ITP population.

Derivation: total number of analysis visits during the treatment phase with platelet counts of $\geq 50 \times 10^9$/L.

Handling of intercurrent events will be as follows:

- early discontinuation of treatment (prior to week 24) due to lack of efficacy or due to an AE: platelet count measured strictly after this intercurrent event will be handled as $<50\times10^9$/L.
- increase of dose and/or frequency of concurrent ITP therapies or start of a new concurrent ITP therapy: platelet count measured strictly after this intercurrent event will be handled as $<50\times10^9$/L.

  Note: This main intercurrent event is defined as described in section 4.1.2.1.
- initiation of rescue therapy: platelet count measured in the 4 weeks strictly following this intercurrent event (start of the administration of the first rescue treatment of every different occurrence initiation) will be handled as $<50\times10^9$/L.

  Note: the platelet count on the start date of the different intercurrent events will be used as is, imputation will only start on the next day

Missing values for reasons other than the main intercurrent events, will be imputed as described in section 4.1.2.5 (approach 1). The main analysis (alpha-controlled) on the first key secondary endpoint extent of disease control will use the composite variable strategy as described above in case of main intercurrent events using the stratified Mann-Whitney test (see also section 4.1.3.4).

A first complementary analysis will be conducted using the stratified Mann-Whitney test where the main intercurrent events are handled differently, ie, using the treatment policy strategy, where platelet counts are used to derive the endpoint regardless of whether or not the intercurrent event occurs.

A second complementary analysis will be conducted where extent of disease control is handled as a time-to-event endpoint (with "loss of disease control" being the event).

Loss of disease control is derived as defined in Table 8.

Table 8: Definition for Loss of Disease control

Situation	Time to Loss of Disease Control or Censoring	Outcome
No occurrence of platelet count of $\geq50\times10^9$/L	0	Event
Early discontinuation of treatment (prior to W24) due to lack of efficacy or due to adverse event	Total number of analysis visits during the treatment phase with platelet counts of $\geq50\times10^9$/L up to date of treatment discontinuation	Event
Rescue therapy	Total number of analysis visits during the treatment phase with platelet counts of $\geq50\times10^9$/L up to date of initiation of rescue therapy (start of the administration of the first rescue treatment)	Event
Dose and/or frequency of concurrent ITP therapy increased or a new ITP therapy	Total number of analysis visits during the treatment phase with platelet counts of $\geq50\times10^9$/L up to	Event

	start date of increase or new ITP therapy	
Disease control at end of 24-week treatment period	Total number of analysis visits during the treatment phase with platelet counts of $\geq 50\times10^9$/L up to date of last assessment (analysis visit)	Censored

Missing values not due to one of the main intercurrent events will be handled as described in section 4.1.2.5 (approach 1).

2) Proportion of participants with a sustained platelet count response (week 19 – 24) in the overall population (chronic and persistent ITP).

Derivation: A participant is considered a responder, ie, has a sustained platelet count response, if he/she shows platelet counts of at least 50×10^9/L for at least 4 of the 6 analysis visits between weeks 19 and 24 of the study. Intercurrent events will be handled with the same composite variable strategy as for the primary endpoint described in section 4.1.2.1. Missing values for reasons other than the main intercurrent events, will be imputed as described in section 4.1.2.5 (approach 1).

3) Proportion of participants achieving platelet counts of at least 50×10^9/L for at least 6 of the 8 visits between weeks 17 and 24 of the study in the overall population.

Derivation: A participant is considered a responder if he/she shows platelet counts of at least 50×10^9/L for at least 6 of the 8 analysis visits between weeks 17 and 24 of the study. Intercurrent events will be handled with the same composite variable strategy as described in section 4.1.2.1. Missing values not due to intercurrent events will be handled as described in section 4.1.2.5 (approach 1).

4) Incidence and severity of the WHO-classified bleeding events (overall population).

Derivation: total number of analysis visits for which WHO bleeding scale ≥ 1. The overall score of the bleeding events per analysis visit will be used, calculated as the maximum bleeding scale over the different body systems available per analysis visit. The data will be used as is, without taking into account intercurrent events (treatment policy strategy). Missing bleeding assessments after one of the main intercurrent events, as described for extent of disease control (section 4.1.2.2) will not be imputed. In case of rescue therapy, the bleeding events will not be imputed for 4 weeks strictly after the initiation of the therapy (the initiation of the therapy is the start date/time of the administration of the first rescue treatment for that occurrence). Missing values for reasons other than the main intercurrent events, will be imputed as described in section 4.1.2.5 (approach 3).

4.1.2.3 OTHER SECONDARY ENDPOINTS (NOT ALPHA CONTROLLED)

All other secondary endpoints will be analyzed using the FAS on the overall population.

1) Overall Response: Proportion of participants with overall platelet count response defined as achieving a platelet count of $\geq 50\times10^9$/L on at least 4 occasions at any time during the 24-week treatment period.

Derivation: a participant is considered a responder if he/she shows platelet count of at least 50×10^9/L on at least 4 analysis visits during the 24-week treatment period. Platelet count after one of the main intercurrent events will be handled in the same way as for extent of disease control (section 4.1.2.2). Missing values not due to intercurrent events will be handled as described in section 4.1.2.5 (approach 1).

2) Extent of disease control defined as the number of cumulative weeks until week 12, with platelet counts of $\geq 50\times10^9$/L.

Derivation: total number of analysis visits during the treatment phase until week 12 with platelet counts of $\geq 50\times10^9$/L. Platelet count after one of the main intercurrent events will be handled in the same way as for extent of disease control (section 4.1.2.2). Missing values not due to intercurrent events will be handled as described in section 4.1.2.5 (approach 1).

3) Proportion of participants with overall platelet response until week 12 defined as achieving a platelet count of $\geq 50\times10^9$/L on at least 4 occasions at any time until week 12.

Derivation: a participant is considered a responder if he/she shows platelet count of at least 50×10^9/L on at least 4 analysis visits during the first 12 weeks in the treatment period. Platelet count after one of the main intercurrent events will be handled in the same way as for extent of disease control (section 4.1.2.2). Missing values not due to intercurrent events will be handled as described in section 4.1.2.5 (approach 1).

4) Mean changes from baseline for platelet count levels. Missing values will only be imputed for the Mixed Model for Repeated Measurements (MMRM). See section 4.1.3.5.

5) Mean changes from baseline in PRO/QoL:
   a) *FACIT-Fatigue*: The FACIT-Fatigue Scale is a short, 13-item, easy to administer tool that measures an individual's level of fatigue during their usual daily activities over the past week. The level of fatigue is measured by recording item responses on a 4-point Likert scale ranging from 0 "not at all" to 4 "very much".
   Total FACIT-Fatigue score[10] = ∑individual scores (range between 0 and 52). The score for all items, except for item 7 (energy) and 8 (able to do usual activities), is reversed. The higher the score, the better the QoL. A total score per analysis visit will be calculated. If 6 or more item scores are missing the total score will not be calculated. Otherwise, scores for missing items will be imputed with the arithmetic average of the non-missing item scores. A total missing score will only be imputed for the Mixed Model for Repeated Measurements (MMRM). See section 4.1.3.5.
   b) *FACT-Th6*: The FACT-Th6 Scale is a 6-item tool rating the individual degree of concern with bleeding or bruising in the past 7 days. The level of

concern is measured on a 4-point Likert scale (4 = not at all concerned to 0 = very much concerned).

Total FACT-Th6 score[10] = ∑individual scores (range between 0 and 24). All scores are reversed, except for item FACTTH61. A total score per analysis visit will be calculated. If 4 or more item scores are missing, the total score will not be calculated. Otherwise, scores for missing items will be imputed with the arithmetic average of the non-missing item scores. A missing total score will only be imputed for the Mixed Model for Repeated Measurements (MMRM). See section 4.1.3.5.

c) *SF-36 (v2.0)*: The SF-36 is a 36-item scale constructed to survey health-related QoL on 8 domains: limitations in physical activities due to health problems; limitations in social activities due to physical or emotional problems; limitations in usual role activities due to physical health problems; bodily pain; general mental health (psychological distress and well-being); limitations in usual role activities due to emotional problems; vitality (energy and fatigue); and general health perceptions. SF-36 scores for the 8 subdomains, and norm-based physical and mental component summaries scores (P-CS and M-CS) will be calculated using a dedicated software: QualityMetric Health Outcomes™ Scoring Software 5.1. 2009 US population norm is used. Missing values are handled in the software: Scale scores can be computed if at least one item in the scale is answered. The Physical Component Summary (P-CS) score can be calculated when seven scale scores are available, and the Physical Functioning (PF) scale is not missing. The Mental Component Summary (M-CS) score can be calculated when at least seven scale scores are available, and the mental Health (MH) scale is not missing. QualityMetric's Missing Data Estimation chooses a unique scoring algorithm to apply to the calculation of the summary scores depending upon which particular scale score is missing from the eight scale profiles[11]. More details on the calculation of SF-36 scores can be found in the OPTUM® PRO CoRE manual.
Missing scores will only be imputed for the Mixed Model for Repeated Measurements (MMRM). See section 4.1.3.5

d) *ITP-PAQ*: The ITP-PAQ Scale is a patient questionnaire composed of 44 questions, grouped into 9 (for male) or 11 (for female) scales: physical health: symptoms, bother, fatigue and activity, emotional health: fear and psychological health, work, social activity, women's reproductive health: menstrual symptoms and fertility, overall QoL. An overview of which questions relate to which scale can be found in appendix 9.2. Each question is asked in a negative way and is scored on a Likert scale with four to seven answering possibilities, the worst outcome (first answer) equaling zero and the best outcome (last answer before NA) equaling the highest score M-1. Each scale score is calculated as follows:

- Item score is converted on a 0-100 scale: score_c = score*100/(M-1)
  Where M is the number of possible answers

- Scale score = mean of all available converted item scores

  A scale score cannot be calculated if less than 50% of the items of the scale are answered. Otherwise, scores for missing items will be imputed with the arithmetic average of the non-missing item scores. Converted item scores are not rounded when calculating the scale score.

6) Rate of receipt of rescue therapy: number of times rescue therapy is given per month, calculated as $\frac{\text{Total number of occurences}}{\text{total days in treatment phase}} \times 30.4$

Occurrence: a period of maximum 5 days where 1 or more rescue treatments are administered simultaneously or consecutively to the study participant. The start date/time of the occurrence is the start of the administration of the first rescue treatment. If this period exceeds the maximum of 5 days, a new occurrence will be assigned, with start date/time of the occurrence being the start date 5 days after the initial occurrence start date.

7) Proportion of participants for whom dose and/or frequency of concurrent ITP therapies have increased at week 12 or later.

Derivation: a participant is counted if (start date concurrent ITP therapy ≥ lower limit ADY of analysis visit corresponding to week 12) AND (dose > previous dose of the specific ITP therapy OR frequency > previous frequency of the specific ITP therapy OR new ITP therapy). Note: Dose and frequency will always be considered in combination (ie, mean daily doses will be compared).

8) Time to platelet count response defined as the time to achieve 2 consecutive platelet counts of $\geq 50\times10^9$/L.

Derivation: It will be calculated as the difference between the first assessment date at which the condition '2 consecutive platelet counts $\geq 50\times10^9$/L' is fulfilled, taking into account all platelet count measurements (also the unscheduled ones), and first IMP intake date.

Time to platelet count response (days) = date (first assessment) – first IMP date + 1:

Table 9: Definition for Time to Platelet Count

Response Situation	Time to Platelet Count Response	Outcome[d]
No occurrence of platelet count of $\geq 50\times 10^9$/L	Date of last available platelet count[c] – first IMP date[b] + 1	Censored
Early discontinuation of treatment (prior to W24) due to lack of efficacy or due to AE[a]	Early treatment discontinuation date – first IMP date[b] + 1	Censored
Dose and/or frequency of concurrent ITP therapy increased or a new ITP therapy[a]	Concurrent ITP therapy start date – first IMP date[b] + 1	Censored
Platelet count response	Date (first assessment) – first IMP date[b] + 1	Event

[a] only applicable if the event (reaching platelet count response) has not occurred before

[b] or date of randomization for participants not treated
[c] or End-of-Study date for participant with no platelet count assessments
[d] If multiple censoring conditions apply, the earliest censoring date is considered.

In case of rescue therapy, the platelet count cannot be used for 4 weeks after the initiation of the therapy (the initiation of the therapy is the start date/time of the administration of the first rescue treatment for that occurrence). The platelet count will be interpreted as $<50\times10^9$/L for the 4 analysis visits following the initiation of the rescue therapy. Missing values not due to one of the main intercurrent events will be handled as described in section 4.1.2.5 (approach 1).

9) Extent of disease control defined as number of cumulative weeks over the planned 24-week treatment period with platelet counts:

   a) $\geq 30\times10^9$/L and at least 20×10^9/L greater than the baseline value

      Derivation: total number of analysis visits during the treatment phase with platelet counts of $\geq 30\times10^9$/L and (platelet count – baseline platelet count) $\geq 20\times10^9$/L. Platelet count after one of the main intercurrent events will be handled in the same way as for extent of disease control (section 4.1.2.2). Missing values not due to intercurrent events will be handled as described in section 4.1.2.5 (approach 1), but imputing with $\geq 30\times10^9$/L / $< 30\times10^9$/L and not with $\geq 50\times10^9$/L / $< 50\times10^9$/L. In the same way, if (platelet count – baseline platelet count) $\geq 20\times10^9$/L for the previous and the next analysis visit, (platelet count – baseline platelet count) will imputed with $\geq 20\times10^9$/L, otherwise with $<20\times10^9$/L.

      The above will be repeated for the selection of participants where baseline platelet count $<15\times10^9$/L.

   b) $\geq 30\times10^9$/L and at least 20×10^9/L greater than the baseline value, where baseline platelet count $<15\times10^9$/L.

[redacted]

Missing values will not be imputed.

11) Number of significant bleeding events where WHO bleeding scale ≥ 2 at any visit.

Derivation: total number of analysis visits for which WHO bleeding scale ≥ 2. The overall score of the bleeding events per analysis visit will be used, calculated as the maximum bleeding scale over the different body systems available per analysis visit. The data will be used as is, without taking into account intercurrent events (treatment policy strategy). Missing bleeding assessments after one of the main intercurrent events will not be imputed. For 'increase of dose and/or frequency of concurrent ITP therapies or start of a new concurrent ITP therapy' and 'initiation of rescue therapy' the whole treatment period should be taken into account. In case of rescue therapy, the bleeding events will not be imputed for 4 weeks strictly after the initiation of the therapy (the initiation of the therapy is the start date/time of the administration of the first rescue treatment for that occurrence). Missing overall score values for reasons

other than the main intercurrent events, will be imputed as described in section 4.1.2.5 (approach 3), but imputing as "scale >=2" instead of "bleeding" and as "bleeding scale<2" instead of "no bleeding".

12) Proportion of participants with an IWG-Complete response[12].

Derivation: a participant is considered a responder if he/she shows platelet count of at least 100×10^9/L and the absence of bleeding events (WHO=0) for at least 2 separate, consecutive occasions which are at least 7 days apart (in case of missing visits (phantom records), the target date will be used). Platelet count after one of the main intercurrent events will be handled in the same way as for extent of disease control (section 4.1.2.2), but imputing $<100\times10^9$/L instead of $<50\times10^9$/L. Missing values not due to one of the main intercurrent events will be handled as follows: if platelet count $\geq100\times10^9$/L for the previous and the next analysis visit, the platelet count will be imputed with $\geq100\times10^9$/L, otherwise with $<100\times10^9$/L. Missing bleeding assessments after one of the main intercurrent events will not be imputed. For 'increase of dose and/or frequency of concurrent ITP therapies or start of a new concurrent ITP therapy' and 'initiation of rescue therapy' the whole treatment period should be taken into account. In case of rescue therapy, the bleeding events will not be imputed for 4 weeks strictly after the initiation of the therapy (the initiation of the therapy is the start date/time of the administration of the first rescue treatment for that occurrence). Missing bleeding assessments for other reasons than the main intercurrent events will be imputed as described in section 4.1.2.5 (approach 3)

13) Proportion of participants with an IWG-Response[12].

Derivation: a participant is considered a responder if he/she shows platelet count of at least 30×10^9/L and at least a 2-fold increase of platelet count from baseline and the absence of bleeding events (WHO=0) for at least 2 separate, consecutive occasions which are at least 7 days apart (in case of missing visits (phantom records), the target date will be used). Platelet count after one of the main intercurrent events will be handled in the same way as for extent of disease control (section 4.1.2.2), but imputing $<30\times10^9$/L instead of $<50\times10^9$/L. If platelet count $\geq30\times109$/L for the previous and the next analysis visit, the platelet count will be imputed with $\geq30\times10^9$/L, otherwise with $<30\times10^9$/L. In the same way, if the previous and the next analysis visit indicates a 2-fold increase, the missing 2-fold increase will be imputed with "Yes", otherwise "No". Missing bleeding assessments after one of the main intercurrent events will not be imputed. For 'increase of dose and/or frequency of concurrent ITP therapies or start of a new concurrent ITP therapy' and 'initiation of rescue therapy' the whole treatment period should be taken into account. In case of rescue therapy, the bleeding events will not be imputed for 4 weeks strictly after the initiation of the therapy (the initiation of the therapy is the start date/time of the administration of the first rescue treatment for that occurrence). Missing bleeding assessments for other reasons than the main intercurrent events will be imputed as described in section 4.1.2.5 (approach 3).

14) Proportion of participants with an Initial Response[13].

Derivation: a participant is considered a responder if he/she shows platelet count of at least 30×10^9/L and a 2-fold increase of platelet count from baseline at analysis visit

Week 5. Platelet count after one of the main intercurrent events will be handled in the same way as for extent of disease control (section 4.1.2.2), but imputing $<30\times10^9$/L instead of $<50\times10^9$/L. If platelet count $\geq30\times10^9$/L for the previous and the next analysis visit, the platelet count will be imputed with $\geq30\times10^9$/L, otherwise with $<30\times10^9$/L. In the same way, if the previous and the next analysis visit indicates a 2-fold increase, the missing 2-fold increase will be imputed with "Yes", otherwise "No".

4.1.2.4 OTHER SECONDARY ANALYSES NOT FORESEEN PER PROTOCOL (NOT ALPHA CONTROLLED)

[redacted]

[redacted]

[redacted]

Table 10: [redacted]

[redacted]

Table 11: [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Table 12: [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.1.2.5 *IMPUTATION*

Missing data (platelet counts) for other reasons than the main intercurrent events will be imputed as follows:

- Approach 1: if platelet count $\geq 50\times10^9$/L for the previous and the next analysis visit, and the previous and next analysis visit are in the treatment phase, the platelet count will be imputed with $\geq 50\times10^9$/L, otherwise with $<50\times10^9$/L.
- Approach 2: all missing data will be imputed with $<50\times10^9$/L. This will only be used as sensitivity analysis for the primary endpoint and the first key secondary endpoint.

Intermittent missing data (overall score of WHO bleeding assessment) for other reasons than the main intercurrent events will be imputed as follows:

- Approach 3: If no bleeding event for previous and next analysis visit with available bleeding assessment result (which can enclose several successive missing bleeding assessments), and the previous and next analysis visit are in the treatment phase, impute with no bleeding event, otherwise impute with bleeding event. No imputation will be done after the last available bleeding assessment in the treatment phase.

4.1.3 *Statistical analysis*

Wherever the stratification factors will be used in the efficacy analyses, the actual values of these will be used and not the ones coming from the randomization.

Summary statistics will be provided in terms of actual values and changes from baseline for platelet count in the chronic and the overall FAS population. All analysis visits as expected per SoA (including the follow-up phase) will be shown.

Frequency tabulations will be provided of the percentage of responders with sustained platelet count (primary endpoint) in participants with chronic ITP and overall and by stratification factors (receiving concurrent ITP therapies at baseline [yes/no], history of splenectomy [yes/no]) and baseline platelet count. The table in the overall population will be repeated by subgroup and ADA participant classification. The table for participants with chronic ITP will be repeated for the complementary analysis using the treatment policy strategy.

Frequency tabulations will be provided of the percentage of responders with sustained platelet count (different definitions excluding primary endpoint) and of the percentage

of responders with overall response (week 1 – 24 and week 1 – 12) in the overall population. Frequency tabulations will also be provided for all different response definitions for platelet count as defined in section 6.1. The response rates and differences in response rate (efgartigimod-placebo) will be shown together with the 95% Agresti-Min[14] confidence limits. The tabulation of the sustained platelet count response (week 19 – 24) in the overall population will be repeated by subgroup.

For the different endpoints on extent of disease control, summary statistics will be provided on the number of cumulative weeks of disease control in the overall population. For the first key secondary endpoint extent of disease control will also be summarized for the chronic population and by stratification factors and baseline platelet count. This first key secondary endpoint summary table for the overall population will also be repeated by subgroup. Furthermore, a table with Kaplan-Meier (KM) estimates will be displayed by randomized treatment arm for the first key secondary endpoint (complementary analysis).

Summary statistics will be provided for the different definitions of number of bleeding events in the overall population. A frequency tabulation will be provided of the number and percentage of bleeding events and repeated for the subgroup on sustained platelet count response (week 19 – 24). The overall severity score at each analysis visit and the worst-case overall severity score will be tabulated.

Summary statistics will be provided in terms of actual values and changes from baseline for PRO scores (FACIT-Fatigue, FACT-Th6) and QoL (SF-36, ITP-PAQ) in the overall population. All analysis visits as expected per SoA (including the follow-up phase) will be shown.

Summary statistics will be provided for the rate of receipt of rescue therapy in the overall population. A frequency tabulation will be provided of the number of rescue therapies (occurrences) received.

Frequency tabulations will be provided of the proportion of participants for whom dose and/or frequency of concurrent ITP therapy have increased at week 12 or later.

KM estimates will be provided for time to platelet count response ($\geq 50\times10^9$/L and $\geq 100\times10^9$/L) and time to platelet count $\geq 50\times10^9$/L or $\geq 100\times10^9$/L in the overall population. KM curves and median time to platelet count response will be displayed by randomized treatment.

Summary statistics will be provided in terms of actual values and changes from baseline for IPF# and IPF% in the overall population. All analysis visits as expected per SoA (including the follow-up phase) will be shown.

Statistical inference will be conducted as described below. All statistical comparisons will be made using two-sided tests at the 0.05 significance level unless specifically stated otherwise. Sensitivity analyses will be done for the primary and key secondary endpoints by using the PP population (PP-chronic). The primary and first key secondary endpoint will also be repeated by use of approach 2 for imputing missing values as sensitivity analysis. A complementary analysis using the treatment policy strategy will be done on the primary and the first key secondary endpoint. Furthermore, a complementary analysis will be done on the first key secondary endpoint extent of disease control using a Cox proportional hazards regression model.

Main intercurrent events occurrence according to the above definitions in section 4.1.2.1 and 4.1.2.2 will be tabulated and listed.

4.1.3.1 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, based on the p-value, subsequent endpoints will no longer be evaluated.

- Primary endpoint: the proportion of participants with chronic ITP with a sustained platelet count response defined as achieving platelet counts of at least 50×10^9/L for at least 4 of the 6 visits between week 19 and 24 of the study.
- The extent of disease control defined as the number of cumulative weeks over the planned 24-week treatment period with platelet counts of $\geq50\times10^9$/L in the participant population with chronic ITP.
- The proportion of participants in the overall population (chronic and persistent ITP) with a sustained platelet count response defined as achieving platelet counts of a least 50×10^9/L for at least 4 of the 6 visits between week 19 and 24 of the study.
- Proportion of participants in the overall population achieving platelet counts of at least 50×10^9/L for at least 6 of the 8 visits between week 17 and 24 of the study.
- The incidence and severity of the WHO-classified bleeding events in the overall population.

4.1.3.2 Cochran-Mantel-Haenszel

The primary endpoint, sustained platelet count, will be analyzed using a Cochran-Mantel-Haenszel statistic stratified for each stratum formed by the combination of the stratification factors. The stratification factors will be history of splenectomy (yes versus no) and receiving concurrent ITP therapies at baseline (yes versus no) and baseline platelet count level category ($<15\times10^9$/L versus $\geq15\times10^9$/L). The treatment effect will be presented as the odds ratio together with its exact 95% confidence interval (CI)[15] and 2-sided p-value. The MH estimator[16] will be used for the odds ratio (OR), except in case of empty cells for all strata within one treatment, in which case the logit estimator[17] will be used. An OR of more than 1 represents a higher response rate for efgartigimod compared to placebo. In addition, an adjusted difference of the proportions with its 95% confidence (Klingenberg approach) will be provided.

Missing data due to a reason of one of the main intercurrent events as described above (see section 4.1.2.1) will be analyzed as a non-responder (composite variable strategy). Missing data for other reasons will be imputed as described in section 4.1.2.5, approach 1. The analysis will be repeated with approach 2 as sensitivity analysis for the primary endpoint.

All secondary endpoints related to sustained platelet count response, overall platelet count response, and IWG derived endpoints (ie, complete IWG response, IWG response and initial response) will be analyzed in the same manner as this primary endpoint.

For the primary endpoint only, the analysis will be repeated where the main intercurrent events will be handled by using the 'treatment policy' strategy (see section 4.1.2.1).

4.1.3.3 EXACT CONDITIONAL LOGISTIC REGRESSION

The primary endpoint, sustained platelet count, is also tested by means of a 2-sided exact test (using exact conditional logistic regression[6]), stratified for the stratification factors (history of splenectomy and receiving concurrent ITP therapies at baseline) and using the baseline platelet count (continuous) and randomized treatment as fixed covariates, at the 2-sided 5% significance level, in the chronic ITP population. A maximum exact conditional likelihood estimate of the OR will be obtained, using the Newton-Raphson algorithm. In the event the algorithm does not converge, the median unbiased estimate will be used[5]. A likelihood ratio test will be conducted to test the null hypothesis that the log OR is equal to zero against the alternative that it is different from zero.[7] In case of empty cells for all strata within one treatment, a Firth regression will be used[18]. The treatment effect will be presented as the OR (by exponentiating the log OR) together with its 95% confidence interval (CI) and 2-sided p-value. An OR of more than 1 represents a higher response rate for efgartigimod compared to placebo.

Missing data due to a reason of one of the main intercurrent events as described above (see section 4.1.2.1) will be analyzed as a non-responder (composite variable strategy). Missing data for other reasons will be imputed as described in section 4.1.2.5, approach 1.

4.1.3.4 STRATIFIED MANN-WHITNEY TEST.

The extent of disease control, the number of bleeding events (WHO bleeding scale ≥1) and the number of significant bleeding events (WHO bleeding scale ≥2) are tested by means of a Wilcoxon-Mann-Whitney test stratified for the stratification factors (history of splenectomy and receiving concurrent ITP therapies at baseline) and baseline platelet count category ($<15\times10^9$/L versus $\geq15\times10^9$/L) included as independent variable. An estimate of the location shift will be provided (Hodges-Lehmann estimator of the treatment difference), along with the associated 95% CI and 2-sided p-value. The 2-sided p-value resulting from this hypothesis test will inform on whether the null hypothesis that the distributions of number of cumulative weeks for both treatment groups are identical can be rejected. The stratified Mann-Whitney test for extent of disease control will be done for both the chronic ITP population and the overall population.

Missing bleeding assessments strictly after of one of the main intercurrent events will not be imputed. For 'increase of dose and/or frequency of concurrent ITP therapies or start of a new concurrent ITP therapy' and 'initiation of rescue therapy' the whole treatment period should be taken into account. In case of rescue therapy, the bleeding events will not be imputed for 4 weeks strictly after the initiation of the therapy (the

initiation of the therapy is the start date/time of the administration of the first rescue treatment for that occurrence).

Missing bleeding assessments for other reasons than the main intercurrent events will be imputed as described in section 4.1.2.5 (approach 3).

4.1.3.5 Mixed Model for Repeated Measurements

For changes from baseline (see section 4.1.2.3), between treatment group differences will be analyzed by means of Mixed Models for Repeated Measurements (MMRM). All available data will be included. Non-missing values after one of the main intercurrent events will be imputed with the baseline value/score. Other (missing) values will not be imputed. The model will include treatment, analysis visit and treatment by visit interaction terms as fixed effects, with baseline value, baseline by visit interaction, and stratification factors as covariates. Only analysis visits within the treatment phase will be considered. Within-participant correlation will be modeled by assuming an unstructured covariance matrix for the error terms and Kenward-Roger degrees of freedom method will be used. Least square (LS) means for placebo and efgartigimod will be reported, along with the difference in LS means, 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 steps will be taken to avoid lack of convergence while maintaining an unstructured variance:

- 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.
- 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).
- If all of the above fail, the variance-and-correlations parameterization will be attempted using TYPE=UNR.

In the rare case where all of the above steps fail, the following covariance structures will be tested for convergence (in order): ANTE(1), 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).

This model will be applied for the mean changes in platelet count levels, PRO (FACIT-Fatigue, FACT-Th6) and QoL (SF-36: 8 subdomain scores, P-CS and M-CS; ITP-PAQ: 9 (for male) or 11 (for female) scales).

4.1.3.6 Cox Proportional Hazards Regression

The Cox proportional hazard model will be used to calculate the estimate of the hazard ratio (HR) and 95% confidence interval for the treatment effect of the extent of disease control as complementary analysis for the first key secondary endpoint (see section 4.1.2.2), and the time to platelet count response (see section 4.1.2.3).

The model will include treatment as fixed effects, with baseline platelet level and stratification factors as covariates. The HR for efgartigimod PH20 SC vs. placebo

PH20 SC will be provided, along with the associated 95% 2-sided Wald-type CI and 2-sided p-value.

4.1.4 Subgroup analyses for efficacy

Subgroups are defined based on the following categorizing factors:

- Fixed dosing regimen (weekly versus bi-weekly): as derived in section 3.6.2
- Recruitment cohort (wave 1 versus wave 2): as derived in section 3.3.2
- History of splenectomy (yes versus no)
- Receiving concurrent ITP therapies at baseline (yes versus no)
- Baseline platelet count: ($<15\times10^9$/L, $\geq15\times10^9$/L)
- Time since diagnosis (chronic versus persistent)
- Number of prior ITP therapies (<3 prior therapies, ≥3 prior therapies)
- Sex at birth (male, female)
- Region (East Asia / Europe / LATAM / MEA / non-EU CEE / North America / rest of the world): as defined in section 3.3.2
- Age category (18-<65 years; 65-<75 years; ≥75 years)
- Race (Asian, Black or African American, White, Other)
- Weight category at baseline (<50 kg, 50-<75 kg, 75 – <100 kg, 100 – <125 kg, ≥ 125 kg)
- Prior Rituximab (yes versus no): as defined in section 3.5.2
- Prior TPO-RA (yes versus no): as defined in section 3.5.2

Note that subgroup categories with less than 5 participants (overall) will not be included in the tables. For region, North America will always be shown. Other regions with less than 15 participants (overall) will be shown in the 'rest of the world' subgroup.

Subgroup analyses will be performed on the following efficacy endpoints:

- Sustained platelet count response (week 19 – 24) in the overall population
- Sustained platelet count response (week 19 – 24) in the ITP chronic population (recruitment cohort only)
- Extent of disease control (first key secondary endpoint) in the overall population (all subgroup analyses except fixed dosing regimen [weekly versus bi-weekly]).

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).

All PK samples are to be collected predose, on the day of IMP administration.

All concentration data-points with deviations outside these permitted ranges will be excluded from the descriptive statistics on concentrations by scheduled timepoint, and a remark will be added in the appropriate listing.

The PK samples taken after a missed dose up to the next administered dose will be excluded from descriptive statistics, a remark will be added in the appropriate listing.

4.2.2 Derivation rules

Not applicable

4.2.3 Presentation of results

For tables by fixed dosing regimen, only visits of the fixed dosing schedule period (ie, baseline up to week 3 and week 16 up to week 24) will be tabulated. In this first period of baseline up to week 3, all participants have weekly dosing per protocol. For the second period, the fixed dosing regimen is defined as explained in section 3.6.2.

Individual concentration data and actual blood sampling times from start of injection for PK assessments will be listed. Data issues like time deviations will be mentioned in the remarks.

Descriptive statistics on concentration data will be presented in tables per visit (and fixed dosing regimen (weekly or every other week)). A similar table will be created by ADA and NAb against efgartigimod, and antibodies against rHuPH20 Participant Classification.

4.3 PHARMACODYNAMICS

4.3.1 Available data

The following PD parameters will be measured:

- Total Immunoglobulin G (IgG)
- antiplatelet antibody levels targeting GPIIb/IIIa, GPIb/IX, GPV and GPIa/IIa.

For the statistical analysis, only the results obtained with the immunoturbidimetry in vitro diagnostic (IVD) assay will be used.

4.3.2 Derivation rules

Antiplatelet antibody positivity at a certain time point is defined as having at least one out of four values of the individually tested glycoproteins above the pre-defined optical density (OD) cutoff at that time point (positive if > 0.129). If at a timepoint one or more individually tested glycoprotein is missing and none is positive, the antiplatelet antibody will be shown as unevaluable.

Antiplatelet antibody positivity for a particular glycoprotein at a certain time point is defined as having an OD value above the pre-defined OD cutoff for that particular glycoprotein at that time point (positive if > 0.129).

For antiplatelet antibodies, a best-case analysis visit will be derived if at least one non-missing postbaseline result is available. The outcome at this visit is negative if at least one postbaseline visit has a negative result. If the outcome is unevaluable at all postbaseline visits, best-case analysis visit result is unevaluable. Otherwise it is positive. All non-missing postbaseline values during the treatment phase, including unscheduled assessments will be considered when deriving the best-case analysis visit.

4.3.3 Presentation of results

Total IgG results after treatment discontinuation will be excluded from the tables.

For tables by fixed dosing regimen, only visits of the fixed dosing schedule period (ie, baseline up to week 3 and week 16 up to week 24) will be tabulated. In this first period of baseline up to week 3, all participants have weekly dosing per protocol. For the second period, the fixed dosing regimen is defined as explained in section 3.6.2.

For Total IgG, summary statistics will be provided in terms of actual values and changes from baseline for each visit per fixed dosing regimen and overall. Moreover, percent changes from baseline will also be presented. The summary statistics for Total IgG will be repeated for all subgroups specified in section 4.1.4.

Antiplatelet antibody results from Chinese participants will be excluded from the tables, as these were obtained with a different assay.

Frequency of antiplatelet antibody categories will be summarized at baseline for each glycoprotein and overall. Frequency of antiplatelet antibody-positive participants will be summarized per analysis visit and for the best-case analysis visit. For antiplatelet antibody-positive participants, a frequency table of the antiplatelet antibodies will be created for each glycoprotein separately (GPIIb/IIIa, GPIb/IX, GPV, GPIa/IIa) per analysis visit and for the best-case analysis visit.

All actual and change from baseline IgG and antiplatelet antibody levels data will be listed.

4.4 IMMUNOGENICITY

4.4.1 Available data

ADA to efgartigimod and antibodies against rHuPH20 (rHuPH20 Ab) is measured per schedule of assessment (see 9.5.1).

Immunogenicity samples are analyzed in a 3-tiered approach:

- All samples are evaluated in the ADA screening assay and are scored ADA screening positive or negative
- If a sample scored positive in the ADA screening assay, it is further evaluated in the confirmatory assay and is scored confirmed positive (positive immuno-depletion) or confirmed negative (negative immuno-depletion)
- 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 (positive or negative). For NAb against efgartigimod, a screening assay is performed and results will be reported as negative or positive. For NAb against rHuPH20,the same 3-tiered approach is implemented: the screening NAb assay, followed by a Nab confirmatory assay, and a titer NAb assay, according to the above described 3-tiered approach.

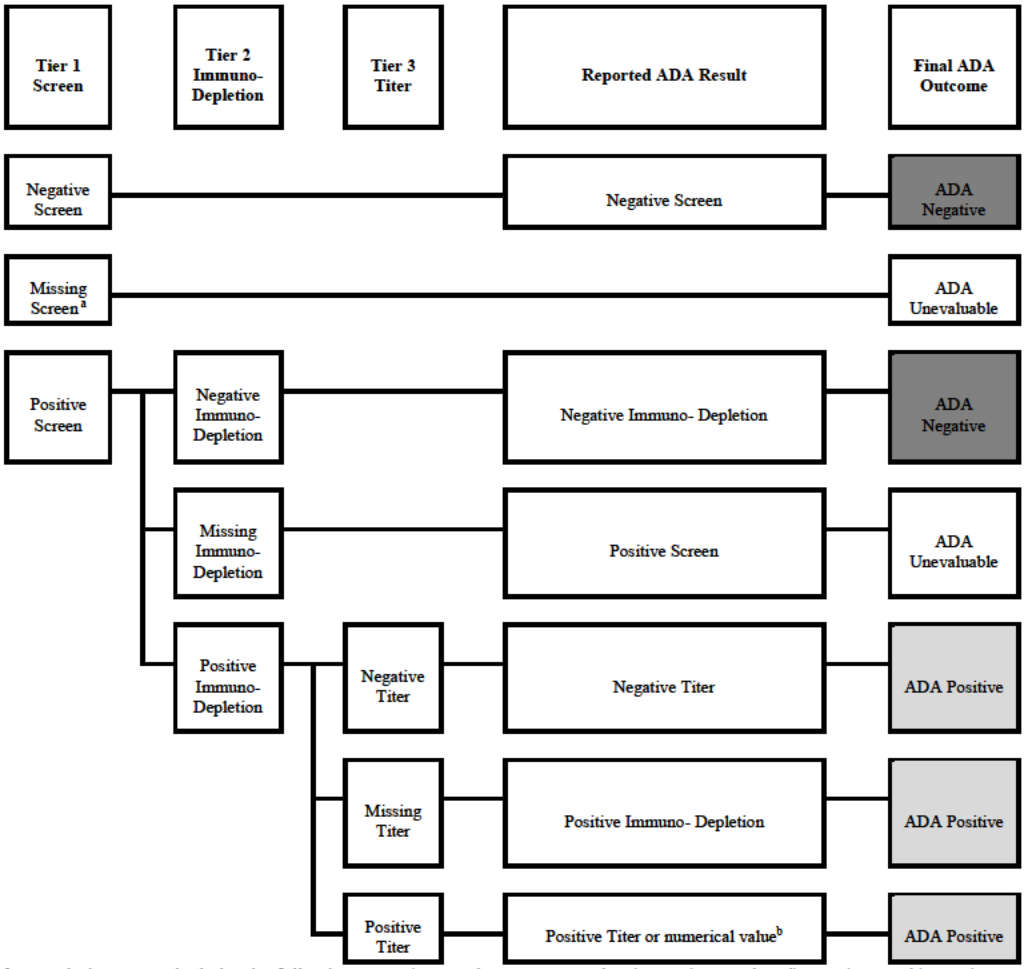
Note: If a sample could not be analyzed or reported as ‘positive screen’, the ADA sample status is ADA unevaluable.

If available, a titer result will be reported for the ADA or rHuPH20 Ab or rHUPH20 NAb confirmed positive samples. However, a titer result is not always available. This is also applicable to rHuPH20 Ab and rHuPH20 NAb results.

- 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.

An overview of this 3-tiered approach and all possible ADA or rHuPH20 Ab or rHuPH20 NAb sample results that will be reported by the laboratory is given below. From these reported ADA or rHuPH20 Ab or rHuPH20 NAb sample results a final ADA or rHuPH20 Ab or rHuPH20 NAb 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 analysed), NR (no result), NS (no sample), and SL (sample lost). More details can be found in the IS data transfer agreement from the specialty labs to SGS SD office.

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

4.4.2 Derivation rules

4.4.2.1 Participant Classification for ADA against Efgartigimod

Table 13 below gives an overview of how the ADA participant classification will be derived, starting from the participant baseline ADA sample status. See also section 4.4.1:

Table 13: 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 numerical titer value)**		**ADA un evaluable**
Baseline ADA sample status					
ADA negative	ADA negative	Treatment-induced ADA	Treatment-induced ADA		*ADA unevaluable*
ADA positive (missing titer[a])	Treatment-unaffectedADA	*ADA unevaluable*	*ADA unevaluable*		*ADA unevaluable*
ADA positive (negative titer[b] or numerical titer value)	Treatment-unaffectedADA	*ADA unevaluable*	**titer < 4 x baseline titer:** Treatment-unaffected ADA	**titer ≥ 4x baseline titer:** Treatment-boosted ADA[d]	*ADA unevaluable*
ADA un evaluable	*ADA unevaluable*	*ADA unevaluable*	*ADA unevaluable*		*ADA unevaluable*

[a] Samples with missing titer will have a reported ADA result of 'positive immunodepletion' or 'positive titer';
[b] Results reported as 'negative titer', ie, 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 ('positive immunodepletion' or 'positive titer'), ADA positive with titer < 1 ('negative titer' as reported ADA result, titer value set to 1), ADA positive with titer ≥ 1 (numerical value and selecting the sample with highest titer)
[d] Note: Fourfold difference in titer values is considered significant in case a twofold serial dilution is applied (= two times the dilution factor) (reference to Shankar et al., 2014)[9].

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

ADA unevaluable participant = participant classified as ADA unevaluable or with missing baseline ADA sample or without postbaseline ADA samples (in case no ADA data are available at all, the participant cannot be classified);

ADA incidence = percentage of participants with treatment-induced or treatment-boosted ADA (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 14 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 14: 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 numerical titer value)**		**rHuPH20 Ab un 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 numerical titer value)	Treatment-unaffected rHuPH20 Ab	rHuPH20 Ab *unevaluable*	**titer < 4x baseline titer:** Treatment-unaffected rHuPH20 Ab	**titer ≥ 4x baseline titer:** Treatment-boosted rHuPH20 Ab[d]	rHuPH20 Ab *unevaluable*
rHuPH20 Ab unevaluable	rHuPH20 Ab *unevaluable*	rHuPH20 Ab *unevaluable*	rHuPH20 Ab *unevaluable*		rHuPH20 Ab *unevaluable*

Ab=antibody; rHuPH20= recombinant human hyaluronidase PH20

[a] Samples with missing titer have as reported rHuPH20 Ab result 'positive immuno-depletion';

[b] Results reported as 'negative titer', ie, 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 immuno-depletion), rHuPH20 Ab positive with titer < 5 ('negative titer' as reported rHuPH20 Ab result, titer value set to 5), rHuPH20 Ab positive with titer ≥ 5 (ie, positive titer and selecting the sample with highest titer)

[d] Note: Fourfold difference in titer values is considered significant in case a twofold serial dilution is applied (reference to Shankar et al., 2014).

rHuPH20 Ab evaluable participant = participant classified in 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', and the latter two are classified as 'rHuPH20 Ab positive'.

rHuPH20 Ab unevaluable participant = participant classified as rHuPH20 Ab unevaluable or with missing baseline rHuPH20 Ab sample or without postbaseline rHuPH20 Ab samples (in case no rHuPH20 Ab data are available at all, the participant cannot be classified);

Anti-rHuPH20 Ab incidence = percentage of participants with treatment-induced or treatment-boosted rHuPH20 Ab (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 (ie, the ADA negative samples) are per default NAb negative. Additionally, if a NAb sample is not reported for ADA confirmed positive samples, the NAb sample status is NAb unevaluable.

All samples evaluated in the NAb assay will be scored as NAb positive, NAb negative or NAb unevaluable. Based on these results, the participants will be categorized according to their baseline and postbaseline sample status as detailed in Table 15.

Table 15: Participant classification for NAb against efgartigimod

Participant NAb classification	**Highest[a] post baseline NAb sample status**		
	NAb negative	**NAb positive**	**NAb unevaluable**
Baseline NAb sample status			
NAb negative	baseline neg – postbaseline neg	baseline neg – postbaseline pos	*NAb unevaluable*
NAb positive	baseline pos – postbaseline neg	baseline pos – postbaseline pos	*NAb unevaluable*
NAb unevaluable	*NAb unevaluable*	*NAb unevaluable*	*NAb unevaluable*

NAb=neutralizing antibody; neg=negative; pos=positive
[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 postbaseline NAb samples (in case no NAb data are available at all, the participant cannot be classified)

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

NAb prevalence = percentage of participant with participant classification 'baseline neg – postbaseline pos', 'baseline pos – postbaseline pos' or 'baseline pos – postbaseline 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 against rHuPH20 assay. All samples that were not analyzed in the rHuPH20 NAb assay (ie, the rHuPH20 Ab negative samples) are by default rHuPH20 NAb negative.

Additionally, if a rHuPH20 NAb sample is not reported, the rHuPH20 NAb sample status is rHuPH20 NAb unevaluable.

For NAb against rHuPH20, all samples evaluated in this NAb assay will be reported by the lab and scored as per Figure 1. Based on these results, participants will be categorized according to their baseline and postbaseline sample status as detailed in following Table 16.

Table 16: 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 numerical titer value)**		**rHuPH20 NAb un 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 < 4x baseline titer:** Treatment-unaffected rHuPH20 NAb	**titer ≥ 4x baseline titer:** Treatment-boosted rHuPH20 NAb	*rHuPH20 NAb unevaluable*
rHuPH20 NAb un evaluable	*rHuPH20 NAb unevaluable*	*rHuPH20 NAb unevaluable*	*rHuPH20 NAb unevaluable*		*rHuPH20 NAb unevaluable*

NAb=neutralizing antibody; rHuPH20= recombinant human hyaluronidase PH20

[a] Samples with missing titer will be reported as having an rHuPH20 NAb result of 'positive immunodepletion' or 'positive titer';

[b] Results reported as 'negative titer', ie, titer value <100 will be set to a 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 (ie, actual titer value and selecting the sample with highest titer) .

rHuPH20 NAb evaluable participant = participant classified in 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', and the latter two as 'rHuPH20 NAb positive';

rHuPH20 NAb unevaluable participant = participant classified as rHuPH20 NAb unevaluable or with missing baseline rHuPH20 NAb sample or without postbaseline rHuPH20 NAb samples (in case no rHuPH20 NAb data are available at all, the participant cannot be classified);

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

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

4.4.3 Presentation of results

Analysis will be performed 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 visit. This will be repeated for following subgroups: receiving concurrent ITP therapies at baseline, and type of concurrent ITP therapies at baseline.

Frequency tabulations (number and percentages) for efgartigimod and rHuPH20 will be provided on:

- participants per ADA or rHuPH20 Ab participants classification
- prevalence and incidence of ADA or rHuPH20 Ab
- ADA or rHuPH20 Ab unevaluable participants
- ADA or rHuPH20 Ab baseline positive/negative/unevaluable 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 efgartigimod ADA participants classification (Treatment-unaffected ADA, Treatment-induced ADA, Treatment-boosted ADA, ADA negative and ADA unevaluable).
- NAb against rHuPH20 Ab positive participants within rHuPH20 Ab participants classification.
- rHuPH20 Ab positive participants within efgartigimod ADA participants classification.

Correlation tables by ADA and NAb participant classification against efgartigimod and by antibodies participant classification against rHuPH20 will be provided for the following parameters:

- Mean drug concentration over time
- Mean percent change from baseline in platelet count
- Mean percent change from baseline in total IgG
- Number and percentage of sustained platelet count response (key secondary endpoint (week 19 – 24) in the overall population)
- Overall Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Overall Anti-Drug Antibodies Participant Classification (All Participants)

- Overall Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Overall Anti-Drug Antibodies Participant Classification (All Participants)
- Overall injection-related reactions (IRR) by Overall Anti-Drug Antibodies Participant Classification (All Participants)
- Overall injection site reactions (ISR) by Overall Anti-Drug Antibodies Participant Classification (All Participants)

Correlation tables on mean drug concentration over time, on mean percent change from baseline in platelet count, on mean percent change from baseline in total IgG and on number and percentage of sustained platelet count response can be restricted to the efgartigimod treated participants only. The other correlation tables must be provided for efgartigimod and placebo treated participants.

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, and rHuPH20 Ab and rHuPH20 NAb will be listed, showing also the ADA and NAb 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 PTs using MedDRA version 26.0. For each AE, start and stop date/times are collected as well as severity National Cancer Institute common toxicity criteria for adverse events [NCI CTCAE] v5.0[8], a seriousness flag, treatment relatedness, relatedness to procedures, action taken towards the study drug, outcome, and AE of special interest (AESI) category (bleeding events, infections).

5.1.2 Derivation rules

Treatment-emergent adverse events (TEAE) are defined as AEs starting on or after first dose of IMP and up to and including 60 days after latest dose prior to the event. In case of a (partially) missing AE start date/time, the event will be considered as treatment-emergent, unless the available parts of the AE start date/time provide evidence not to do so.
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 1 phase. Phases are defined in section 2.2.1, Table 2. In case the AE start date/time is incomplete or missing and the AE could consequently be allocated to more than 1 phase, a worst-case allocation will be done: 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 screening phase/follow-up phase. AESIs will also be allocated to analysis periods (see section 2.2.1, Table 3). In case the AESI start date/time is incomplete or missing and the AESI could consequently be allocated to more than 1 period, it will be allocated to the first possible period.

Death is not considered an AE in itself but a 'fatal' outcome of an SAE.

An AE for which the study drug was discontinued is defined as an AE with action taken 'drug withdrawn'.

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

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

AND occurring within 48 hours of an injection, 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 PTs in the MedDRA high level term of "injection site reactions", regardless of the time of onset.

Two AESI types will be used: 'Bleeding events' as recorded on the AE section of the CRF and 'Infections' as defined using the MedDRA system organ class (SOC) 'Infections and infestations'.

Adverse events of hypersensitivity are defined as AEs with a MedDRA preferred term listed in the MedDRA Hypersensitivity SMQ broad selection.

Anaphylactic adverse events are defined as AEs with a MedDRA preferred term listed in the MedDRA Anaphylactic reaction SMQ broad selection

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

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

- AE onset day (versus first administration) =
  - AE start date ≥ date of first administration: AE start date – date of first study drug administration + 1 day
  - AE start date < date of first administration: AE start date – date of first study drug administration
- AE duration (days) =
  - AE end date – AE start date + 1 day
  - 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) is defined as 100 * the number of treatment-emergent events divided by the sum of the follow-up time during which an event is considered treatment-emergent of all participants per treatment expressed in years (ie, divided by 365.25).

5.1.3 Presentation of results

Tables will present TEAEs only. The AEs will be presented for the overall study duration, including AEs during the follow up. Pre-treatment AEs will only be listed.

An overview table will show the number and percentage of participants with at least 1 event and the number of events for the following:

- TEAEs
- Serious TEAEs
- Non serious TEAEs
- Grade ≥ 3 TEAEs
- Fatal TEAEs
- Treatment related TEAEs according to the principal investigator
- Procedures related TEAEs

- Serious treatment related TEAEs
- TEAEs for which the study was discontinued
- TEAEs for which the study drug was discontinued
- TEAEs for which the study drug was interrupted
- TEAEs of special interest: bleeding events
- TEAEs of special interest: infections
- ISR TEAEs
- IRR TEAEs
- TEAEs of hypersensitivity
- TEAEs of anaphylactic reaction

In addition, the number of events per participant years on study will be added to the overview table.
The overview table will be repeated, overall and by 12-week period (as defined in Table 3), specifically for ISR events, omitting the records related to TEAEs of special interest and ISR events.
Summary tables by MedDRA SOC and PT will show the number and percentage of participants with at least one event. The table of TEAEs will additionally show the number of events. The table of ISR events will be presented overall and by 12-week period (as defined in Table 3).

Summary tables by MedDRA SOC and PT will show the number and percentage of participants with at least 1 event. The table of TEAEs will additionally show the number of events.

Separate tables will be prepared for the following TEAEs:

- Serious TEAEs
- Non serious TEAEs
- Grade ≥3 TEAEs
- Fatal TEAEs
- Treatment related TEAEs according to the Principal Investigator
- TEAEs related to study procedures
- Serious treatment-related TEAEs
- TEAEs leading to discontinuation from the study
- TEAEs leading to discontinuation of study drug
- TEAEs for which the study drug was interrupted
- TEAEs of special interest: bleeding events
- TEAEs of special interest: infections
- ISR events
- Serious ISR events
- IRR events
- Serious IRR events
- TEAEs of hypersensitivity

- TEAEs of anaphylactic reaction

Tables on TEAEs, serious TEAEs, hypersensitivity and anaphylactic events will be repeated by ADA and NAb against efgartigimod participant classification and by antibodies against rHuPH20 participant classification.

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

5.2 CLINICAL LABORATORY EVALUATION

5.2.1 Available data

Per CTP, the following laboratory parameters are expected:

- Biochemistry: creatinine, creatinine clearance (BSA adjusted), 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), uric acid, albumin, potassium, sodium, total calcium, hemoglobin A1c (HbA1c), cholesterol (total cholesterol, high density lipoprotein [HDL], low density lipoprotein [LDL]), triglycerides, apolipoprotein B, lipoprotein A.
- Hematology: hemoglobin, white blood cell (WBC) count with WBC differentials, fibrinogen, von Willebrand factor, D-dimer.
- Urinalysis: color, clarity/appearance, specific gravity, pH, protein, glucose, ketones, blood, bilirubin, urobilinogen, nitrite, leukocyte esterase, and microscopic examination including red blood cell (RBC) count, WBC, casts, crystals, bacteria.

Normal ranges are available as provided by the laboratory.

5.2.2 Derivation rules

The following parameters will be derived:

- Estimated glomerular filtration rate (eGFR) (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]) (mL/min/1.73m^2) = 141 * minimum(creatinine [mg/dL]/ K; 1)$^{\alpha}$ * maximum(creatinine [mg/dL]/K; 1) $^{-1.209}$ * 0.993 $^{\text{age (years)}}$ * [1.018 if female] * [1.159 if race = black]

  where K = 0.7 if female and K = 0.9 if male; α = -0.329 if female and α = -0.411 if male
- The following abnormality categories will be defined:
  - 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

  Note:
  - Classification will be done in standardized units, using non-imputed values and limits.
  - 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 postbaseline values.

Toxicity grades will be computed according to the NCI CTCAE toxicity grading list (version 5.0[8]). The implementation of these toxicity grades for analysis is presented in appendix 9.3. Additional study-specific toxicity gradings will be applied as defined in appendix 9.4. Only the parameters described in appendices 9.3 and 9.4 will be computed, according to the declared limits for each grade.

5.2.3 Presentation of results

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

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. Categorical urinalysis results will be listed only. Only central lab (ie, CERBA research) assessments will be considered in the table, except for the worst-case analysis visit, where specific rules hold.

Laboratory abnormalities will be presented as cross-tabulations of the abnormality at each postbaseline analysis visit and at the worst-case analysis visit versus the baseline abnormality. Numbers of participants with treatment-emergent abnormalities (see Definition of terms) will also be shown. The denominator for the percentage is the total number of participants having data for the parameter per treatment and per analysis visit in the safety analysis set. Both central laboratory and local laboratory assessments will be considered in the table.

Laboratory toxicity grades will be presented as cross-tabulations (shift table) of the toxicity (NCI-CTCAE grades) at each postbaseline analysis visit and at the worst-case analysis visit versus the baseline toxicity. Numbers and cumulative numbers over decreasing toxicity grading of participants with treatment-emergent toxicities

will also be shown. The denominator for the percentage is the total number of participants having data for the parameter 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 central laboratory assessments and the subset of local laboratory assessments for which toxicity grades are defined based on local normal ranges only (ie, parameters flagged in appendix 9.3 and 9.4) will be considered in the table. The worst-case analysis visit of a participant will only be considered in the cross-tabulation if the laboratory parameter is flagged in appendix 9.3 or 9.4 or if the parameter is not flagged but all the baseline and postbaseline assessments of the participant are from the central lab.

The tables will only show analysis visits as expected per SoA (including the follow-up phase).

All laboratory data will be listed, but only for participants with any postbaseline abnormality.

5.3 VITAL SIGNS

5.3.1 Available data

The following VS parameters are collected: systolic (SBP) and diastolic blood pressure (DBP) in supine position, pulse rate, body temperature and weight (weight will be measured at screening and at any IMP injection visit).

5.3.2 Derivation rules

Abnormalities are defined in Table 17.

Table 17: Abnormalities for VS parameters

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

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

5.3.3 Presentation of results

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

Abnormalities will be presented as cross-tabulations of the abnormality at each postbaseline analysis visit versus the baseline abnormality and as cross-tabulations of the worst-case abnormality versus the baseline abnormality. Numbers of participants with treatment-emergent abnormalities will also be shown.

The tables will only show analysis visits as expected per SoA (including the follow-up phase).

All VS data will be listed, but only for participants with any postbaseline abnormality.

5.4 ELECTROCARDIOGRAMS

5.4.1 Available data

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

5.4.2 Derivation rules

Abnormalities for HR, QRS and PR interval are defined in Table 18.

Table 18: Abnormalities for ECG parameters

	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 postbaseline values.

For QTcF and QTcB interval (ms), the following categories are defined:

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

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

5.4.3 Presentation of results

Uncorrected QT interval and RR 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 cross-tabulations of the abnormality at each postbaseline analysis visit, and at the worst-case analysis visit versus the baseline abnormality. Numbers and cumulative numbers over decreasing abnormalities (QTcF and QTcB only) of participants with treatment-emergent abnormalities will also be shown. 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 tabulations of the change from baseline abnormality at each postbaseline analysis visit and at the worst-case analysis visit. Cumulative numbers over decreasing change from baseline abnormalities of participants will also be shown. The denominator for the percentage is the total number of participants per treatment and per analysis visit in the safety analysis set.

The tables will only show analysis visits as expected per SoA (including the follow-up phase).

All ECG data will be listed, but only for participants with any postbaseline 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 CTP AMENDMENTS BEFORE DATABASE LOCK

The primary endpoint will be analyzed using a Cochran-Mantel-Haenszel statistic stratified for each stratum formed by the combination of the stratification factors and by stratification factors. The stratification factors will be history of splenectomy (yes versus no) and receiving concurrent ITP therapies at baseline (yes versus no), and baseline platelet count level category ($<15\times10^9$/L versus $\geq15\times10^9$/L). See section 4.1.3.2 for more details.

Following extra analyses are not covered in the CTP. See section 4.1.2.4 for derivation details.

[redacted]

The definition of the PK analysis set as specified in this SAP deviates from the definition of the CTP. The definition was updated to specify that placebo participants are excluded from the PK analysis set.

6.2 CHANGES NOT COVERED BY CTP AMENDMENTS AFTER DATABASE LOCK

NA

6.3 CHANGES TO THE FINAL STATISTICAL ANALYSIS PLAN

NA

7. REFERENCES

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14.3.1.19	Serious Injection Related Reactions by MedDRA System Organ Class and Preferred Term	SAF	
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16.2.2.2	Violations on Eligibility Criteria	FAS
16.2.2.3	No-Treatment Participants	SCR minus SAF
16.2.3.1	Participants Excluded from the Efficacy Analysis	FAS
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16.2.4.2	Baseline Disease Characteristics	SAF
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9. APPENDICES

9.1 SAS CODE

9.1.1 Cochran-Mantel-Haenszel test

9.1.2 *Exact conditional logistic regression*

[redacted]

9.1.3 *Stratified Mann-Whitney Test*

[redacted]

9.1.4 *Mixed Model for Repeated Measurements*

[redacted]

9.1.5 Cox Proportional Hazards Regression

[redacted]

9.1.6 95% CI for difference in proportions (Agresti-Min)

[redacted]

9.1.7 Kaplan-Meier estimates

[redacted]

9.2 ITP-PAQ SCALES AND QUESTIONS

SCALE		QUESTIONS	N[c]	M[d]
Physical health:	Symptoms	Q1-Q6	6	5
	Bother	Q11-Q13	3	5 (Q11) or 7 (Q12; Q13)
	Fatigue	Q7-Q10	4	5
	Activity	Q14-Q15	2	5
Emotional health:	Fear	Q21-Q25	5	5
	Psychological health	Q16-Q20	5	5
Work[a]		Q41-Q44	4	5
Social activity		Q31-Q34	4	5
Women's reproductive health:	Menstrual symptoms[b]	Q35-Q37	3	5
	Fertility[b]	Q38-Q40	3	5
Overall QoL		Q26-Q30	5	7 (Q26; Q27) or 4 (Q28-Q30)

[a] For those who work for pay
[b] For women only
[c] N is the number of questions in the scale
[d] M is the number of possible answers

9.3 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.

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

Creatinine[3]		>1.0-1.5 *ULN	>1.5-3.0 *ULN	>3.0-6.0 *ULN	>6.0 *ULN
Gamma-glutamyl transferase[3]		>1.0-2.5 *ULN	>2.5-5.0 *ULN	>5.0-20.0 *ULN	>20.0 *ULN
Glucose (fasting) low [1,2]	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[3]		>1.0-1.5 *ULN	>1.5-2.0 *ULN	>2.0-5.0 *ULN	>5.0 *ULN
Magnesium low [1]	mmol/L	<LLN-0.5	<0.5-0.4	<0.4-0.3	<0.3
	mg/dL	<LLN-1.2	<1.2-0.9	<0.9-0.7	<0.7
Magnesium high [1]	mmol/L	>ULN-1.23	-	>1.23-3.30	>3.30
	mg/dL	>ULN-3.0	-	>3.0-8.0	>8.0
Potassium low [1]	mmol/L	-	<LLN-3.0	<3.0-2.5	<2.5
	mEq/L	-	<LLN-3.0	<3.0-2.5	<2.5
Potassium high [1]	mmol/L	>ULN-5.5	>5.5-6.0	>6.0-7.0	>7.0
	mEq/L	>ULN-5.5	>5.5-6.0	>6.0-7.0	>7.0
Sodium low [1]	mmol/L	<LLN-130	-	<130-120	<120
	mEq/L	<LLN-130	-	<130-120	<120
Sodium high [1]	mmol/L	>ULN-150	>150-155	>155-160	>160
	mEq/L	>ULN-150	>150-155	>155-160	>160
Triglycerides	mmol/L	1.71-3.42	>3.42-5.70	>5.70-11.4	>11.4
	mg/dL	150-300	>300-500	>500-1000	>1000
Partial thromboplastin time (activated or not specified[3]		>1.0-1.5 *ULN	>1.5-2.5 *ULN	>2.5 *ULN	-
CD4 count [1]	giga/L	<LLN-0.50	<0.50-0.20	<0.20-0.05	<0.05

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

[1] In case ULN/LLN is higher/lower than the upper/lower limit of grade 1 (or even higher grades), ULN/LLN will be ignored and only the fixed values of CTCAE will be considered. In case ULN/LLN is missing, a grade will only be derived if the value leaves no doubt on which grade is to be assigned.
[2] 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).

[3] Local lab assessments of this lab parameter can be considered in the lab toxicity table.

9.4 TOXICITY GRADES THAT ARE NOT COVERED BY CTCAE, V5.0

Table 19: Toxicity Graded that are not Covered by CTCAE, v5.0

PARAMETER	Unit	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Hemoglobin decreased (anemia)	g/L	<LLN – 100	<100 – 80	<80	-
Hemoglobin increased[1]	g/L	>ULN – (ULN + 20)	>(ULN + 20) – (ULN + 40)	>(ULN + 40)	-
White blood cell (WBC decreased)	giga/L	<LLN – 3.0	<3.0 – 2.0	<2.0 – 1.0	<1.0
White blood cell (WBC) (leukocytosis)	giga/L	-	-	>100	-
Prothrombin Time (PT)[1]		>ULN – 1.5 *ULN	>1.5 *ULN – 2.5 *ULN	>2.5 *ULN	-
BSA adjusted creatinine clearance decreaseddecreased	mL/min/1.73m^2	< LLN – 60	<60 – 30	<30 – 15	<15
Blood urea nitrogen[1]		>ULN - ≤1.5 *ULN	>1.5 *ULN - ≤3.0 *ULN	>3.0 *ULN - ≤6.0 *ULN	>6.0 *ULN

[1] Local lab assessments of this lab parameter can be considered in the lab toxicity table.

9.5 SCHEDULE OF ASSESSMENTS

9.5.1 Global study ARGX-113-2004 V6.0

Trial Period[a]		Treatment Period																							End-of-Treatment	Early Discontinuation	Follow-up 1	Follow-up 2	Unscheduled
Visit	Screening	1 Baseline	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24					
Trial day	*-14 to -1*	*1*	*8*	*15*	*22*	*29*	*36*	*43*	*50*	*57*	*64*	*71*	*78*	*85*	*92*	*99*	*106*	*113*	*120*	*127*	*134*	*141*	*148*	*155*	*162*	*169*				
Visit window, days			+2																											
Informed consent form[b]	X																													
Inclusion/exclusion criteria	X	X[c]																												
Medical/surgical history	X																													
Demographic data	X																													
Platelet count[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
			Can be performed within 1 day of the next procedure																											
SF-36(v2)		X								X								X							X	X				
ITP-PAQ[e]		X												X											X	X				
FACT-Th6/FACIT-fatigue scale		X				X				X				X				X				X				X	X			
Weight	X									X								X							X	X	X			
Vital signs, including height[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X				X				X								X							X	X	X			X
Electrocardiogram	X	X[g]				X[g]				X[g]				X[g]				X[g]				X[g]			X[g]	X	X	X		X
General bleeding assessment (WHO)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[h]	X[i]	X	X	X	X		X		X		X		X		X		X		X		X		X		X	X	X	X	X	X
Urine pregnancy test[j]		X				X				X				X				X				X				X	X	X	X	X
Hematology and chemistry test[h]	X[i,k]	X	X	X	X		X		X		X		X		X		X		X		X		X		X	X	X	X	X	X
Serum pregnancy test[h,j]	X[i]																													
Follicle-stimulating hormone[h,l]	X[i]																													
Coagulation, thyroid, and autoimmune antibody testing[h]	X[i]																													
Viral tests[h]	X[i]																													
Tuberculosis QuantiFERON test[h]		X																												
Pharmacodynamics[h,m,n]		X	X	X	X		X[o]		X[o]		X[o]		X[o]		X[o]		X[o]		X[o]		X[o]		X[o]		X[p]	X	X	X	X	X
Antiplatelet antibodies[h,n]		X							X[o]								X[o]								X[p]	X	X			X
Immunogenicity[h,n]	X	X			X				X[o]				X[o]				X[o]				X[o]				X[p]	X	X	X	X	X
[redacted]																														

SGS	Statistical Analysis Plan	
ARGX-113-2004	Final analysis	Final 1.0 of 7NOV2023

Trial Period[a]	Screening	Treatment Period																							End-of-Treatment	Early Discontinuation	Follow-up 1	Follow-up 2	Unscheduled
Visit		1 Baseline	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24					
Trial day	*-14 to -1*	*1*	*8*	*15*	*22*	*29*	*36*	*43*	*50*	*57*	*64*	*71*	*78*	*85*	*92*	*99*	*106*	*113*	*120*	*127*	*134*	*141*	*148*	*155*	*162*	*169*				
Visit window, days			+2																											
Pharmacokinetics[h,n]		X	X	X	X		X[o]		X[o]		X[o]		X[o]		X[o]		X[o]		X[o]		X[o]		X[o]		X[p]	X	X	X	X	X
Randomization[r]		X																												
IMP administration[s]		X	X	X	X	‹---------- qw or q2w administration ----------›																									
Caregiver informed consent form[t]																‹---------- X ----------›														
IMP (self-)administration training[s,u]																‹---------- X ----------›														
Collecting information related to hospitalization for ITP management	‹---------- X ----------›																													
Concomitant therapies/procedures[v]	‹---------- X ----------›																													
Adverse events[v]	‹---------- X ----------›																													

FACIT-Fatigue=Functional Assessment of Chronic Illness Therapy-Fatigue; FACT-Th6=Functional Assessment of Cancer Therapy-Th6; IMP=investigational medicinal product; ITP=immune thrombocytopenia; ITP-PAQ=ITP-Patient Assessment Questionnaire; qw=weekly; q2w=every other week; SF-36 (v2)=Short Form 36 (version 2); WHO=World Health Organization

[a] **Trial Period:**

Screening Period: maximum 14 days

Treatment Period: Weekly subcutaneous (SC) IMP administrations for visit 1 up to and including visit 4. As of visits 5 to 16, a qw or q2w IMP administration schedule will be followed. From visits 17 to 24, participants will be fixed on the dose schedule they were receiving at visit 16 or at the last visit at which IMP was administered (ie, either qw or q2w). There is a permissible visit window of +2 days during the treatment phase as well as the follow-up period. Every effort should be made to schedule every visit on the exact day (which is relative to baseline randomization [visit 1]).

The frequency (ie, qw or q2w) of IMP administrations depends on predefined criteria set forward in Section 6.5 of the protocol.

End-of-Treatment: This visit should be performed on trial day 169 (+2 days) (ie, 7 days [+2 days] after the last dosing visit) for all participants who have completed the 24-week treatment period, whether they were still receiving IMP or not. Every effort should be made to schedule every visit on the exact day (which is relative to baseline randomization [visit 1]).

Early Discontinuation: This visit should be performed on the day of early discontinuation for all participants that discontinue the trial early.

Follow-up Period: For participants discontinuing the trial early (with the exception of participants who withdraw their consent) or who do not roll over to the open-label extension trial. The follow-up period will consist of 2 visits q4w (ie, 8 weeks of follow-up).

[b] No trial-related assessment must be carried out before signing the informed consent form (ICF).

[c] For further confirmation of eligibility at visit 1, the assessment of inclusion and exclusion criteria should be performed prior the start of any trial-related procedure and randomization.

[d] [redacted]

[redacted]

[e] If available at baseline.
[f] Height will only be measured at the screening visit.
[g] If IMP is administered, the ECG will be performed after the IMP administration.
[h] Laboratory assessments include all parameters mentioned in Section 10.2. On days that IMP is administered, samples for laboratory assessments should be collected before dosing, unless otherwise requested.
[i] At the screening visit, if the investigator detects 1 or more screening laboratory abnormalities which are not aligned with the medical history and clinical evaluation of the participant, the result(s) should be confirmed if still within the screening window. For rescreening criteria see Section 5.4.
[j] Only for women of childbearing potential.
[k] At the screening visit, the total IgG level must be determined by the central laboratory (exclusion criterion 9).
[l] Only for women of non-childbearing potential.
[m] To maintain the blind, the IgG testing cannot be performed locally.
[n] To be collected predose, on the day of IMP administration.
[o] If the visit does not coincide with an IMP administration, then the assessment should be performed at the next IMP visit.
[p] If the visit does not coincide with an IMP administration, then the assessment should **NOT** be performed.
[q] Only in investigative sites participating in the platelet functionality substudy. To be collected as the last sample predose.
[r] Randomization to be completed before administration of IMP.
[s] Participants or their caregivers will be invited to receive training to (self-)administer the IMP while under supervision at least 4 times in the last 10 weeks, until they are capable of and comfortable with the (self-)administration ([self-]administration without supervision is foreseen only in the open-label extension trial ARGX-113-2005, not in ARGX-113-2004).
[t] To be obtained before initiation of the IMP administration training.
[u] The IMP (efgartigimod PH20 SC or placebo PH20 SC) will be administered as an SC injection at each IMP administration visit. Participants will remain at the trial site for at least 30 minutes following the end of the injection for routine safety monitoring based on the participant's clinical status. Assessment of the dosing regimen as described in Section 6.5 will be applied.
[v] Adverse events, procedures, and intake of concomitant medication(s) will be monitored continuously from signing the ICF until the last trial-related activity, unless the participant withdraws consent. In case of early discontinuation, any adverse events/serious adverse events should be assessed until the participant has ended the trial or until satisfactory resolution or stabilization. All available vaccination history will be recorded as part of the participant's prior medication for vaccinations received in the past, or concomitant medication for vaccinations received during the trial.

9.5.2 Specific protocol amendments

Refer to the specific CTP amendments for a detailed SoA per country.