# STATISTICAL ANALYSIS PLAN

**A Phase 3, Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Efgartigimod (ARGX-113) 10 mg/kg Intravenous in Adult Patients With Primary Immune Thrombocytopenia**

| | |
|---|---|
| **Protocol:** | ARGX-113-1801 |
| **SGS CR number:** | BE-80-1807371 |
| **Development phase:** | Phase 3 |
| **Sponsor:** | argenx |
| **Analysis purpose:** | Final analysis |
| **SAP version number:** | Final 1.0 |
| **SAP version date:** | 28MAR2022 |

# SIGNATURE PAGE

| **Name and function** | **Date (ddMMMyyyy) and Signature** |
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| Sponsor's approval:<br>The approver agrees the statistical analysis will be performed according to this statistical analysis plan. | |
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# PROTOCOL HISTORY

| **Protocol:** | | |
|---|---|---|
| **Version or ID** | **Date (ddMMMyyyy)** | **Impact of the changes on the statistical analysis** |
| Final 1.0 | 23MAY2019 | NAP |
| Final 2.0 | 09SEP2019 | No |
| Final 3.0 | 18SEP2019 | No |
| Final 4.0 | 27MAY2020 | No |
| Final 5.0 | 16NOV2020 | No |
| Final 6.0 | 15JUL2021 | Change in analysis of primary endpoint and definition of FAS, per FDA recommendations |

| **Japan specific protocol:** | | |
|---|---|---|
| **Version or ID** | **Date (ddMMMyyyy)** | **Impact of the amendment on the statistical analysis** |
| Final 3.1 | 4OCT2019 | Japan-specific |
| Final 3.2 | 12NOV2019 | Japan-specific |
| Final 4.1 | 17JUN2020 | Japan-specific |
| Final 5.1 | 25NOV2020 | Japan-specific |
| Final 6.1 | 20JUL2021 | Japan-specific |

| **France specific protocol:** | | |
|---|---|---|
| **Version or ID** | **Date (ddMMMyyyy)** | **Impact of the amendment on the statistical analysis** |
| Final 3.1 | 16JAN2020 | France-specific |
| Final 4.1 | 10JUN2020 | France-specific |
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| **Serum Pregnancy Test protocol:** | | |
|---|---|---|
| **Version or ID** | **Date (ddMMMyyyy)** | **Impact of the amendment on the statistical analysis** |
| Final 4.1 | 03JUL2020 | Serum Pregnancy-specific |
| Final 5.1 | 26NOV2020 | 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 toxicity 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 | infusion-related reaction |
| IRT | interactive response technology |
| ITP | immune thrombocytopenia |
| 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 |
| SAP | statistical analysis plan |
| SAE | serious adverse event |
| SAF | safety analysis set |
| SBP | systolic blood pressure |
| SCR | all screened patients 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 patient. |
| display | Analysis table, figure or listing. |
| 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 post-baseline abnormality/toxicity that was not present at baseline (e.g. hemoglobin normal at baseline and grade 1 post-baseline; glucose low at baseline and high post-baseline; QTcFri ]450; 480] ms at baseline and >500 ms post-baseline) |

# TABLE OF CONTENTS

# 1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the final statistical analysis to be performed for the ARGX-113-1801 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 compared to placebo in achieving a sustained platelet count response in patients with primary chronic immune thrombocytopenia (ITP), with a sustained platelet count response defined as platelet counts of at least $50\times10^9$/L for at least 4 of the 6 visits between week 19 and 24 of the study.

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

- To evaluate the efficacy of efgartigimod compared to placebo in overall platelet count response.
- To evaluate the safety and tolerability of efgartigimod administered intravenously (IV) weekly (qw) or every other week (q2w).
- To evaluate the incidence and severity of bleeding events while receiving treatment with efgartigimod compared to placebo.
- To evaluate the use of rescue treatment and changes in concurrent ITP therapy while receiving treatment with efgartigimod compared to placebo.
- To evaluate the effects of efgartigimod treatment on Quality of Life (QoL) measures and Patient Reported Outcomes (PRO) compared to placebo.
- To assess the immunogenicity of efgartigimod.
- To assess the PK of efgartigimod.
- To assess the PD effects of efgartigimod.

According to the CTP, the exploratory objective is:

- [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 $50\times10^9$/L for at least 4 of the 6 visits between week 19 and 24 of the study.

Patients 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. Patients 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 $50\times10^9$/L for at least 4 of the 6 visits between week 19 and 24 of the study.
- Incidence and severity of the WHO-classified bleeding events in the overall population.
- Proportion of patients in the overall population achieving platelet counts of at least $50\times10^9$/L for at least 6 of the 8 visits between week 17 and 24 of the study

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

- Percentage 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.
- Percentage 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 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 $\geq50\times10^9$/L.
- 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.
- The number of cumulative weeks over the planned 24-week treatment period with platelet counts $\geq30\times10^9$/L and at least $20\times10^9$/L above baseline.

- In patients with baseline platelet count of $<15\times10^9$/L, the number of cumulative weeks over the planned 24-week treatment period with platelet counts of $\geq30\times10^9$/L and at least $20\times10^9$/L above baseline.
- Change from baseline in PROs (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 of anti-drug antibodies (ADA) to efgartigimod.
- Pharmacokinetic parameters of efgartigimod: maximum observed serum concentration ($C_{max}$) and serum concentration observed predose ($C_{trough}$).
- Pharmacodynamics markers: Total IgG, IgG isotypes (IgG1, IgG2, IgG3, IgG4), antiplatelet antibody levels.

**Safety Evaluation:**

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

**Exploratory Endpoint:**

- [redacted]

## 1.3 STUDY DESIGN

This is a phase 3, multicenter, randomized, double-blinded, placebo-controlled, parallel-group, up to 31-week study to evaluate the efficacy, safety, and impact on QoL of efgartigimod 10 mg/kg IV treatment in adult patients with primary ITP.

The total maximum study duration per patient is up to 31 weeks:

- a screening period of up to 2 weeks
- a treatment period of 24 weeks where all patients will receive IV infusions of efgartigimod 10 mg/kg or placebo
- an End-of-Treatment visit 1 week after visit 24
- a follow-up period of 4 weeks

The target population are adult patients with persistent or chronic primary ITP, having an average platelet count of $<30\times10^9$/L, and at the start of the study being on concurrent ITP treatment(s) and having received at least 1 prior therapy for ITP in the past, or not being on treatment for ITP but having received at least 2 prior treatments for ITP. If patients are receiving concurrent ITP therapies at baseline, these therapies should have been maintained at a stable dose and dosing frequency for 4 weeks prior to randomization. As of week 12, the start or an increase in the dose and/or schedule of permitted concurrent ITP therapy is allowed for patients who have an 'insufficient response' (i.e. no platelet count of $\geq30\times10^9$/L in any of the visits during the last 4 weeks). These patients will be considered as 'non-responders' for the primary endpoint analysis (cfr. section 4.1).

After confirmation of eligibility, the patients enter a 24-week treatment period and will be randomized to receive either efgartigimod 10 mg/kg IV of or placebo, 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, patients will be fixed on the dosing schedule they were receiving at visit 16 or at the last visit at which investigational medicinal product (IMP) was administered (i.e. either qw or q2w). Assessment of the dosing regimen is described in clinical trial protocol (CTP) section 5.4.1. Permitted concurrent ITP medications are described in CTP section 6.8.1.

"Rescue therapy" is defined as an occurrence where the patient 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 study patient. The start date/time of the occurrence is the start of the administration of the first rescue treatment.

Rescue therapy is allowed post-baseline during the 24-week treatment period for patients 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 study 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

Patients completing the 24-week treatment period will perform the End-of-Treatment visit and can enter the open-label extension study (ARGX-113-1803) to receive efgartigimod 10 mg/kg IV. The platelet counts from the ARGX-113-1801 study will be taken into account to assess the dosing frequency in ARGX-113-1803.

Patients who complete the 24-week treatment period but who do not enter the open-label extension study ARGX-113-1803, or patients who discontinue the study early, with the exception of patients who withdraw their consent, will be followed for 4 weeks for ongoing safety and efficacy monitoring.

For patients who discontinue the study early, all the assessments listed for the Early Discontinuation visit as specified in the schedule of assessments (SoA, see appendix 9.4), will be performed.

## 1.4 EXPECTED SAMPLE SIZE

Approximately 117 patients with chronic ITP and up to 39 patients with persistent ITP will be randomized in a 2:1 ratio to receive efgartigimod or placebo, respectively. Recruitment will end as from 117 patients with chronic ITP have been randomized.

Non-Japanese patients will be 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 will be no stratification, i.e. randomization will be 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 $\pi_1$ and $\pi_2$ are the population probabilities to achieve a sustained platelet count response (primary efficacy endpoint) for patients with chronic ITP receiving placebo and for patients with chronic ITP receiving efgartigimod, respectively.

The response rate of placebo patients with chronic ITP reaching the primary endpoint is expected to be [redacted]%, while for efgartigimod patients with chronic ITP a response rate of [redacted]% is expected (i.e. $\pi_1$ = [redacted] and $\pi_2$ = [redacted]). Given these assumptions, a total of N = 117 patients with chronic ITP randomized will ensure a power of at least 90% to reject the null hypothesis at a 1-sided significance level α of 0.025.

For the first key secondary endpoint "extent of disease control," assuming a median 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 of 10 weeks for patients receiving efgartigimod and 3 weeks for patients receiving placebo, a total of N=117 patients will ensure a power of >99% (two-sided α of 0.05) to detect a significant difference between both treatment groups. For ensuring a power of at least 90%, a total number of N=54 patients 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 versus placebo.

## 1.5 RANDOMIZATION AND BLINDING

Approximately 117 patients with chronic ITP and up to 39 patients with persistent ITP will be randomized in a 2:1 ratio to receive efgartigimod or placebo, 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-113-1801 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 patients set (SCR):* | Patients who *signed an informed consent* to participate in this study |
| *Full analysis set (FAS):* | All randomized patients |
| *FAS-chronic* | Patients from the full analysis set including only patients with chronic ITP |
| *Per-Protocol (PP):* | Patients from the full analysis set, excluding the patients having any major protocol deviations |
| *PP-chronic* | Patients from the PP analysis set including only patients with chronic ITP |
| *Safety analysis set (SAF):* | All patients who received at least 1 dose or part of a dose |
| *PK analysis set (PK):* | Safety analysis set excluding placebo patients and including patients with at least one serum post dose PK measurement |
| *PD analysis set (PD):* | Safety analysis set including patients 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 done on the FAS, or FAS-chronic, where applicable. Sensitivity analyses of primary and key secondary efficacy endpoints will be done on the PP, or PP-chronic, where applicable. General characteristics, safety and immunogenicity analyses (ADA, Neutralizing 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 done on the SAF, PK and PD the actual treatment of the patient received will be considered. For analyses on the FAS, and PP, the planned treatment of the patient will be considered.

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

## 2.2 PHASES AND TIME POINTS

### *2.2.1 Phases*

All events and assessments will be allocated to phases (see Table 2). The treatment phase consists of 24 weeks where all patients will receive IV infusions of efgartigimod 10 mg/kg or placebo, including the End-of-Treatment visit, 1week after visit 24. Only for patients who discontinue from the study or do not roll-over to ARGX-113-1803 a follow-up phase of 4 weeks is foreseen.

**Table 2: Phase definition**

| Phase | Start | End |
|---|---|---|
| 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 date of last contact, with 23:59 added as time part (for patients not treated) |
| Treatment | First administration of the IMP date/time | End-of-Treatment visit end date, with 23:59 added as time part (for patients completing the treatment phase and not rolling over to 1803), or End-of-Study date, with 23:59 added as time part (for patients completing the treatment phase rolling over to 1803) or Early Discontinuation visit date, with 23:59 added as time part (for patients 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 patients completing the treatment phase but not rolling over to study ARGX-113-1803). | Date of last contact, with 23:59 added as time part |

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 IgG (total and subtypes), only results from IVD assays will be considered, including 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. Allocation of assessments will be done using their relative day in the phase (see section 2.2.3).

**Table 3: Analysis visits**

| Phase | Analysis window | Target ADY | Lower limit ADY | Upper limit ADY |
|---|---|---|---|---|
| *Screening* | Screening* | -14 | -INF | 1 |
| *Treatment* | Baseline* | 1 | -INF | 1** |
| | Week 1 | 8 | 1** | 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 2 | 14 | 1 | 21 |
| | SEFU Week 4 | 28 | 22 | n[c] |

[a] x=1,…,18; [b]Relative day of End-of-Treatment phase; [c]Relative day of end of follow-up phase
*: As the interval of screening and baseline are overlapping, it may be that the same assessment will be attributed to both timepoints.
**: An assessment on day 1 will be attributed to baseline in case it is before the infusion, to Week 1 otherwise, unless the assessment is related to questionnaires for which time will not be considered and therefore be allocated to baseline. In addition, baseline pre and post dose PK assessments will be attributed to the baseline.

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 patient can have 2 worst-case analysis visits for a same parameter. For toxicity grades the worst-case is the value associated to the highest toxicity grade and is derived per parameter and toxicity direction (hypo / hyper).

All non-missing post-baseline values, including unscheduled assessments will be considered when deriving the worst-case analysis visit.

## 2.3 IMPUTATION AND ROUNDING RULES

### *2.3.1 Missing values*

No imputation will be done of missing values (i.e. observed cases analysis) for safety. 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*

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.

### *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.
- 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 region (Japanese / Non-Japanese 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 submissons 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.

Mean, median, Q1 and Q3 will be presented with 1 more decimal place than the individual values. The SD and SE will be presented with 2 more decimal places than the individual values. Minimum and maximum will be presented with the same number of decimal places as the individual values.

Descriptive statistics for PK concentrations and PK parameters 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 and PK parameters 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. If more than half of the values per time point are BLQ, the arithmetic mean will be reported as BLQ and SD, CV%, geometric mean and geometric CV% will not be calculated. If (one or more) BLQ is reported at a time point, the geometric mean and geometric CV% will not be calculated for that time point.

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

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

### *2.4.2 Presentation of treatments*

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

- efgartigimod
- placebo

In the general characteristics analysis, a grand total will be added to summarize all patients 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 patient, unless specified otherwise.

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

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

The efgartigimod treatment group will always be shown first, then the placebo treatment group.

# 3. GENERAL CHARACTERISTICS ANALYSES

## 3.1 PATIENT DISPOSITION

The following patient data will be tabulated:

- The number of patients in each analysis set
- The number and percentage of patients by country and site
- The number and percentage of patients 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 patients randomized but not treated and of patients who completed or discontinued the trial as documented on the study termination page and the number and percentage of patients for each trial discontinuation reason (including reasons for screen failures).
- The number and percentage of patients who completed or discontinued the treatment as documented on the end of treatment page and the number and percentage of patients for each treatment discontinuation reason.
- The number and percentage of patients who roll over to study ARGX-113-1803.

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 patients with major and minor protocol deviations will be tabulated, overall and per class of deviation.

All available information concerning major and minor protocol deviations, violations on eligibility criteria, patients not treated and patients 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), patient with chronic or persistent ITP, received prior ITP therapy (yes versus no), baseline platelet level, baseline SF-36 (v2), baseline PRO: Functional Assessment of Cancer Therapy questionnaire-Th6 (FACT Th6) questionnaire (Total FACT Th6 score) and Functional Assessment of Chronic Illness Therapy (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: 18-<65 years; 65-<75 years; ≥75 years
- Weight category at baseline: <50 kg, 50-<75 kg, 75 – <120 kg, ≥ 120 kg
- Baseline platelet level category: (<$15\times10^9$/L versus ≥$15\times10^9$/L)
- Ethnicity category: Japanese versus non-Japanese (including Hispanic or Latino, Not Hispanic or Latino, and Not allowed to ask per local regulations)
- Region: country will be categorized into the following regions: United States / Japan / Europe / rest of the world
  - Europe includes EU countries, and EFTA countries (Norway, Iceland, Liechtenstein and Switzerland)
- 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.
- See section 4.1.2.3 for the definitions of FACT Th6, FACIT and the WHO-classified bleeding events.

### *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 and region.

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
- patient 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 24.1. 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

### *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

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

For primary ITP history the following data will be tabulated:

- The number and percentage of patients with chronic and persistent ITP.

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

## 3.5 PRIOR AND CONCOMITANT THERAPIES

### *3.5.1 Available data*

All therapies are coded using the September 2021 version of the WHO-DRUG Dictionary. 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 after first IMP dose date
- New concurrent ITP therapy: started after first IMP dose date

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.

Type of ITP therapy:

- Corticosteroids: selection based on ATC2 = 'H02'
- IVIG, anti-D: selection based on ATC2 = 'J06' or CMDECOD = 'ANTI-D IMMUNOGLOBULIN'
- Thrombopoietin-receptor agonists (TPO-RA): selection based on CMDECOD = ('AVATROMBOPAG MALEATE' or 'AVATROMBOPAG' or 'ELTROMBOPAG' or 'ELTROMBOPAG OLAMINE' or 'ROMIPLOSTIM')
- Fostamatinib: selection based on CMDECOD = ('FOSTAMATINIB' or 'FOSTAMATINIB DISODIUM')
- Other immunosuppressants (azathioprine, cyclophosphamide, cyclosporine A, mophetil mycophenolate, vinca alkaloids): selection based on CMDECOD = ('AZATHIOPRINE' or 'CICLOSPORINE' or 'CYCLOPHOSPHAMIDE' or 'MYCOPHENOLATE MOFETIL' or 'MYCOPHENOLATE SODIUM' or 'SIROLIMUS' or 'VINBLASTINE SULFATE' or 'VINCRISTINE' or 'VINCRISTINE SULFATE')
- Danazol: selection based on ATC4 = 'G03XA'
- Dapsone: selection based on ATC4 = 'J04BA'
- Anti-CD20 (Rituximab): selection based on ATC4 = 'L01XC'
- Other: ITP therapies that are not in any of the previous 9 categories

Rescue ITP therapy will be allocated to the following categories:

- methylprednisolone, dexamethasone, 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'
- 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 patient. 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 6.8.4.

### *3.5.3 Presentation of results*

Prior and concomitant therapies will be tabulated (separately), by ATC class (level 1 and 3) and generic term.

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

Similarly, prior and concurrent ITP therapy and rescue ITP therapy will be tabulated and listed separately. For splenectomy, the generic term is non-informative ('ALL OTHER NON-THERAPEUTIC PRODUCTS') and therefore the analysis category 'splenectomy' will be shown instead.

Prior ITP therapy and concurrent ITP therapy at baseline will also be tabulated (separately) by type of ITP therapy.

## 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.

### *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 q2w administration.

  *Notes*:
  - Dosing is expected at a visit except if reason not done is "DUE TO BIWEEKLY ADMINISTRATION" or "DUE TO PLATELET COUNT > 400X10^9/L"
  - Only visits up to treatment discontinuation are considered in the compliance calculation.
- Cumulative duration of q2w dosing: number of weeks for which the patient was on the q2w dosing regimen
- Dosing frequency will be derived for subjects still being dosed at or after visit 17, based on dosing at CRF visits 14, 15, 16 and 17:
  - Biweekly (q2w): if the patient was not dosed at visit 15 or at visit 16 "DUE TO BIWEEKLY ADMINISTRATION"
  - Else, Weekly: if the patient was dosed at both visit 15 and 16

    Note: in case of missing information at visit 15 and/or 16, a missed visit 15 or 16 is considered as dosed and visits 14 and 17 are also

taken into account. If the patient was dosed at two subsequent visits in this timeframe, dosing frequency is set to weekly.

- Else, Unknown: in case dosing frequency cannot be determined based on the above rules.

### *3.6.3 Presentation of results*

Overall number of administrations, compliance, cumulative duration of q2w dosing and dosing regimen between week 17 and 24 will be summarized using descriptive statistics.

All study drug administration data will be listed.

# 4. EFFICACY, PHARMACOKINETIC, PHARMACODYNAMIC AND IMMUNOGENICITY ANALYSES

## 4.1 EFFICACY

### *4.1.1 Available data*

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

### *4.1.2 Endpoints and derivation rules*

All efficacy endpoints will be analyzed on the overall FAS population or a subset of patients 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 defining the different responses and time to response parameters.

#### *4.1.2.1 PRIMARY ENDPOINT*

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

A patient is considered a responder, i.e. has a sustained platelet count response, if he/she shows platelet counts of at least $50\times10^9$/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 patient is considered a non-responder, if the patient 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 ≥ target 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 ≥ target 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 ≥ target 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 worse-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').*

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 ≥50×109/L in the chronic ITP population.

*Derivation*: total number of analysis visits during the treatment phase with platelet counts of $\geq 50\times10^9$/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.

- 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, i.e. 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 4.

**Table 4: 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) | 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 | Total number of analysis visits during the treatment phase with platelet counts of $\geq50\times10^9$/L up to start date of increase | Event |
| Disease control at end of 24-week treatment period | Total number of analysis visits during the treatment phase with platelet counts of $\geq50\times10^9$/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 patients with a sustained platelet count response (week 19 – 24) in the overall population (chronic and persistent ITP).

*Derivation*: A patient is considered a responder, i.e. has a sustained platelet count response, if he/she shows platelet counts of at least $50\times10^9$/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) 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 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 values for reasons other than the main intercurrent events, will be imputed as described in section 4.1.2.5 (approach 3).

4) Proportion of patients achieving platelet counts of at least 50×109/L for at least 6 of the 8 visits between weeks 17 and 24 of the study in the overall population.

*Derivation*: A patient is considered a responder if he/she shows platelet counts of at least $50\times10^9$/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).

#### *4.1.2.3 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 patients with overall platelet count response defined as achieving a platelet count of ≥50×109/L on at least 4 occasions at any time during the 24-week treatment period.

*Derivation*: a patient is considered a responder if he/she shows platelet count of at least $50\times10^9$/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 ≥50×109/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 patients 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 patient is considered a responder if he/she shows platelet count of at least $50\times10^9$/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 4.1.3.6.

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 items [An5] and [An7] is reversed. A score of more than 30 indicates severe fatigue. The higher the score, the worse 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 4.1.3.6.

   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 4.1.3.6.

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 4.1.3.6

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 patient. 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 patients for whom dose and/or frequency of concurrent ITP therapies have increased at week 12 or later.

*Derivation*: a patient is counted if (start date concurrent ITP therapy ≥ target 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).

8) Time to platelet count response defined as the time to achieve 2 consecutive platelet counts of ≥50×$10^9$/L.

*Derivation*: It will be calculated as the difference between the first assessment date at which the condition '2 consecutive platelet counts ≥50×$10^9$/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 5: Definition for Time to Platelet Count**

| Response Situation | Time to Platelet Count Response | Outcome |
|---|---|---|
| No occurrence of platelet count of ≥ 50× $10^9$/L | Date of last available platelet count*** – first IMP date** + 1 | Censored |
| Early discontinuation of treatment (prior to W24) due to lack of efficacy or due to AE* | Early discontinuation date – first IMP date** + 1 | Censored |
| Dose and/or frequency of concurrent ITP therapy increased* | Concurrent ITP therapy start date – first IMP date** + 1 | Censored |
| Platelet count response | Date (first assessment) – first IMP date** + 1 | Event |

* only applicable if the event (reaching platelet count response) has not occurred before
** or date of randomization for subjects not treated
*** or date of last contact for subject with no platelet count assessments

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×$10^9$/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) ≥ 30×109/L and at least 20×109/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 patients where baseline platelet count $<15\times10^9$/L.

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

10) Mean changes from baseline for:

a) [redacted]

b) [redacted]

Missing values will not be imputed.

11) Number of significant bleeding events where WHO bleeding scale $\geq 2$ at any visit.

*Derivation*: total number of analysis visits for which WHO bleeding scale $\geq 2$. The overall score of the bleeding events per analysis visit will be used, calculated as the max 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 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".

#### *4.1.2.4 OTHER SECONDARY ENDPOINTS NOT FORESEEN PER PROTOCOL (NOT ALPHA CONTROLLED)*

1) Proportion of patients achieving platelet counts of $\geq 30\times10^9$/L on at least one occasion during the 24-week study period.

*Derivation*: a patient is considered a responder if he/she shows platelet count of at least $30\times10^9$/L on at least 1 analysis visit during the 24-week study 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), but imputing $<30\times10^9$/L instead of $<50\times10^9$/L. Missing values not due to intercurrent events will not be imputed.

2) Proportion of patients achieving platelet counts of $\geq50\times10^9$/L on at least one occasion during the 24-week study period.

*Derivation*: a patient is considered a responder if he/she shows platelet count of at least $50\times10^9$/L on at least 1 analysis visit during the 24-week study 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 not be imputed.

3) Proportion of patients achieving platelet counts of $\geq80\times10^9$/L on at least one occasion during the 24-week study period.

*Derivation*: a patient is considered a responder if he/she shows platelet count of at least $80\times10^9$/L on at least 1 analysis visit during the 24-week study 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), but imputing $<80\times10^9$/L instead of $<50\times10^9$/L. Missing values not due to intercurrent events will not be imputed.

4) Proportion of patients achieving platelet counts of $\geq100\times10^9$/L on at least one occasion during the 24-week study period.

*Derivation*: a patient is considered a responder if he/she shows platelet count of at least $100\times10^9$/L on at least 1 analysis visit during the 24-week study 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), but imputing $<100\times10^9$/L instead of $<50\times10^9$/L. Missing values not due to intercurrent events will not be imputed.

5) Proportion of patients achieving platelet counts of $\geq30\times10^9$/L on at least 2 occasions during the 24-week study period.

*Derivation*: a patient is considered a responder if he/she shows platelet count of at least $30\times10^9$/L on at least 2 analysis visits during the 24-week study 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), but imputing $<30\times10^9$/L instead of $<50\times10^9$/L. Missing values not due to intercurrent events will not be imputed.

6) Proportion of patients achieving platelet counts of $\geq50\times10^9$/L on at least 2 occasions during the 24-week study period.

*Derivation*: a patient is considered a responder if he/she shows platelet count of at least $50\times10^9$/L on at least 2 analysis visits during the 24-week study 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 not be imputed.

7) Proportion of patients achieving platelet counts of $\geq80\times10^9$/L on at least 2 occasions during the 24-week study period.

*Derivation*: a patient is considered a responder if he/she shows platelet count of at least $80\times10^9$/L on at least 2 analysis visits during the 24-week study 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), but imputing $<80\times10^9$/L instead of $<50\times10^9$/L. Missing values not due to intercurrent events will not be imputed.

8) Proportion of patients achieving platelet counts of ≥100×109/L on at least 2 occasions during the 24-week study period.

*Derivation*: a patient is considered a responder if he/she shows platelet count of at least $100\times10^9$/L on at least 2 analysis visits during the 24-week study 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), but imputing $<100\times10^9$/L instead of $<50\times10^9$/L. Missing values not due to intercurrent events will not be imputed.

9) Proportion of patients achieving platelet counts of at least $\geq100\times10^9$/L for at least 3 out of 4 consecutive weekly visits during the 24-week study period.

*Derivation*: a patient is considered a responder if he/she shows platelet count of at least $100\times10^9$/L on at least 3 out of any 4 consecutive weekly visits during the 24-week study period. All possible windows of 4 consecutive weekly visits will be taken into account. 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 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.

10) Proportion of patients achieving platelet counts of at least $\geq80\times10^9$/L for at least 3 out of 4 consecutive weekly visits during the 24-week study period.

*Derivation*: a patient is considered a responder if he/she shows platelet count of at least $80\times10^9$/L on at least 3 out of any 4 consecutive weekly visits during the 24-week study period. All possible windows of 4 consecutive weekly visits will be taken into account. 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 $<80\times10^9$/L instead of $<50\times10^9$/L. Missing values not due to intercurrent events will be handled as follows: if platelet count $\geq80\times10^9$/L for the previous and the next analysis visit, the platelet count will be imputed with $\geq80\times10^9$/L, otherwise with $<80\times10^9$/L.

11) Time to achieve a platelet count of $\geq50\times10^9$/L.

*Derivation*: It will be calculated as the difference between the first assessment date at which the platelet counts is $\geq50\times10^9$/L, taking into account all platelet count measurements (also the unscheduled ones), and first IMP intake date.

Time to achieve a platelet count of $\geq50\times10^9$/L (days) = date (first assessment with platelet count of $\geq50\times10^9$/L) – first IMP date + 1.

**Table 6: Definition for Time to Platelet Count Response**

| Situation | Time to Platelet Count Response | Outcome |
|---|---|---|
| No occurrence of platelet count of ≥50× 109/L | Date of last available platelet count*** – first IMP date** + 1 | Censored |
| Early discontinuation of treatment (prior to W24) due to lack of efficacy or due to AE* | Early discontinuation date – first IMP date** + 1 | Censored |
| Dose and/or frequency of concurrent ITP therapy increased* | Concurrent ITP therapy start date – first IMP date** + 1 | Censored |
| Platelet count ≥50×109/L | Date (first assessment) – first IMP date** + 1 | Event |

* only applicable if the event (reaching platelet count of $\geq 50\times10^9$/L) has not occurred before
** or date of randomization for subjects not treated
*** or date of last contact for subject with no platelet count assessments

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 intercurrent events will not be imputed.

12) Time to achieve a platelet count of $\geq 100\times10^9$/L.

*Derivation*: It will be calculated as the difference between the first assessment date at which the platelet counts is $\geq 100\times10^9$/L, taking into account all platelet count measurements (also the unscheduled ones), and first IMP intake date.

Time to achieve a platelet count of $\geq 100\times10^9$/L (days) = date (first assessment with platelet count of $\geq 100\times10^9$/L) – first IMP date + 1.

**Table 7: Definition for Time to Platelet Count Response**

| Situation | Time to Platelet Count Response | Outcome |
|---|---|---|
| No occurrence of platelet count of ≥100× 109/L | Date of last available platelet count*** – first IMP date** + 1 | Censored |
| Early discontinuation of treatment (prior to W24) due to lack of efficacy or due to AE* | Early discontinuation date – first IMP date** + 1 | Censored |
| Dose and/or frequency of concurrent ITP therapy increased* | Concurrent ITP therapy start date – first IMP date** + 1 | Censored |
| Platelet count ≥100×109/L | Date (first assessment) – first IMP date + 1 | Event |

* only applicable if the event (reaching platelet count of $\geq 100\times10^9$/L) has not occurred before
** or date of randomization for subjects not treated
*** or date of last contact for subject with no platelet count assessments

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 $<100\times10^9$/L for the 4 analysis visits following the initiation of the rescue therapy. Missing values not due to intercurrent events will not be imputed.

13) Time to platelet count response defined as the time to achieve 2 consecutive platelet counts of $\geq100\times10^9$/L.

*Derivation*: It will be calculated as the difference between the first assessment date at which the condition '2 consecutive platelet counts ≥100×109/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 8: Definition for Time to Platelet Count Response**

| Situation | Time to Platelet Count Response | Outcome |
|---|---|---|
| No occurrence of platelet count of ≥100× 109/L | Date of last available platelet count*** – first IMP date** + 1 | Censored |
| Early discontinuation of treatment (prior to W24) due to lack of efficacy or due to AE* | Early discontinuation date – first IMP date** + 1 | Censored |
| Dose and/or frequency of concurrent ITP therapy increased* | Concurrent ITP therapy start date – first IMP date** + 1 | Censored |
| Platelet count response | Date (first assessment) – first IMP date** + 1 | Event |

* only applicable if the event (reaching platelet count response) has not occurred before
** or date of randomization for subjects not treated
*** or date of last contact for subject with no platelet count assessments

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 $<100\times10^9$/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) but imputing $<100\times10^9$/L instead of $<50\times10^9$/L.

14) Proportion of patients achieving platelet counts of at least $\geq50\times10^9$/L for at least 8 out of 12 visits between weeks 13 and 24 of the study.

*Derivation*: a patient is considered a responder if he/she shows platelet count of at least $50\times10^9$/L for at least 8 of the 12 analysis visits between weeks 13 and 24 of the study. 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).

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

*Derivation*: a patient is considered a responder if he/she shows platelet count of at least $100\times10^9$/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. If platelet count ≥100×109/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)

16) Proportion of patients with an IWG-Response[12].

*Derivation*: a patient is considered a responder if he/she shows platelet count of at least $30\times10^9$/L and 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 ≥30×109/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).

17) Proportion of patients with an IWG-Initial Response[13].

*Derivation*: a patient is considered a responder if he/she shows platelet count of at least $30\times10^9$/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".

#### *4.1.2.5 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 (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 (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 randomisation.

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 chronic patients 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 patient classification. The table for chronic patients 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) 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 patients 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 [redacted] and [redacted] 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, subsequent endpoints will no longer be evaluated.

- Primary endpoint: the proportion of patients with chronic ITP with a sustained platelet count response defined as achieving platelet counts of at least $50\times10^9$/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 patient population with chronic ITP.
- The proportion of patients in the overall population (chronic and persistent ITP) with a sustained platelet count response defined as achieving platelet counts of a least $50\times10^9$/L for at least 4 of the 6 visits between week 19 and 24 of the study.
- The incidence and severity of the WHO-classified bleeding events in the overall population.
- Proportion of patients in the overall population achieving platelet counts of at least $50\times10^9$/L for at least 6 of the 8 visits between week 17 and 24 of the study.

#### *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 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). 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 and overall platelet count 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 is 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. This stratified Mann-Whitney test will be done for both the chronic ITP population and the overall population.

#### *4.1.3.5 ZERO-INFLATED NEGATIVE BINOMIAL MODEL*

Number of bleeding events (WHO bleeding scale ≥1) and number of significant bleeding events (WHO bleeding scale ≥2) will be analyzed using a zero-inflated negative binomial model, which is a mixture model consisting of two components: a negative binomial count model (using the log link) and a binary model (using the logit link) for predicting excess zeros. The model will include the number of bleeding events (see section 4.1.2.2 and 4.1.2.3) as dependent variable, and treatment, the stratification factors and baseline platelet count (continuous) as explanatory factors. An offset term (number of visits with data on bleeding) will be used to take into account the patient exposure. The rate of bleeding over 24 weeks on placebo and efgartigimod will be reported, along with the rate ratio, 95% 2-sided Wald-type CI, and 2-sided p-value.

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).

#### *4.1.3.6 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. Data 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 and stratification factors as covariates. Only analysis visits within the treatment phase will be considered. Within-patient correlation will be modeled by assuming an unstructured covariance matrix for the error terms. If the model does not converge upon using UN, the following covariance structures will be tested for convergence (in order): toeph, arh(1), csh, toep, ar(1) and cs. 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.

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).

#### *4.1.3.7 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 vs. placebo 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:

- Dosing frequency (weekly versus bi-weekly): as derived in section 3.6.2
- 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 (United States / Japan / Europe / rest of the world)
- Age category (18-<65 years; 65-<75 years; ≥75 years)
- Race (American Indian or Alaska Native, Asian, Black or African American, White, Other)
- Ethnicity category (Japanese versus non-Japanese)
- Weight category at baseline (<50 kg, 50-<75 kg, 75 – <120 kg, ≥ 120 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 patients (overall) will not be included in the tables.

Subgroup analyses will be performed on the following efficacy endpoints:

- Sustained platelet count response (week 19 – 24) in the overall population
- Extent of disease control (first key secondary endpoint) in the overall population (all subgroup analyses except dosing frequency [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 9.4).

Time windows for PK samples are specified as follows:

- Dosing days: within 2 hours prior to the start of infusion for the pre-dose PK sample; within 30 minutes after end of infusion for the post-dose PK sample.

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 and excluded from PK parameter derivation, a remark will be added in the appropriate listing.

### *4.2.2 Derivation rules*

The following parameters from the individual serum drug concentration versus time profile for efgartigimod:

- $C_{max}$: maximum observed serum concentration
- $C_{trough}$: Serum concentration observed pre-dose

Concentration data-points with deviations outside the permitted time window (see section 4.2.1) will be excluded for the PK parameter derivation. $C_{trough}$ will not be calculated at baseline and if the post-dose sample is missing, $C_{max}$ will not be estimated.

### *4.2.3 Presentation of results*

For tables by dosing frequency, only visits of the fixed dosing schedule period (i.e. 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 patients have weekly dosing per protocol. For the second period, the dosing frequency is defined as explained in section 3.6.2.

Individual concentration data and actual blood sampling times from start of IV infusion 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 dosing frequency (weekly or q2w)) and per time point. A similar table will be created by ADA and by NAb Patient Classification.

Individual PK parameters will be listed.

Descriptive statistics on PK parameters will be presented in tables per visit (and dosing frequency (weekly of q2w)).

## 4.3 PHARMACODYNAMICS

### *4.3.1 Available data*

The following PD parameters will be measured:

- total immunoglobulin G (IgG), IgG subtypes (IgG1, IgG2, IgG3, and IgG4)
- antiplatelet antibody levels targeting GPIIb/IIIa, GPIb/IX, GPV and GPIa/IIa.

For total IgG, it was decided to reanalyze the samples using an alternative assay. For the statistical analysis, only the results obtained with the immunoturbidimetry in vitro diagnostic (IVD) assay will be used and not the ELISA results.

### *4.3.2 Derivation rules*

BLQ or ALQ values will not be imputed but excluded from the analysis.

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 (0.128) at that time point.

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 (0.128) for that particular glycoprotein at that time point.

### *4.3.3 Presentation of results*

IgG subtypes will be listed only.

For tables by dosing frequency, only visits of the fixed dosing schedule period (i.e. 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 patients have weekly dosing per protocol. For the second period, the dosing frequency 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 dosing frequency 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.

Frequency of antiplatelet antibody positive patients will be summarized per analysis visit and for the worst-case analysis visit. For antiplatelet antibodies against each glycoprotein (GPIIb/IIIa, GPIb/IX, GPV, GPIa/IIa) separately, frequency of patients

positive for antiplatelet antibodies against the particular glycoprotein will be summarized per analysis visit and for the worst-case analysis visit.

All actual and change from baseline IgG and antiplatelet antibody levels data will be listed. Note that IgG results obtained with an ELISA assay will not be shown in the listings.

## 4.4 ANTI-DRUG ANTIBODIES

### *4.4.1 Available data*

Presence of anti-drug antibodies (ADA) to efgartigimod is measured at visits 1, 4, 8, 13, 19, 23, End-of-Treatment visit and follow-up visit 2.

ADA samples are analyzed in a 3-tiered approach:

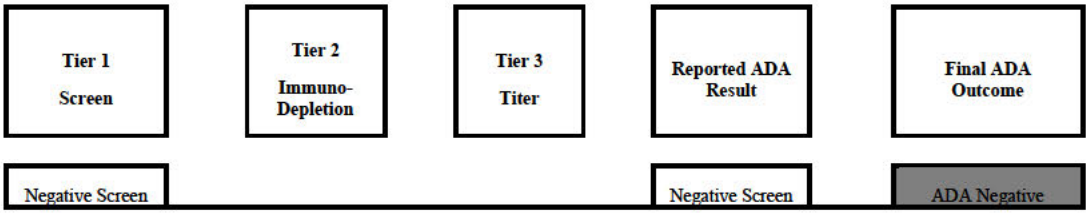
- All samples are evaluated in the ADA screening assay and are scored ADA screening positive or negative
- If a sample scored positive in the ADA screening assay, it is further evaluated in the confirmatory assay and is scored confirmed positive (positive immunodepletion) or confirmed negative (negative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

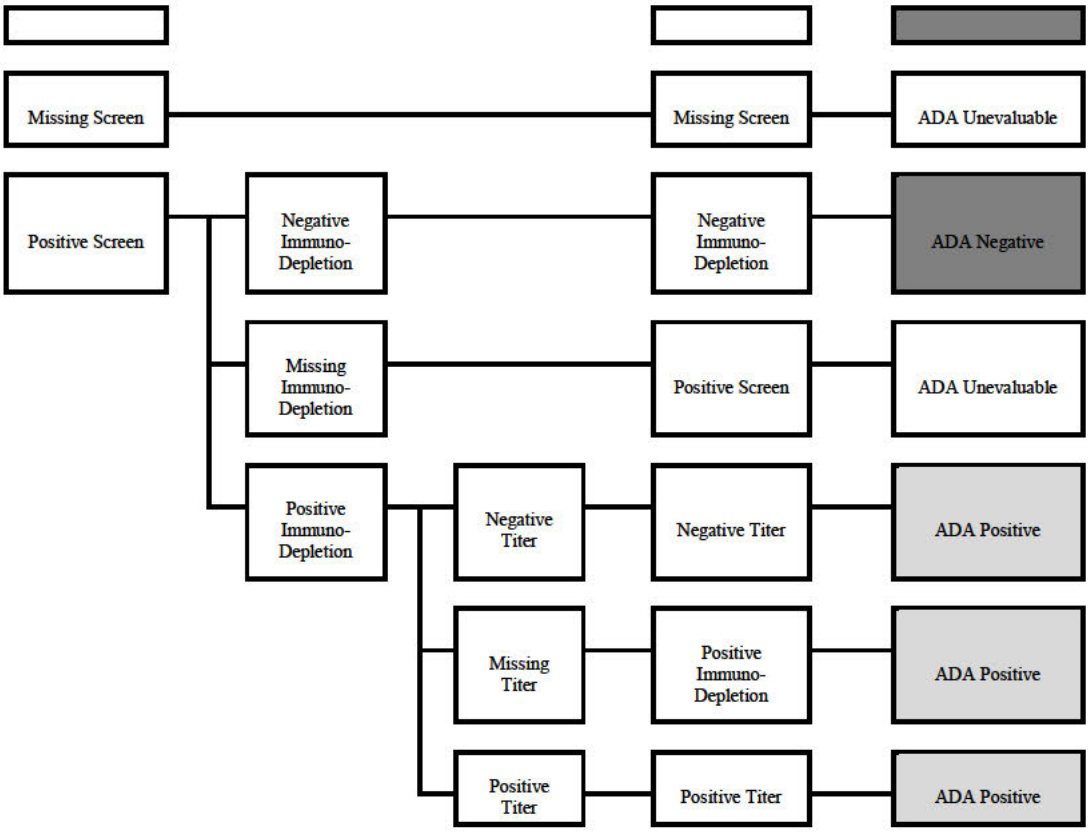
If available, a titer result will be reported for the ADA confirmed positive samples. However, a titer result is not always available:

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

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

**Figure 1: ADA sample status**






## *4.4.2 Derivation rules*

### *4.4.2.1 PATIENT CLASSIFICATION FOR ADA*

Table 9 below gives an overview of how the ADA patient classification will be derived, starting from the patient baseline ADA sample status. See also section 4.4.1:

**Table 9: Patient classification for ADA**

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

[a] Samples with missing titer have as reported ADA result 'positive immunodepletion';
[b] Results reported as 'negative titer', i.e. titer value <1 will be set to value of 1;
[c] Highest sample status, with order: (from low to high): ADA unevaluable, ADA negative, ADA positive (missing titer /positive immunodepletion), ADA positive with titer < 1 ('negative titer' as reported ADA result, titer value set to 1), ADA positive with titer ≥ 1 (i.e. positive titer and selecting the sample with highest titer)

ADA evaluable patient = patient classified as any of following categories: ADA negative, treatment unaffected ADA, treatment induced ADA, treatment boosted ADA.

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

Note: Fourfold difference in titer values is considered significant in case a twofold serial dilution is applied (= two times the dilution factor) (reference to Shankar et al., 2014)[9].

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

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

#### *4.4.2.2 PATIENT CLASSIFICATION FOR NAB*

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

All samples evaluated in the NAb assay will be scored as NAb positive, NAb negative or NAb unevaluable by the laboratory. Based on these results, the patients

will be categorized based on their baseline and post-baseline sample status as detailed in Table 10.

**Table 10: Patient classification for NAb**

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

a: Highest sample status in order: (from low to high): NAb unevaluable, NAb negative, NAb positive.

Note: At least 1 sample (which is not unevaluable) should be present.

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

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

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

### *4.4.3 Statistical analysis*

Frequency tabulations (number and percentages) will be provided with ADA negative/positive/unevaluable samples per visit.

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

- patients per ADA patient category
- prevalence and incidence of ADA
- ADA unevaluable patients
- ADA baseline positive/negative/unevaluable samples

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

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

In addition, a frequency tabulation (number and percentages) will be provided of NAb positive patients within the ADA patient category (ADA negative, treatment-unaffected, treatment-induced, treatment-boosted and unevaluable).

Correlation tables (restricted to the efgartigimod treated patients only) by ADA patient category (ADA negative, treatment-unaffected , treatment-induced, treatment-boosted and unevaluable) 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)

The above tables will be repeated for NAb patient category as defined in previous section.

# 5. SAFETY ANALYSES

## 5.1 ADVERSE EVENTS

### *5.1.1 Available data*

Adverse events (AEs) are coded into SOC and PTs using MedDRA version 24.1. 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 administration of any study drug.

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. 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 as detailed below:

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

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’.

Infusion-related reactions (IRR) will be defined as all AEs with a MedDRA preferred term that are listed in either:

- MedDRA Hypersensitivity SMQ broad selection
- MedDRA Anaphylactic SMQ broad selection
- MedDRA Extravasation SMQ broad selection, excluding implants

AND occurring within 48 hours of an infusion, 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 infusion.

Two AESI types will be used: ‘Bleeding events’ as recorded on 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.

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 patient years of follow-up (PYFU) is defined as the number of events divided by the sum of follow-up time (duration of treatment + FU phase) of all patients per treatment expressed in years.

### *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 patients 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 principle 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
- IRR events

In addition, the number of events per patient years on study will be added to the overview table.

Summary tables by MedDRA SOC and PT will show the number and percentage of patients 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 Principle 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
- IRR events
- Serious IRR events
- Hypersensitivity events

Tables on TEAEs, serious TEAEs and hypersensitivity events will be repeated by ADA patient classification and by NAb patient 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.
- Hematology: hemoglobin, white blood cell (WBC) count with WBC differentials.
- 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 post-baseline values.

Toxicity grades will be computed according to the NCI CTCAE toxicity grading list (version 5.0[5]). The implementation of these toxicity grades for analysis is presented in appendix 9.2. Additional study-specific toxicity gradings will be applied as defined in appendix 9.3. Only the parameters described in appendices 9.2 and 9.3 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/1.73m$^2$.

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.

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

Laboratory toxicity grades will be presented as cross-tabulations (shift table) of the toxicity (NCI-CTCAE grades) at each post-baseline analysis visit and at the worst-case analysis visit versus the baseline toxicity. Numbers and cumulative numbers over decreasing toxicity grading of patients with treatment-emergent toxicities will also be shown. The denominator for the percentage is the total number of patients 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.

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 patients with any post-baseline 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 infusion visit).

### *5.3.2 Derivation rules*

Abnormalities are defined in Table 11.

**Table 11: 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 post-baseline 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 post-baseline analysis visit versus the baseline abnormality and as cross-tabulations of the worst-case abnormality versus the baseline abnormality. Numbers of patients 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 patients with any post-baseline 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 12.

**Table 12: 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 post-baseline 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 post-baseline 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 post-baseline 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 patients with treatment-emergent abnormalities will also be shown. The denominator for the percentage is the total number of patients 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 post-baseline analysis visit and at the worst-case analysis visit. Cumulative numbers over decreasing change from baseline abnormalities of patients will also be shown. The denominator for the percentage is the total number of patients 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 patients with any post-baseline abnormality.

## 5.5 PHYSICAL EXAMINATIONS

### *5.5.1 Available data*

Physical examination results per body system will be available.

### *5.5.2 Presentation of results*

Abnormal physical examination results will be listed.

# 6. CHANGES TO THE PLANNED ANALYSIS

## 6.1 CHANGES NOT COVERED BY 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.

1) Proportion of patients achieving platelet counts of $\geq30\times10^9$/L on at least one occasion during the 24-week study period.

2) Proportion of patients achieving platelet counts of $\geq50\times10^9$/L on at least one occasion during the 24-week study period.

3) Proportion of patients achieving platelet counts of $\geq80\times10^9$/L on at least one occasion during the 24-week study period.

4) Proportion of patients achieving platelet counts of $\geq100\times10^9$/L on at least one occasion during the 24-week study period.

5) Proportion of patients achieving platelet counts of $\geq30\times10^9$/L on at least 2 occasions during the 24-week study period.

6) Proportion of patients achieving platelet counts of $\geq50\times10^9$/L on at least 2 occasions during the 24-week study period.

7) Proportion of patients achieving platelet counts of $\geq80\times10^9$/L on at least 2 occasions during the 24-week study period.

8) Proportion of patients achieving platelet counts of $\geq100\times10^9$/L on at least 2 occasions during the 24-week study period.

9) Proportion of patients achieving platelet counts of at least $\geq100\times10^9$/L for at least 3 out of 4 consecutive weekly visits during the 24-week study period.

10) Proportion of patients achieving platelet counts of at least $\geq80\times10^9$/L for at least 3 out of 4 consecutive weekly visits during the 24-week study period.

11) Time to achieve a platelet count of $\geq50\times10^9$/L.

12) Time to achieve a platelet count of $\geq100\times10^9$/L.

13) Time to platelet count response defined as the time to achieve 2 consecutive platelet counts of $\geq100\times10^9$/L.

14) Proportion of patients achieving platelet counts of at least ≥$50\times10^9$/L for at least 8 out of 12 visits between weeks 13 and 24 of the study.

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

16) Proportion of patients with an IWG-Response[11].

17) Proportion of patients with an IWG-Initial Response[13].

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 subjects 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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2 ICH Topic E6(R2) Guideline for Good Clinical Practice – Step 4: 9 November 2016.

3 ICH Topic E9 Statistical Principles for Clinical Trials – Step 4 –September 1998.

4 ICH Topic E9 (R1) Statistical Principles for Clinical Trials, Addendum on Estimands and Sensitivity Analysis is Clinical Trials: Step 4 – November 2019.

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6 Cox D, Snell E. *Analysis of Binary Data*. New York: Chapman & Hall; 1970.

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|---|---|---|---|
| 14.3.1.5 | Grade 3 or More Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term | SAF | TL |
| 14.3.1.6 | Fatal Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term | SAF | TL |
| 14.3.1.7 | Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term | SAF | TL |
| 14.3.1.8 | Procedure-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term | SAF | |
| 14.3.1.9 | Serious Treatment-Related Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term | SAF | TL |
| 14.3.1.10 | Treatment-Emergent Adverse Events for Which the Study Was Discontinued by MedDRA System Organ Class and Preferred Term | SAF | |
| 14.3.1.11 | Treatment-Emergent Adverse Events for Which the Study Drug Was Discontinued by MedDRA System Organ Class and Preferred Term | SAF | TL |
| 14.3.1.12 | Treatment-Emergent Adverse Events for Which the Study Drug Was Interrupted by MedDRA System Organ Class and Preferred Term | SAF | |
| 14.3.1.13 | Treatment-Emergent Adverse Events of Special Interest by MedDRA System Organ Class and Preferred Term: Bleeding Events | SAF | TL |
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| 14.3.1.15 | Infusion-Related Reactions by MedDRA System Organ Class and Preferred Term | SAF | TL |
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|---|---|---|---|
| 14.3.2.2 | Cross-Tabulation of Laboratory Abnormalities Versus Baseline | SAF | |
| 14.3.2.3 | Cross-Tabulation of Laboratory Toxicity Grades Versus Baseline | SAF | TL |
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| 14.3.3.1 | Descriptive Statistics of Vital Signs Actual Values and Changes from Baseline | SAF | |
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| 14.3.4.1 | Descriptive Statistics of ECG Actual Values and Changes from Baseline | SAF | |
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| | | | |
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| 16.2.2.1 | Protocol Deviations | FAS | |
| 16.2.2.2 | Violations on Eligibility Criteria | FAS | |
| 16.2.2.3 | No-Treatment Patients | SCR minus SAF | |
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| 16.2.4.1 | Demographic Data | SAF | |
| 16.2.4.2 | Baseline Disease Characteristics | SAF | |
| 16.2.4.3 | Medical History | SAF | |
| 16.2.4.4 | ITP History | SAF | |
| 16.2.4.5 | Prior Vaccinations | SAF | |
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| | | |
|---|---|---|
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# 9. APPENDICES

## 9.1 SAS CODE

### *9.1.1 Cochran-Mantel-Haenszel test*

[redacted]

RUN;

[redacted]

RUN;

[redacted]

RUN;

[redacted]

RUN;

[redacted]

RUN;

### *9.1.2 Exact conditional logistic regression*

[redacted]

RUN;

[redacted]

RUN;

### *9.1.3 Stratified Mann-Whitney Test*

[redacted]

RUN;

### *9.1.4 Zero-inflated Negative Binomial Model*

[redacted]

RUN;

### *9.1.5 Mixed Model for Repeated Measurements*

[redacted]

RUN;

### *9.1.6 Cox Proportional Hazards Regression*

[redacted];

[redacted];

[redacted]

RUN;

### *9.1.7 95% CI for difference in proportions (Agresti-Min)*

[redacted]

RUN;

### *9.1.8 Kaplan-Meier estimates*

[redacted]

RUN;

## 9.2 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) | | >1.0-1.5 *ULN | >1.5-2.0 *ULN | >2.0-5.0 *ULN | >5.0 *ULN |
| Alanine amino transferase | | >1-3 *ULN | >3-5 *ULN | >5-20 *ULN | >20 *ULN |
| Albumin [1] | g/L | <LLN-30 | <30-20 | <20 | - |
| | g/dL | <LLN-3 | <3-2 | <2 | - |
| Alkaline phosphatase | | >1.0-2.5 *ULN | >2.5-5.0 *ULN | >5.0-20.0 *ULN | >20.0 *ULN |
| Aspartate amino transferase | | >1-3 *ULN | >3-5 *ULN | >5-20 *ULN | >20 *ULN |
| Bilirubin (total) | | >1.0-1.5 *ULN | >1.5-3.0 *ULN | >3.0-10.0 *ULN | >10.0 *ULN |
| Calcium 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 high [1] | mmol/L | >ULN-1.5 | >1.5-1.6 | >1.6-1.8 | >1.8 |
| | mg/dL | >ULN-6.0 | >6.0-6.4 | >6.4-7.2 | >7.2 |
| Calcium (corrected) low [1] | mmol/L | <LLN-2.00 | <2.00-1.75 | <1.75-1.50 | <1.50 |
| | mg/dL | <LLN-8 | <8-7 | <7-6 | <6 |
| Calcium (corrected) high [1] | mmol/L | >ULN-2.9 | >2.9-3.1 | >3.1-3.4 | >3.4 |
| | mg/dL | >ULN-11.5 | >11.5-12.5 | >12.5-13.5 | >13.5 |
| Cholesterol [1] | mmol/L | >ULN-7.75 | >7.75-10.34 | >10.34-12.92 | >12.92 |

| | | | | | |
|---|---|---|---|---|---|
| | mg/dL | >ULN-300 | >300-400 | >400-500 | >500 |
| Creatine kinase | | >1.0-2.5 *ULN | >2.5-5.0 *ULN | >5.0-10.0 *ULN | >10.0 *ULN |
| Creatinine | | >1.0-1.5 *ULN | >1.5-3.0 *ULN | >3.0-6.0 *ULN | >6.0 *ULN |
| Gamma-glutamyl transferase | | >1.0-2.5 *ULN | >2.5-5.0 *ULN | >5.0-20.0 *ULN | >20.0 *ULN |
| Glucose (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 | | >1.0-1.5 *ULN | >1.5-2.0 *ULN | >2.0-5.0 *ULN | >5.0 *ULN |
| Magnesium low [1] | mmol/L | <LLN-0.5 | <0.5-0.4 | <0.4-0.3 | <0.3 |
| | mg/dL | <LLN-1.2 | <1.2-0.9 | <0.9-0.7 | <0.7 |
| Magnesium high [1] | mmol/L | >ULN-1.23 | - | >1.23-3.30 | >3.30 |
| | mg/dL | >ULN-3.0 | - | >3.0-8.0 | >8.0 |
| Potassium low [1] | mmol/L | - | <LLN-3.0 | <3.0-2.5 | <2.5 |
| | mEq/L | - | <LLN-3.0 | <3.0-2.5 | <2.5 |
| Potassium high [1] | mmol/L | >ULN-5.5 | >5.5-6.0 | >6.0-7.0 | >7.0 |
| | mEq/L | >ULN-5.5 | >5.5-6.0 | >6.0-7.0 | >7.0 |
| Sodium low [1] | mmol/L | <LLN-130 | - | <130-120 | <120 |
| | mEq/L | <LLN-130 | - | <130-120 | <120 |
| Sodium high [1] | mmol/L | >ULN-150 | >150-155 | >155-160 | >160 |
| | mEq/L | >ULN-150 | >150-155 | >155-160 | >160 |
| Triglycerides | mmol/L | 1.71-3.42 | >3.42-5.70 | >5.70-11.4 | >11.4 |
| | mg/dL | 150-300 | >300-500 | >500-1000 | >1000 |

| | | | | | |
|---|---|---|---|---|---|
| Partial thromboplastin time (activated or not specified | | >1.0-1.5 *ULN | >1.5-2.5 *ULN | >2.5 *ULN | - |
| CD4 count [1] | giga/L | <LLN-0.50 | <0.50-0.20 | <0.20-0.05 | <0.05 |
| | counts/mm$^3$ | <LLN-500 | <500-200 | <200-50 | <50 |
| Fibrinogen | | <1.00-0.75 *LLN | <0.75-0.50 *LLN | <0.50-0.25 *LLN | <0.25 *LLN |
| International normalized ratio | | >1.2-1.5 *ULN | >1.5-2.5 *ULN | >2.5 *ULN | - |
| Lymphocytes (absolute count) low [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.
[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).

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

**Table 13: 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 | 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 | - |
| Neutrophils (neutrophil decreased) | giga/L | <LLN – 1.5 | <1.5 – 1.0 | <1.0 – 0.5 | <0.5 |
| Lymphocytes (lymphocytes decreased) | giga/L | <LLN – 0.8 | <0.8 – 0.5 | <0.5 – 0.2 | <0.2 |
| Lymphocytes (lymphocytes increased) | giga/L | - | >4 – 20 | >20 | - |
| Partial Thromboplastin Time (aPTT Activated or not specified) | | >ULN – 1.5 *ULN | >1.5 – 2.5 *ULN | >2.5 *ULN | - |
| Prothrombin Time (PT) | | >ULN – 1.5 *ULN | >1.5 *ULN – 2.5 *ULN | >2.5 *ULN | - |
| International Normalized Ratio (INR) (INR increased) | | >1.2 – 1.5 | >1.5 – 2.5 | >2.5 | - |
| Creatinine clearance (eGFR (estimated Glomerular Filtration rate) or CrCl (creatinine clearance)) | mL/min/1.73m$^2$ | <LLN – 60 | <60 – 30 | <30 – 15 | <15 |
| Blood urea nitrogen | | >ULN - ≤1.5 *ULN | >1.5 *ULN - ≤3.0 *ULN | >3.0 *ULN - ≤6.0 *ULN | >6.0 *ULN |

## 9.4 SCHEDULE OF ASSESSMENTS

### *9.4.1 Global study ARGX-113-1801 V6.0*

| Trial Period[a] | Screening | IV Treatment Period | | | | | | | | | | | | | | | | | | | | | | End-of-Treatment/ Early Discontinuation | Follow-up 1 | Follow-up 2 | Unscheduled Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visits | | 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 (+2 days) | *-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* | | | | |
| 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 |
| | | | Can be performed within 1 day of the next procedure | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SF-36(v2)[e] | | X | | | | | | | | X | | | | | | | | X | | | | | | | | X | | | |
| FACT-Th6 and FACIT-Fatigue Scale[e] | | X | | | | X | | | | X | | | | X | | | | X | | | | X | | | | | X | | |
| Weight | X | X | X | X | X | Performed only on visits with an IMP infusion | | | | | | | | | | | | | | | | | | | | | 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 |
| Physical examination | 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 |
| Urinalysis[h] | X[i] | 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 |
| Hematology and chemistry tests[k] | X[i,k] | X | X | X | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | | X | X | X | X | X |
| Serum pregnancy test[h] | X[i] | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Follicle-stimulating hormone[h] | X[i] | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Coagulation, thyroid, and autoimmune antibody testing[h] | X[i] | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Viral tests[h] | X[i] | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Tuberculosis QuantiFERON test[h] | | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pharmacodynamics[h,l] | | X | X | X | X | Performed only on visits with an IMP infusion | | | | | | | | | | | | | | | | | | | | | X | X | X | X |
| Antiplatelet antibodies[h] | | X | | | | | | | X[m] | | | | | | | | X[m] | | | | | | | X[m] | | X | | | |
| Anti-drug antibodies[h,n] | X | X | | | X | | | | X[m] | | | | | X[m] | | | | | | X[m] | | | | X[m] | | X | | X | X |
| [redacted] | | X | X | | | X | | | | | | | | X | | | | | | | | | | | | X | | | |
| Pharmacokinetics | | X[p] | X[p] | X[p] | X[p] | Performed only on visits with an IMP infusion[p] | | | | | | | | | | | | | | | | | | | | | X | X | X | X |
| Randomization[q] | | X | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| IMP infusions[r] | | X | X | X | X | (----------Weekly or q2w infusion----------) | | | | | | | | | | | | | | | | | | | | | | | | |
| Concomitant therapies[s] | (----------X----------) | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adverse events[s] | (----------X----------) | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

ADA=anti-drug antibodies; ECG=electrocardiogram; FACT-Th6=Functional Assessment of Cancer Therapy questionnaire-Th6; FACIT-Fatigue Scale=Functional Assessment of Chronic Illness Therapy Fatigue Scale; ICF=informed consent form; IgG=immunoglobulin G; IMP=investigational medicinal product; IV=intravenous; q2w=every other week; SF-36(v2)=Short Form-36 version 2; SoA=schedule of assessments; WHO=World Health Organization.

[a] **Screening Period**: maximum 14 days
**IV Treatment Period**: Weekly IV IMP administrations for visit 1 up to and including visit 4. As of visits 5 to 16, a weekly or q2w schedule will be followed . From visits 17 to 24, patients will be fixed on the dosing schedule they were receiving at visit 16 or at the last visit at which IMP was administered (ie, either weekly 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, weekly or q2w) of IMP infusions depends on predefined criteria set forward in Section 5.4.1 (Screening and Treatment) of the protocol.
**End-of-Treatment:** This visit should be performed on trial day 169 (+2 days) for all patients who have completed the 24-week trial period, whether they were still on 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 patients that discontinue the trial early.

**Follow-up Period**: For patients discontinuing the trial early (with the exception of patients who withdraw their consent) or who do not roll over to the open-label extension trial (ARGX-113-1803). The follow-up period will consist of 2 q2w visits (ie, 4 weeks).

[b] No trial-related assessment must be carried out before signing the 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] Platelet count is measured locally. Post-baseline platelet count can be performed within 1 day of the next procedure as per the SoA (both dosing and non-dosing visits). Eligible patients should have a mean platelet count of $<30\times10^9$/L from 2 counts: 1 platelet count during the screening period and the predose platelet count on the day of randomization (visit 1).
In addition, the absolute immature platelet count (IPF#) and the fraction of immature platelets related to mature platelets (IPF%) will be measured locally in facilities equipped with a hematology analyzer which can determine this platelet subset.

[e] Patient-reported outcomes and QoL assessments need to be performed preferably after the platelet count assessment.

[f] Height will only be measured at the screening visit.

[g] Electrocardiogram will be assessed after the end of the IMP infusion, if any. If no IMP is administered, the ECG will be assessed preferably after the blood sample for platelet counts has been taken.

[h] Laboratory assessments include all parameters mentioned in Appendix 1 of the protocol.

[i] At the screening visit, if the investigator detects 1 or more screening laboratory abnormalities, the result(s) should be confirmed if still within the screening window. For rescreening criteria see Section 4.7.

[j] Only for women of childbearing potential. To be done at least every 4 weeks.

[k] At the screening visit, the total IgG level must be determined by the central laboratory (exclusion criterion 10).

[l] In order to maintain the blind, the IgG testing cannot be performed locally.

[m] If the visit does not coincide with an IMP infusion, then the assessment should be performed at the next IMP visit.

[n] In samples having a positive ADA titer, samples will be tested for neutralizing ADAs.

[redacted]

[p] Both pre- and post-dose to be collected (within 2 hours prior to the start of the IMP infusion and within 30 minutes after the end of IMP infusion, respectively).

[q] Randomization to be completed before administration of IMP.

[r] The IMP (ARGX-113 or placebo) will be administered as an IV infusion over a period of approximately 1 hour at each IMP administration visit. Patients will remain at the site for at least 30 minutes following the end of the infusion for safety monitoring based on the patient's clinical status. Assessment of the dosing regimen as described in Section 5.4.1 will be applied.

[s] Adverse events and intake of concomitant medication(s) will be monitored continuously from signing the ICF until the last trial-related activity. In case of early discontinuation, any adverse events/serious adverse events should be assessed for 30 days following the Early Discontinuation visit or until satisfactory resolution or stabilization.

### *9.4.2 Specific protocol amendments*

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

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| Reason for signing: Approved | Name: [redacted]<br>Role: B<br>Date of signature: 28-Mar-2022 09:29:10 GMT+0000 |
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| Reason for signing: Approved | Name: [redacted]<br>Role: P<br>Date of signature: 28-Mar-2022 09:39:26 GMT+0000 |
| Reason for signing: Approved | Name: [redacted]<br>Role: S<br>Date of signature: 28-Mar-2022 10:05:10 GMT+0000 |
| Reason for signing: Approved | Name: [redacted]<br>Role: P<br>Date of signature: 28-Mar-2022 10:06:06 GMT+0000 |
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