Clinical Trial Protocol

Protocol Title:	**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 Number:	**ARGX-113-1801 (ADVANCE)**
Date of Protocol:	**15 July 2021, Version 6.0, Final**
IND No:	[redacted]
EudraCT No:	**2019-002100-41**
Investigational Product:	**ARGX-113**
Indication	**Primary immune thrombocytopenia**
Trial Phase:	**3**
Sponsor:	**argenx BVBA** **Industriepark Zwijnaarde 7** **9052 Zwijnaarde (Ghent)** **BELGIUM** **Phone: +32 (0)9 310 34 00**
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The following additional numbers are also available for urgent contact:

24-Hour Urgent Medical Helpline Number:	**(+1) 857 957 5013** **For the country-specific toll-free AT&T Direct Access code, please always refer to the latest version available on https://icophone.iconplc.com/ under ‘‘24/7 Medical Help Desk”**

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Safety Mailbox/Fax:	**Email: safety@argenx.com** **Fax: + 1 833 874 7325**

SIGNATURE OF SPONSOR

PROTOCOL TITLE: 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 NO: ARGX-113-1801 (ADVANCE)

SPONSOR REPRESENTATIVE [redacted]

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[redacted], **MD** **Signature** **Date**

Chief Medical Officer, argenx BVBA

SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: 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 NO: ARGX-113-1801 (ADVANCE)

This protocol is a confidential document of argenx BVBA. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from argenx BVBA.

Instructions to the investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the site in which the trial will be conducted. Return the signed original copy to the local representative of your sponsor's designated CRO.

I have read this protocol in its entirety and agree to conduct the trial accordingly:

Signature of Investigator: _____ Date: _____
Printed Name: _____
Investigator Title: _____
Name/Address of Site: _____
_____
_____

DOCUMENT HISTORY

Previous Version Number	Effective Date
1.0	23 May 2019
2.0	09 September 2019
3.0	18 September 2019
4.0	27 May 2020
5.0	16 November 2020
6.0	15 July 2021

SUMMARY OF CHANGES

The major changes from Protocol Version 5.0 compared to Protocol Version 6.0 are summarized below.

The protocol amendment Summary of Changes table for the previous amendments can be found in Appendix 5.

A strikethrough font is used to indicate deleted text and a bold font to indicate added text. Minor administrative editorial changes are not summarized in the following table:

Summary of Changes Between Protocol Version 5.0 and Protocol Version 6.0

Section(s)	Change	Rationale
• Front Page	Safety Mailbox/Fax: Email: ~~248700ADR@parexel.com~~ **safety@argenx.com** Fax: (+1) 833 ~~644 0806~~ 874 7325	As per argenx safety requirements.
• Synopsis • 4.1. Summary of Trial Design • 6.8.4. Rescue Therapy	• IV anti-D: up to 50-75 mcg/kg/day × 1-2 days **Note: Anti-D rescue therapy should not be given to Rh(D)-positive patients**	Clarification upon request of the German competent authorities.
• Synopsis	**Efgartigimod treatment induces reductions in IgG levels, and there is a potential risk for infections associated with low IgG levels. As such, infections are considered AESI in this trial.** **Due to the nature of underlying disease (ie, ITP), any occurrence of bleeding will also be considered an adverse event of special interest (AESI).**~~Any bleeding or infection will be considered as adverse event of special interest (AESI).~~	Clarification.
• Synopsis • 4.3.1. Inclusion Criteria	7. Women of childbearing potential … . Follicle-stimulating hormone can be used to confirm postmenopausal status in amenorrheic patients **not** on hormonal replacement therapy.	Correction.

Section(s)	Change	Rationale
• Synopsis • 4.3.2. Exclusion Criteria	16. ~~Patients with known serum positivity or who test p~~**P**ositive **serum test at screening** for an active viral infection ~~at screening~~ with **any of the following conditions**: a. Hepatitis B virus (HBV) **that is indicative of an acute or chronic infection, unless associated with a negative HBV DNA test (https://www.cdc.gov/hepatitis/HBV/PDFs/SerologicChartv8.pdf)**~~(except patients who are anti HBs Ab positive because of HBV vaccination), Hepatitis C Virus, HIV~~ b. **Hepatitis C virus (HCV) based on HCV-antibody assay (unless associated with a negative HCV RNA test)** c. **Human immunodeficiency virus (HIV) based on test results that are associated with an acquired immunodeficiency syndrome (AIDS)-defining condition or a CD4 count ≤200 cells/mm^3**	Clarification.
• Synopsis • 8.4.1. Primary Endpoint Analysis	The primary endpoint will be **analyzed using a Cochran-Mantel-Haenszel statistic test stratified for the stratification factors history of splenectomy (yes versus no), receiving concurrent ITP therapies at baseline (yes versus no), and for baseline platelet count level category (<15×10^9/L versus ≥15×10^9/L). The treatment effect will be presented as the odds ratio together with its 95% confidence interval (CI) and two-sided p-value. In addition, an adjusted difference of the proportions with its 95% CI will be provided** ~~tested by means of exact logistic regression, also known exact conditional logistic regression.[15] The model will contain fixed effect terms for randomized treatment and baseline platelet count level and will be stratified by history of splenectomy (yes versus no) and receiving concurrent ITP therapies at baseline (yes versus no). Parameter estimation and hypothesis testing will be performed on the log odds ratio (OR) of a sustained platelet count response for patients receiving efgartigimod PH20 SC versus patients receiving placebo PH20 SC. Using the Newton-Raphson algorithm, a maximum exact conditional likelihood estimate of the log OR will be obtained. In the event the algorithm does not converge, the median unbiased estimate will be used.[14] 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.[16] The OR (by exponentiating the log OR) will be provided, along with the 95% two-sided CI and two-sided p-value.~~	As per FDA recommendations.

Section(s)	Change	Rationale
• Synopsis • 8.4.2. Key Secondary Endpoint Analysis Subject to Alpha Control	A Wilcoxon-Mann-Whitney test stratified by receiving concurrent ITP therapies at baseline (yes versus no), ~~and~~ history of splenectomy (yes versus no)**, and baseline platelet count level category (<15×10^9/L versus ≥15×10^9/L)** will be used to compare the extent of disease control between both treatment groups.	Addition of baseline platelet count level category to the analysis model to be consistent with the primary endpoint analysis approach (CMH test).
	~~It will have~~**The model will consist of** the number of events as the dependent variable and ~~both~~ **of** randomized treatment**,** ~~and~~ the stratification variables (history of splenectomy; receiving concurrent ITP therapies at baseline)**, and baseline platelet count as independent variables** ~~as factors in the model~~.	Inclusion of baseline platelet count in the model to have an analysis approach consistent with the primary and other key secondary endpoints.
• Definition of Terms	Childbearing potential: … Determination of FSH levels can be used to confirm postmenopausal status in amenorrheic patients **not** on hormonal replacement therapy.	Correction.
• 5.4.2. Rollover to the Open-Label Extension Trial (ARGX-113-1803)	- For patients on a q2w dosing regimen, the baseline visit including first IMP dose administration of the ARGX-113-1803 trial will be done 7 days after the End-of-Treatment visit of the current trial **if visit 24 of the ARGX-113-1801 trial was a dosing visit. If visit 24 of the ARGX-113-1801 trial was a non-dosing visit, the End-of-Treatment visit will coincide with visit 1 of the ARGX-113-1803 trial**.	Clarification.
• 7.2.1. Platelet Count	The assessment of platelet count can be performed within 1 day prior to any other trial-specific assessment (except at screening, where the informed consent should be obtained and weight assessed first**, and at randomization**) at each visit as specified in the SoA (Table 1).	Correction.
• 7.3.1. Adverse Events	Definition of AE The following events will NOT be collected as AEs: • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition. **Note: Except for any occurrence of bleeding, which will be considered as an AESI as per section 7.3.1.1.**	Clarification.
	Definition of SAE • Requires inpatient hospitalization or prolongation of existing hospitalization. In general, hospitalization signifies that the patient has been admitted ~~(usually involving at least an overnight stay)~~ at the hospital or emergency ward for observation and/or treatment that	To clarify the term "hospitalization" in the definition of SAE.

Section(s)	Change	Rationale
	would not have been appropriate in the physician's office or outpatient setting.	
• 7.3.1. Adverse Events	Definition of SAE • Other situations: … **Suspected transmission of any infectious agent via the IMP will also be treated as an SAE.**	To fulfill the requirements of section VI.C.2.2.5 of Module V of EMA's Guideline on good pharmacovigilance practices (GVP).
	Definition of SAE An unexpected AE is any adverse drug event, which is not listed in the reference safety information in the current IB **section 7** or is not listed at the specificity or intensity that has been observed. **The assessment of expectedness will be the responsibility of the sponsor.**	To clarify that the assessment of expectedness is the responsibility of the sponsor.
• 7.3.1.1. Adverse Events of Special Interest	Due to the nature of underlying disease (**ie,** ITP), any ~~AE~~ **occurrence** of bleeding will also be ~~treated~~ **considered** an AESI.	Clarification.
• 7.3.2. Clinical Laboratory Evaluations	The actual sample collection date and time must be entered in the patient's source documents and on the central/local lab assessment eCRF page. **For urinalysis samples, only the date of collection is to be entered.**	Correction.
• 8.2. Analysis Populations	The full analysis set (FAS) consists of all randomized patients ~~who have a baseline efficacy observation~~.	As per FDA recommendations.
• 8.4.1. Primary Endpoint Analysis	Complementary analyses **Furthermore, an exact logistic regression analysis in which the continuous baseline platelet count level is added as covariate instead of the baseline platelet count category will be conducted as supportive analysis.**	
• 8.4.2. Key Secondary Endpoint Analysis Subject to Alpha Control	When 1 of the **main** intercurrent events ~~described in Section 8.4.1~~occurs, platelet count levels measured after the occurrence will be censored (or, they will not be taken into account for the calculation of the number of cumulative weeks).	Correction.
• 12. References	~~15. Cox D, Snell E. *Analysis of Binary Data*. New York: Chapman & Hall; 1970.~~ ~~16. Agresti A. Categorical Data Analysis. Second Edition. *New York: John Wiley & Sons*. 2002.~~	Update
	15~~.~~ **International Committee of Medical Journal Editors. Defining the role of authors and contributors. ICMJE website, http://www icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html.**~~200699388, argenx BVBA. Tissue Cross-reactivity of ARGX-113 with Human and~~	Correction.

Section(s)	Change	Rationale
	~~Cynomolgus Monkey Tissues In Vitro. Final Report. Testing Facility Study No. 200699388. 2016.~~	
• 13. Appendices Appendix 2: Administrative Structure	Analysis of Pharmacokinetics**, IgG Subtypes,**~~-Pharmacodynamics~~ and Anti-Drug Antibodies LGC	Administrative change
	Analysis of Total IgG **PPD Laboratories - US** **2 Tesseneer Road** **Highland Heights, KY 41076** **United States**	
	Home Care Vendor: **Accellacare In-Home Services (previously known as** Symphony Clinical Research**)** (an ICON company)	

SYNOPSIS

Name of Sponsor:	**argenx BVBA**
Name of Investigational Medicinal Product (IMP):	ARGX-113
Active Ingredient:	Efgartigimod
Indication:	Primary immune thrombocytopenia
Title of Trial:	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 No:	ARGX-113-1801 (ADVANCE)
Trial Sites:	This is a global, multicenter trial
Trial Duration: The total maximum trial duration per patient is up to 31 weeks: - Up to 2 weeks of screening - 24 weeks treatment period - End-of-Treatment visit 1 week after visit 24 - 4 weeks of follow-up	Phase: 3

Objectives:

Primary Objective:

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

Secondary Objectives:

- 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 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 pharmacokinetics (PK) of efgartigimod.

* "week" instead of "visits" are used in the endpoints, ensuring that the platelet count of the End-of-Treatment visit is regarded as week 24 platelet count (eg, platelet count after 19 weeks of treatment corresponds with platelet count of visit 20).

- To assess the pharmacodynamic (PD) effects of efgartigimod.

Exploratory Objective:

- [redacted]

Trial Design:

DESCRIPTION

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

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 trial 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" (ie, 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.

After confirmation of eligibility, the patients enter a 24-week treatment period and will be randomized to receive efgartigimod 10 mg/kg IV or placebo, weekly from visits 1 to 4 and then from visits 5 to 16 either weekly 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 IMP was administered (ie, either weekly or q2w).

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

Patients who complete the 24-week trial period but who do not enter the open-label extension trial ARGX-113-1803, or patients who discontinue the trial 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 trial early, all the assessments listed for the Early Discontinuation visit as specified in the schedule of assessments (SoA, Table 1), will be performed.

SAMPLE SIZE AND STRATIFICATION

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 when 117 patients with chronic ITP have been randomized.

Patients will be stratified according to the following factors:

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

SCREENING AND TREATMENT

During the screening period (up to 2 weeks) the patient's eligibility for trial participation will be evaluated.

All eligible patients will be randomized to receive IV infusions of either efgartigimod 10 mg/kg body weight or matching placebo throughout the trial.

All patients will initially receive weekly IV infusions from visits 1 to 4. Based on the platelet counts as of visit 2, the dosing frequency can be altered from visits 5 to 16 according to following rules (the change in dosing frequency will occur at the current visit):

- Reduce from weekly to q2w in patients achieving platelet counts of $\geq 100\times10^9$/L for 3 out of 4 consecutive visits (the fourth visit being the current visit) and having a platelet count of $\geq 100\times10^9$/L at the last of these 4 visits

  – OR –

  3 consecutive visits.
- Increase from q2w to weekly in patients whose platelet counts drop below 100×10^9/L on 2 consecutive visits

  – OR –

  $<30\times10^9$/L at 1 visit

  – OR –

  in patients who receive rescue therapy (see Section 6.8.4)
- Temporary withholding treatment:
  - for reasons described in Section 4.5, IMP should be reintroduced once the investigator considers the undue risk to the patient has passed
  - in patients with platelet counts greater than 400×10^9/L, IMP should be resumed at the 10 mg/kg q2w dose when the platelet count falls to fewer than 150×10^9/L
- Post-baseline platelet count can be performed within 1 day of the next procedure as the SoA (both dosing and non-dosing visit), allowing the results to be incorporated into the criteria above.

From visits 17 to 24, the dosing frequency is fixed for each individual patient (ie, either the weekly or q2w regimen), based on the regimen the patient was receiving at visit 16 or at the last visit at which IMP was administered.

Exceptions to the fixed dosing frequency are:

1. Continued weekly dosing for patients requiring rescue therapy.
2. Continued q2w dosing for patients resuming IMP when the platelet count falls to fewer than 150×10^9/L after having had platelet counts greater than 400×10^9/L.

CONCURRENT ITP THERAPY

Patients receiving at least 1 permitted concurrent ITP therapy are eligible for the trial, if the dose and schedule have remained unchanged in the last 4 weeks before randomization (ie, visit 1). Permitted concurrent ITP medications include oral corticosteroids, oral immunosuppressants, dapsone/danazol, fostamatinib and/or oral thrombopoietin receptor agonists (TPO-RAs; inclusion criterion n°6, Section 4.3.1).

Dose and frequency of permitted concurrent ITP therapies should remain unchanged during the trial.

Exceptions are patients who are receiving concurrent treatment with oral TPO-RAs in whom dose changes are permitted at label-defined platelet thresholds, and patients who are receiving concurrent treatment with fostamatinib, in whom dose changes or stopping of treatment is allowed in label-defined conditions.

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" (ie, no platelet count of $\geq 30\times10^9$/L in any of the visits during the last 4 weeks). These patients will be considered as "non-responders" for the primary endpoint analysis. At the discretion of the investigator, the dose and/or schedule of the concurrent ITP therapy can be returned to the baseline levels.

Patients not receiving concurrent ITP therapy are also eligible for the trial.

RESCUE THERAPY

"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 trial 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 trial 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 trial completion)

The following rescue therapies are permitted:

- IV methylprednisolone up to 1 g/day × 1-3 days, oral dexamethasone up to 40 mg/day × 1-3 days, or oral prednisone up to 1 mg/kg/day × 1-2 days
- immunoglobulins given IV (IVIg): up to 1 g/kg/day × 1-2 days
- IV anti-D: up to 50-75 mcg/kg/day × 1-2 days
  Note: Anti-D rescue therapy should not be given to Rh(D)-positive patients
- platelet transfusions

It is encouraged to inform the sponsor's designated Contract Research Organization (CRO) medical monitor prior to initiating rescue therapy.

In the event of rescue with IVIg or IV anti-D:

- If given at a visit where the IMP was due to be administered, the IMP should be withheld and administered at the next visit.

For rescue therapy with methylprednisolone, dexamethasone, prednisone, or platelet transfusions:

- Administration of the IMP continues during rescue therapy.

Patients who were receiving q2w dosing at the time of rescue therapy will have the IMP administration frequency increased to weekly.

For patients who receive rescue therapy, the platelet counts for 4 weeks after the first day of rescue treatment will not be used (ie, are censored) to assess whether or not the patient can transition to q2w treatment.

Patients requiring more than 3 occurrences of rescue therapy will discontinue from IMP.

SAFETY

The administration of IMP may be temporarily withheld if, in the opinion of the investigator, it could put the patient at undue risk in the following circumstances:

- clinically significant disease, including evidence of infection
- severe bleeding, grade 3 or 4 on the WHO bleeding scale, requiring urgent medical and/or surgical intervention
- thrombosis

If the IMP is being withheld, it can be reintroduced once the investigator considers the undue risk to the patient has passed.

The administration of IMP must be temporary withheld from patients with platelet counts greater than 400×10^9/L, IMP should be resumed at the 10 mg/kg q2w dose when the platelet count falls to fewer than 150×10^9/L.

Efgartigimod treatment induces reductions in IgG levels, and there is a potential risk for infections associated with low IgG levels. As such, infections are considered AESI in this trial.

Due to the nature of underlying disease (ie, ITP), any occurrence of bleeding will also be considered an adverse event of special interest (AESI).

ASSESSMENT OF BLEEDING

Signs and symptoms of bleeding are the predominant clinical manifestation of ITP and are typically related to platelet counts.

The occurrence and severity of any bleeding symptoms will be assessed and recorded at every visit using the World Health Organization (WHO) bleeding scale as specified in the SoA (Table 1).

EARLY DISCONTINUATION FROM THE TRIAL

Any patient prematurely discontinuing the trial should perform the assessments listed for the Early Discontinuation visit.

TRIAL END

End-of-Trial is defined as last patient last visit in the ARGX-113-1801 trial.

Planned Number of Patients:	Approximately 117 patients with chronic ITP and up to 39 patients with persistent ITP will be randomized.
Planned Number of Sites:	Approximately 125 sites
Planned Countries:	This trial is a global, multicenter trial.
Target Population	Adult patients with persistent or chronic primary ITP, who have an average platelet count of $<30\times10^9$/L, and who, at the start of the trial, are on concurrent ITP treatment(s) and have received at least 1 prior therapy for ITP in the past, or are not on treatment for ITP but have received at least 2 prior treatments for ITP.

Criteria for Inclusion and Exclusion:	Inclusion Criteria: 1. Ability to understand the requirements of the trial, to provide written informed consent (including consent for the use and disclosure of research-related health information), and to comply with the trial protocol procedures (including required trial visits). 2. Male or female patient aged ≥18 years. 3. Confirmed ITP diagnosis, at least 3 months before randomization and according to the American Society of Hematology Criteria, and no known other etiology for thrombocytopenia. 4. Diagnosis supported by a response to a prior ITP therapy (other than thrombopoietin receptor agonists [TPO-RAs]), in the opinion of the investigator. 5. Mean platelet count of $<30\times10^9$/L from 2 counts: 1 platelet count collected during the screening period and the predose platelet count on the day of randomization (visit 1). 6. At the start of the trial, the patient is either on concurrent ITP treatment(s) and has received at least 1 prior therapy for ITP in the past, or the patient is not on treatment for ITP but has received at least 2 prior treatments for ITP. Patients receiving permitted concurrent ITP treatment(s) at baseline, must have been stable in dose and frequency for at least 4 weeks prior to randomization. Permitted concurrent ITP medications include oral corticosteroids, oral immunosuppressants, dapsone/danazol, fostamatinib, and/or oral TPO-RAs. Patients not receiving concurrent ITP therapy are also eligible for the trial if they have not received prior ITP therapy for at least 4 weeks prior to baseline, and 6 months in case of prior ITP therapy with an anti-CD20 therapy (eg, rituximab). 7. Women of childbearing potential must have a negative serum pregnancy test at the screening visit and a negative urine pregnancy test at baseline before trial medication (infusion) can be administered. Women are considered of childbearing potential unless they are postmenopausal (defined by continuous amenorrhea) for at least 1 year with a follicle-stimulating hormone (FSH) of >40 IU/L or are surgically sterilized (ie, women who had a hysterectomy, a bilateral salpingectomy, both ovaries surgically removed, or have a documented permanent female sterilization procedure including tubal ligation). Follicle-stimulating hormone can be used to confirm postmenopausal status in amenorrheic patients not on hormonal replacement therapy.

	8. Women of childbearing potential should use a highly effective or acceptable method of contraception during the trial and for 90 days after the last administration of the IMP. They must be on a stable regimen, for at least 1 month: • combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation o oral o intravaginal o transdermal • progestogen-only hormonal contraception associated with inhibition of ovulation: o oral o injectable o implantable • intrauterine device (IUD) • intrauterine hormone-releasing system • bilateral tubal occlusion • vasectomized partner (provided that the partner is the sole sexual partner of the trial participant and documented aspermia post procedure) • continuous abstinence from heterosexual sexual contact. Sexual abstinence is only allowable if it is the preferred and usual lifestyle of the patient. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not acceptable • male or female condom with or without spermicide • cap, diaphragm, or sponge with spermicide 9. Non-sterilized male patients who are sexually active with a female partner of childbearing potential must use an acceptable method of contraception, ie, a condom. Male patients practicing true sexual abstinence (when this is in line with the preferred and usual lifestyle of the participant) can be included. Sterilized male patients who have had a vasectomy with documented aspermia post procedure can be included. In addition, male patients are not allowed to donate sperm during this period from signing of ICF, throughout the duration of the trial, and for 90 days after the last administration of IMP.
	Exclusion Criteria: 1. ITP/thrombocytopenia associated with another condition, eg, lymphoma, chronic lymphocytic leukemia, viral infection, hepatitis, induced or alloimmune thrombocytopenia, or thrombocytopenia associated with myeloid dysplasia. 2. Use of anticoagulants (eg, vitamin K antagonists, direct oral anticoagulants) within 4 weeks prior to randomization. 3. Use of any transfusions within 4 weeks prior to randomization. 4. Use of Ig (IV, subcutaneous, or intramuscular route) or plasmapheresis (PLEX), 4 weeks prior to randomization.

	5. Use of anti-CD20 therapy (eg, rituximab) within 6 months prior to randomization. 6. Use of romiplostim within 4 weeks prior to randomization. 7. Undergone splenectomy less than 4 weeks prior to randomization. 8. Use of any other investigational drug within 3 months or 5 half lives of the drug (whichever is longer) prior to randomization. 9. Use of monoclonal antibodies or crystallized fragment (Fc) fusion proteins, other than those previously indicated, within 3 months prior to randomization. 10. At the screening visit, clinically significant laboratory abnormalities as below: • Hemoglobin ≤9 g/dL. - OR - • International normalized ratio >1.5 or activated partial thromboplastin time >1.5×ULN. - OR - • Total IgG level <6 g/L. 11. Patients who have a history of malignancy, including malignant thymoma, or myeloproliferative or lymphoproliferative disorders, unless deemed cured by adequate treatment with no evidence of recurrence for ≥3 years before screening. Patients with completely excised non-melanoma skin cancer (such as basal cell carcinoma or squamous cell carcinoma) or cervical carcinoma in situ would be permitted at any time. 12. Uncontrolled hypertension, defined as a repeated elevated blood pressure exceeding 160 mmHg (systolic) and/or 100 mmHg (diastolic) despite appropriate treatments. 13. History of any major thrombotic or embolic event (eg, myocardial infarction, stroke, pulmonary embolism, deep venous thrombosis) within 12 months prior to randomization. 14. History of coagulopathy or hereditary thrombocytopenia or a family history of thrombocytopenia. 15. History of a recent or planned major surgery (that involves major organs eg, brain, heart, lung, liver, bladder, or gastrointestinal tract) within 4 weeks of randomization. 16. Positive serum test at screening for an active viral infection with any of the following conditions: a. Hepatitis B virus (HBV) that is indicative of an acute or chronic infection, unless associated with a negative HBV DNA test (https://www.cdc.gov/hepatitis/HBV/PDFs/SerologicChartv8.pdf) b. Hepatitis C virus (HCV) based on HCV-antibody assay (unless associated with a negative HCV RNA test)

	c. Human immunodeficiency virus (HIV) based on test results that are associated with an acquired immunodeficiency syndrome (AIDS)-defining condition or a CD4 count $\leq$200 cells/mm^3 17. Clinical evidence of significant unstable or uncontrolled acute or chronic diseases other than ITP (eg, cardiovascular, pulmonary, hematologic, gastrointestinal, endocrine, hepatic, renal, neurological, malignancy, infectious diseases, uncontrolled diabetes) despite appropriate treatments which could put the patient at undue risk. 18. Patients with known medical history of hypersensitivity to any of the ingredients of the IMP. 19. Patients who previously participated in a clinical trial with efgartigimod and have received at least 1 administration of the IMP. 20. Pregnant or lactating females. 21. Employees of the investigator or trial center, with direct involvement in the proposed trial or other trials under the direction of that investigator or trial center, as well as family of the employees or the investigator. 22. Patients who received a live/live-attenuated vaccine within 4 weeks before screening. The receipt of any inactivated, sub-unit, polysaccharide, or conjugate vaccine at any time before screening is not considered an exclusion criterion.
Test Product, Dose, and Mode of Administration:	**Test product**: efgartigimod (ARGX-113), a modified human IgG1 Fc fragment **Dose:** 10 mg/kg body weight at infusion visits. The maximum total dose per infusion for IMP is 1200 mg for patients with body weight $\geq$120 kg measured at infusion visits **Mode of Administration**: IV infusion over a period of 1 hour
Comparator, Dose, and Mode of Administration:	Matching placebo with same excipients as the test product but without the active substance and will be administered as an IV infusion over a period of 1 hour.
Criteria for Evaluation: Primary Endpoint: • Proportion of patients with chronic ITP with a sustained platelet count response defined as achieving platelet counts of at least 50×10^9/L for at least 4 of the 6 visits between week 19 and 24 of the trial. Patients who discontinue treatment prior to visit 24 due to lack of efficacy (eg, 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.	

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 $\geq 50\times10^9$/L in the chronic ITP population.
- Proportion of patients in the overall population (chronic and persistent ITP) with a sustained platelet count response defined as achieving platelet counts of at least 50×10^9/L for at least 4 of the 6 visits between week 19 and 24 of the trial.
- 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 50×10^9/L for at least 6 of the 8 visits between week 17 and 24 of the trial.

Other Secondary Endpoints Not Subject to Alpha Control:

- Percentage of patients with overall platelet response defined as achieving a platelet count of $\geq 50\times10^9$/L on at least 4 occasions at any time during the 24-week treatment period.
- Extent of disease control defined as the number of cumulative weeks until week 12, with platelet counts of $\geq 50\times10^9$/L.
- Percentage of patients with overall platelet response defined as achieving a platelet count of $\geq 50\times10^9$/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 $\geq 50\times10^9$/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 of $\geq 30\times10^9$/L and at least 20×10^9/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 $\geq 30\times10^9$/L and at least 20×10^9/L above baseline.
- Change from baseline in PRO (FACIT-Fatigue, 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 AEs, AESIs, and serious AEs (SAEs).
- Evaluate vital signs, electrocardiogram (ECG), and laboratory assessments.

Exploratory Endpoint

- [redacted].

Statistical Methods and Plan

All patients starting at least 1 infusion of efgartigimod or placebo will be assessed for safety according to their actual treatment.

The efficacy analysis will be performed on the full analysis set (FAS) or the subset of patients in the FAS with chronic ITP; supportive analyses will be conducted in the per protocol population. The safety analysis will be performed on the safety analysis set.

The PK analysis set will include all patients from the safety analysis set who have at least 1 serum post-dose PK measurement.

Efficacy:

The efficacy analysis will be performed on the FAS or the subset of patients in the FAS with chronic ITP (baseline primary efficacy observation) and analyzed with intent-to-treat principle (ie, patients will be analyzed according to their planned treatment irrespective of the treatment actually received).

Sample Size

The null and alternative hypotheses are defined as H_0: $\pi_1 = \pi_2$ *vs.* H_A: $\pi_1 \neq \pi_2$, where π_1 and π_2 are the population probabilities to achieve a sustained platelet count response (primary efficacy endpoint) for 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 (ie, π_1 = [redacted] and π_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.

Primary Endpoint

The primary endpoint will be analyzed using a Cochran-Mantel-Haenszel statistic test stratified for the stratification factors history of splenectomy (yes versus no), receiving concurrent ITP therapies at baseline (yes versus no), and for 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 95% confidence interval (CI) and two-sided p-value. In addition, an adjusted difference of the proportions with its 95% CI will be provided.

Key Secondary Endpoints Subject to Alpha Control

Extent of disease control is defined as the number of cumulative weeks over the planned 24-week treatment period with platelet counts of $\geq50\times10^9$/L. For each patient this number will be calculated by counting the number of analysis visits from week 1 until week 24 (End-of-Treatment visit) at which the platelet count level is $\geq50\times10^9$/L. A Wilcoxon-Mann-Whitney test stratified by receiving concurrent ITP therapies at baseline (yes versus no), history of splenectomy (yes versus no), and baseline platelet count level category ($<15\times10^9$/L versus $\geq15\times10^9$/L) will be used to compare the extent of disease control between both treatment groups. The 2-sided p-value resulting from this hypothesis test will inform on whether the null hypothesis that the distributions of number of cumulative weeks for both treatment groups are identical can be rejected. The test will be conducted at a significance level α=0.05. An estimate of the location shift will be provided, along with the associated 95% confidence interval.

The key secondary endpoints on proportion of patients in the overall population with a sustained platelet count response and on proportion of patients in the overall population achieving platelet counts of at least 50×10^9/L for at least 6 of the 8 visits between week 17 and 24 of the trial will be analyzed in the same manner as the primary endpoint.

The number of bleeding events per patient (assessed using the WHO bleeding scale; where WHO scale ≥1 at any visit is considered a new bleeding event) will be analyzed using a zero-inflated negative binomial model. This model will account for the large expected number of patients with zero bleeding events. It is a mixture model consisting of 2 components: a negative binomial count model and a binary model for predicting excess zeros. The model will consist of the number of events as the dependent variable and of randomized treatment, the stratification variables (history of splenectomy; receiving concurrent ITP therapies at baseline), and baseline platelet count as independent variables. An offset term will be used to allow for patient exposure. Both the count model, using the log link, and the binary model, using the logit link, will contain the same independent variables. The probability of no bleeding will be estimated for each randomized treatment group. A Wald test will be used to test the null hypothesis that the log of the bleeding rate ratio on placebo and efgartigimod is equal to zero against the alternative that it is different from zero. The rate of bleeding over 24 weeks on placebo and efgartigimod will be provided, along with the rate

ratio, 95% 2-sided CI, and 2-sided p-value. Incidence of bleeding will also be summarized descriptively by visit. Severity of bleeding will be summarized descriptively by visit. In addition, a summary of within-subject maximum severity will be provided.

The primary endpoint analysis will act as gatekeeper for the testing of the key secondary endpoints. Subject to meeting statistical significance for the primary endpoint, the key secondary endpoints will be analyzed using a fixed-sequence testing procedure to maintain the overall type I error rate at 5%. The type I error rate of each individual test will be 5%, but the test will only be conducted if the analysis for all previous endpoints in the pre-defined hierarchy resulted in a p-value <0.05. The order in the testing hierarchy of the key secondary endpoints is as follows:

1. The extent of disease control defined as the number of cumulative weeks over the planned 24-week treatment period with platelet counts of $\geq 50\times10^9$/L in the population with chronic ITP.
2. The proportion of patients in the overall population (chronic and persistent ITP) with a sustained platelet count response defined as achieving platelet counts of $\geq 50\times10^9$/L for at least 4 of the 6 visits between week 19 and week 24 of the trial.
3. The incidence and severity of the WHO-classified bleeding events in the overall population.
4. The proportion of patients in the overall population achieving platelet counts of $\geq 50\times10^9$/L for at least 6 of the 8 visits between week 17 and 24 of the trial.

Other Secondary Endpoints Not Subject to Alpha Control

The mean changes from baseline in platelet count levels at planned time points and the mean changes from baseline in PRO at planned time points will be analyzed by means of mixed models for repeated measurements. The model will include fixed effect terms for randomized treatment, baseline platelet level or baseline PRO, history of splenectomy (yes vs. no), and receiving concurrent ITP therapies at baseline (yes vs. no). Least square (LS) means for placebo and efgartigimod will be provided, along with the difference in LS means, 95% 2-sided CI, and 2-sided p-value.

Time to response (defined as the time to achieve 2 consecutive platelet counts of $\geq 50\times10^9$/L) will be analyzed via Cox proportional hazards regression with fixed effect terms for randomized treatment and baseline platelet level. The model will be stratified by history of splenectomy (yes vs. no) and receiving concurrent ITP therapies at baseline (yes vs. no), at randomization. The hazard ratio for efgartigimod vs. placebo will be provided, along with the associated 95% 2-sided CI and 2-sided p-value. The data will also be displayed using Kaplan-Meier curves and the median time to response will be displayed by randomized treatment arm. The number of cumulative weeks over the planned 24-week treatment period with platelet counts of $\geq 30\times10^9$/L and at least 20×10^9/L above baseline will be analyzed in the same way as described for the key secondary endpoint "extent of disease control." Assessment of number of cumulative weeks over the planned 24-week treatment period with platelet counts of $\geq 30\times10^9$/L and at least 20×10^9/L above baseline within the group of patients with a baseline platelet count of $<15\times10^9$/L will also be analyzed as described for the key secondary endpoint.

Pharmacodynamics, Pharmacokinetics, and Immunogenicity

Descriptive statistics will be provided for PD parameters (total IgG and subtypes, and antiplatelet antibodies), and ADA. Efgartigimod serum concentration data will be summarized.

Safety

Incidence and severity of AEs, AESIs, and SAEs will be summarized descriptively. Laboratory parameters, vital signs, and ECG data will also be analyzed descriptively.

Exploratory Endpoint

Descriptive statistics will be presented for [redacted]. The analysis of [redacted] will be performed at a later stage than the analyses of the other endpoints and will be described in a separate report.

Table 1 Schedule of Assessments

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[h]	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).
[redacted]

[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.

[o] [redacted].

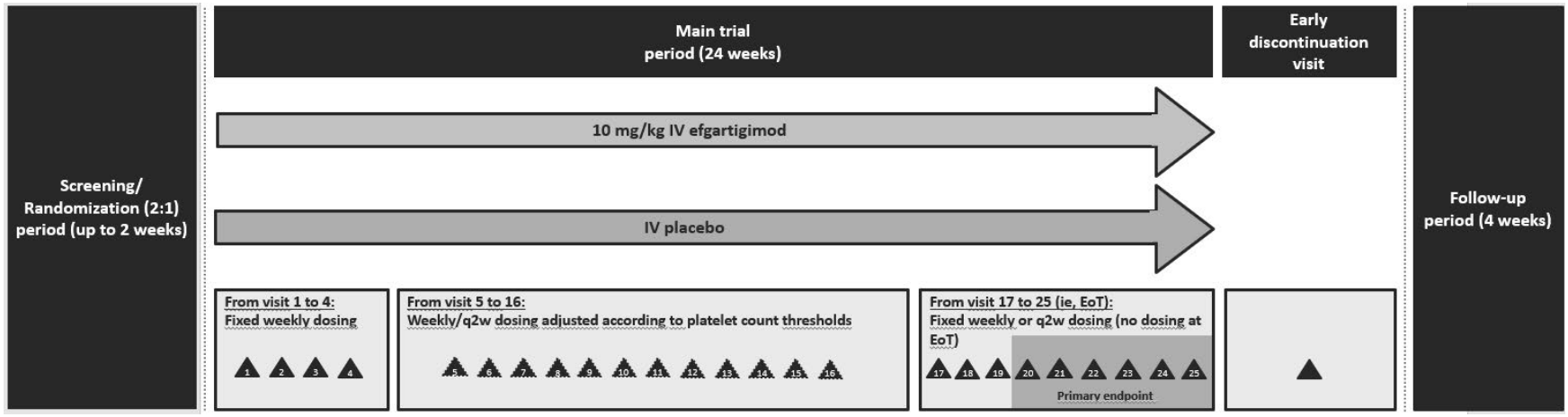
[p] Both pre- and post-dose to be collected (within 2 hours prior to the start of the IMP infusion and within 30 minutes after the end of IMP infusion, respectively).

[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.

Figure 1 A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial to Evaluate the Efficacy and Safety of Efgartigimod (ARGX-113) 10 mg/kg IV in Adult Patients With Primary Immune Thrombocytopenia



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ADA	anti-drug antibodies
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ASH	American Society of Hematology
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CRO	contract research organization
CTCAE	common terminology criteria for adverse events
CTR	clinical trial report
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
FAS	full analysis set
Fc	crystallized fragment
FcRn	neonatal crystallized fragment receptor
FSH	follicle-stimulating hormone
GCP	good clinical practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification number
IEC	Independent Ethics Committee
Ig	immunoglobulin
IMP	investigational medicinal product
IND	investigational new drug
[redacted]	[redacted]
IRB	Institutional Review Board
IRT	interactive response technology
ITP	immune thrombocytopenia
IUD	intrauterine device

IV	intravenous
IVIg	immunoglobulins given intravenously
LS	least square
MG	myasthenia gravis
NCI	National Cancer Institute
OR	odds ratio
PD	pharmacodynamic
PK	pharmacokinetics
PLEX	plasmapheresis
PP	per protocol
PRO	patient-reported outcomes
q2w	biweekly/every other week
QoL	quality-of-life
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SoA	schedule of assessments
SOP	standard operating procedure
TEAE	treatment-emergent adverse event
TPO-RA	thrombopoietin receptor agonist
US	United States
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

DEFINITION OF TERMS

Blinding:	A procedure in which 1 or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased trial outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a (serious) adverse event ([S]AE). In a double-blind trial, the patient, the investigator, site staff, and sponsor staff who are involved in the treatment or clinical evaluation of the patients and the review or analysis of data are all unaware of the treatment assignment.
Childbearing potential:	Women of childbearing potential are defined as all female participants unless they are postmenopausal (defined by continuous amenorrhea) for at least 1 year with a follicle-stimulating hormone (FSH) of >40 IU/L or are surgically sterile (ie, who had a hysterectomy, a bilateral salpingectomy, a bilateral oophorectomy, or have current documented tubal ligation or any other permanent female sterilization procedure). Determination of FSH levels can be used to confirm postmenopausal status in amenorrheic patients not on hormonal replacement therapy.
Council for International Organizations of Medical Sciences:	The Council for International Organizations of Medical Sciences (CIOMS) is an international, non-governmental, non-profit organization established jointly by the World Health Organization (WHO) and United Nations Educational, Scientific and Cultural Organization in 1949. They provide a set of ethical principles regarding human experimentations, including International Reporting of adverse drug reactions (ADRs) and International Reporting of Periodic Drug-Safety Update Summaries. The CIOMS form provides a standardized format for the reporting of suspected adverse reactions to any particular medicinal product and is the accepted and widely used format for reporting suspected ADR/suspected unexpected serious adverse reaction in clinical trials.

Contract Research Organization:	A person, or a group of persons (commercial, academic, or other), who as an independent contractor with argenx BVBA, assume(s) 1 or more obligations of argenx BVBA, eg, development of a protocol, selection and/or monitoring of investigators, evaluation of reports, preparation of materials to be submitted to regulatory authorities.
Database lock:	An action taken to prevent further changes to a trial database. A database is locked after review, query resolution, data cleaning and determination that it is ready for analysis.
Data Safety Monitoring Board:	Independent group of experts that advises and whose responsibilities are to periodically review and evaluate the accumulated trial data for participant safety, trial conduct and progress and, when appropriate, efficacy, and to make recommendation to the sponsor concerning the continuation, modification or termination of the trial.
Eligible:	Qualified for randomization into the trial based upon strict adherence to inclusion/exclusion criteria.
Good Clinical Practice:	A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial patients are protected. (International Council for Harmonisation of Technical Requirements for Human Use [ICH] E6).
Institutional Review Board/Independent Ethics Committee:	An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving / providing favorable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.
Informed Consent/ Informed Consent Form:	A process by which a clinical investigation participant voluntarily confirms his or her willingness to participate in a particular clinical trial, after having been informed of all

	aspects of the trial that are relevant to the participant's decision to participate. Informed consent is documented by means of a dated and signed informed consent form (ICF).
International Council for Harmonisation:	The ICH is a project that brings together the regulatory authorities of Europe, Japan, and the United States (US), and experts from the pharmaceutical industry in the 3 regions to discuss scientific and technical aspects of pharmaceutical product registration.
Investigational Medicinal Product:	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Protocol amendment:	A written description of a change(s) to or formal clarification of a protocol.
Randomization:	Process of random attribution of treatment to subjects in order to reduce bias of selection.
Treatment:	Term used throughout the clinical trial to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a subject.

1. INTRODUCTION

1.1. Background Information

Efgartigimod (ARGX-113) is a modified human immunoglobulin (Ig) G1-derived crystallized fragment (Fc) of the za allotype that binds with nanomolar affinity to the human neonatal crystallized fragment receptor (FcRn). Efgartigimod encompasses IgG1 residues D221-K447 (EU numbering scheme) and has been modified with the so-called ABDEG™ technology (ABDEG™ = antibody that enhances IgG degradation)[1] to increase its affinity for FcRn at both physiological and acidic pH. The increased affinity for FcRn of efgartigimod at both acidic and physiological pH results in a blockage of FcRn-mediated recycling of IgGs.

Given the essential role of the FcRn receptor in IgG homeostasis, inhibiting this FcRn function, as is achieved by efgartigimod, leads to rapid degradation of all IgGs, including disease-associated autoantibodies of the IgG isotype. This approach is thought to result in alleviation of signs and symptoms in IgG-driven autoimmune diseases.

The safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of intravenous (IV) administrations of efgartigimod have been investigated in a first-in-human study in healthy adult subjects. A second study in healthy adult subjects investigated the bioavailability, safety, tolerability, immunogenicity, PK, and PD of a subcutaneous (SC) administration of efgartigimod and evaluated the reduction of the IV infusion time from 2 hours to 1 hour.

Phase 2 trials in immune thrombocytopenia (ITP) and myasthenia gravis (MG) have indicated that efgartigimod administered by IV infusion is well tolerated; induces a specific, rapid, and profound PD effect (ie, reduction in IgG levels, including autoantibody levels); and is associated with improvement in clinical signs and symptoms in ITP and MG patients,[2] separately (see Section 1.3). Additionally, the safety and tolerability of efgartigimod is currently being evaluated for the treatment of patients with pemphigus in a phase 2 trial.

Primary ITP is an acquired autoimmune bleeding disorder characterized by an isolated low platelet count ($<100\times10^9$/L) in the absence of other causes or disorders associated with thrombocytopenia.[3] Prevalence of ITP is estimated at 9.5 per 100 000 adults, and incidence rates have been reported at 3.3 per 100 000 adults/year.[4] In adults, the prevalence of ITP increases with age[5]. Adult ITP can persist for years. Even with best available care, patients rarely achieve long-term remission, and often require multiple treatment options.[6] ITP can be described based on the duration of disease: newly diagnosed (within 3 months of diagnosis), persistent (between 3 and 12 months from diagnosis), and chronic (lasting for more than 12 months).[3]

In primary ITP, platelet destruction and impaired platelet production are driven by IgG autoantibodies targeting surface receptors on platelets and their progenitor cells. The resulting, often severe, thrombocytopenia may be accompanied by a variety of symptoms including evidence of bleeding in the skin and mucosa, and risk of serious intracranial and

gastrointestinal bleeding complications. The highest concern is the risk of significant bleeding, such as intracranial hemorrhage. The 5-year fatal hemorrhage rate is higher in older patients with ITP, especially in those with comorbid conditions.[6-8] Other clinically significant concerns include complications from internal bleeding and elevated risk of arterial thrombosis and venous thromboembolism.[9] Immune thrombocytopenia is also associated with fatigue, reported in up to 39% of adults with ITP,[6] as well as impaired quality-of-life (QoL). These comorbidities interfere with work and social life, which can lead to feelings of embarrassment, isolation, and sexual inadequacy.[6-8]

Several drugs and medical procedures are routinely used in the management of ITP. First-line therapy in primary ITP is corticosteroids, as well as immunoglobulins given intravenously (IVIg) and anti-D. Second-line treatments include broad immunosuppressants and thrombopoietin receptor agonists (TPO-RAs). There is limited evidence to guide the use of these treatments, as described in the American Society of Hematology (ASH) guidelines.[10] There is no evidence to guide a sequence of treatments for patients who have recurrent or persistent thrombocytopenia associated with bleeding after an initial treatment course with corticosteroids (or IVIg or anti-D). Patients may cycle through different treatment regimens seeking any that is efficacious and tolerable. Immune thrombocytopenia remains a chronic disease despite the availability of several treatments with differing mechanisms of action. According to the ASH ITP guidelines only splenectomy has provided evidence of remission at 1 year. Additionally, a significant proportion of patients develop resistance to treatment. Furthermore, existing treatments are associated with burdensome side-effects limiting their use (eg, long-term steroid treatment) and/or concern about use in patient populations (eg, TPO-RAs in patients with elevated cardiovascular risk).

Targeted and selective IgG reduction, as achieved by efgartigimod, has the potential as an effective new treatment in ITP seen the central role of IgG autoantibodies in the pathophysiology of ITP. It represents a novel mechanism of action distinct from that of other existing treatments which are either broadly immunosuppressive or stimulate thrombopoiesis.

1.2. Benefit-Risk Assessment

Efgartigimod has been shown to effectively reduce IgG antibodies in several clinical trials, including healthy volunteers, patients with MG, and with ITP.

More specifically, a phase 2 trial (ARGX-113-1603) in patients with ITP enrolled a patient population who was predominantly refractory to previous lines of ITP therapy, with the majority of patients having long-standing disease, prior ITP treatment exposure and approximately half with baseline platelet count of $<15\times10^9$/L.

Efgartigimod resulted in a rapid and marked reduction of IgG antibodies (maximum mean reduction of 65%) and of all IgG subtypes.

Treatment with efgartigimod, whether 5 mg/kg or 10 mg/kg, was associated with an increase in platelet counts in more patients than occurred in the placebo group, with greater numerical separation from placebo as the platelet count threshold stringency was increased. Additional post hoc analyses further supported these observations, showing a longer duration of clinically meaningful effect and statistically significantly more active-treated patients achieving a platelet count of $\geq 50 \times 10^9$/L for more than 10 cumulative days compared to the placebo group.

In each of the subgroups of patients based on ITP classification (newly diagnosed, persistent, or chronic ITP) or those with or without historical or concomitant use of TPO-RA, there were examples of efgartigimod-treated patients with an increase in platelet count.

In the open-label treatment period patients received 4 weekly infusions of efgartigimod 10 mg/kg, either as first exposure in patients who previously received placebo or retreatment with efgartigimod. In this part of the trial, the majority of patients (58%) had improved platelet counts.

Efgartigimod is under investigation in MG, another disease driven by IgG autoantibodies. In a phase 2 trial ARGX-113-1602, 4 weekly IV infusions of 10 mg/kg efgartigimod led to statistically significant improvements in clinical scales and were well tolerated. A phase 3 trial ARGX-113-1704 and accompanying open-label extension trial ARGX-113-1705 are ongoing in this indication.

In clinical trials to date, efgartigimod has been well tolerated in healthy adult subjects and patients with MG and ITP, separately: the majority of treatment-emergent AEs (TEAEs) were considered to be mild (grade 1) in severity. In the completed phase 1 trials ARGX-113-1501, ARGX-113-1702, and ARGX-113-1901 in healthy volunteers, and in the phase 2 trial ARGX-113-1602 in patients with MG, no grade ≥3 TEAEs were reported and no TEAE led to discontinuation. In the phase 2 trial ARGX-113-1603 in patients with ITP, 1 TEAE with grade 4 was reported (thrombocytopenia), considered unrelated to treatment, and led to treatment discontinuation.

No clinically significant changes in vital signs and/or electrocardiogram (ECG) findings have been observed in clinical trials to date.

Safety for use during pregnancy has not been established. Therefore, efgartigimod should not be administered to pregnant or lactating women.

Please refer to the current Investigator's Brochure for more information regarding the preclinical and clinical trials, and the potential risks and benefits of efgartigimod. In summary, the favorable balance between risks and anticipated efficacy/benefits supports the use of efgartigimod in clinical development.

1.3. Trial Rationale

The proposed phase 3 trial aims to establish the efficacy, safety, and impact on patient-reported outcomes (PRO) of efgartigimod administered as IV infusions in adult patients with primary

ITP who have had an insufficient response or who are intolerant to existing ITP treatments, evidenced by a platelet count that is below the clinically accepted level for intervention ($<30\times10^9$/L).

Patients classified as having persistent ITP (between 3 and 12 months since diagnosis) and chronic ITP (greater than 12 months since diagnosis) will be recruited. At the start of the trial, the patients are either on concurrent ITP treatment(s) and have received at least 1 prior therapy for ITP in the past, or the patients are not on treatment for ITP but have received at least 2 prior treatments for ITP.

Treatments for ITP are often used in combination and efgartigimod has the potential to be used in combination with other ITP therapies or offer a new stand-alone modality. Therefore, patients with and without concurrent ITP therapy will be enrolled. Experience to date of efgartigimod treatment in combination with steroids and immunosuppressants in phase 2 ITP and MG trials has not raised any safety concerns with these combinations of treatments.

This trial will utilize an IV dosing schedule aiming to maximize PD effect (ie, reduction of autoantibody levels) and seeking to result in an improvement in platelet count. In patients who achieve a prespecified threshold of maintained platelet count improvement, the frequency of efgartigimod administration will be altered (ie, increased or decreased) according to prespecified criteria, after which the frequency of administration will be unchanged for the last 7 weeks (visits 17 to 24) of trial treatment. Assessment of the dosing regimen as described in Section 5.4.1 will be applied. The aim is to achieve the maximum possible proportion of patients with a platelet count improvement and then assess whether this can be sustained in the last 5 weeks of trial treatment.

Based on the results of the phase 1 trial in healthy adult subjects, the phase 2 trial in patients with ITP, as well as the PK/PD modeling analysis, a dose of 10 mg/kg efgartigimod was selected as it is considered safe and well tolerated, achieved consistently a close to maximal IgG reduction (ie, 65-70%), and resulted in a clinical response (eg, increase in platelet count) in a significant proportion of patients. This dose is also being utilized in the ongoing phase 3 trials in MG (see Section 1.2).

A continuous dosing regimen of weekly or biweekly (q2w) IV infusions of 10 mg/kg efgartigimod is anticipated to be safe. In a long-term toxicity trial (26-weeks with 8-weeks recovery period), cynomolgus monkeys were dosed with weekly efgartigimod infusions of up to 100 mg/kg. The no observed adverse effect level was set at the highest administered dose of 100 mg/kg. The exposures achieved in this toxicity study were between 35.5 (female animals) and 40.8 (male animals) times the simulated area under the curve values in ITP patients using the clinical dose of 10 mg/kg.

2. TRIAL OBJECTIVES

2.1. Primary Objective

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

2.2. Secondary Objectives

- To evaluate the efficacy of efgartigimod compared to placebo in overall platelet count response.
- To evaluate the safety and tolerability of efgartigimod administered IV weekly or 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 QoL measures and PRO compared to placebo.
- To assess the immunogenicity of efgartigimod.
- To assess the PK of efgartigimod.
- To assess the PD effects of efgartigimod.

2.3. Exploratory Objective

- [redacted].

[*] "week" instead of "visits" are used in the endpoints, ensuring that the platelet count of the EoT visit is regarded as week 24 platelet count. (eg, platelet count after 19 weeks of treatment corresponds with platelet count of visit 20).

3. TRIAL ENDPOINTS

3.1. Primary Endpoint

- Proportion of patients with chronic ITP with a sustained platelet count response defined as achieving platelet counts of at least 50×10^9/L for at least 4 of the 6 visits between week 19 and 24 of the trial.

Patients who discontinue treatment prior to visit 24 due to lack of efficacy (eg, 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.

3.2. Secondary Endpoints

Key Secondary Efficacy Endpoints Subject to Alpha Control:

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

Other Secondary Endpoints Not Subject to Alpha Control:

- 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 $\geq 30\times10^9$/L and at least 20×10^9/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 $\geq 30\times10^9$/L and at least 20×10^9/L above baseline.
- Change from baseline in PRO (FACIT-Fatigue, 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 AEs, AESIs, and SAEs.
- Evaluate vital signs, ECG, and laboratory assessments.

3.3. Exploratory Endpoint

- [redacted]

4. INVESTIGATIONAL PLAN

4.1. Summary of Trial Design

DESCRIPTION

This is a phase 3, multicenter, randomized, double-blinded, placebo-controlled, parallel-group, up to 31-week trial 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 trial 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
- 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 trial 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" (ie, 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.

After confirmation of eligibility, the patients enter a 24-week treatment period and will be randomized to receive 10 mg/kg IV of efgartigimod or placebo, weekly from visits 1 to 4 and then from visits 5 to 16 either weekly 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 IMP was administered (ie, either weekly or q2w). Assessment of the dosing regimen as described in Section 5.4.1 will be applied.

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

Patients who complete the 24-week trial period but who do not enter the open-label extension trial ARGX-113-1803, or patients who discontinue the trial 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 trial early, all the assessments listed for the Early Discontinuation visit as specified in the schedule of assessments (SoA, Table 1), will be performed.

SAMPLE SIZE AND STRATIFICATION

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 when 117 patients with chronic ITP have been randomized.

Patients will be stratified according to the following factors:

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

SCREENING AND TREATMENT

During the screening period (up to 2 weeks) the patient's eligibility for trial participation will be evaluated.

All eligible patients will be randomized to receive IV infusions of either efgartigimod 10 mg/kg body weight or matching placebo throughout the trial.

All patients will initially receive weekly IV infusions from visits 1 to 4.

Based on the platelet counts as of visit 2, the dosing frequency can be altered from visits 5 to 16 according to the following rules (the change in dosing frequency will occur at the current visit):

- Reduce from weekly to q2w in patients achieving platelet counts of $\geq 100\times10^9$/L for 3 out of 4 consecutive visits (the fourth visit being the current visit), and have a platelet count of $\geq 100\times10^9$/L at the last of these 4 visits
  – OR –
  3 consecutive visits
- Increase from q2w to weekly in patients whose platelet counts drop below 100×10^9/L on 2 consecutive visits
  – OR –
  $<30\times10^9$/L at 1 visit
  – OR –
  in patients who receive rescue therapy (see Section 6.8.4)

- Temporary withholding treatment
    - for the reasons described in Section 4.5, IMP should be reintroduced once the investigator considers the undue risk to the patient has passed
    - in patients with platelet counts greater than 400×10^9/L, IMP should be resumed at the 10 mg/kg q2w dose when the platelet count falls to fewer than 150×10^9/L
- Post-baseline platelet count can be performed within 1 day of the next procedure as per the SoA (both dosing and non-dosing visit), allowing the results to be incorporated into the criteria above.

From visits 17 to 24, the dosing frequency is fixed for each individual patient (ie, either weekly or q2w regimen), based on the regimen the patient was receiving at visit 16 or at the last visit at which IMP was administered.

Exceptions to the fixed dosing frequency are:

- Continued weekly dosing for patients requiring rescue therapy.
- Continued q2w dosing for patients resuming IMP when the platelet count falls to fewer than 150×10^9/L after having had platelet counts greater than 400×10^9/L.

ROLLOVER TO THE OPEN-LABEL EXTENSION TRIAL (ARGX-113-1803)

Patients who complete the 24-week trial period have the possibility to enter the open-label extension trial (ARGX-113-1803) to receive efgartigimod 10 mg/kg IV. The platelet counts from the ARGX-113-1801 trial will be taken into account to assess the dosing frequency in ARGX-113-1803.

CONCURRENT ITP THERAPY

Patients receiving at least 1 permitted concurrent ITP therapy are eligible for the trial, if the dose and schedule have remained unchanged in the last 4 weeks before randomization (ie, visit 1). Permitted concurrent ITP medications include oral corticosteroids, oral immunosuppressants, dapsone/danazol, fostamatinib and/or oral TPO-RAs (inclusion criterion n°6, Section 4.3.1). Dose and frequency of permitted concurrent ITP therapies should remain unchanged during the trial.

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” (ie, 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. At the discretion of the investigator, the dose and/or schedule of the concurrent ITP therapy can be returned to the baseline levels.

Exceptions are patients who are receiving concurrent treatment with oral TPO-RAs in whom dose changes are permitted at label-defined platelet thresholds, and patients who are receiving concurrent treatment with fostamatinib, in whom dose changes or stopping of treatment is allowed in label-defined conditions.

All changes or discontinuations in concurrent ITP therapy (type, dose, frequency, date of discontinuation and resumption) should be appropriately indicated in the electronic case report form (eCRF). The patient does not need to be discontinued from the trial.

Patients not receiving concurrent ITP therapy are also eligible for the trial.

RESCUE THERAPY

"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 trial 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 trial 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 trial completion)

The following rescue therapies are permitted:

- IV methylprednisolone up to 1 g/day×1-3 days, or oral dexamethasone up to 40 mg/day×1-3 days, or oral prednisone up to 1 mg/kg/day×1-2 days
- IVIg: up to 1 g/kg/day×1-2 days
- IV anti-D: up to 50-75 mcg/kg/day×1-2 days
  Note: Anti-D rescue therapy should not be given to Rh(D)-positive patients
- platelet transfusions

It is encouraged to inform the sponsor's designated contract research organization (CRO) medical monitor prior to initiating any rescue therapy.

In the event of rescue with IVIg or IV anti-D:

- If given at a visit where the investigational medicinal product (IMP) was due to be administered, the IMP should be withheld and administered at the next visit.

For rescue therapy with methylprednisolone, dexamethasone, prednisone, or platelet transfusions:

- Administration of the IMP continues during rescue therapy.

Patients who were receiving q2w dosing at the time of rescue therapy will have the IMP administration frequency increased to weekly.

For patients who receive rescue therapy, the platelet counts for 4 weeks after the first day of rescue treatment will not be used (ie, are censored) to assess whether or not the patient can transition to q2w treatment.

Patients requiring more than 3 occurrences of rescue therapy will discontinue from IMP.

EARLY DISCONTINUATION FROM THE TRIAL

Any patient prematurely discontinuing the trial should perform the assessments listed for the Early Discontinuation visit as mentioned in the SoA (Table 1).

TRIAL END

End-of-Trial is defined as last patient last visit in the ARGX-113-1801 trial.

4.2. Discussion of Trial Design

In the current trial, efgartigimod or placebo will be administered in patients with primary ITP, with the aim to evaluate the efficacy, safety, and impact on QoL of efgartigimod versus placebo.

This trial is designed as a randomized, double-blinded trial to evaluate the effect of efgartigimod and placebo administered as an IV infusion. The trial consists of a treatment period where all patients will initially receive weekly IV infusions from visits 1 to 4. From visits 5 to 16, the dosing frequency can be altered (ie, increased or decreased) according to specified rules.

The primary endpoint in this trial is the proportion of patients with chronic ITP that have a sustained platelet count response defined as achieving platelet counts of at least 50×10^9/L for at least 4 of the 6 visits between week 19 and 24 of the trial. Patients who discontinue treatment prior to visit 24 due to lack of efficacy (eg, 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.

The key secondary endpoints assess the efficacy of efgartigimod focusing on measures of response derived from platelet counts, and the incidence and severity of bleeding.

The choice of a 10-mg/kg IV dose of efgartigimod was made because it has been shown to be well tolerated, to consistently achieve close to maximal PD effect, and to be associated with a clinical meaningful effect on platelet counts (see Section 1.3). Based on the transient clinical responses observed following short term 4-week treatment in the phase 2 trial, a personalized chronic dosing regimen guided by treatment response is proposed in line with the chronic nature of the disease: a continuous weekly or q2w dosing regimen of 10 mg/kg.

Platelet count is an objective measure and is the accepted marker of treatment effect in ITP.

4.3. Selection of Trial Population

Approximately 117 patients with chronic ITP and up to 39 patients with persistent ITP will be randomized. Recruitment will end when 117 patients with chronic ITP have been randomized.

Patients who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive any trial medication.

4.3.1. Inclusion Criteria

Patients will be randomized in this trial only if they meet **all** of the following criteria:

1. Ability to understand the requirements of the trial, to provide written informed consent (including consent for the use and disclosure of research-related health information), and to comply with the trial protocol procedures (including required trial visits).
2. Male or female patient aged ≥18 years.
3. Confirmed ITP diagnosis, at least 3 months before randomization and according to the ASH Criteria, and no known other etiology for thrombocytopenia.
4. Diagnosis supported by a response to a prior ITP therapy (other than TPO-RAs), in the opinion of the investigator.
5. Mean platelet count of $<30\times10^9$/L from 2 counts: 1 platelet count collected during the screening period and the predose platelet count on the day of randomization (visit 1).
6. At the start of the trial, the patient is either on concurrent ITP treatment(s) and has received at least 1 prior therapy for ITP in the past, or the patient is not on treatment for ITP but has received at least 2 prior treatments for ITP. Patients receiving permitted concurrent ITP treatment(s) at baseline, must have been stable in dose and frequency for at least 4 weeks prior to randomization.
   Permitted concurrent ITP medications include oral corticosteroids, oral immunosuppressants, dapsone/danazol, fostamatinib and/or oral TPO-RAs.
   Patients not receiving concurrent ITP therapy are also eligible for the trial if they have not received prior ITP therapy for at least 4 weeks prior to baseline, and 6 months in case of prior ITP therapy with an anti-CD20 therapy (eg, rituximab).
7. Women of childbearing potential (see DEFINITION OF TERMS) must have a negative serum pregnancy test at the screening visit and a negative urine pregnancy test at baseline before trial medication (infusion) can be administered. Women are considered of childbearing potential unless they are postmenopausal (defined by continuous amenorrhea) for at least 1 year with an FSH of >40 IU/L or are surgically sterilized (ie, women who had a hysterectomy, a bilateral salpingectomy, both ovaries surgically removed, or have a documented permanent female sterilization procedure including tubal

ligation). Follicle-stimulating hormone can be used to confirm postmenopausal status in amenorrheic patients not on hormonal replacement therapy.

8. Women of childbearing potential should use a highly effective or acceptable method of contraception during the trial and for 90 days after the last administration of the IMP. They must be on a stable regimen, for at least 1 month, of:
   - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
     - oral
     - intravaginal
     - transdermal
   - progestogen-only hormonal contraception associated with inhibition of ovulation:
     - oral
     - injectable
     - implantable
   - intrauterine device (IUD)
   - intrauterine hormone-releasing system
   - bilateral tubal occlusion
   - vasectomized partner (provided that the partner is the sole sexual partner of the trial participant and documented aspermia post procedure)
   - continuous abstinence from heterosexual sexual contact. Sexual abstinence is only allowable if it is the preferred and usual lifestyle of the patient. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not acceptable
   - male or female condom with or without spermicide
   - cap, diaphragm, or sponge with spermicide.
9. Non-sterilized male patients who are sexually active with a female partner of childbearing potential must use an acceptable method of contraception, ie, a condom. Male patients practicing true sexual abstinence (when this is in line with the preferred and usual lifestyle of the participant) can be included. Sterilized male patients who have had a vasectomy with documented aspermia post procedure can be included. In addition, male patients are not allowed to donate sperm during this period from signing of ICF, throughout the duration of the trial, and for 90 days after the last administration of IMP.

4.3.2. Exclusion Criteria

Patients will not be enrolled in this trial if they meet **any** of the following criteria:

1. ITP/thrombocytopenia associated with another condition, eg, lymphoma, chronic lymphocytic leukemia, viral infection, hepatitis, induced or alloimmune thrombocytopenia, or thrombocytopenia associated with myeloid dysplasia.
2. Use of anticoagulants (eg, vitamin K antagonists, direct oral anticoagulants) within 4 weeks prior to randomization.
3. Use of any transfusions within 4 weeks prior to randomization.
4. Use of Ig (IV, SC, or intramuscular route) or plasmapheresis (PLEX), 4 weeks prior to randomization.
5. Use of anti-CD20 therapy (eg, rituximab) within 6 months prior to randomization.
6. Use of romiplostim within 4 weeks prior to randomization.
7. Undergone splenectomy less than 4 weeks prior to randomization.
8. Use of any other investigational drug within 3 months or 5 half-lives of the drug (whichever is longer) prior to randomization.
9. Use of monoclonal antibodies or Fc fusion proteins, other than those previously indicated, within 3 months prior to randomization.
10. At the screening visit, clinically significant laboratory abnormalities as below:
    - Hemoglobin ≤9 g/dL

      - OR -
    - International normalized ratio >1.5 or activated partial thromboplastin time >1.5×ULN

      - OR -
    - Total IgG level <6 g/L
11. Patients who have a history of malignancy, including malignant thymoma, or myeloproliferative or lymphoproliferative disorders, unless deemed cured by adequate treatment with no evidence of recurrence for ≥3 years before screening. Patients with completely excised non-melanoma skin cancer (such as basal cell carcinoma or squamous cell carcinoma) or cervical carcinoma in situ would be permitted at any time.
12. Uncontrolled hypertension, defined as a repeated elevated blood pressure exceeding 160 mmHg (systolic) and/or 100 mmHg (diastolic) despite appropriate treatments.
13. History of any major thrombotic or embolic event (eg, myocardial infarction, stroke, pulmonary embolism, deep venous thrombosis) within 12 months prior to randomization.
14. History of coagulopathy or hereditary thrombocytopenia or a family history of thrombocytopenia.
15. History of a recent or planned major surgery (that involves major organs eg, brain, heart, lung, liver, bladder, or gastrointestinal tract) within 4 weeks of randomization.
16. Positive serum test at screening for an active viral infection with any of the following conditions:

a. Hepatitis B virus (HBV) that is indicative of an acute or chronic infection, unless associated with a negative HBV DNA test (https://www.cdc.gov/hepatitis/HBV/PDFs/SerologicChartv8.pdf)

b. Hepatitis C virus (HCV) based on HCV-antibody assay (unless associated with a negative HCV RNA test)

c. Human immunodeficiency virus (HIV) based on test results that are associated with an acquired immunodeficiency syndrome (AIDS)-defining condition or a CD4 count $\leq$200 cells/mm^3

17. Clinical evidence of significant unstable or uncontrolled acute or chronic diseases other than ITP (eg, cardiovascular, pulmonary, hematologic, gastrointestinal, endocrine, hepatic, renal, neurological, malignancy, infectious diseases, uncontrolled diabetes) despite appropriate treatments which could put the patient at undue risk.
18. Patients with known medical history of hypersensitivity to any of the ingredients of the IMP.
19. Patients who previously participated in a clinical trial with efgartigimod and have received at least 1 administration of the IMP.
20. Pregnant or lactating females.
21. Employees of the investigator or trial center, with direct involvement in the proposed trial or other trials under the direction of that investigator or trial center, as well as family of the employees or the investigator.
22. Patients who received a live/live-attenuated vaccine within 4 weeks before screening. The receipt of any inactivated, sub-unit, polysaccharide, or conjugate vaccine at any time before screening is not considered an exclusion criterion.

4.4. Early Discontinuation

The criteria for screening and enrollment are to be followed explicitly. If it is noted that a patient who does not meet 1 or more of the inclusion criteria and/or meets 1 or more of the exclusion criteria is inadvertently enrolled and dosed, the sponsor's designated CRO monitor and the sponsor's medical director must be contacted immediately.

4.4.1. Early Discontinuation From Trial

Early discontinuation from the trial is defined as the permanent cessation of further participation in the trial prior to its planned completion and without the possibility to roll over to the open-label extension trial (ARGX-113-1803).

The reason for early discontinuation from the trial will be clearly documented by the investigator.

- Patients **must** be discontinued early from the **trial** and complete the Early Discontinuation visit as specified in the SoA (Table 1) if:

- they withdraw their consent

  All patients are free to withdraw consent from participation in the trial at any time, for any reason, specified or unspecified, and without prejudice to further treatment. Prior to actual withdrawal of consent, an effort should be made to perform a final set of assessments as per Early Discontinuation visit.

  Investigators will make and document all efforts made to contact those patients who do not return for scheduled visits.

- Patients **must** be discontinued early from the **trial**, complete the Early Discontinuation visit as specified in the SoA (Table 1), and have to be followed-up for 4 weeks (2 q2w visits) for ongoing safety and efficacy monitoring if:

  - it is in the patient's best interest, discussion with the sponsor's medical director is encouraged prior to discontinuation
  - unblinding occurred
  - prohibited medication is taken (see Section 6.8.2)
  - a severe hypersensitivity reaction to IMP occurs
  - the patient became pregnant

4.4.2. Early Discontinuation From Treatment

Early discontinuation from treatment means that the patient stops receiving the ongoing IMP treatment and does not restart IMP treatment, however, informed consent is not withdrawn. These patients will continue the weekly trial visits as specified in the SoA (Table 1) without IMP-related assessments.

Patients **must** be discontinued early from **treatment** in the following circumstances:

- on the request of the sponsor (eg, following data safety monitoring board [DSMB] advice, see Section 7.3.5)
- patient has missed more than 2 consecutive scheduled doses of IMP treatment
- patient has received more than 3 occurrences of rescue therapy

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

4.5. Temporary Withholding Treatment

- The administration of IMP may be temporary withheld if, in the opinion of the investigator, it could put the patient at undue risk in the following circumstances:
  - clinically significant disease, including evidence of infection
  - severe bleeding, grade 3 or 4 on the WHO bleeding scale, requiring urgent medical and/or surgical intervention
  - thrombosis

  If the IMP is being withheld, it can be reintroduced once the investigator considers the undue risk to the patient has passed.
- The administration of IMP must be temporary withheld from patients with platelet counts greater than 400×10^9/L. IMP should be resumed at the 10 mg/kg q2w dose when the platelet count falls to fewer than 150×10^9/L.

4.6. Protocol Deviations

The investigator should not implement any deviation from, or changes to the approved protocol without agreement of the sponsor, and prior review and documented approval of an amendment from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) and regulatory authority as per local regulation, except where necessary to eliminate an immediate hazard to trial patients, or when the change involves only logistical or administrative aspects of the trial (eg, change of telephone numbers, …). The investigator (or designee) should document and explain any deviation from the approved protocol.

Planned protocol exemptions or waivers will not be approved by the sponsor.

4.7. Screen Failures, Rescreening, and Retesting

Evaluations at screening and confirmation at baseline (visit 1) will be used to determine the eligibility of each patient for randomization at visit 1. Patients who fail to meet the eligibility criteria by visit 1 will be considered screen failures.

Patients may be retested once (ie, redoing 1 test) if still within the screening period.

Retesting may be considered in the following case:

- A patient who has clinical laboratory tests values meeting 1 or more exclusion criteria which are not in line with the medical history and clinical evaluation of the patient, may be retested to confirm the value of the test (to be confirmed by the central laboratory, except for the platelet count for which 1 retesting can be done at the local laboratory), if still within the screening period. If not feasible, the patient should be rescreened.

Examples of conditions under which rescreening may be considered include the following:

- Patients who required treatment for an acute illness (eg, a urinary tract infection) or have a chronic medical problem (eg, uncontrolled hypertension) may be rescreened once the illness has resolved or the medical problem is stabilized.

The decision to rescreen patients may be optional, based on the clinical state of the patient and the decision to rescreen will solely be made per the investigator's discretion on a case-by-case basis. For the purpose of rescreening, a new ICF should be completed, and a new patient identification number (ID) generated.

4.8. Early Termination of Trial or Site

The trial may be terminated at any time by the sponsor for safety concerns as recommended by the DSMB, inability to achieve the recruitment target within a reasonable time, or if in the sponsor's judgment there are no further benefits to be expected from the trial. In such a case, the sponsor or designee will inform the trial investigators, institutions, and all regulatory authorities.

The trial can also be terminated by the regulatory authority for any reason or at a site level by the IRB/IEC. The sponsor may close individual trial sites prematurely for reasons such as poor protocol compliance or unsatisfactory recruitment of patients.

4.9. End-of-Trial Definition

The End-of-Trial is defined as last patient last visit in the ARGX-113-1801 trial.

5. TRIAL PROCEDURES

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. When a protocol-required procedure cannot be performed, the investigator will document the reason, and any corrective and preventive actions that he/she has taken to ensure that the normal processes are adhered to in source documents. The trial team should be informed of these incidents in a timely manner.

Each patient should attend each trial visit, whether he/she is on a weekly or q2w IMP administration regimen, on the designated days. 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]) as described in the SoA (Table 1).

The treatment phase consists of a 24-week IV treatment period with either efgartigimod 10 mg/kg or matching placebo, administered weekly from visits 1 to 4 and either weekly or q2w from visits 5 to 16, adjusted according to the patient's platelet count. 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). Assessment of the dosing regimen as described in Section 5.4.1 will be applied.

At screening, all eligibility assessments should be performed after obtaining informed consent as well as the weight assessment.

The platelet count needs to be performed within 1 day prior to any other assessment.

As from the signature of informed consent until the last trial-related activity, all AEs that occur and all concomitant medications, whether allowed or not, that are taken during the trial are to be recorded on the appropriate pages in the eCRF.

5.1. Informed Consent

The patient must sign the ICF prior to any trial-related assessment.

Prior to signing the ICF, the trial patients will be instructed not to participate in any other clinical trial that involves an intervention or collection of data until the completion of the current trial.

Any patient who provides informed consent is being assigned a unique patient ID via the interactive response technology (IRT) system.

5.2. Screening

After the informed consent has been obtained, the patient will be screened at the site for eligibility based on the inclusion and exclusion criteria defined in Section 4.3.1 and Section 4.3.2, respectively.

The assessments as specified in the SoA (Table 1) will be performed during screening.

Patients being screened will be registered in the IRT system. The IMP treatment can be started upon confirmation of eligibility at visit 1.

5.3. Randomization

The results of all screening procedures have to be available prior to randomization (visit 1) to determine the eligibility for randomization into the trial. 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 IRT. If a patient is not eligible, the patient should be recorded as a screen failure in the IRT system.

5.4. Treatment Period

The assessments as specified in the SoA (Table 1) will be performed during the IMP treatment period.

During the IMP treatment period, all assessments and procedures have to be performed before the start of the IMP administration, except for:

- Pharmacokinetic sampling, which will be performed both pre- and post-dose (within 2 hours prior to the start of the IMP infusion and within 30 minutes after the end of IMP infusion, respectively)
- the continuous assessment of AEs and the recording of concomitant therapy

If the IMP is being withheld, it can be reintroduced once the investigator considers the undue risk to the patient has passed (see also Section 4.5). If a patient misses more than 2 consecutive scheduled doses, then he/she will be discontinued early from further IMP treatment as defined in Section 4.4.2.

The End-of-Treatment/Early Discontinuation visit should be completed for all patients, whether they roll over to the open-label extension trial (ARGX-113-1803), discontinue the trial early, or complete the 24-week trial period.

5.4.1. Screening and Treatment

During the screening period (up to 2 weeks) the patient's eligibility for trial participation will be evaluated.

All eligible patients will be randomized to receive IV infusions of either efgartigimod 10 mg/kg body weight or matching placebo throughout the trial.

All patients will initially receive weekly IV infusions from visits 1 to 4.

Based on the platelet counts as of visit 2, the dosing frequency can be altered from visits 5 to 16 according to the following rules (the change in dosing frequency will occur at the current visit):

- Reduce from weekly to q2w in patients achieving platelet counts of ≥100×10⁹/L for 3 out of 4 consecutive visits (the fourth visit being the current visit), and have a platelet count of ≥100×10⁹/L at the last of these 4 visits
  – OR –
  3 consecutive visits
- Increase from q2w to weekly in patients whose platelet counts drop below 100×10⁹/L on 2 consecutive visits
  – OR –
  <30×10⁹/L at 1 visit
  – OR –
  in patients who receive rescue therapy (see Section 6.8.4)
- Temporary withholding treatment
  - for reasons described in Section 4.5, IMP should be reintroduced once the investigator considers the undue risk to the patient has passed
  - in patients with platelet counts greater than 400×10^9/L, IMP should be resumed at the 10 mg/kg q2w dose when the platelet count falls to fewer than 150×10^9/L
- Post-baseline platelet count can be performed within 1 day of the next procedure as per the SoA (both dosing and non-dosing visit), allowing the results to be incorporated into the criteria above.

From visits 17 to 24, the dosing frequency is fixed for each individual patient (ie, either weekly or q2w regimen), based on the regimen the patient was receiving at visit 16 or at the last visit at which IMP was administered.

Exceptions to the fixed dosing frequency are:

- Continued weekly dosing for patients requiring rescue therapy
- Continued q2w dosing for patients resuming IMP when the platelet count falls to fewer than 150×10^9/L after having had platelet counts greater than 400×10^9/L

5.4.2. Rollover to the Open-Label Extension Trial (ARGX-113-1803)

Patients who complete the 24-week trial period have the possibility to enter the open-label extension trial (ARGX-113-1803) to receive efgartigimod 10 mg/kg IV. The platelet counts from the ARGX-113-1801 trial will be taken into account to assess the dosing frequency in ARGX-113-1803.

Eligible patients who consent to roll over into the open-label extension trial ARGX-113-1803 should complete the End-of-Treatment visit of the current trial.

- For patients on a weekly dosing regimen, the baseline visit including first IMP dose administration of the ARGX-113-1803 trial will be done on the same day.
- For patients on a q2w dosing regimen, the baseline visit including first IMP dose administration of the ARGX-113-1803 trial will be done 7 days after the End-of-Treatment visit of the current trial if visit 24 of the ARGX-113-1801 trial was a dosing visit. If visit 24 of the ARGX-113-1801 trial was a non-dosing visit, the End-of-Treatment visit will coincide with visit 1 of the ARGX-113-1803 trial.

The platelet counts from the ARGX-113-1801 trial will be taken into account to assess the dosing frequency in ARGX-113-1803.

Patients who do not enter the open-label extension trial (ARGX-113-1803) will remain in the current trial to be followed for 4 weeks (2 q2w visits).

5.5. Follow-up Period

Patients who complete the 24-week trial period but who do not enter the open-label extension trial ARGX-113-1803, or patients who discontinue the trial early, with the exception of patients who withdraw their consent, will be followed for 4 weeks for ongoing safety and efficacy monitoring. The follow-up period will consist of 2 q2w visits.

The assessments as specified in the SoA (Table 1) will be performed during the follow-up period.

5.6. Unscheduled Visit

It is at the investigator's discretion or on request of the patient to initiate an unscheduled visit, if deemed necessary for the patient's safety and well-being. All such visits will be entered in the eCRF with any additional required documentation based on the nature of the unscheduled visit.

The assessments as specified in the SoA (Table 1) can be performed at the unscheduled visit.

6. TRIAL TREATMENT

6.1. Treatment Administered

The IMP infusions (efgartigimod or placebo) will be administered weekly from visits 1 to 4, either weekly or q2w from visits 5 to 16, and fixed on the dosing schedule of visit 16 (or the last visit at which IMP was administered) from visits 17 to 24 (ie, either weekly or q2w). Patients should receive each IV infusion of IMP at a dose of 10 mg/kg over a period of approximately 1 hour.

The maximum total dose per efgartigimod infusion is 1200 mg for patients with a body weight ≥120 kg measured at infusion visits. A variation of ± 10% of the amount of efgartigimod will not be considered an overdose/underdose. In case of a change in body weight, the dose will automatically be recalculated by the IRT system.

The matching placebo infusion will contain the same excipients as the efgartigimod infusion but without the active substance.

All IMP treatment will be fully blinded.

Details on infusion rate and time will be given in the IMP management manual (pharmacy manual).

6.2. Identity of Investigational Medicinal Product

The IMP (efgartigimod or placebo) will be supplied to the pharmacy at the investigational site (and stored at a temperature of 2°C to 8°C or 35°F to 46°F), by and under the responsibility of the sponsor's designated IMP supply vendor. For each IMP batch at the site, the investigator will receive the certificate of analysis, certificate of conformity, and European Union qualified person release documents.

Efgartigimod for IV administration will be provided as a sterile, colorless, clear concentrate for solution for IV infusion in glass vials. Appropriate dilutions in a 0.9% saline solution in an infusion bag will be prepared on site prior to administration with an IV pump.

Matching placebo will be provided as a sterile, colorless, clear concentrate solution for IV administration in glass vials with the same formulation as the efgartigimod solution, but without the active ingredient that is present in efgartigimod. Appropriate dilutions in a 0.9% saline solution in an infusion bag will be prepared on site prior to administration with an IV pump.

The IMP will be manufactured in accordance with Good Manufacturing Practice regulations. Detailed instructions on IMP management on site (including preparation of the IMP) will be included in the IMP management manual (pharmacy manual).

6.3. Packaging and Labeling

The IMP will be labeled and secondary packed in accordance to local laws and regulatory requirements.

6.4. Storage of Investigational Medicinal Products

The investigator (or his/her designee) is responsible for the correct and safe storage of the IMP assigned to the clinical site, in a locked, secure storage facility with access limited to those individuals authorized to dispense the IMP and maintained within the appropriate temperature ranges.

The IMP must be stored refrigerated (2°C to 8°C or 35°F to 46°F) in its secondary packaging, should not be exposed to freezing temperatures, should not be shaken, and should be protected from direct sunlight during storage at the clinical site.

The IMP temperature will be recorded on a continuous basis at the site pharmacy and minimum/maximum temperature ranges should be registered.

Further requirements on temperature logging during storage and information on how to handle temperature excursions can be found in the IMP management manual (pharmacy manual).

6.5. Method of Assigning Patients to Treatment Group

Once the patient has provided informed consent, the site will enroll the patient and a screening number will be allocated through IRT. Upon confirmation of eligibility at baseline (visit 1), the patient will be randomized through IRT by generating a unique patient randomization ID.

This randomization ID will be stored in the IRT system.

Patients will be randomized in a 2:1 ratio to receive efgartigimod (10 mg/kg) or matching placebo. No trial team members from the sponsor, nor from the sponsor's designated CRO, or pharmacy personnel will have access to this IMP treatment assigned until after database lock.

6.6. Dosing Administration for Each Patient

During the IMP treatment period, the IMP will be administered as an IV infusion over a period of approximately 1 hour. Patients will be asked to remain at the site for at least 30 minutes after the end of the infusion as part of routine safety monitoring.

6.7. Blinding

This is a randomized, double-blinded, placebo-controlled trial with limited access to the IMP treatment assigned (see also DEFINITION OF TERMS).

An independent unblinded DSMB and statistician will review all unblinded safety data as specified in Section 7.3.5.

6.7.1. Emergency Unblinding

The process of breaking the blind will be handled through the IRT.

Investigators are strongly discouraged from breaking the blind for an individual patient, unless there is a patient safety issue that via knowledge of the IMP treatment assignment would change patient management. The investigator is encouraged to discuss with the monitor at the sponsor's designated CRO or the sponsor's medical expert before utilizing IRT to break the blind. If the blind is broken by the investigator it may be broken only for the patient concerned, and the IMP treatment assignment should not be revealed to the trial team members from the sponsor, nor from the sponsor's designated CRO, pharmacy personnel, or other site staff. Once unblinded, the patient will be discontinued from the trial and will be followed for 4 weeks for ongoing safety and efficacy monitoring.

The sponsor and monitor at the sponsor's designated CRO must be notified immediately if a patient and/or investigator is unblinded during the course of the trial. Pertinent information regarding the circumstances of unblinding must be documented in the patient's source documents and eCRF. Once unblinded, the patient will be early discontinued from the trial and followed-up for 4 weeks (2 q2w visits).

6.8. Prior Treatments and Concomitant Medications

All prior ITP procedures and therapies received by the patient since diagnosis, before baseline must be recorded in the eCRF, including the name, dose/schedule, duration (including start and stop dates), and whether patient responded to them.

The washout periods as specified in exclusion criteria 2 to 9 must be followed.

The patient's history of TPO-RA and other ITP therapy response and intolerance will be collected separately in the eCRF.

All vaccinations received by the patient in the 6 months prior to baseline should be recorded.

All concomitant medications whether allowed or not must be recorded in the eCRF (including the name, dose/schedule, start and stop dates).

6.8.1. Concurrent ITP Therapy

Patients receiving at least 1 permitted concurrent ITP therapy are eligible for the trial, if the dose and schedule have remained unchanged in the last 4 weeks before randomization (ie, visit 1).

Permitted concurrent ITP medications include oral corticosteroids, oral immunosuppressants, dapsone/danazol, fostamatinib and/or oral TPO-RAs.

Patients not receiving concurrent ITP therapy are also eligible for the trial if they have not received prior ITP therapy for at least 4 weeks prior to baseline (inclusion criterion 6).

Dose and frequency of permitted concurrent ITP therapies should remain unchanged during the trial.

Exceptions are patients who are receiving concurrent treatment with TPO-RAs in whom dose changes are permitted at label-defined platelets thresholds, and patients who are receiving concurrent treatment with fostamatinib, in whom dose changes or stopping of treatment is allowed in label-defined conditions.

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" (ie, no platelet count of $\geq 30 \times 10^9$/L in any of the visits during the last 4 weeks). These patients will be considered as "non-responders" for the primary endpoint analysis. At the discretion of the investigator, the dose and/or schedule of the concurrent ITP therapy can be returned to the baseline levels.

Any change in concurrent ITP therapy should appropriately be recorded in the eCRF.

6.8.2. Prohibited Medications and Therapy Prior to Randomization

The following medications or treatments are not permitted within the specified time window prior to randomization:

- Use of anticoagulants (eg, vitamin K antagonists, direct oral anticoagulants) within 4 weeks prior to randomization.
- Use of any transfusions within 4 weeks prior to randomization.
- Use of Ig (IV, SC, or intramuscular route) or PLEX, 4 weeks prior to randomization.
- Use of anti-CD20 therapy (eg, rituximab) within 6 months prior to randomization.
- Use of romiplostim within 4 weeks prior to randomization.
- Undergone splenectomy less than 4 weeks prior to randomization.
- Use of any other investigational drug within 3 months or 5 half-lives of the drug (whichever is longer) prior to randomization.
- Use of monoclonal antibodies or Fc fusion proteins, other than those previously indicated, within 3 months prior to randomization.
- Live/live-attenuated vaccines within 4 weeks prior to screening.

6.8.3. Prohibited Medications and Therapy During the Trial

The following medications or treatments are not permitted during the trial:

- Anti-CD20 therapy (eg, rituximab)
- Romiplostim
- Any monoclonal antibodies or Fc fusion proteins or investigational drug
- Live/live-attenuated vaccines

6.8.4. Rescue Therapy

"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 trial patient. The start date/time of the occurrence is the start of the administration of the first rescue treatment.

Rescue therapy is allowed for patients having protocol-defined ITP clinical deterioration AND if in addition the treating physician believes that the patient's health is in jeopardy if rescue therapy is not given.

Rescue therapy is allowed post-baseline during the 24-week trial 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 trial completion)

The following rescue therapies are permitted:

- IV methylprednisolone up to 1 g/day × 1-3 days, oral dexamethasone up to 40 mg/day × 1-3 days, or oral prednisone up to 1 mg/kg/day × 1-2 days
- IVIg: up to 1 g/kg/day × 1-2 days
- IV anti-D: up to 50-75 mcg/kg/day × 1-2 days
  Note: Anti-D rescue therapy should not be given to Rh(D)-positive patients
- platelet transfusions

If a patient needs rescue therapy according to the investigator, it is encouraged to inform the medical monitor at the sponsor's designated CRO, whenever possible prior to actual implementation of the rescue therapy.

In the event of rescue with IVIg or IV anti-D:

- If given at a visit where the IMP was due to be administered, the IMP should be withheld and administered at the next visit (see also Section 4.5 and Section 6.11).

For rescue therapy with methylprednisolone, dexamethasone, prednisone, or platelet transfusions:

- Administration of the IMP continues during rescue therapy

Patients who were receiving q2w dosing at the time of rescue therapy will have the IMP administration frequency increased to weekly.

For patients who receive rescue therapy, the platelet counts for 4 weeks after the first day of the rescue treatment will not be used (ie, are censored) to assess whether or not the patient can transition to q2w treatment.

Patients requiring more than 3 occurrences of rescue therapy will discontinue from IMP.

6.9. Medical Care of Patients After End-of-Treatment or Early Discontinuation

After a patient has completed the trial, has withdrawn/discontinued early, or does not roll over to the open-label extension trial (ARGX-113-1803) usual treatment will be administered if required, in accordance with the trial site's standard of care and generally accepted medical practice depending on the patient's individual needs.

6.10. Treatment Compliance

The investigator should promote treatment compliance by stating that compliance is necessary for the patient's safety and the validity of the trial. The prescribed dose, timing, and mode of administration cannot be changed. All dates, start and end time of IMP administration, and any deviations from the intended regimen must be recorded in the eCRF.

A sponsor's designated CRO monitor will review the pharmacy records at each site including the drug accountability and dispensing records on which the pharmacist or designated person should record all IMP released for patient use. The sponsor's designated CRO monitor will compare the dispensing record and vials with the individual patient's identifiers, kit number, and visit schedule to confirm that the patient received the correct treatment and dose, and that the dosing schedule is correct.

Errors that are identified will be communicated to the site personnel to ensure that the errors are not repeated. The sponsor's designated CRO monitor's report will include details of any missed doses, errors in dose, treatment or scheduling errors, and the associated explanations. It will be evaluated if these dosing errors will be reported as protocol deviations in the clinical database. All supplies and pharmacy documentation must be made available throughout the trial for the sponsor's designated CRO monitor to review.

6.11. Handling Missed Doses of the Investigational Medicinal Product

All efforts will be made to ensure that the patient receives all administrations of IMP within the allowed visit windows. However, if a patient misses more than 2 consecutive scheduled doses, then he/she will be discontinued early from further IMP treatment (see Section 4.4.2).

6.12. Accountability of Investigational Medicinal Product

Detailed instructions on accountability of the IMP will be included in the IMP management manual (pharmacy manual).

6.13. Storage of Blood Samples in the Trial

Any samples remaining after the laboratory analyses as defined in the protocol have been completed may be stored for up to 15 years for future additional research to address any scientific questions related to efgartigimod, FcRn biology, or ITP, unless this would not be allowed according to local regulations or the patient would not agree.

In addition, blood samples may be used to validate methods to measure efgartigimod, antibodies, and biomarkers.

7. TRIAL ASSESSMENTS

7.1. Demography

Demographic characteristics comprise age, year of birth, gender, race, and ethnicity (per local regulations).

7.2. Efficacy

Procedures assessing the efficacy of efgartigimod will mainly focus on measures of response derived from platelet counts. These assessments will be performed at the weekly visits predose on all IMP administration days, and at the unscheduled visits (if needed), as specified in the SoA (Table 1).

7.2.1. Platelet Count

The assessment of platelet count can be performed within 1 day prior to any other trial-specific assessment (except at screening, where the informed consent should be obtained and weight assessed first, and at randomization) at each visit as specified in the SoA (Table 1). The samples will be analyzed locally. For a single patient, baseline and post-baseline platelet count assessments need to be performed at the same facility throughout the trial.

In addition, the absolute [redacted] and the [redacted] will be measured locally in facilities equipped with a hematology analyzer which can determine this [redacted].

7.2.2. General Bleeding Assessment

Signs and symptoms of bleeding are the predominant clinical manifestation of ITP and are typically related to low platelet counts.

The WHO bleeding scale is a widely recognized tool to assess bleeding and has been used in many previous ITP trials. The occurrence and severity of any bleeding symptoms will be assessed and recorded at each visit using the WHO bleeding scale (Appendix 3) as specified in the SoA (Table 1). The WHO bleeding scale was originally developed to assess bleeding in patients undergoing treatment for cancer and has been used extensively.[11]

The wide use of the scale and incorporation into the common terminology criteria for AEs (CTCAE) suggest that it is commonly used by clinicians, is applicable across populations and cultures, and is responsive to changes in bleeding severity. While validated for mild to moderate bleeding in ITP, validation for severe bleeding events in ITP has not yet been performed.[12]

7.3. Safety

Safety assessments will consist of monitoring and recording all safety information including pregnancies, safety laboratory testing, measurement of vital signs, ECG, physical examination, and other tests that are deemed critical to the safety evaluation of the trial treatment in all patients. As discussed in Section 7.3.1.5, any pregnancy in a female patient (or partner of a male patient) that occurs while the patient is enrolled in the trial will also be monitored and reported according to the appropriate regulations. Although a pregnancy is not considered as an (S)AE, any adverse pregnancy outcome, complication, or elective termination of a pregnancy for medical reasons will be recorded and reported as an (S)AE.

An independent unblinded DSMB will periodically review the safety data as described in the DSMB charter (Section 7.3.5).

The investigator is responsible for recording all AE(SI)s observed during the trial from the time the patient signs the ICF until the last contact with the patient.

7.3.1. Adverse Events

Definition of AE

An AE is any untoward medical occurrence in a clinical trial patient, temporally associated with the use of IMP, whether or not considered related to the medicinal product or IMP.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of IMP, whether or not considered related to the medicinal product or IMP.

The following events will be collected as AEs:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after IMP administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either IMP or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

The following events will NOT be collected as AEs:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition.
  Note: Except for any occurrence of bleeding, which will be considered an AESI as per section 7.3.1.1.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

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

Definition of SAE

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (the term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it was more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization. In general, hospitalization signifies that the patient has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event will be considered as serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

  Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not collected as an AE.
- Results in persistent or significant disability or incapacity

  The term disability means a substantial disruption of a person's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital abnormality or birth defect
- Other situations: Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the patient or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition.

  Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

  Suspected transmission of any infectious agent via the IMP will also be treated as an SAE.

An unexpected AE is any adverse drug event, which is not listed in the reference safety information in the current IB section 7 or is not listed at the specificity or intensity that has been observed. The assessment of expectedness will be the responsibility of the sponsor.

Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE.

Each AE is to be evaluated for duration, severity (using the CTCAE criteria version 5.0), seriousness, and causal relationship to the IMP or trial procedures. The action taken with the investigational drug and the outcome of the event must also be recorded.

Overdose or Medication Error

For this trial, a variation of less than ±10% of the amount of efgartigimod will not be considered an overdose/underdose or medication error, while a variation greater than ±10% of the intended amount of efgartigimod will be considered a medication error and/or overdose without AE (see Section 6.1).

An overdose is defined as a deliberate or accidental administration of IMP to a patient, at a dose greater than that which was assigned to that patient per the trial protocol.

A medication error is any preventable incident that may cause or lead to inappropriate IMP use or patient harm while the IMP is in the control of health care professionals. Such incident may be due to health care professional practice, product labeling, packaging and preparation, dispensing, distribution, administration, education, monitoring, and use.

In case of suspected overdose or medication error, the patient should be treated according to standard medical practice based on the investigator's judgment. The suspected overdose or medication error with the quantity of the excess dose should be documented in the eCRF including the additional AE, if any.

Severity

All AEs observed will be graded using the National Cancer Institute (NCI) CTCAE version 5.0. The NCI CTCAE is a descriptive terminology, which can be utilized for AE reporting. A grading (severity) scale is provided for each AE term. The grade refers to the severity of the AE. If a particular AE's severity is not specifically graded by the guidance document, the investigator is to use the general NCI CTCAE definitions of grade 1 through grade 5 following his or her best medical judgment. The CTCAE displays grades 1 through 5 with unique clinical descriptions of severity for each AE based on the following general guideline:

- Grade 1: mild; asymptomatic or mild symptoms clinical or diagnostic observations only; intervention not indicated
- Grade 2: moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living

- Grade 4: life-threatening consequences; urgent intervention indicated
- Grade 5: death related to AE

Note: a semi-colon indicates "or" within the description of the grades.

Relationship

The causal relationship between the IMP/trial procedures and the AE has to be characterized as unrelated, unlikely, possible, probable, and related.

- Events can be classified as "unrelated" if there is no reasonable possibility that the IMP caused the AE.
- An "unlikely" relationship suggests that only a remote connection exists between the IMP and the reported AE. Other conditions, including chronic illness, progression or expression of the disease state, or reaction to concomitant medication, appear to explain the reported AE.
- A "possible" relationship suggests that the association of the AE with the IMP is unknown; however, the AE is not reasonably supported by other conditions.
- A "probable" relationship suggests that a reasonable temporal sequence of the AE with drug administration exists and, in the investigator's clinical judgment, it is likely that a causal relationship exists between the drug administration and the AE, and other conditions (concurrent illness, progression or expression of disease state, or concomitant medication reactions) do not appear to explain the AE.
- A "related" relationship suggests that the AE follows a reasonable temporal sequence from administration of IMP, it follows a known or expected response pattern to the IMP, and it cannot reasonably be explained by known characteristics of the patient's clinical state.

In the final evaluation for reporting, the relationship will be converted into a "binary determination" as per CIOMS. Unrelated and unlikely will be clubbed into "unrelated," and related, possible, and probable will be clubbed into "(at least possibly) related" for final reporting purpose.

7.3.1.1. Adverse Events of Special Interest

An AESI (serious or non-serious, related or not related) is an event of scientific and medical concern specific to the sponsor's product or program (eg, an underlying condition being investigated, a mechanism of action like potential immunosuppression, etc). Further characterizing information will be collected in the eCRF. This event could be expected due to the natural progression of the underlying disease, disorder, or condition of the patient(s) and the patient's predisposing risk factor profile including concomitant medications (eg, bruising in patients with ITP).

Efgartigimod treatment induces reductions in IgG levels, and there is a potential risk for infections associated with low IgG levels. As such, infections are considered AESI in this trial.

Due to the nature of underlying disease (ie, ITP), any occurrence of bleeding will also be considered an AESI.

7.3.1.2. Reporting of Adverse Events and Serious Adverse Events

All AEs that occur during the trial, from signature of the ICF until the last trial-related activity are to be recorded on the appropriate AE pages (either "serious" or "non-serious") of the eCRF. The investigator should complete all the details requested, including date of onset, time of onset, stop date (when applicable), stop time (when applicable), severity, action taken, outcome, and relationship to IMP and to trial procedures. Each event should be recorded separately in the eCRF.

Any SAE, including death due to any cause, which occurs during this trial after signature of the ICF, whether or not related to the IMP, must be reported immediately (within 24 hours of the trial site's knowledge of the event). All SAEs will be recorded on the paper SAE report form and the AE form in the eCRF. The investigator or designated site staff should check that all entered data is consistent. An alert email for the SAE report in the eCRF will then automatically be sent by email to the sponsor's designated CRO safety mailbox via the electronic data capture (EDC) system. The paper SAE report form should be faxed or emailed to the sponsor's designated CRO (see the Safety Mailbox/Fax details on the title page of this protocol).

The report will contain as much available information concerning the SAE as possible, to enable the sponsor (or an authorized representative) to file a report, which satisfies regulatory reporting requirements. These timelines apply to initial reports of SAEs and to all follow-up reports.

Criteria for documenting the relationship to IMP as well as severity, outcome, and action taken will be the same as those previously described.

All SAEs that are spontaneously reported within 30 days after the last trial visit are to be collected and reported in the safety database, and all efforts should be made to follow-up until resolution.

Additional follow-up information should be completed and entered on a paper SAE report form and sent by fax/email to the sponsor's designated CRO.

7.3.1.3. Reporting of Serious Adverse Events to Regulatory Authorities and Investigators

The sponsor's designee will be responsible for reporting all suspected ADRs that are both serious and unexpected, and any other applicable reports to regulatory authorities, IRB/IEC, and investigators, in accordance with national regulations in the countries where the trial is conducted. Relative to the first awareness of the event by/or further provision to the sponsor's designee, these events will be submitted within 7 days for fatal and life-threatening events and 15 days for other events, unless otherwise required by national regulations. The sponsor's designee will also prepare an expedited report for other safety issues where applicable.

The investigational site will also forward a copy of all expedited reports to his or her IRB/IEC in accordance with national regulations.

7.3.1.4. Follow-up of Adverse Events and Serious Adverse Events

Any AEs observed from signing the ICF to the last trial-related activity will be followed-up until resolution, until the patient is lost to follow-up, or until the patient withdraws consent. Resolution means that the patient has returned to a baseline state of health or the investigator does not expect any further improvement or worsening of the AE.

Every effort should be made to follow all (S)AEs considered to be related to the IMP or trial procedures until an outcome can be reported. If the patient is lost to follow-up, all AEs will be categorized based on the investigator's last assessment.

During the trial period, resolution of SAEs (with dates) should be documented on the AE page of the eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to the baseline status or stabilization cannot be established, an explanation should be recorded on the SAE form.

All pregnancies reported during the trial should be followed until pregnancy outcome.

For SAEs, AESI, non-serious AEs, and pregnancies, the sponsor's designee may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (eg, from hospital discharge summaries, consultant reports, or autopsy reports) in order to perform an independent medical assessment of the reported case.

7.3.1.5. Reporting and Follow-up Requirements for Pregnancies

7.3.1.5.1. Pregnancies in Female Patients

A serum pregnancy test will be performed centrally at screening. A urine pregnancy test will be conducted and analyzed locally at the visits detailed in the SoA (Table 1).

If a patient becomes pregnant during the administration of IMP and up to 90 days after the patient received the last IMP, the sponsor and/or sponsor's designee should be informed immediately (ie, within 24 hours of the trial site's knowledge of the event). The following actions will be performed:

- The patient should immediately be discontinued from IMP treatment.
- The patient should have the Early Discontinuation assessments and enter the 4-week follow-up period.
- All assessments for Early Discontinuation (see Section 4.4.1) must be performed unless contraindicated by pregnancy (harmful to fetus) or unless the patient withdraws informed consent.

The investigator must update the patient with information currently known about potential risks and available treatment alternatives. The pregnancy should be followed-up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

If required by local regulations, the female participant will be requested to sign a separate pregnancy ICF.

Full details will be recorded on a paper pregnancy report form and submitted via email or fax (see the Safety Mailbox/Fax details on the title page of this protocol), and reporting details will be specified in the trial manual. The investigator will update the pregnancy report form with additional information as soon as the outcome of the pregnancy is known.

If the outcome of the pregnancy is an SAE, then this must be additionally reported as an SAE on the appropriate SAE report form.

7.3.1.5.2. Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the ICF to immediately inform the investigator if their partner becomes pregnant during the trial or up to 90 days after they received the last IMP. A pregnancy report form should be completed by the investigator within 24 hours after learning of the pregnancy and submitted via email or fax (see the Safety Mailbox/Fax details on the title page of this protocol). Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to the IMP.

The pregnant partner will need to sign an ICF to allow for follow-up on her pregnancy, its outcome, including if appropriate, the birth and health of the baby. Once the ICF has been signed, the investigator will update the pregnancy report form with additional information on the course and outcome of the pregnancy. An investigator, who is contacted by the male patient or his pregnant partner, may provide information on the risks of the pregnancy and

the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

7.3.2. Clinical Laboratory Evaluations

Blood and urine samples for determination of clinical chemistry, hematology, urinalysis, coagulation, thyroid, autoimmune antibody testing, FSH (only for women of non-childbearing potential), PK, PD, antiplatelet antibodies, viral testing, tuberculosis QuantiFERON test, and ADA will be collected and analyzed at a central lab as indicated in the SoA (Table 1) and Appendix 1. The blood sample for platelet counts and the urine sample for the pregnancy test will be analyzed locally.

In addition, the IPF# and IPF% will be measured locally in the facilities equipped with a hematology analyzer which can determine this platelet subset.

Patients may be rescreened (ie, redoing the full assessments as per SoA, Table 1) or retested once (ie, repeating 1 test, see Section 4.7) if still within the screening period.

On days that IMP is administered, blood for laboratory assessments should be collected before dosing.

Additional safety samples may be collected if clinically indicated, at the discretion of the investigator.

For all female patients of childbearing potential, a serum pregnancy test will be performed centrally at screening (on the samples taken for clinical laboratory tests), and a urine pregnancy test will be conducted and analyzed locally at the site at the visits specified in the SoA (Table 1).

The estimated total maximum blood volume needed for a patient during the trial (when completing the trial) is approximately 618 mL.

Clinical laboratory tests will be reviewed for results of potential clinical significance at all time points throughout the trial. The investigator will evaluate any change in laboratory values. If the investigator determines a laboratory abnormality to be clinically significant, it will be considered as a laboratory AE, however, if the abnormal laboratory value is consistent with a current diagnosis, it may be documented accordingly without being reported as an AE.

The details of sampling, handling, storage, and transportation of the samples will be described in the laboratory manual. The actual sample collection date and time must be entered in the patient's source documents and on the central/local lab assessment eCRF page. For urinalysis samples, only the date of collection is to be entered.

Refer to Appendix 2 for the addresses of the laboratories used for sample analyses.

7.3.3. Vital Signs, Physical Examination, and Electrocardiogram

The assessment of vital signs (supine blood pressure, heart rate, and body temperature) physical examination, and ECG will be performed at the time points indicated in the SoA (Table 1).

Supine blood pressure and heart rate will be measured using standard equipment after at least 10 minutes rest.

It is recommended that the method used to measure body temperature at screening is maintained throughout the trial for each patient.

A physical examination will include at a minimum an assessment of general appearance, skin, lymph nodes, musculoskeletal/extremities, abdomen, cardiovascular, respiratory, and neurological system.

Height will be measured at screening only. Weight will be measured at screening and at any IMP infusion visit. For the assessment of height and weight, patients will be required to remove their shoes and wear light indoor clothing.

A single 12-lead ECG will be taken post-dose at a paper speed of 25 mm/sec in the supine position after the patient has rested in this position for at least 10 minutes. The ECG will be analyzed centrally. The assessments on heart rate, PR, QT, and QRS intervals will be recorded. If no IMP is administered, the ECG will be assessed preferably after the blood sample for platelet counts has been taken.

Clinically significant abnormalities in physical examination, vital signs, and ECG at screening will be reported as medical history in the eCRF. At all other trial visits, new abnormal or worsened pre-existing conditions which are clinically significant as judged by the investigator, will be reported as an AE.

7.3.4. Medical and Surgical History

All significant findings, surgeries, and pre-existing conditions present at screening must be reported on the relevant medical history/current medical conditions page of the eCRF, including start and end dates, if known. The date of ITP diagnosis as well as the date of confirmation of the diagnosis according to the ASH criteria[10] will be collected separately.

The patient will be asked if he/she has been vaccinated for Streptococcus pneumoniae, Neisseria meningitidis, and Hemophilus influenzae. Bleeding events such as gastrointestinal bleeding, intracranial hemorrhage, and hemorrhage for coagulation disorder will be prespecified in the eCRF.

Information should be provided on medical and surgical history and concomitant medical conditions specifying those ongoing at screening.

7.3.5. Data Safety Monitoring Board

The sponsor will appoint an independent DSMB consisting of an independent group of clinical experts who are not involved in the trial management. They will be supplemented by an independent statistician. The objective of the DSMB will be to review all unblinded safety data (including the overall number of patients treated up to that point, rates, and patient-level details) and the evaluation of IgG. The planning and frequency of the meetings will be detailed in a DSMB charter. In addition, ad hoc meetings can be requested at any time during the trial by either the sponsor or the DSMB. The DSMB will advise the sponsor regarding continuation, modification, or termination of the trial after every meeting.

Additionally, the composition, objectives, role, and responsibilities of the independent DSMB will be described in the DSMB charter, agreed with the DSMB members and the sponsor. The DSMB charter will also define and document the content of the safety summaries and general procedures (including communications).

7.3.6. Visit Reminder/Patient ID Card

Patients must be provided with the address and telephone number of the main contact for information about the clinical trial. The investigator must therefore provide a "Visit Reminder/Patient ID Card" to each patient. In an emergency situation this card serves to inform the responsible attending physician that the patient is in a clinical trial and that relevant information may be obtained by contacting the investigator. Patients must be instructed to keep the card in their possession at all times.

7.4. Pharmacokinetics

Blood samples for PK will be collected from each patient as presented in the SoA (Table 1). Concentrations of efgartigimod will be determined using a validated assay. The actual date and time of collection of the blood sample will be recorded in the relevant section of the eCRF, as well as the reason in case no sample was taken.

The PK samples will be taken predose (within 2 hours prior to start of IMP infusion) and post-dose (within 30 minutes after the end of IMP infusion).

7.5. Pharmacodynamics

Blood samples for the determination of the PD markers (total IgG, IgG subtypes [IgG1, IgG2, IgG3, and IgG4]) will be collected as indicated in the SoA (Table 1). Sampling will be done predose on IMP administration visits. Samples will be analyzed by the central laboratory. In order to maintain the blind, the IgG testing cannot be performed locally.

These PD markers will be determined using validated assays.

Additionally, presence, nature, and level of antiplatelet antibodies will be tested as indicated in the SoA (see Table 1).

The actual date and time of collection of the blood sample will be recorded in the relevant section of the eCRF, as well as the reason in case no sample was taken.

7.6. Anti-Drug Antibodies

Blood samples to assess ADA will be collected as indicated in the SoA (Table 1). Sampling will be done predose on IMP administration visits.

All samples will be analyzed first in a validated screening assay, followed by an assessment of specificity of the measured ADA response in positive samples in a confirmation assay. Finally, in samples scoring positive in both abovementioned assays, a titration of the ADA response will be performed and samples will be tested for neutralizing ADAs.

The actual date and time of collection of the blood sample will be recorded in the relevant section of the eCRF, as well as the reason in case no sample was taken.

7.7. [redacted]

The sample to measure the [redacted] has to be collected as the last sample predose as indicated in the SoA (Table 1) in sites participating in the [redacted].

The actual date and time of collection of the blood sample will be recorded in the relevant section of the eCRF, as well as the reason in case no sample was taken.

The sample will be used for an exploratory endpoint and will be analyzed in a specialty lab.

7.8. Quality-of-Life and Patient-Reported Outcomes

The patient will complete the QoL questionnaire (SF-36 v2.0) and the PRO (FACT-Th6 and FACIT-Fatigue Scale) as indicated in the SoA (Table 1).

FACT-Th6: The FACT-Th6 uses the Likert scale, with patients rating their degree of concern in the past 7 days. The 6 selected items pertain to ability to do usual activities, worry about problems with bleeding or bruising, worry about the possibility of serious bleeding, avoidance of physical or social activity because of concern with bleeding or bruising and frustration due to the inability to carry out usual activities.[13]

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.[13]

FACIT-Fatigue Scale: 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."

8. STATISTICS

The statistical analyses will be performed by the sponsor's designated CRO using statistical analysis systems SAS® (SAS Institute, Cary, NC, US) version 9.4 or higher, and the software package R, if applicable. The standard operating procedures (SOPs) and work instructions of the sponsor's designated CRO will be used as the default methodology if not otherwise specified.

Any change to the data analysis methods described underneath will be mentioned in the statistical analysis plan (SAP). Any additional analysis and the justification for making the change, will be described in the clinical trial report (CTR). Additional exploratory analyses of the data may be conducted as deemed appropriate. The below paragraphs contain the main general features of the statistical analysis. More details will be provided as needed in the SAP.

8.1. Determinations of Sample Size

The null and alternative hypotheses are defined as H_0: $\pi_1 = \pi_2$ *vs.* H_A: $\pi_1 \neq \pi_2$, where π_1 and π_2 are the population probabilities to achieve a sustained platelet count response (primary efficacy endpoint) for 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 (ie, π_1 = [redacted] and π_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[14] was taken to compute the power, taking into account a 2:1 allocation ratio to receive efgartigimod versus placebo.

8.2. Analysis Populations

The full analysis set (FAS) consists of all randomized patients. In general, the FAS will be used for efficacy analyses. For the primary and first key secondary endpoint the subset of all

patients in the FAS with chronic ITP will be used. The analysis will follow the intent-to-treat principle, ie, patients will be analyzed according to their randomized treatment, irrespective of the treatment they actually received.

The per protocol (PP) population is a subset of the FAS, ie, all patients from the FAS without a major protocol deviation. The PP population will be used for sensitivity analyses for the primary and key secondary endpoints.

The safety analysis set comprises all patients in the randomized population who have received at least 1 dose or part of a dose of IMP. Patients will be analyzed according to the actual treatment received for safety analyses.

8.3. Patient Disposition, Characteristics, and Concomitant Medication

A tabular presentation of the patient disposition will be provided. It will include the number of patients screened, randomized, received IMP treatment, completed the trial, as well as the number of early discontinuations from IMP treatment (including rescued patients) and trial, with reasons for discontinuation from IMP treatment or trial, and major protocol deviations.

A listing will be presented to describe dates of screening, screen failure with reason, randomization or assigned treatment, completion or early discontinuation, and the reason for discontinuation, if applicable, for each patient.

Patient characteristics will be listed and summarized (by treatment group and overall). Summaries will include descriptive statistics for continuous measures (number of observations, mean, standard deviation, median, 1st quartile, 3rd quartile, minimum, and maximum) and for categorical measures (frequency and percentage). Patient characteristics include, but are not limited to, age, sex, race, weight, body mass index, and baseline platelet level.

Use of concomitant medication will be summarized by treatment group with frequency and percentage. Separate summaries of concurrent ITP therapies and rescue therapy by treatment group will be provided. All concomitant medications used will be listed.

8.4. Statistical Methods

All patients starting at least 1 infusion of efgartigimod or placebo will be assessed for safety according to their actual treatment.

The efficacy analysis will be performed on the FAS or the subset of patients in the FAS with chronic ITP, and analyzed with intent-to-treat principle (ie, patients will be analyzed according to their planned treatment irrespective of the treatment actually received). Supportive analyses will be conducted in the PP population. The safety analysis will be performed on the safety analysis set.

The PK analysis set will include all patients from the safety analysis set who have at least 1 serum post-dose PK measurement.

8.4.1. Primary Endpoint Analysis

Definition of the estimand for the primary endpoint

- Population: adult patients with chronic ITP, having an average platelet count of $<30\times10^9$/L, and, at the start of the trial, either 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
- Variable: sustained platelet count response defined as achieving platelet counts of at least 50×10^9/L for at least 4 of the 6 visits between week 19 and 24 of the trial
- Main intercurrent events:
  i. early discontinuation of treatment (prior to visit 24) due to lack of efficacy (eg, more than 3 occurrences of rescue therapy) or due to an AE
  ii. initiation of rescue therapy at week 12 or later
  iii. increase of dose and/or frequency of concurrent ITP therapies at week 12 or later
- Population-level summary: proportion of patients with sustained platelet count response

Handling of main intercurrent events

A composite strategy approach will be taken to address the main intercurrent events described above. This implies that patients who discontinue treatment prior to visit 24 due to lack of efficacy (eg, more than 3 occurrences of rescue therapy) or due to an AE, as well as 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, will be considered non-responders for the primary endpoint analysis.

Estimation of treatment effect and statistical inference

The primary endpoint will be analyzed using a Cochran-Mantel-Haenszel statistic test stratified for the stratification factors history of splenectomy (yes versus no), receiving concurrent ITP therapies at baseline (yes versus no), and for 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 95% confidence interval (CI) and two-sided p-value. In addition, an adjusted difference of the proportions with its 95% CI will be provided.

Handling of missing data

Missing data for reason of 1 of the main intercurrent events will be handled as described above. Details on handling other missing data will be provided in the SAP.

Complementary analyses

To facilitate interpretation of the estimated treatment effect in the primary analysis, complementary analyses will be conducted where the main intercurrent events are handled differently, eg, by using the hypothetical and/or 'treatment policy' strategy. Furthermore, an exact logistic regression analysis in which the continuous baseline platelet count level is added as covariate instead of the baseline platelet count category will be conducted as supportive analysis. Details will be provided in the SAP.

8.4.2. Key Secondary Endpoint Analyses Subject to Alpha Control

Extent of disease control is defined as the number of cumulative weeks over the planned 24-week treatment period with platelet counts of $\geq 50\times10^9$/L. For each patient this number will be calculated by counting the number of analysis visits from week 1 until week 24 (End-of-Treatment visit) at which the platelet count level is $\geq 50\times10^9$/L. A Wilcoxon-Mann-Whitney test stratified by receiving concurrent ITP therapies at baseline (yes versus no), history of splenectomy (yes versus no), and baseline platelet count level category ($<15\times10^9$/L versus $\geq 15\times10^9$/L) will be used to compare the extent of disease control between both treatment groups. The 2-sided p-value resulting from this hypothesis test will inform on whether the null hypothesis that the distributions of number of cumulative weeks for both treatment groups are identical can be rejected. The test will be conducted at a significance level $\alpha=0.05$. An estimate of the location shift will be provided, along with the associated 95% confidence interval. When 1 of the main intercurrent events occurs, platelet count levels measured after the occurrence will be censored (or, they will not be taken into account for the calculation of the number of cumulative weeks). In other words, they will be handled as if the platelet count level were $<50\times10^9$/L. Missing platelet counts because of early discontinuation due to lack of efficacy or due to an AE will be handled in the same way.

Sensitivity analyses will be conducted to assess the robustness of the analysis results to the proposed handling of intercurrent events and missing platelet counts.

Furthermore, a complementary analysis will be performed where extent of disease control is handled as a time-to-event endpoint (with "loss of disease control" being the event). Cox proportional hazards regression methodology will be applied for this complementary analysis. Details on the model and the event and censoring scheme for this complementary analysis will be provided in the SAP.

The key secondary endpoints on proportion of patients in the overall population with a sustained platelet count response and on proportion of patients in the overall population achieving platelet counts of at least 50×10^9/L for at least 6 of the 8 visits between week 17 and 24 of the trial will be analyzed in the same manner as the primary endpoint.

The number of bleeding events per patient (assessed using the WHO bleeding scale; where WHO scale ≥ 1 at any visit is considered a new bleeding event) will be analyzed using a zero-inflated negative binomial model. This model will account for the large expected number of patients with zero bleeding events. It is a mixture model consisting of 2 components: a

negative binomial count model and a binary model for predicting excess zeros. The model will consist of the number of events as the dependent variable and of randomized treatment, the stratification variables (history of splenectomy; receiving concurrent ITP therapies at baseline), and baseline platelet count as independent variables. An offset term will be used to allow for patient exposure. Both the count model, using the log link, and the binary model, using the logit link, will contain the same independent variables. The probability of no bleeding will be estimated for each randomized treatment group. A Wald test will be used to test the null hypothesis that the log of the bleeding rate ratio on placebo and efgartigimod is equal to zero against the alternative that it is different from zero. The rate of bleeding over 24 weeks on placebo and efgartigimod will be provided, along with the rate ratio, 95% 2-sided Wald-type CI, and 2-sided p-value. Missing bleeding assessments for reasons of 1 of the main intercurrent events will not be imputed, but the offset term will be adapted accordingly to reflect the assessment period until the occurrence or start of the intercurrent event. Incidence of bleeding will also be summarized descriptively by visit. Severity of bleeding will be summarized descriptively by visit. In addition, a summary of within-subject maximum severity will be provided.

The primary endpoint analysis will act as gatekeeper for the testing of the key secondary endpoints. Subject to meeting statistical significance for the primary endpoint, the key secondary endpoints will be analyzed using a fixed-sequence testing procedure to maintain the overall type I error rate at 5%. The type I error rate of each individual test will be 5%, but the test will only be conducted if the analysis for all previous endpoints in the pre-defined hierarchy resulted in a p-value <0.05. The order in the testing hierarchy of the key secondary endpoints is as follows:

1. The extent of disease control defined as the number of cumulative weeks over the planned 24-week treatment period with platelet counts of $\geq 50 \times 10^9$/L in the population with chronic ITP.
2. The proportion of patients in the overall population (chronic and persistent ITP) with a sustained platelet count response defined as achieving platelet counts of $\geq 50 \times 10^9$/L for at least 4 of the 6 visits between week 19 and week 24 of the trial.
3. The incidence and severity of the WHO-classified bleeding events in the overall population.
4. Proportion of patients in the overall population achieving platelet counts of $\geq 50 \times 10^9$/L for at least 6 of the 8 visits between week 17 and 24 of the trial.

Complementary analyses for the key secondary endpoints will be conducted. Subgroup analyses for the primary and/or the key secondary endpoints may be conducted. Details will be provided in the SAP.

8.4.3. Other Secondary Endpoint Analyses Not Subject to Alpha Control

The secondary endpoints on overall platelet count response will be analyzed in the same manner as the primary endpoint. The secondary endpoint on extent of disease control will analyzed in the same manner as the corresponding key secondary endpoint.

The mean changes from baseline in platelet count levels at planned time points and the mean changes from baseline in PRO at planned time points will be analyzed by means of mixed models for repeated measurements. The model will include fixed effect terms for randomized treatment, baseline platelet level or baseline PRO, history of splenectomy (yes vs. no), and receiving concurrent ITP therapies at baseline (yes vs. no). Least square (LS) means for placebo and efgartigimod will be provided, along with the difference in LS means, 95% 2-sided CI, and 2-sided p-value.

Time to response (defined as the time to achieve 2 consecutive platelet counts of $\geq 50\times10^9$/L) will be analyzed via Cox proportional hazards regression with fixed effect terms for randomized treatment and baseline platelet level. The model will be stratified by history of splenectomy (yes vs. no) and receiving concurrent ITP therapies at baseline (yes vs. no), at randomization. The hazard ratio for efgartigimod vs. placebo will be provided, along with the associated 95% 2-sided CI and 2-sided p-value. The data will also be displayed using Kaplan-Meier curves and the median time to response will be displayed by randomized treatment arm.

The number of cumulative weeks over the planned 24-week treatment period with platelet counts of $\geq 30\times10^9$/L and at least 20×10^9/L above baseline will be analyzed in the same way as described for the key secondary endpoint "extent of disease control." Assessment of number of cumulative weeks over the planned 24-week treatment period with platelet counts of $\geq 30\times10^9$/L and at least 20×10^9/L above baseline within the group of patients with a baseline platelet count of $<15\times10^9$/L will also be analyzed as described for the key secondary endpoint.

The number of significant bleeding events per patient (assessed using the WHO bleeding scale; where WHO scale ≥2 at any visit is considered a new significant bleeding event) will be analyzed in the same manner as the corresponding key secondary endpoint.

8.4.4. Pharmacodynamics, Pharmacokinetics, and Immunogenicity

Descriptive statistics will be provided for PD parameters (total IgG and subtypes, and antiplatelet antibodies) and ADA. Efgartigimod serum concentration data will be summarized.

8.4.5. Safety

Incidence and severity of AEs, AESIs, and SAEs will be summarized descriptively. Laboratory parameters, vital signs, and ECG data will also be analyzed descriptively.

8.4.6. Exploratory Endpoint Analysis

Descriptive statistics will be presented for [redacted]. The analysis of [redacted] will be performed at a later stage than the analyses of the other endpoints and will be described in a separate report.

8.5. Interim Analyses

Not applicable.

9. QUALITY CONTROL AND QUALITY ASSURANCE

9.1. Investigator's Responsibility

The investigator will comply with the protocol which has been approved/given favorable opinion by the IRB/IEC, according to ICH Good Clinical Practice (GCP) and applicable regulatory requirements. The investigator is ultimately responsible for the conduct of all aspects of the trial at the trial site and verifies by signature the integrity of all data transmitted to the sponsor. The term "investigator" as used in this protocol as well as in other trial documents, refers to the investigator or site staff that the investigator has designated to perform certain duties. Sub-investigators or other designated site staff are eligible to sign for the investigator, except where the investigator's signature is specifically required.

9.2. Quality Control

Quality control will be applied to each stage of trial-related activities.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- investigator meetings
- central laboratories for clinical laboratory parameters
- site initiation visit
- routine site monitoring
- ongoing site communication and training
- ongoing oversight by sponsor's designated CRO monitors of safety parameters and adherence to selection criteria
- data management quality control checks
- continuous data acquisition and cleaning
- quality control check of the CTR
- to avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all efficacy and safety evaluations, eg, for the completion of the WHO scale

In addition, periodic audits can be performed as specified in Section 9.5.

When audits or inspections are conducted, access must be authorized for all trial-related documents including medical history and concomitant medication documentation to authorized sponsor's representatives and regulatory authorities.

9.3. Monitoring

The sponsor has engaged the services of a CRO to perform all clinical trial monitoring functions within this clinical trial. The sponsor's designated CRO monitors will work in accordance with the SOPs of the CRO.

Monitoring visits must be conducted according to the applicable ICH GCP guidelines to verify that, among others, the:

- data are authentic, accurate, and complete
- safety and rights of patients are being protected
- the trial is conducted in accordance with the currently approved protocol, any other trial agreements, and all applicable regulatory requirements

The investigator and the head of the medical institution (where applicable) agree to allow the sponsor's designated CRO monitor direct access to all relevant documents.

The investigator must ensure provision of reasonable time, space, and qualified personnel for monitoring visits.

The sponsor's designated CRO monitor will perform an eCRF review, source document verification, and source document review.

The source documentation agreement form describes the source data for the different data in the eCRF. This document should be completed and signed by the sponsor's designated CRO monitor and investigator, and should be filed in the investigator's trial file. Any data item for which the eCRF will serve as the source must be identified, agreed, and documented in the source documentation agreement form.

Upon completion or premature discontinuation from the trial, the sponsor's designated CRO monitor will conduct site closure activities with the investigator and site staff as appropriate, in accordance with applicable regulations, ICH GCP guidelines, and CRO/sponsor procedures.

9.4. Data Management

Data generated within this clinical trial will be processed according to the SOPs of the data management and biostatistics departments of the sponsor's designated CRO.

Case report forms are provided for each patient in electronic format (ie, eCRF). Data will be transcribed by the trial site staff from the source documents onto the eCRF. Data must be entered in English. Guidelines for eCRF completion, including the collection of the investigator's e-signature, will be provided by the CRO. Appropriate training and security measures will be completed by the investigator and all designated site staff prior to the trial being initiated, and any data being entered into the system for any trial patient at the site.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the investigator or hospital that relate to the patient's medical history, that verify the existence of the patient, the inclusion and exclusion criteria, and all records covering the patient's participation in the trial. They can include laboratory notes, ECG results, memoranda, pharmacy dispensing records, patient files, etc. The eCRFs should be completed by the investigator or a qualified designee from the site as soon as the data are available.

As a matter of regulation, the investigator is responsible for the accuracy and authenticity of all clinical data entered onto eCRFs. Prior to database lock, each completed eCRF must be reviewed for accuracy by the investigator, corrected as necessary, and then approved. The investigator's e-signature serves to attest that the information contained in the eCRFs has been reviewed by the investigator, and is true and accurate. The investigator will be required to electronically sign off the eCRF.

The data will be verified for missing data, inconsistencies, and for necessary medical clarifications. Queries arising from these checks will be flagged to the trial site, and the trial site staff will correct data, confirm, or clarify data as appropriate. The CRO will provide the details of the review process in a data management plan and a monitoring plan. Any change, including the issuing of queries, will be fully audit-trailed by the EDC system, meaning the name of the person, time, and date stamp are captured, as well as the reason for change.

Data will also be provided by third party vendors, such as the results generated by the central laboratories, ECG reader, and IRT provider. This data will need to be reconciled with the data recorded in the eCRF before it can be merged with the eCRF data into the clinical database. The CRO will provide a data management plan detailing this reconciliation.

Adverse events, concomitant diseases, and medical history terms will be assigned to a lowest level term and a preferred term, and will be classified by high level term, high level group term, and primary system organ class according to the medical dictionary for regulatory activities thesaurus.

Prior and concomitant medications will be classified according to active drug substance using the WHO drug dictionary (WHO-DD). The generic name, the preferred name, and the WHO name will be assigned using the WHO-DD thesaurus.

The anatomical therapeutic chemical classes will be assigned to the prior and concomitant medications.

9.5. Quality Assurance Audit

Trial processes, trial sites (including, but not limited to site visits, central laboratories, vendors), the trial database, and trial documentation may be subject to quality assurance audit during the course of the trial by the sponsor or sponsor's designee (CRO or other vendor) on behalf of sponsor. In addition, inspections may be conducted by regulatory bodies at their

discretion. Such audits/inspections can occur at any time during or after completion of the trial.

10. ETHICS

10.1. Institutional Review Board or Independent Ethics Committee

The investigator will provide the sponsor or designee with documentation of IRB/IEC approval of the protocol and informed consent documents before the trial may begin at the trial sites. The investigator will supply documentation to the sponsor or designee of the required IRB/IEC's annual renewal of the protocol, and any approvals of revisions to the informed consent document or amendments to the protocol.

The investigator will report promptly to the IRB/IEC, any new information that may adversely affect the safety of patients or the conduct of the trial. Similarly, the investigator will submit written summaries of the trial status to the IRB/IEC annually, or more frequently if requested by the IRB/IEC. Upon completion of the trial, the investigator will provide the IRB/IEC with a brief report of the outcome of the trial, if required.

10.2. Ethical Conduct of the Trial

This trial will be conducted and the informed consent will be obtained according to the ethical principles stated in the Declaration of Helsinki (2013), the applicable guidelines for GCP, or the applicable drug and data protection laws and regulations of the countries where the trial will be conducted.

To comply with the Declaration of Helsinki (2013), argenx is currently assessing the appropriateness and possibility of making the trial drug available for clinical trial participants post-trial.

10.3. Patient Information and Informed Consent

The investigator must explain to each patient the nature of the trial, its purpose, the procedures involved, the expected duration, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available, and the extent of maintaining confidentiality of the patient's records. Each patient must be informed that participation in the trial is voluntary, that he/she may withdraw from the trial at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

The ICF will be used to explain the potential risks and benefits of trial participation to the patient in simple terms before the patient is screened. A separate ICF will be given in case of pregnancy of a female partner of a male patient. The ICF contains a statement that the consent is freely given, that the patient is aware of the risks and benefits of entering the trial, and that the patient is free to withdraw from the trial at any time. Written consent must be given by the patient, after the receipt of detailed information on the trial.

All patient information and ICFs must be available in the local and vernacular languages required at the site and include patient information sheets/brochures that outline the trial procedures. All ICF(s) must be signed and dated by the patient.

Confirmation of a patient's informed consent must also be documented in the patient's medical record prior to any trial-related procedure under this protocol, including screening tests and assessments.

The investigator is responsible for ensuring that the informed consent is obtained from each patient and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of IMP. The investigator will provide each patient with a copy of the signed and dated ICF(s).

10.4. Patient Data Protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

11. TRIAL ADMINISTRATION

11.1. Data Handling and Record Keeping

It is the investigator's responsibility to maintain essential trial documents (records and documents pertaining to the conduct of this trial and the distribution of IMP, including regulatory documents, eCRFs, signed patient ICFs, laboratory test results, IMP inventory records, source documents, relevant correspondence, AE reports, and all other supporting documentation) as required by the applicable national regulatory requirements. The trial site should plan on retaining such documents for approximately 25 years after trial completion. The trial site should retain such documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years after the formal discontinuation of clinical development of the IMP. The sponsor will notify the principal investigator of these events.

These documents should be retained for a longer period if required by the applicable regulatory requirements or the hospital, institution, or private practice in which the trial is being conducted. Patient identification codes (patient names and corresponding trial numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to the sponsor, who agrees to abide by the retention policies. The investigator is required to notify the sponsor (or an authorized representative) in writing prior to changing the location or status of any essential clinical trial documents. The investigator must contact the sponsor prior to disposing of any trial records.

No records should be disposed without the written approval of argenx BVBA.

For trials conducted outside the US under a US investigational new drug (IND), the principal investigator must comply with US Food and Drug Administration IND regulations and with those of the relevant national and local health authorities.

11.2. Direct Access to Source Data/Documents

The sponsor or designee, and auditor may access patient records for the purpose of monitoring this trial, auditing, and managing progress details. The investigator must be fully aware that the sponsor or designee and auditor can inspect or verify documents to verify patient's chart and eCRF records. Such information must be kept confidential and must have locked facilities that allow for this. The investigator will prepare and maintain adequate and accurate source documents to record all observations and other pertinent data for each patient enrolled into the trial.

The investigator is responsible for maintaining source documents. These will be made available for verification by the sponsor's designated CRO monitor at each monitoring visit. The investigator must submit a completed eCRF for each patient who receives IMP,

regardless of duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the trial and patient number. Any personal information, including patient name, should be removed or rendered illegible to preserve individual confidentiality.

11.3. Investigator Information

11.3.1. Investigator Obligations

This trial will be conducted by qualified investigators under the sponsorship of argenx BVBA (the sponsor).

The name and telephone/fax numbers of the sponsor's designated CRO monitor and other contact personnel at the sponsor and the CRO are listed in the investigator trial file provided to each site.

The investigator is responsible for ensuring that all trial site personnel, including sub-investigators, adhere to all applicable regulations and guidelines, including local laws and regulations, regarding the trial, both during and after trial completion. The investigator is responsible for informing the IRB/IEC of the progress of the trial and for obtaining annual IRB/IEC renewal. The investigator is responsible for informing the IRB/IEC of completion of the trial and will provide the IRB/IEC with a summary of the results of the trial.

11.3.2. Protocol Signatures

After reading the protocol, each investigator will sign the protocol signature page and send a copy of the signed page to the sponsor or representative. By signing the protocol, the investigator confirms in writing that he/she has read, understands, and will strictly adhere to the trial protocol, and will conduct the trial in accordance with ICH tripartite guidelines for GCP and applicable regulatory requirements. The trial will not be able to start at any site where the investigator has not signed the protocol.

11.3.3. Publication Policy

All information regarding efgartigimod supplied by the sponsor to the investigator and all data generated as a result of this trial, are considered confidential and remain the sole property of the sponsor. The results of the trial will be reported in a CTR.

The CTR written in accordance with the ICH E3 guideline, will be submitted in accordance with local regulations.

Any manuscript, abstract or other publication, presentation of results, or information arising in connection with the trial must be prepared in conjunction with the sponsor after the trial has been analyzed and reported and must be submitted to the sponsor for review and

comment prior to submission for publication or presentation. Trial patient identifiers will not be used in the publication of results.

Authorship will be granted according to the International Committee of Medical Journal Editors criteria,[15] based on scientific input and recruitment efforts.

The sponsor will register and/or disclose the existence of and the results of clinical trials as required by law.

11.3.4. Financing and Insurance

The sponsor will fund the trial as outlined in the clinical trial agreement.

The sponsor will obtain adequate global/local insurance for the trial participants including the trial patients for the required duration of time.

The sponsor maintains an insurance coverage for this trial in accordance with the laws and regulations of the countries in which the trial is performed. Liability and insurance provisions for this trial are specified in the investigator's contract. The terms and conditions will apply as specified in the policy document.

12. REFERENCES

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13. APPENDICES

Appendix 1 Laboratory Evaluations

Hematology	Hemoglobin, white blood cell (WBC) count with WBC differential
Coagulation	activated partial thromboplastin time (aPTT), prothrombin time (PT INR)
Clinical Chemistry	Creatinine, creatinine clearance, blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, gamma-glutamyl transferase (GGT), C-reactive protein (CRP), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), uric acid, albumin, potassium, sodium, calcium
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
Serology	Human immunodeficiency virus (HIV) antibodies (1 and 2), hepatitis B surface antigen (HBsAg), antibodies to the surface and core antigens of the hepatitis B virus (anti-HBs and anti-HBc), hepatitis C virus antibody (HCV-Ab)
Other	Serum human chorionic gonadotrophin (ß-HCG), follicle-stimulating hormone (FSH) test, autoimmune antibody testing, antinuclear antibody, thyroglobulin, thyroid stimulating hormone (TSH), tuberculosis QuantiFERON test
Pharmacokinetics	Serum levels of efgartigimod
Pharmacodynamic markers	Serum levels of total IgG and IgG subtypes (IgG1, IgG2, IgG3, and IgG4)
Antiplatelet antibodies	Presence, nature, and level of antiplatelet antibodies
Anti-drug antibodies	Serum levels of anti-ARGX-113 binding antibodies, neutralizing antibodies (Nab)
Local evaluations	Platelet count [redacted] urine pregnancy
Other exploratory	Whole blood flow cytometry for [redacted]

Appendix 2 Administrative Structure

Central Laboratories
Cerba Research NV Industriepark Zwijnaarde 3 9052 Gent Belgium
Analysis of Pharmacokinetics, IgG Subtypes, and Anti-Drug Antibodies
LGC Newmarket Road Fordham Cambridgeshire CB7 5WW United Kingdom
Analysis of Total IgG
PPD Laboratories - US 2 Tesseneer Road Highland Heights, KY 41076 United States
Antiplatelet Antibodies
Sanquin Diagnostic Services Plesmanlaan 125 1066 CX Amsterdam The Netherlands
Long-Term Storage of Pharmacokinetics-Pharmacodynamics (PK-PD), Anti-Drug Antibodies (ADA), Antiplatelet Antibodies Samples
Brooks Life Sciences, BioStorage Technologies GmbH Im Leuschnerpark 1B 64347 Griesheim Germany
[redacted]
[redacted] Boston, MA 02115 USA
Central ECG Reading
ERT Clinical Peterborough Business Park Lynchwood House Peterborough PE2 6FZ United Kingdom

Trial Monitoring/Medical Monitoring
ICON plc South County Business Park Leopardstown Dublin 18 Ireland
Home Care Vendor
Accellacare In-Home Services (previously known as Symphony Clinical Research) (an ICON company) 700 Deerpath Drive Vernon Hills, IL 60061-1802 USA
Clinical Trial Supply Management
Fisher Clinical Services GmbH Steinbühlweg 69 4123 Allschwil Switzerland
Data Management, Biostatistics, Medical Data Review
SGS Life Sciences (SGS LS), a division of SGS Belgium NV Generaal de Wittelaan 19 – A5 Mechelen, 2800 Belgium
Drug Safety Reporting
Parexel International 1 Federal Street Billerica, MA 01821 USA

Appendix 3 World Health Organization Bleeding Scale

	Grade 1	Grade 2	Grade 3
Oral and nasal	➢ Oropharyngeal bleeding – total duration of all episodes in previous 24 hours ≤ 30 minutes* ➢ Petechiae of oral mucosa ➢ Epistaxis – total duration of all episodes in previous 24 hours < 30 minutes*	➢ Oropharyngeal bleeding – total duration of all episodes in previous 24 hours > 30 minutes* ➢ Epistaxis – total duration of all episodes in previous 24 hours > 30 minutes*	➢ Any bleeding requiring RBC transfusion over routine transfusion needs†
Skin, soft tissue, musculoskeletal	➢ Petechiae of skin ➢ Purpura ≤ 1 inch diameter ➢ One or more spontaneous hematomas in the soft tissue or muscle > 1 inch	➢ Purpura > 1 inch diameter ➢ Spontaneous hematoma in deeper tissues ➢ Joint bleeding (confirmed by aspiration, imaging study or other accepted technique)	➢ Any bleeding requiring RBC transfusion over routine transfusion needs†
Gastrointestinal	➢ Positive stool occult blood test‡	➢ Melanotic stool ➢ Hematochezia – visible red blood mixed in stool, not requiring a transfusion ➢ Hematemesis – grossly visible blood in emesis or in nasogastric drainage tube (not related or secondary to swallowed blood)	➢ Any bleeding requiring RBC transfusion over routine transfusion needs†
Genitourinary	➢ Any biochemical or microscopic Hb/RBCs without red urine‡ ➢ Abnormal vaginal bleeding (Unexpected bleeding out of normal cycle *or* bleeding heavier than normal *or* breakthrough bleeding (patient on hormonal therapy to prevent bleeding)) with spotting	➢ Gross/visible hematuria without need for transfusion ➢ Abnormal vaginal bleeding (Unexpected bleeding out of normal cycle *or* bleeding heavier than normal *or* breakthrough bleeding (patient on hormonal therapy to prevent bleeding)) more than spotting	➢ Any bleeding requiring RBC transfusion over routine transfusion needs†
Pulmonary		➢ Hemoptysis – visible blood ➢ Blood in broncho-pulmonary lavage, or blood tinged sputum (excluding those with nose or oropharyngeal bleeding)	➢ Any bleeding requiring RBC transfusion over routine transfusion needs†
Body cavity		➢ Visible blood in body cavity fluid (e.g. red cells apparent in fluid aspirate) short of criteria for Grade 3 or 4	➢ Grossly bloody body cavity fluids and organ dysfunction with symptoms, and/or need to intervene (e.g. to aspirate), and/or need for transfusion
Central nervous system		➢ Retinal bleeding without visual impairment ➢ Lumbar puncture with blood (>5 RBC/μL in CSF on microscopic analysis and non-traumatic tap), no symptoms and no visible red color	➢ Lumbar puncture with visible red color in absence of symptoms, and non-traumatic tap
Invasive sites		➢ Bleeding at invasive sites (venipuncture sites, intravenous lines or catheter exit sites): active oozing at site for a cumulative total of > 1 hour in the previous 24 hours	➢ Any bleeding requiring RBC transfusion over routine transfusion needs†
Hemodynamic instability			➢ Any bleeding associated with moderate hemodynamic instability (hypotension; >30mmHg fall or >30% decrease in either systolic or diastolic blood pressure) and requiring RBC transfusion over routine transfusion needs†

Grade 4:

- Any bleeding associated with severe hemodynamic instability (hypotension; >50mm/Hg fall or >50% decrease in either systolic or diastolic blood pressure, with associated tachycardia (heart rate increase of ≥ 20% for 20 minutes) and requiring RBC transfusion over routine transfusion needs
- Fatal bleeding from any source
- Retinal bleeding with visual impairment (Visual impairment is defined as a field deficit, and patients with suspected visual impairment require an ophthalmologic consult for documentation)
- CNS symptoms with non-traumatic bloody lumbar puncture
- CNS bleeding on imaging study with or without dysfunction

RBC indicates red blood cell; Hb, hemoglobin; CSF, cerebrospinal fluid; Hg, mercury; and CNS, central nervous system

* Count actual bleeding (i.e. "running out" or need for basin, Kleenex, towel, etc.) not minor bleeding

†Red cell transfusion must be specifically related to treatment of bleeding within 24 hours of onset of bleeding

‡Not assessed in PLADO

Appendix 4 Possible Adaptations of Trial Protocol During COVID-19 Pandemic

The aim of the ARGX-113-1801 trial is to evaluate the efficacy and safety of efgartigimod (ARGX-113) 10 mg/kg intravenous (IV) in adult patients with primary immune thrombocytopenia (ITP).

During the COVID-19 pandemic, it may not be possible to perform site visits as planned for this trial (see SoA, Table 2). The main adaptation presented in this appendix is the shift from site visits to home visits.

Argenx has performed a critical assessment of the use of efgartigimod during the COVID-19 pandemic. From discussions within the company, the physician community, and patient associations it has been concluded that the risk/benefit profile of efgartigimod in ongoing clinical trials has not changed in the context of this pandemic. This decision was made based on efgartigimod's mechanism of action, the safety data generated to date, and provisions made in all clinical trials with efgartigimod regarding safety reporting and withholding treatment upon evidence of infection. This assessment will be reviewed regularly to consider new information about the pandemic and the ongoing, continuous assessment of adverse events (AEs) reported during argenx clinical trials.

Based on this risk/benefit assessment, the clinical trial ARGX-113-1801 can continue. However, it may not always be possible to perform all visits at the trial site during the pandemic.

In order to allow patients with ITP to receive treatment with the IMP during the COVID-19 pandemic, this appendix to the protocol has been developed. Only in case a visit to the trial site is absolutely not possible, a home visit or a visit at an alternative convenient location can be allowed. This proposed flexibility in executing the trial will be temporary and will only last as long as the COVID-19 pandemic affects the ability of the patients to attend the trial visits at the trial site. As soon as the situation returns to normal, the measures specified here will not apply any more.

It remains at the investigator's discretion to assess if it is in the best interest of the patient to participate/continue in the trial. Note that the home nurse, who will go to the patient in case of a home visit, could also be another qualified person to perform all tasks (eg, a trained qualified physician).

Possible Adaptations in ARGX-113-1801 Trial Protocol During COVID-19 Pandemic

Permission and Duration to Use the "Updated" Protocol Version

This appendix to the protocol is intended for countries and/or sites in geographical areas where COVID-19 has affected the trial sites' workload or travel restrictions are imposed. Prior to implementation of this protocol appendix, the trial site first needs to inform and obtain approval from the sponsor or the CRO. The initial duration of implementation of the protocol appendix will be agreed upon and can potentially be extended (upon written agreement) based on the local epidemic status. When a home visit is performed under this COVID-19 appendix it should be documented as a COVID-19 home visit in the eCRF for the applicable visit.

Testing for COVID-19

Additional testing for COVID-19 beyond that mandated by relevant local authorities for the patient's screening and randomization is not required. See also Figure 2.

Based on the exclusion criterion "Clinical evidence of significant unstable or uncontrolled acute or chronic diseases other than ITP (eg, cardiovascular, pulmonary, hematologic, gastrointestinal, endocrine, hepatic, renal, neurological, malignancy, infectious diseases, uncontrolled diabetes) despite appropriate treatments, which could put the patient at undue risk," patients with ongoing COVID-19 would be excluded from participation in the trial.

Protecting Home Nurse and Site Staff From COVID-19

The home nurse and site staff should use personal protective equipment as directed by the local guidelines.

Patients With COVID-19 (Either a Positive Test or With Symptoms)

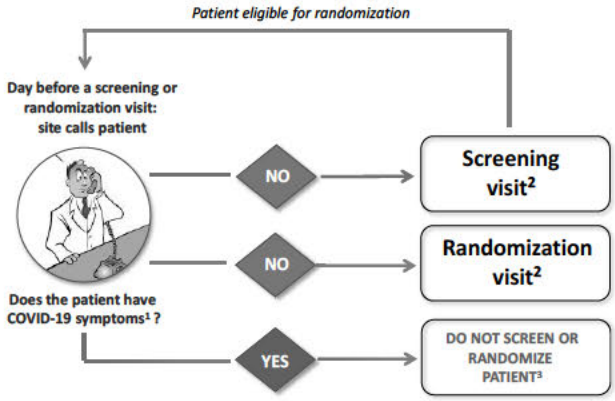
The instructions to manage infections in the main protocol are also applicable in case of COVID-19 (ie, it will be considered as an AESI). The administration of IMP may be temporarily withheld if, in the opinion of the investigator, it could put the patient at undue risk in circumstances as clinically significant disease, including evidence of infection (see Section 4.5).

During the pandemic, site staff or home nurse should call patients prior to each visit to enquire about COVID-19 symptoms, and to check for exposure and infection with the virus before deciding to proceed with the visit using the flow charts below. In case the patient is placed in quarantine and is not able to receive IMP, the investigator can specify in the eCRF that there was no intention to administer IMP due to COVID-19.

For all assessments not performed at the trial site, "COVID-19: home visit" or "COVID-19: phone call" will be added as a comment in the eCRF.

Figure 2 Decision Tree for the Treatment of Patients

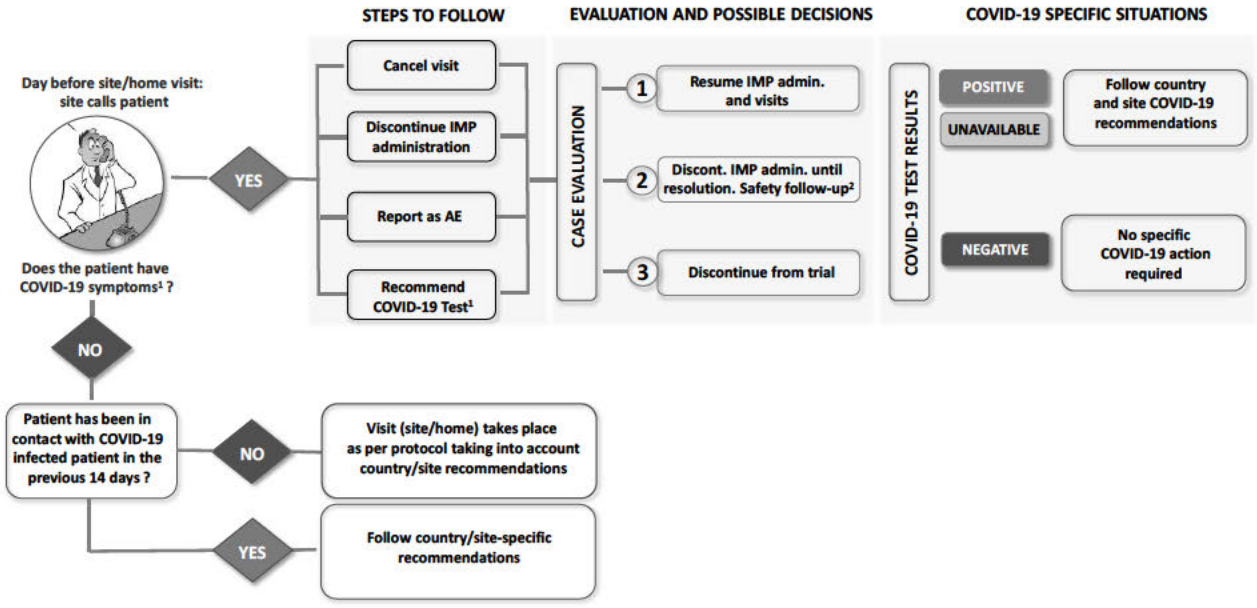
COVID-19 OUTBREAK: IMPACT ON ARGENX STUDIES – SCREENING AND RANDOMIZATION OF PATIENTS



Footnotes:

1. *No COVID-19 test for screening or randomization visit unless required/recommended by country or site*
2. *Visit (trial site) takes place as per protocol following country/site recommendation, if applicable*
3. *Screening / randomization can be reconsidered at a later time following country/site recommendation if applicable*

COVID-19 OUTBREAK: IMPACT ON ARGENX STUDIES – PATIENTS ALREADY IN THE STUDY



[1]*Encourage and facilitate execution of COVID-19 test (PCR):* [2]*In COVID-19 positive patients, consider resuming IMP administration, visits, and trial assessments after recovery*

In case of (suspected) COVID-19, the patient will be treated as guided by the local health care system. Patients will be observed for safety follow-up by the trial site by phone or by video call, if available and compliant with applicable regulations, eg, 21 CFR part 11, data protection regulation. In case the patient has to be isolated for a period longer than 2 weeks, it will be discussed on a case-by-case basis with the medical monitor from the sponsor, and/or when appropriate the CRO, whether the patient can remain in the trial.

The investigator can be contacted by the patient at any time by phone/video call in case of concerns.

Forms completed at the patient's home have to be taken back to the site for data entry. In case the trial site would be closed due to the COVID-19 situation, the completed forms have to be stored in a safe location until reopening of the trial site.

Relevant records should be archived in the investigator site's Trial Master File. The investigator/institution or delegate should maintain adequate and accurate source documentation.

Screening Visit
The screening assessments should be performed at the trial site. In case the trial site is closed due to the COVID-19 situation, an alternative convenient location considered appropriate by the investigator and the patient (and confirmed and approved by the sponsor) can be used (eg, an infusion center, local clinic, patient's home).

If it is not possible for the patient to go to the trial site and the patient cannot be screened or treated at an alternative convenient location due to the COVID-19 situation, the patient cannot start screening and has to wait until the situation changes and the patient is able to go to the trial site for the screening assessments.

Please note that prospective protocol waivers remain unacceptable and that patients should not be included in trials without proper eligibility assessment, including performance of planned tests, and written informed consent according to national laws and regulations. The investigator remains ultimately responsible for obtaining informed consent, even when delegating this task to another individual knowledgeable about the research.

Baseline Visit
The baseline visit should be performed at the trial site. In case the trial site would be closed due to the COVID-19 situation, an alternative convenient location considered appropriate by the investigator and the patient (and confirmed and approved by the sponsor) can be used (eg, an infusion center, local clinic, patient's home).

Possible Home Visits/Home Assessments
All other trial visits can be performed at home (or at an alternative convenient location) during the COVID-19 pandemic. A home nurse will travel to the patient's home (or an alternative convenient location) to conduct the visit(s). The investigator will talk to the patient via an audio or video interview to elicit AEs, concomitant medications, and the general well-being of the patient. The investigator will perform the WHO bleeding assessments using a video interview with the patient. This will be mentioned in the source documents as such.

All assessments performed at home, should preferably be performed by the same qualified trained nurse or another authorized person. This person will get all materials and equipment needed in order to perform the home assessments.

Blood and urine samples (except the urine pregnancy test, samples for platelet counts) will preferably be shipped to and analyzed by a central laboratory. Only in exceptional cases a certified local laboratory can be used; laboratory reports should be reviewed by the investigator, any abnormalities will be evaluated for clinical significance, and any significant laboratory findings should be recorded as AEs. The laboratory report should be kept as a source document.

The division of tasks between the trained qualified physician and home nurse are indicated in the following scheme should be in line with applicable local regulations.

Scheme for Home Visits[a]		
Assessment	**Performed by**	**Place/Method of Assessment**[a]
• Patient eligibility	Trained qualified physician	Preferably at the trial site
• Quality-of-life and patient-reported outcomes	Patient	At patient's home
• Weight • Electrocardiogram • Urinalysis • Urine pregnancy test • Blood sample (platelet count, hematology, chemistry, serum pregnancy, viral tests, pharmacodynamics, antiplatelet antibodies, anti-drug antibodies, pharmacokinetics) • IMP infusion	Trained qualified nurse	In person at patient's home
• Vital signs • Physical examination	Trained qualified nurse/trained qualified physician	In person at patient's home
• General bleeding assessment (WHO)	Trained qualified physician	In person at patient's home or video call with investigator
• Concomitant therapies • Adverse events		Audio/video call

[a] Note that a home visit can also be a visit at an alternative convenient location (eg, an infusion center, local clinic).

Platelet Count
A trained qualified nurse can draw the sample at the patient's home, within 1 day before the next procedure as per the SoA. If IMP is to be administered, the IMP can be prepared and administered the day after, based on the platelet count and weight from the day before or all can be done on the day on which IMP should be administered according to the SoA. The platelet count should be performed at the same local laboratory throughout the trial.

Quality-of-Life and Patient-Reported Outcomes
SF-36, FACT-Th6, and FACIT-Fatigue can be completed at home (or an alternative convenient location) by the patient.

Weight
Calibrated scales can be provided to the home nurse or the patient.

Vital Signs
Vital signs can be performed at home (or an alternative convenient location) by a trained qualified nurse. The investigator can be contacted by phone/video call in case of concerns.

Physical Examination
Physical examination can be performed at home (or an alternative convenient location) by a trained qualified nurse or, if not allowed per local regulations, a trained qualified physician. The investigator can be contacted by phone/video call in case of concerns.

Electrocardiogram
An ECG can be taken at home (or an alternative convenient location) by a trained qualified nurse. The investigator can be contacted by phone/video call in case of concerns.

General Bleeding Assessment (WHO)
The general bleeding assessment can be performed at home (or an alternative convenient location) by a trained qualified physician or by means of a video call with the investigator.

Urinalysis
A trained qualified nurse can take a urine sample at home (or an alternative convenient location) using the laboratory kits/requisition forms supplied by the central lab. The testing should preferably be done by the initially appointed laboratory.

Urine Pregnancy Test
A trained qualified nurse can perform the urine pregnancy test on a urine sample taken at home (or an alternative convenient location).

Hematology and Chemistry Tests
A trained qualified nurse can take the blood sample at home (or an alternative convenient location) using the laboratory kits/requisition forms supplied by the central lab. The testing should preferably be done by the initially appointed central laboratory.

Serum Pregnancy Test
A trained qualified nurse can take a blood sample at home (or an alternative convenient location) using the laboratory kits/requisition forms supplied by the central lab. The testing should preferably be done by the initially appointed central laboratory.

Viral Tests
A trained qualified nurse can take a blood sample at home (or an alternative convenient location) using the laboratory kits/requisition forms supplied by the central lab. The testing should preferably be done by the initially appointed central laboratory.

Tuberculosis QuantiFERON Test
The test for tuberculosis can be omitted if the baseline visit cannot be done at the trial site. This sample requires specific processing at a high technical level, which could not be feasible outside the trial site.

Pharmacodynamics
A trained qualified nurse can take a blood sample at home (or an alternative convenient location) using the laboratory kits/requisition forms supplied by the central lab. The testing should be done by the initially appointed central laboratory.

Antiplatelet Antibodies
A trained qualified nurse can take a blood sample at home (or an alternative convenient location) using the laboratory kits/requisition forms supplied by the central lab. The testing should be done by the initially appointed laboratory.

Anti-Drug Antibodies
A trained qualified nurse can take a blood sample at home (or an alternative convenient location) using the laboratory kits/requisition forms supplied by the central lab. The testing should be done by the initially appointed laboratory.

Pharmacokinetics
A trained qualified nurse can take the blood samples at home (or an alternative convenient location) (pre- and post-dose) using the laboratory kits/requisition forms supplied by the central lab. The testing should be done by the initially appointed laboratory.

IMP Infusions
A trained qualified nurse can administer the IMP at the patient's home (or an alternative convenient location). Detailed instructions on IMP management can be found in the Home Guide for Preparation and Administration. The patient has to be observed for infusion-related reactions by the trained qualified nurse for at least 30 minutes following the end of the infusion for safety monitoring based on the patient's clinical status. The investigator can be contacted by phone/video call in case of concerns.

Concomitant Therapies
The assessment of concomitant therapies can be performed at home (or an alternative convenient location) through a phone/video call with the investigator.

Adverse Events
The assessment of adverse events can be performed at home (or an alternative convenient location) through a phone/video call with the investigator.

Schedule of Assessments
In the SoA below, the assessments preferably performed at the trial site are indicated with a solid dot "●"(ie, mandatory). The assessments that can be omitted in case it is not possible to perform them, are indicated with a circle "**O**"(ie, optional). The assessments that can be performed at home (or an alternative convenient location) are indicated with a triangle "Δ." However, if possible and feasible, it is preferred to perform as many assessments as possible on site.

Table 2 Schedule of Assessments

Trial Period[a]	Screening[b]	IV Treatment Period																						End-of-Treatment/ Early Discontinuation	Follow-up 1	Follow-up 2	Unscheduled Visit
Visits		1[b] (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[c]	●																												
Inclusion/exclusion criteria	●	●[d]																											
Medical/surgical history	●																												
Demographic data	●																												
Platelet count[e]	●	●	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ
			Can be performed within 1 day of the next assessment																										
SF-36(v2)[f]		●								Δ								Δ								Δ			
FACT-Th6 and FACIT-Fatigue Scale[f]		●				Δ				Δ				Δ				Δ				Δ				Δ			
Weight[g]	●	●	Δ	Δ	Δ	Performed only on visits with an IMP infusion																				Δ			
Vital signs, including height[h]	●	●	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ
Physical examination	●	●				Δ				Δ								Δ							Δ	Δ			Δ
Electrocardiogram	●	●[i]				Δ[i]				Δ[i]				Δ[i]				Δ[i]				Δ[i]			Δ[i]	Δ	Δ	Δ	Δ
General bleeding assessment (WHO)	●	●	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ
Urinalysis[j]	●[k]	●	Δ	Δ	Δ		Δ		Δ		Δ		Δ		Δ		Δ		Δ		Δ		Δ		Δ	Δ	Δ	Δ	Δ
Urine pregnancy test[l]		●				Δ				Δ				Δ				Δ				Δ				Δ		Δ	Δ
Hematology and chemistry tests[j]	●[k,m]	●	Δ	Δ	Δ		Δ		Δ		Δ		Δ		Δ		Δ		Δ		Δ		Δ		Δ	Δ	Δ	Δ	Δ
Serum pregnancy test[j]	●[k]																												
Follicle-stimulating hormone[j]	●[k]																												
Coagulation, thyroid, and autoimmune antibody testing[j]	●[k]																												
Viral tests[j]	●[k]																												
Tuberculosis QuantiFERON test[j]		●[n]																											
Pharmacodynamics[j,o]		●	Δ	Δ	Δ	Performed only on visits with an IMP infusion																				Δ	Δ	Δ	Δ
Antiplatelet antibodies[j]		●							Δ[p]								Δ[p]							Δ[p]		Δ			
Anti-drug antibodies[j,q]	●	●			Δ				Δ[p]					Δ[p]						Δ[p]				Δ[p]		Δ		Δ	Δ
[redacted]		O	O			O								O												O			
Pharmacokinetics		●[s]	Δ[s]	Δ[s]	Δ[s]	Performed only on visits with an IMP infusion[s]																				Δ	Δ	Δ	Δ
Randomization[t]		●																											
IMP infusions[u]		●	Δ	Δ	Δ	‹----------Weekly or q2w infusion----------›																							
Concomitant therapies[v]	●	●	‹----------Δ----------›																										
Adverse events[v]	●	●	‹----------Δ----------›																										

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. ●=mandatory; **O**=optional; Δ=home assessment

[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] The screening and baseline visits are preferably performed at the trial site or an alternative convenient location.

[c] No trial-related assessment must be carried out before signing the ICF.

[d] 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 through a phone/video call with the investigator, if the baseline visit cannot be performed at the trial site.

[e] 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)
[redacted]
.

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

[g] Weight can be measured, together with the platelet count, within 1 day before the next procedure.

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

[i] 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.

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

[k] 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.

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

[m] At the screening visit, the total IgG level must be determined by the central laboratory (exclusion criterion 11).

[n] Optional in case the baseline visit is held at an alternative convenient location.

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

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

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

[r] [redacted]

[s] 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).

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

[u] 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 home (or an alternative convenient location) 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.

[v] 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.

Appendix 5 Protocol Amendment History

The protocol amendment Summary of Changes table for the current amendment is located directly before the Synopsis. The protocol amendment Summary of Changes table for the previous amendments can be found in this section.

The major changes from Protocol Version 4.0 compared to Protocol Version 5.0 are summarized below.

A strikethrough font is used to indicate deleted text and a bold font to indicate added text. Minor administrative editorial changes are not summarized in the following table:

Summary of Changes Between Protocol Version 4.0 and Protocol Version 5.0

Section(s)	Change	Rationale
• Front page	Medical Director: [redacted], MD argenx BVBA Industriepark Zwijnaarde 7 B-9052 Zwijnaarde BELGIUM Phone: office [redacted] Email: [redacted]	Internal restructure.
	24-Hour Urgent Medical Helpline Number: (+1) ~~919 674 5468~~**857 957 5013**	Administrative change.
	Safety Mailbox/Fax: Email: ~~be.life.saefax-ma@sgs.com~~ **248700ADR@parexel.com** Fax: +~~32 (0)15 29 93 94~~**1 833 644-0806**	Change in safety vendor.
• Section DEFINITION OF TERMS	Childbearing potential: Women of childbearing potential are defined as all female participants unless they are postmenopausal (defined by continuous amenorrhea) for at least 1 year with a follicle-stimulating hormone (FSH) of >40 IU/L or are surgically sterile (ie, who had a hysterectomy, **a bilateral salpingectomy, a** bilateral oophorectomy, or have current documented tubal ligation or any other permanent female sterilization procedure). Determination of FSH levels can be used to confirm postmenopausal status in amenorrheic patients ~~not~~ on hormonal replacement therapy.	Clarification.

Section(s)	Change	Rationale
• Synopsis • Section 4.1. Summary of Trial Design • Section 6.8.4. Rescue Therapy	**"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 trial patient. The start date/time of the occurrence is the start of the administration of the first rescue treatment.**	Clarification.
	Patients requiring **more than 3 occurrences of** rescue therapy ~~more than 3 times~~ will discontinue from IMP.	
• Synopsis • Section 3.1. Primary Endpoint • Section 4.2. Discussion of Trial Design • Section 8.4.1. Primary Endpoint Analysis	Patients who discontinue treatment prior to visit 24 due to lack of efficacy (eg, ~~need rescue therapy more than 3 times~~**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.	
• Section 4.4.2. Early Discontinuation from Treatment	• patient has received **more than 3 occurrences of** rescue therapy ~~more than 3 times~~	
• Section 8.4.1. Primary Endpoint Analysis	• Main intercurrent events: i. early discontinuation of treatment (prior to visit 24) due to lack of efficacy (eg, ~~need for rescue therapy more than 3 times~~**more than 3 occurrences of rescue therapy**) or due to an AE	
• Synopsis • Section 4.3.1. Inclusion Criteria	5. Mean platelet count of <30×10⁹/L ~~(and no single platelet count of >35×10⁹/L)~~ from **2**~~3 qualifying~~ counts**: 1 platelet count collected**~~,~~ 2 during the screening period and the predose platelet count ~~at~~**on the day of randomization (**visit 1**)**. ~~The 3 platelet counts must be over the course of 7 to 14 days, with at least 2 days between any 2 counts.~~	To allow more flexibility.
• Synopsis • Section 4.3.1. Inclusion Criteria	7. Women of childbearing potential (see DEFINITION OF TERMS) must have a negative serum pregnancy test at the screening visit and a negative urine pregnancy test at baseline before trial medication (infusion) can be administered. Women are considered of childbearing potential unless they are postmenopausal (defined by continuous amenorrhea) for at least 1 year with a follicle-stimulating hormone (FSH) of >40 IU/L or are surgically sterilized (ie, women who had a hysterectomy, **a bilateral salpingectomy,** both ovaries surgically removed, or have a documented permanent female sterilization procedure including tubal ligation). Follicle-stimulating hormone can be used to confirm postmenopausal status in amenorrheic patients ~~not~~ on hormonal replacement therapy.	Clarification

Section(s)	Change	Rationale
	8. Women of childbearing potential should use a highly effective **or acceptable** method of contraception ~~(ie, pregnancy rate of less than 1% per year)~~ during the trial and for 90 days after the last administration of the IMP. They must be on a stable regimen, for at least 1 month: … • **male or female condom with or without spermicide** • **cap, diaphragm, or sponge with spermicide.**	As per results of reproductive toxicology studies.
	9. Non-sterilized male patients who are sexually active with a female partner of childbearing potential must use **an acceptable method of** ~~effective double~~ contraception, **ie,** ~~being~~ a condom ~~for male patients and a highly effective form of contraception for the female partner of childbearing potential (same as for female patients described in inclusion criterion 8)~~. Male patients practicing true sexual abstinence (when this is in line with the preferred and usual lifestyle of the participant) can be included. Sterilized male patients who have had **a** vasectomy with documented aspermia post procedure can be included. In addition, male patients are not allowed to donate sperm during this period from signing of ICF, throughout the duration of the trial, and for 90 days after the last administration of IMP.	
• Synopsis	22. Patients who received a **live/**live-attenuated vaccine within 4 weeks before ~~randomization~~ **screening**. The receipt of any inactivated, sub-unit, polysaccharide, or conjugate vaccine at any time **before** ~~prior to~~ **screening**~~randomization~~ is not considered an exclusion criterion.	Correction.
• Section 4.3.2. Exclusion Criteria	22. Patients who received a **live/**live-attenuated vaccine **within**~~less than~~ 4 weeks before screening. The receipt of any inactivated, sub-unit, polysaccharide, or conjugate vaccine at any time **before** ~~prior to~~ screening is not considered an exclusion criterion.	
• Synopsis • Section 4.3.2. Exclusion Criteria	19. Patients who previously participated in a clinical trial with efgartigimod **and have received at least 1 administration of the IMP**.	Clarification.
• Synopsis • Section 8.4.2. Key Secondary Endpoint Analyses Subject to Alpha Control	**The primary endpoint analysis will act as gatekeeper for the testing of the key secondary endpoints. Subject to meeting statistical significance for the primary endpoint,**~~If the primary endpoint is met,~~ the key secondary endpoints will be analyzed using a fixed-sequence testing procedure to maintain the overall type I error rate at 5%. The type I error rate of each individual test will be 5%, but the test will only be conducted if the analysis for all previous endpoints in the pre-defined hierarchy resulted in a p-value <0.05. The order in the testing hierarchy **of the key secondary endpoints** is as follows:	Clarification.

Section(s)	Change	Rationale
	~~1. The proportion of patients with chronic ITP with a sustained platelet count response defined as achieving platelet counts of at least 50×109/L for at least 4 of the 6 visits between week 19 and 24 of the trial (primary endpoint).~~ ~~2.~~**1.** The extent of disease control defined as the number of cumulative weeks over the planned 24-week treatment period with platelet counts of ≥50×10^9/L in the population with chronic ITP. ~~3.~~**2.** The proportion of patients in the overall population (chronic and persistent ITP) with a sustained platelet count response defined as achieving platelet counts of ~~≥at least~~ 50×10^9/L for at least 4 of the 6 visits between ~~visits~~ **week** 19 and **week** 24 of the trial. ~~4.~~**3.** The incidence and severity of the WHO-classified bleeding events **in the overall population**. ~~5.~~**4.** The proportion of patients in the overall population achieving platelet counts of ~~≥at least~~ 50×10^9/L for at least 6 of the 8 visits between week 17 and 24 of the trial.	
• Table 1 Schedule of Assessments • Appendix 4 Possible Adaptations of Trial Protocol During COVID-19 Pandemic	Footnote a: **<u>Screening Period</u>: maximum 14 days**	
	Physical examination: assessment removed at visits 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22; assessment added at visits 5, 9, and 17.	To allow more flexibility.
Table 2 Schedule of Assessments	Urine pregnancy test: assessment removed at visits 2, 3, 4, "performed only on visits with an IMP infusion", and Follow-up 1; assessment added at visits 5, 9, 13, 17, 21, and End-of-Treatment/Early Discontinuation.	

Section(s)	Change	Rationale
• Table 1 Schedule of Assessments	Footnote d: Platelet count is measured locally**. Post-baseline platelet count** ~~and~~ can be performed within 1 day of the next procedure as per **the SoA**~~schedule of assessments~~ (both dosing and non-dosing visits). Eligible patients should have a mean platelet count of $<30\times10^9$/L ~~(and no single platelet count of $>35\times10^9$/L)~~ from **2**~~3 qualifying~~ counts**:**~~, of which 2~~**1 platelet count** during the screening period and the predose platelet count ~~at~~**on the day of randomization (**visit 1**)**. ~~The 3 platelet counts must be over the course of 7 to 14 days, with at least 2 days between any 2 counts. The last platelet count is to be collected on the day of the randomization.~~	To allow more flexibility.
	Footnote e: Patient-reported outcome**s** and QoL assessments need to be performed **preferably** after the platelet count assessment.	
	Footnote 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.	
	Footnote r: Patients will remain at the site for at least ~~1 hour~~**30 minutes** following the end of the infusion for safety monitoring based on the patient's clinical status.	To shorten the visit duration for the patient, based on supporting safety data.
• Section 6.6. Dosing Administration for Each Patient	Patients will be asked to remain at the site for at least ~~1 hour~~**30 minutes** after the end of the infusion as part of routine safety monitoring.	
• Appendix 4. Possible Adaptations of Trial Protocol During COVID-19 Pandemic	IMP Infusions The patient has to be observed for infusion-related reactions by the trained qualified nurse for at least ~~1 hour~~**30 minutes** following the end of the infusion for safety monitoring based on the patient's clinical status.	
• Table 2 Schedule of Assessments	Footnote u: Patients will remain at home (or an alternative convenient location) for at least ~~1 hour~~**30 minutes** following the end of the infusion for safety monitoring based on the patient's clinical status.	

Section(s)	Change	Rationale
• Table 1 Schedule of Assessments	Footnote i: At the screening visit, if the investigator detects 1 or more screening laboratory abnormalities, the result(s) should be confirmed ~~by the central laboratory~~ if still within the screening window.	Correction.
	Footnote j: **Only for women of childbearing potential. To be done at least every 4 weeks.**	Clarification.
• Figure 1	From visit 17 to 25 (ie, EoT): Fixed weekly or q2w dosing **(no dosing at EoT)**	
• Section 1.1. Background Information	Efgartigimod encompasses IgG1 residues D22~~0~~**1**-K447 (EU numbering scheme) and has been modified with …	Correction.
	Prevalence of ITP is estimated at 9.5 per 100 000 adults, and incidence rates have been reported at 3.3 ~~adults~~ per 100 000 **adults**/year~~s~~.	
• Section 1.2. Benefit-Risk Assessment	Safety for use during pregnancy has not been established. Therefore, efgartigimod should not be administered to pregnant or lactating women~~. Reproductive toxicity trials are completed and in reporting phase~~.	Update.
• Section 7.3.1. Adverse Events	Definition of AE: An AE is any untoward medical occurrence in a clinical trial patient**, temporally associated with the use of IMP,** ~~whether or not a pharmaceutical product is administered and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product or IMP,~~ whether or not considered related to the medicinal product or IMP. **Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of IMP, whether or not considered related to the medicinal product or IMP.** **The following events will be collected as AEs:** • **Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the**	Clarification.

Section(s)	Change	Rationale
	medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • **Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.** • **New conditions detected or diagnosed after IMP administration even though it may have been present before the start of the study.** • **Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.** • **Signs, symptoms, or the clinical sequelae of a suspected overdose of either IMP or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.** • **"Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.** **The following events will NOT be collected as AEs:** • **Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.** • **The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition.** • **Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.** • **Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).** • **Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.** ~~An AE can also be a new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), if considered clinically relevant by the investigator.~~	

Section(s)	Change	Rationale
	~~Abnormal laboratory values, or test results, physical examination findings, and other abnormal investigational findings (ie, ECG) should not be reported as AEs unless they are considered clinically significant, eg, require therapy (eg, hematologic abnormality that requires transfusion or hematological stem cell support) or lead to treatment discontinuation.~~ Death is not considered an AE in itself but a (fatal) outcome of an SAE. <u>Definition of SAE</u> An SAE~~, experience or reaction,~~ is **defined as** any untoward medical occurrence ~~(whether considered to be related to the IMP or not)~~ that at any dose: • **R**~~r~~esults in death • **I**~~i~~s life-threatening (the **term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event,** ~~patient is at risk of death at the time of the event; it does not refer to an event,~~ which hypothetically might have caused death if it was more severe) • ~~r~~**R**equires inpatient hospitalization or prolongation of existing hospitalization. **In general, hospitalization signifies that the patient has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event will be considered as serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.**~~However, a planned hospitalization related to the administration of IMP, is not considered an SAE.~~ **Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not collected as an AE.**~~(Hospital admissions and/or surgical operations planned before a trial are not considered SAEs or if the illness or disease, which caused hospitalization, existed before the patient was enrolled in the trial, provided that it did not deteriorate in an unexpected way during the trial. However, the condition for which the surgery is required may be an AE).~~ • **R**~~r~~esults in persistent or significant disability or incapacity	

Section(s)	Change	Rationale
	The term disability means a substantial disruption of a person's ability to conduct normal life functions. **This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.** • **I**~~i~~s a congenital abnormality or birth defect • ~~o~~**O**ther **situations**: **Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that** ~~medically significant events, which do not meet any of the criteria above, but~~ may jeopardize the patient ~~and~~ **or** may require medical or surgical intervention to prevent 1 of the other ~~serious~~ outcomes listed in the **above** definition ~~above~~. Examples of such events **include invasive or malignant cancers, intensive treatment for allergic bronchospasm,**~~are~~ blood dyscrasias ~~(eg, neutropenia or anemia requiring blood transfusion, etc.) or~~**,** convulsions**, or development of intervention dependency or intervention abuse** ~~that do not result in inpatient hospitalization~~. An unexpected AE is any adverse drug event, which is not listed in the reference safety information in the current IB or is not listed at the specificity or intensity that has been observed. Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Each AE is to be evaluated for duration, severity **(using the CTCAE criteria version 5.0)**, seriousness, and causal relationship to the IMP or trial procedures ~~using the CTCAE criteria~~. The action taken with the investigational drug and the outcome of the event must also be recorded. <u>Severity</u> **Note: a semi-colon indicates "or" within the description of the grades.**	

Section(s)	Change	Rationale
• Section 7.3.3. Vital Signs, Physical Examination, and Electrocardiogram	If no IMP is administered, the ECG will be assessed **preferably** after the blood sample for platelet counts has been taken.	To allow more flexibility.
• Section 8.4.3.	~~The mean change from baseline for IPF# and IPF% will be analyzed by means of mixed models for repeated measurements similar to the mean change from platelet count analysis described above.~~	Correction.
• Appendix 2. Administrative Structure	**Home Care Vendor** **Symphony Clinical Research (an ICON company)** **700 Deerpath Drive** **Vernon Hills, IL 60061-1802** **Illinois** **USA**	Administrative update.
	Data Management, Biostatistics~~, Drug Safety Reporting~~, Medical Data Review	Change in safety vendor.
	Drug Safety Reporting **Parexel International** **8 Federal Street** **Billerica, MA 01821** **USA**	
• Appendix 4 Possible Adaptations of Trial Protocol During COVID-19 Pandemic	Testing for COVID-19 Based on **the** exclusion criterion ~~18~~ "Clinical evidence of significant unstable or uncontrolled acute or chronic diseases other than ITP (eg, cardiovascular, pulmonary, hematologic, gastrointestinal, endocrine, hepatic, renal, neurological, malignancy, infectious diseases, uncontrolled diabetes) despite appropriate treatments, which could put the patient at undue risk," patients with ongoing COVID-19 would be excluded from participation in the trial.	Generalization.
	Screening Visit The screening assessments should be performed at the trial site. In case the trial site is closed due to the COVID-19 situation, an alternative convenient location considered appropriate by the investigator and the patient (and confirmed and approved by the sponsor) can be used (eg, an infusion center, local clinic**, patient's home**).	Clarification.

Section(s)	Change	Rationale
• Appendix 4 Possible Adaptations of Trial Protocol During COVID-19 Pandemic	Baseline visit The baseline visit should be performed at the trial site. In case the trial site would be closed due to the COVID-19 situation, an alternative convenient location considered appropriate by the investigator and the patient (and confirmed and approved by the sponsor) can be used (eg, an infusion center, local clinic**, patient's home**).	Clarification.
	Possible Home Visits/Home Assessments The investigator will perform the WHO bleeding assessments using a video interview with the patient. ~~The assessments via an audio or video interview will be conducted before the home nurse administers the IMP.~~ This will be mentioned in the source documents as such.	Correction.
• Appendix 4 Possible Adaptations of Trial Protocol During COVID-19 Pandemic Table 2 Schedule of Assessments	Footnote e: Platelet count is measured locally**. Post-baseline platelet count** ~~and~~ can be performed within 1 day of the next procedure as per **the SoA**~~schedule of assessments~~ (both dosing and non-dosing visits). Eligible patients should have a mean platelet count of $<30\times10^9$/L ~~(and no single platelet count of $>35\times10^9$/L)~~ from **2**~~3 qualifying~~ counts**:**~~, of which 2~~**1 platelet count** during the screening period and the predose platelet count ~~at~~**on the day of randomization (**visit 1**)**. ~~The 3 platelet counts must be over the course of 7 to 14 days, with at least 2 days between any 2 counts. The last platelet count is to be collected on the day of the randomization.~~	To allow more flexibility.
	Footnote f: Patient-reported outcome**s** and QoL assessments need to be performed **preferably** after the platelet count assessment.	
	Footnote g: **Weight can be measured, together with the platelet count, within 1 day before the next procedure.**	
	Footnote i: 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.	

Section(s)	Change	Rationale
• Appendix 4 Possible Adaptations of Trial Protocol During COVID-19 Pandemic Table 2 Schedule of Assessments	Footnote k: At the screening visit, if the investigator detects 1 or more screening laboratory abnormalities, the result(s) should be confirmed ~~by the central laboratory~~ if still within the screening window.	Correction.
	Footnote l: **Only for women of childbearing potential. To be done at least every 4 weeks.**	Clarification.

The major changes from Protocol Version 3.0 compared to Protocol Version 4.0 are summarized below.

A strikethrough font is used to indicate deleted text and a bold font to indicate added text. Minor administrative editorial changes are not summarized in the following table:

Summary of Changes Between Protocol Version 3.0 and Protocol Version 4.0

Section(s)	Change	Rationale
• Overall	"biweekly" has been replaced with "q2w."	Clarification.
	"Eltrombopag" has been replaced with "oral TPO-RA."	To consider all oral TPO-RAs.
• Synopsis	Secondary Objectives: To evaluate the safety and tolerability of efgartigimod administered intravenously (IV) weekly or ~~biweekly~~ **every other week (q2w)**.	Clarification.
• Synopsis • Section 2.1. Primary Objective	To evaluate the efficacy of efgartigimod compared to placebo in achieving a sustained platelet count response in patients with chronic primary immune thrombocytopenia (ITP), with a sustained platelet count response defined as platelet counts of at least 50×10^9/L for at least 4 of the 6 visits between week 19 and 24 of the trial.* *** "week" instead of "visits" are used in the endpoints, ensuring that the platelet count of the End-of-Treatment visit is regarded as week 24 platelet count (eg, platelet count of week 19 corresponds with platelet count of visit 20).**	To take into account the effect of the full 24-week treatment period for the efficacy evaluation.
• Synopsis • **Section 2.3. Exploratory Objective** • **Section 3.3. Exploratory Endpoint**	The following exploratory objective and endpoint was added: Objective: [redacted] Endpoint: [redacted]	To investigate whether (1) efgartigimod can [redacted] and (2) if [redacted]

Section(s)	Change	Rationale
• Synopsis • Section 3.2. Secondary Endpoints • Section 8.4.2. Key Secondary Endpoint Analyses Subject to Alpha Control	Incidence and severity of the WHO-classified bleeding events **in the overall population**.	Clarification.
• Synopsis • Section 4.1. Summary of Trial Design • Section 4.3. Selection of Trial Population	Approximately 117 patients with chronic ITP and up to 39 patients with persistent ITP will be randomized. Recruitment will end as from 117 patients with chronic ITP have been ~~included~~**randomized**.	Correction.
• Synopsis • Section 4.1. Summary of Trial Design • Section 6.8.4. Rescue Therapy	Rescue therapy is allowed post-baseline during the 24-week ~~treatment~~ **trial** period for patients with a platelet count of <30×10⁹/L and 1 of the following:	For consistency.
• Synopsis • Section 4.1. Summary of Trial Design • Section 5.4.1. Screening and Treatment	**Post-baseline p**~~P~~platelet count **can be performed**~~will be assessed~~ **within 1 day of the next procedure as per schedule of assessments (both dosing and non-dosing visits)** ~~at the start of each visit before the administration of the IV infusion~~, allowing the results to be incorporated into the criteria above.	To allow more flexibility.
	Continued weekly dosing for patients requiring rescue therapy~~, unless deemed medically inappropriate by the investigator~~.	Covered already in the protocol by the provision that the administration of IMP may be temporary withheld if, in the opinion of the investigator, it could put the patient at undue risk.
• Synopsis • Section 4.1. Summary of Trial Design • Section 6.8.1. Concurrent ITP Therapy	Permitted concurrent ITP medications include oral corticosteroids, oral immunosuppressants, dapsone/danazol, **fostamatinib**, and/or ~~eltrombopag~~ **oral thrombopoietin receptor agonists** (**TPO-RAs;** inclusion criterion n°6, Section 4.3.1). ~~The only e~~**E**xceptions are patients who are receiving concurrent treatment with ~~the thrombopoietin receptor agonist~~ **oral** ~~(~~TPO-RAs~~) eltrombopag~~ in whom dose ~~reduction~~ **changes are** ~~of eltrombopag is~~ permitted at label-defined platelet thresholds ~~(see SAFETY section)~~**, and patients who are receiving concurrent treatment with fostamatinib, in whom dose changes or stopping of treatment is allowed in label-defined conditions**.	To consider all oral TPO-RAs. Fostamatinib has been added upon request of the US sites. Specifying that fostamatinib has label-specific dosing changes to be taken into account.

Section(s)	Change	Rationale
• Synopsis • Section 4.1. Summary of Trial Design • Section 6.8.4. Rescue Therapy	Patients who were receiving ~~biweekly~~ **q2w** dosing at the time of rescue therapy will have the IMP administration frequency increased to weekly.~~, unless deemed medically inappropriate by the investigator.~~	Covered already in the protocol by the provision that the administration of IMP may be temporary withheld if, in the opinion of the investigator, it could put the patient at undue risk.
• Synopsis • Section 4.1. Summary of Trial Design • Section 5.4. Treatment Period	~~If the platelet count is >250×10^9/L in a patient receiving eltrombopag, the dose of eltrombopag should be reduced in line with clinical practice recommendations.~~	"Eltrombopag" has been replaced with "oral TPO-RAs" and Section 6.8.1. Concurrent ITP Therapy describes that the dose needs to be adjusted at label-specific thresholds, which makes this statement redundant.
• Synopsis	Planned Number of Sites: Approximately ~~95~~ **125** sites	Update based on current site selection.
• Synopsis • Section 4.3.1. Inclusion Criteria	3. Confirmed ITP diagnosis, at least 3 months before randomization and according to the American Society of Hematology Criteria ~~2011~~, and no known other etiology for thrombocytopenia.	Removed the year of release of the American Society of Hematology Criteria and updated the references with the most recent publication on the American Society of Hematology Criteria
• Synopsis • Section 4.3.1. Inclusion Criteria • Section 4.1. Summary of Trial Design • Section 6.8.1. Concurrent ITP Therapy	Permitted concurrent ITP medications include oral corticosteroids, oral immunosuppressants, dapsone/danazol, **fostamatinib,** and/or oral **TPO-RAs**~~eltrombopag~~.	Regulatory approval of fostamatinib as ITP therapy.
• Synopsis • Section 4.3.2. Exclusion Criteria	1. ITP/thrombocytopenia associated with another condition, eg, lymphoma, chronic lymphocytic leukemia, viral infection, ~~autoimmune disorders, thyroid disease, human immunodeficiency virus (HIV),~~ hepatitis, induced or alloimmune thrombocytopenia, or thrombocytopenia associated with myeloid dysplasia.	Correction.
	History of any **major** thrombotic or embolic event **(eg, myocardial infarction, stroke, pulmonary embolism, deep venous thrombosis)** within 12 months prior to randomization.	

Section(s)	Change	Rationale
• Synopsis • Section 4.3.2. Exclusion Criteria • Section 6.8.2. Prohibited Medication and Therapy prior to Randomization	Use of ~~IV~~Ig~~,~~ **(IV,** subcutaneous**,** or intramuscular route**)~~,~~** or plasmapheresis (PLEX), 4 weeks prior to randomization.	Administrative change.
	~~Use of fostamatinib within 4 weeks prior to randomization.~~	Regulatory approval of fostamatinib as ITP therapy.
• Synopsis • Section 4.3.2. Exclusion Criteria	The following exclusion criterion was added: **Patients who received a live-attenuated vaccine within 4 weeks before randomization. The receipt of any inactivated, sub-unit, polysaccharide, or conjugate vaccine at any time prior to randomization is not considered an exclusion criterion.**	Preventive protection measure for patients.
• Synopsis (Objectives/Criteria for Evaluation/ Statistical Methods and Plan) • Section 2.1. Primary Objective • Section 3.1. Primary Endpoint • Section 3.2. Secondary Endpoints • Section 4.2. Discussion of Trial Design • Section 8.4.1. Primary Endpoint Analysis • Section 8.4.2. Key Secondary Endpoint Analyses Subject to Alpha Control	"visit" has been replaced with "week."	To take into account the effect of the full 24-week treatment period for the efficacy evaluation.
• Synopsis • Section 3.2. Secondary Endpoints	Pharmacokinetic parameters of efgartigimod: **maximum observed serum concentration (C_{max}) and serum concentration observed predose (C_{trough})**.	Clarification.
• Synopsis • Section 5.4. Treatment Period	The End-of-Treatment/Early Discontinuation visit should be completed for all patients, whether they roll-over to the open-label extension trial (ARGX-113-1803), discontinue the trial early, or complete the 24-week ~~treatment~~ **trial** period.	For consistency.

Section(s)	Change	Rationale
• Synopsis • Section 8.4.2. Key Secondary Endpoint Analysis Subject to Alpha Control	Key Secondary Endpoints Subject to Alpha Control **Extent of disease control is defined as the number of cumulative weeks over the planned 24-week treatment period with platelet counts of ≥50×10^9/L. For each patient this number will be calculated by counting the number of analysis visits from week 1 until week 24 (End-of-Treatment visit) at which the platelet count level is ≥50×10^9/L. A Wilcoxon-Mann-Whitney test stratified by receiving concurrent ITP therapies at baseline (yes versus no) and history of splenectomy (yes versus no) will be used to compare the extent of disease control between both treatment groups. The 2-sided p-value resulting from this hypothesis test will inform on whether the null hypothesis that the distributions of number of cumulative weeks for both treatment groups are identical can be rejected. The test will be conducted at a significance level α=0.05. An estimate of the location shift will be provided, along with the associated 95% confidence interval.** ~~Extent of disease control defined as the number of cumulative weeks over the planned 24-week treatment period with platelet counts of ≥50×10^9/L, will be analyzed using Cox regression methodology. The 2 treatment groups will be compared using a Cox proportional hazards regression model with fixed effect terms for randomized treatment and baseline platelet level. The model will be stratified by history of splenectomy (yes vs. no) and receiving concurrent ITP therapies at baseline (yes vs. no), at randomization. A Wald test will be used to test the null hypothesis that the log of the hazard ratio on placebo and efgartigimod is equal to zero (or, equivalently, that the hazard ratio is equal to one) against the alternative that it is different from zero (or, equivalently, that the hazard ratio is different from one). From the model, the hazard ratio for efgartigimod vs. placebo will be provided, along with the associated 95% 2-sided Wald-type CI and 2-sided p-value. The hazard ratio will estimate the relative probability of disease control with efgartigimod as compared to placebo. The data will also be displayed using Kaplan-Meier curves and the median length of disease control will be displayed by randomized treatment arm.~~	To allow patients who are in disease control during much of the trial, but lose it near the end, to contribute more to the final estimate for length of disease control. In the original time-to-event analysis these patients would be censored at the time when they lose the response. The time-to-event analysis is still planned as complementary analysis.

Section(s)	Change	Rationale
• Synopsis Section 8.4.3. Other Secondary Endpoint Analyses Not Subject to Alpha Control	Other Secondary Endpoints Not Subject to Alpha Control … The number of cumulative weeks over the planned 24-week treatment period with platelet counts of $\geq 30\times10^9$/L and at least 20×10^9/L above baseline will be analyzed ~~via the same Cox regression methodology~~**in the same way** as described for the key secondary endpoint "e~~E~~xtent of disease control." Assessment of number of cumulative weeks over the planned 24-week treatment period with platelet counts of $\geq 30\times10^9$/L and at least 20×10^9/L above baseline within the group of patients with a baseline platelet count of $<15\times10^9$/L will also be analyzed ~~via the same Cox regression methodology~~ as described for the key secondary endpoint.	Administrative change.
• Synopsis • Section 8.4.4. Pharmacodynamics, Pharmacokinetics, and Immunogenicity	Pharmacodynamics, Pharmacokinetics, and Immunogenicity Descriptive statistics will be provided for PD parameters (total IgG and subtypes, and antiplatelet antibodies) and ADA. Efgartigimod serum concentration data will be summarized ~~and PK parameters will be calculated with standard non-compartmental methods~~.	In this study, PK samples will be collected within 2 hours prior to the start of the IMP infusion (representing trough concentration) and within 30 minutes after the end of IMP infusion (representing peak concentration). With the limited PK sampling, derivation of PK parameters by non-compartmental methods becomes less appropriate. Therefore, efgartigimod serum concentration data will only be summarized.
• Synopsis • **Section 8.4.6. Exploratory Endpoint Analysis**	**Exploratory Endpoint/Analysis** **Descriptive statistics will be presented for [redacted]. The analysis of [redacted] will be performed at a later stage than the analyses of the other endpoints and will be described in a separate report.**	To investigate whether (1) efgartigimod [redacted] and (2) if [redacted]
• Table 1 Schedule of Assessments	Table footnote n The assessment [redacted] has been added at baseline, visit 2, visit 5, and visit 13, as well as a respective footnote "[n] [redacted]"	

Section(s)	Change	Rationale
• Table 1 Schedule of Assessments	Table footnote a **IV Treatment Period**: Weekly IV IMP administrations for visit 1 up to and including visit 4 ~~(consecutive administrations should be at least 7 days apart)~~. As of visits 5 to 16, a weekly or ~~biweekly~~ **q2w** schedule will be followed ~~(consecutive administrations should be at least 7 or 14 days apart, respectively)~~. 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 ~~biweekly~~**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 ~~biweekly~~**q2w**) of IMP infusions depends on pre-defined 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** ~~7 days~~ (+2 days) ~~after visit 24~~ 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]).**	Correction.
	Assessment "Platelet count[d]" **Can be performed within 1 day of the next assessment** Table footnote d: Platelet count **is measured locally and can** ~~should~~ be performed ~~locally~~ within **1 day of the next procedure as per schedule of assessments** ~~at the start of each visit~~ (both dosing and non-dosing visits) ~~to facilitate quick turnaround time. For a single patient, the platelet count needs to be performed at the same facility throughout the study~~. Eligible patients should have a mean platelet count of $<30\times10^9$/L (and no single platelet count of $>35\times10^9$/L) from 3 qualifying counts, of which 2 during the screening period and the predose platelet count at visit 1. The 3 platelet counts must be over the course of 7 to 14 days, with at least 2 days between any 2 counts. **The last platelet count is to be collected on the day of the randomization.** In addition, the absolute [redacted] and the [redacted] ill be measured locally in **facilities** ~~sites~~ equipped with a hematology analyzer which can determine this [redacted].	To allow more flexibility.
	Table footnote e: Patient-reported outcome and QoL assessments need to be performed after the platelet count assessment~~, before any other assessments at the visit~~.	Correction.

Section(s)	Change	Rationale
• Table 1 Schedule of Assessments	Table footnote k has been added to the assessment "Pharmacodynamics": **In order to maintain the blind, the IgG testing cannot be performed locally.**	To avoid unintentional unblinding.
• List of Abbreviations	**q2w biweekly/every other week**	Administrative change.
• Definition of Terms	Blinding: … In a double-blind trial, the patient, the investigator, **site staff,** and sponsor staff who are involved in the treatment or clinical evaluation of the patients and the review or analysis of data are all unaware of the treatment assignment.	Administrative change.
• Section 1.2. Benefit-Risk Assessment	More specifically, a phase 2 trial (ARGX-113-1603) in patients with ITP enrolled a patient population who was predominantly refractory to previous lines of ITP therapy, with the majority of patients having long-standing disease, prior ITP treatment exposure and approximately half with baseline platelet count of $<15\times10^9$/L. ~~Thirty-seven out of 38 patients (97.4%) had a history of receiving at least 1 ITP therapy, either historical or ongoing at baseline. The median number of prior unique treatments for ITP was 2.0 (range 0-10). Twenty-seven out of 38 patients (71.1%) were receiving at least 1 concomitant ITP therapy at baseline, including corticosteroids, immunosuppressants, and TPO-RAs.~~ … In clinical trials to date, efgartigimod has been well tolerated in healthy adult subjects and patients with MG and ITP, separately: the majority of treatment-emergent AEs (TEAEs) were considered to be mild (grade 1) in severity. In the **completed phase 1 trials ARGX-113-1501, ARGX-113-1702, and ARGX-113-1901 in healthy volunteers, and in the** phase 2 trial ARGX-113-1602 in **patients with** MG, no grade ≥3 TEAEs were reported and no TEAE led to discontinuation. In **the phase 2 trial ARGX-113-1603 in patients with** ITP, 1 TEAE with grade 4 was reported (thrombocytopenia), considered unrelated to treatment, and led to treatment discontinuation. ~~In the MG trial ARGX-113-1602, the most common TEAE was headache, reported in 4 of 12 patients (33%) treated with efgartigimod 10 mg/kg and 3 of 12 patients (25%) who received placebo. In the ITP trial ARGX-113-1603, headache was reported in 1 of 13 patients (7.7%) treated with efgartigimod 5 mg/kg and 2 of 12 patients (16.7%) who received placebo. In the ITP trial, the most common TEAEs were petechiae 2 of 13 patients (15.4%) in the 5 mg/kg group and 2 of 13 patients (15.4%) in the efgartigimod 10 mg/kg groups, hypertension in 2 of 13 patients (15.4%) treated with efgartigimod 10 mg/kg and 1~~	To refer to the latest version of the Investigator's Brochure to ensure the latest information is available.

Section(s)	Change	Rationale
	~~of 12 patients (8.3%) with placebo, and vomiting in 2 of 13 patients (15.4%) treated with efgartigimod 10 mg/kg.~~ ~~No deaths have occurred in any efgartigimod trial as of data cut-off date. There is no evidence of an increased risk of infection.~~ ~~The only clinically relevant laboratory findings, observed after repeated administration of efgartigimod 10 mg/kg, were decreased monocyte count (reported for 1 patient with MG) and abnormal differential white blood cell count in individual healthy volunteers after administration of a single dose of 25 and 50 mg/kg efgartigimod, which was associated with decreased CD8, CD3, CD56, CD4, and CD19 lymphocyte levels. All events were short-lasting and resolved within 2 to 4 days. An increase in C-reactive protein was reported in individual healthy volunteers administered 25 and 50 mg/kg efgartigimod. All events resolved within 3 to 6 days and were in general not associated with signs of fever or serious infections.~~ ~~In non-clinical toxicology trials repeated administration of 100 mg/kg (15 infusions, every 2 days) efgartigimod was associated with reversible Kupffer cell hypertrophy/hyperplasia in rat, as well as hepatic cytoplasmic alterations and degeneration, and diffuse mixed inflammatory cell infiltrates (correlating with alanine aminotransferase [ALT] increase) in cynomolgus monkey. No such observations were made in a 6-month chronic dosing trial where cynomolgus monkeys were treated with 100 mg/kg efgartigimod once every week. In healthy volunteers, patients with MG, or with ITP, no clinically significant changes were observed in liver enzyme levels (including ALT and aspartate aminotransferase), serum lipids, or electrolytes (including potassium).~~ No clinically significant changes in vital signs and/or electrocardiogram (ECG) findings have been observed in clinical trials to date. Safety for use during pregnancy has not been established. Therefore, efgartigimod should not be administered to pregnant or lactating women. ~~No fertility trials have been performed so far~~ **Reproductive toxicity trials are completed and in reporting phase.** ~~In summary, taking into account the efficacy and safety data collected up to date, the benefit risk assessment allows further testing of efgartigimod.~~ **Please refer to the current Investigator's Brochure for more information regarding the preclinical and clinical trials, and the potential risks and benefits of efgartigimod. In summary, the favorable balance between risks and anticipated efficacy/benefits supports the use of efgartigimod in clinical development.**	

Section(s)	Change	Rationale
• Section 1.3. Trial Rationale	The aim is to achieve the maximum possible proportion of patients with a platelet count improvement and then assess whether this can be sustained in the last 5 weeks ~~(visits 19 to 24)~~ of trial treatment.	Correction.
• Section 4.2. Discussion of Trial Design	The ~~chosen~~ primary endpoint in this trial is the proportion of patients with chronic ITP that have a sustained platelet count response …	Administrative change.
• Section 4.4.1. Early Discontinuation from Trial	~~the IMP treatment code is broken~~ **unblinding occurred**	Correction.
• Section 4.7. Screen failures, Rescreening, and Retesting	Patients may be ~~rescreened (ie redoing the full assessments as per SoA, Table 1) or~~ retested once (ie redoing 1 test) if still within the screening period.	
	A patient who has clinical laboratory tests values meeting 1 or more exclusion criteria which are not in line with the medical history and clinical evaluation of the patient, may be retested to confirm the value of the test (to be confirmed by the central laboratory**, except for the platelet count for which 1 retesting can be done at the local laboratory**), if still ~~allowed~~ within the screening period. If not feasible, the patient should be rescreened.	
• Section 5. Trial Procedures	Every effort should be made to schedule every visit on the exact day (which is relative to baseline **randomization** [visit 1]) as described in the SoA (Table 1).	Clarification.
	~~At all visits after screening, t~~**T**he platelet count need~~s~~ to be performed **within 1 day** prior to any other assessment ~~followed by the weight assessment (only on IMP dosing visits)~~.	To allow more flexibility.
• Section 6.2. Identity of Investigational Medicinal Product	The IMP (efgartigimod or placebo) will be supplied to the pharmacy at the investigational site (and stored at a temperature of 2**°C** to 8°C or 35**°F** to 46°F), by and under the responsibility of the sponsor's designated IMP supply vendor~~, who will also provide~~**. For each IMP batch at the site,** the investigator ~~with~~ **will receive** the certificate of analysis, certificate of conformity, and European Union qualified person release documents.	Clarification.
• Section 6.4. Storage of Investigational Medicinal Products	The IMP must be stored refrigerated (2**°C** to 8°C or 35**°F** to 46°F) in its secondary packaging, …	Administrative change.

Section(s)	Change	Rationale
• Section 6.7. Blinding	This is a randomized, double-blinded, placebo-controlled trial with limited access to the IMP treatment assigned (see also DEFINITION OF TERMS). ~~The IMP treatment each patient receives will not be disclosed to the blinded site staff, including the investigator, trial coordinator, patient, sponsor, or sponsor's designee.~~ ~~The storage and preparation of IMP will be at a secured location that is not accessible to blinded investigational staff.~~	Clarification
• Section 6.7.1. Emergency Unblinding	If the blind is broken by the investigator it may be broken only for the patient concerned, and the IMP treatment assignment should not be revealed to the trial team members from the sponsor, nor from the sponsor's designated CRO, ~~or~~ pharmacy personnel**, or other site staff**. Once unblinded, the patient will be discontinued from the trial and will be followed for 4 weeks for ongoing safety and efficacy monitoring. ~~The follow-up period will consist of 2 biweekly visits.~~ The sponsor and monitor at the sponsor's designated CRO must be notified immediately if a patient and/or investigator is unblinded during the course of the trial. Pertinent information regarding the circumstances of unblinding ~~of a patient's IMP treatment code~~ must be documented in the patient's source documents and eCRF. Once unblinded, the patient will be early discontinued from the trial and followed-up for 4 weeks (2 ~~biweekly~~ **q2w** visits).	Correction.
• Section 6.8. Prior Treatments and Concomitant Medications	"TPO" has been replaced with "TPO-RA."	Correction.
• Section 6.8. Prior Treatments and Concomitant Medications • Section 6.8.1. Concurrent ITP Therapy	The sentence "The washout periods as specified in exclusion criteria 2 to 9 must be followed." Has been moved from Section 6.8.1. to Section 6.8.	Clarification.

Section(s)	Change	Rationale
• Section 6.8.2. Prohibited Medications and Therapy prior to Randomization	The following bullet-point was added: **Live/live-attenuated vaccines within 4 weeks prior to screening.**	Preventive protection measure for patients.
• Section 6.8.3. Prohibited Medications and Therapy during the Trial	The following bullet-point was added: **Live/live-attenuated vaccines**	
	~~• Fostamatinib~~	Regulatory approval of fostamatinib as ITP therapy.
• Section 6.13. Storage of Blood Samples in the Trial	**In addition, blood samples may be used to validate methods to measure efgartigimod, antibodies, and biomarkers.**	For consistency with the master ICF version 3.0.
• Section 7.2.1. Platelet Count	The assessment of platelet count ~~should~~ **can** be performed **within 1 day** prior to any other trial-specific assessment ~~procedures as per schedule of assessments~~ (except at screening, where the informed consent should be obtained and weight assessed first) at each visit as specified in the SoA (Table 1). The samples will be analyzed locally. **For a single patient, baseline and post-baseline platelet count assessments needs to be performed at the same facility throughout the trial.** In addition, the absolute [redacted] and the [redacted] related to [redacted] will be measured locally in **facilities** ~~sites~~ equipped with a hematology analyzer which can determine this platelet subset.	To allow more flexibility.
• Section 7.3.1.1. Adverse Events of Special Interest	~~Any bleeding or infection will be considered as AESI.~~ **Due to the nature of underlying disease (ITP), any AE of bleeding will also be treated as an AESI.**	Clarification.
• Section 7.3.1.2. Reporting of Adverse Events and Serious Adverse Events	All SAEs that are spontaneously reported within 30 days after the last trial visit are to be collected and reported ~~as previously described~~**in the safety database,** and all efforts should be made to follow-up until resolution.	This information will not be captured in the clinical database after the last trial-related visit.
• Section 7.3.2. Clinical Laboratory Evaluations	In addition, the [redacted] will be measured locally in the ~~sites~~ **facilities** equipped with a [redacted] which can determine this [redacted]	Correction.
	The estimated total maximum blood volume needed for a patient during the trial (when completing the trial) is approximately **618**~~543~~ mL.	

Section(s)	Change	Rationale
• Section 7.3.3. Vital Signs, Physical Examination, and Electrocardiogram	Supine blood pressure and heart rate will be measured using standard equipment after **at least** 10 minutes rest ~~on a bed~~. … **Clinically significant a~~A~~**bnormalities in physical examination, vital signs, and ECG at screening will be reported as medical history in the eCRF. At all other trial visits, new abnormal or worsened pre-existing conditions **which are clinically significant as judged by the investigator,** will be reported as an AE.	Clarification.
• Section 7.3.4. Medical and Surgical History	… The date of ITP diagnosis as well as the date of confirmation of the diagnosis according to the ASH criteria[13~~11~~] (~~2011~~) will be collected separately.	Removed the year of release of the American Society of Hematology Criteria and updated the references with the most recent publication on the American Society of Hematology Criteria.
• Section 7.5. Pharmacodynamics	Blood samples for the determination of the PD markers (total IgG, IgG subtypes [IgG1, IgG2, IgG3, and IgG4]) will be collected as indicated in the SoA (Table 1). Sampling will be done predose on IMP administration visits. **Samples will be analyzed by the central laboratory. In order to maintain the blind, the IgG testing cannot be performed locally.**	Clarification.
• **Section 7.7.** [redacted]	**The sample to measure the** [redacted] **has to be collected as the last sample predose as indicated in the SoA (Table 1) in sites participating in the** [redacted]. **The actual date and time of collection of the blood sample will be recorded in the relevant section of the eCRF, as well as the reason in case no sample was taken.** **The sample will be used for an exploratory endpoint and will be analyzed in a specialty lab.**	To investigate whether (1) efgartigimod can [redacted].
• Section 7.8. Quality-of-Life and Patient-Reported Outcomes	FACIT-Fatigue Scale: 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 "**~~(4 =~~ not at all**" to 4 "**~~fatigued to 0 =~~ very much.**"** ~~Fatigued)~~	Correction.

Section(s)	Change	Rationale
• Section 8.1. Determinations of Sample Size	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 ~~14~~ **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~~.9~~% (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=~~27~~ **54** patients would be needed, given these assumptions. **Calculations are based on the Wilcoxon-Mann-Whitney test, where the O'Brien-Castelloe approach[14] was taken to compute the power, taking into account a 2:1 allocation ratio to receive efgartigimod versus placebo.**	To allow patients who are in disease control during much of the trial, but lose it near the end, to contribute more to the final estimate for length of disease control. In the original time-to-event analysis these patients would be censored at the time when they lose the response. The time-to-event analysis is still planned as complementary analysis.
• Section 8.4.1. Primary Endpoint Analysis	Handling of missing data Missing data for reason of 1 of the main intercurrent events will be handled as described above. ~~Missing data for other reasons will be imputed by multiple imputation.~~ Details **on handling other missing data** will be provided in the SAP.	Correction.

<table>
<tr><th>Section(s)</th><th>Change</th><th>Rationale</th></tr>
<tr>
<td>• Section 8.4.2. Key Secondary Endpoint Analysis Subject to Alpha Control</td>
<td>
~~The main event and censoring rules are as follows, where event is defined as "loss of disease control":~~
<table>
<tr><th>~~Situation~~</th><th>~~Date of event or censoring~~</th><th>~~Outcome~~</th></tr>
<tr><td>~~No occurrence of platelet count of ≥50×10^9/L throughout 24-week treatment period~~</td><td>~~Date of baseline~~</td><td>~~Event~~</td></tr>
<tr><td>~~Early discontinuation of treatment (prior to W24)~~</td><td>~~Date of treatment discontinuation~~</td><td>~~Event~~</td></tr>
<tr><td>~~Rescue therapy started~~</td><td>~~Date of initiation of rescue therapy~~</td><td>~~Event~~</td></tr>
<tr><td>~~Dose and/or frequency of concurrent ITP therapy increased~~</td><td>~~Start date of increase~~</td><td>~~Event~~</td></tr>
<tr><td>~~Disease control at end of 24-week treatment period~~</td><td>~~Date of last assessment (analysis visit)~~</td><td>~~Censored~~</td></tr>
</table>
~~Missing platelet counts for other reasons than those mentioned in the final event and censoring rules table (as detailed in the SAP) will be imputed by multiple imputation. Sensitivity analyses will be conducted to assess the robustness of the analysis results to the applied imputation method.~~

When 1 of the intercurrent events described in Section 8.4.1 occurs, platelet count levels measured after the occurrence will be censored (or, they will not be taken into account for the calculation of the number of cumulative weeks). In other words, they will be handled as if the platelet count level were <50×10^9/L. Missing platelet counts because of early discontinuation due to lack of efficacy or due to an AE will be handled in the same way.

Sensitivity analyses will be conducted to assess the robustness of the analysis results to the proposed handling of intercurrent events and missing platelet counts.

Furthermore, a complementary analysis will be performed where extent of disease control is handled as a time-to-event endpoint (with "loss of disease control" being the event). Cox proportional hazards regression methodology will be applied for this complementary analysis. Details on the model and the event and censoring scheme for this complementary analysis will be provided in the SAP.

Missing bleeding assessments for reasons of 1 of the main intercurrent events will not be imputed, but the offset term will be adapted accordingly to reflect the assessment period until the occurrence or start of the intercurrent event. ~~Missing bleeding assessment for other reasons will be imputed by multiple imputation.~~
</td>
<td>To allow patients who are in disease control during much of the trial, but lose it near the end, to contribute more to the final estimate for length of disease control. In the original time-to-event analysis these patients would be censored at the time when they lose the response. The time-to-event analysis is still planned as complementary analysis.</td>
</tr>
</table>

Section(s)	Change	Rationale
• Section 12. References	~~Neunert C, Lim W, Crowther M, Cohen A, Solberg L, Crowther MA. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood*. 2011:blood-2010-2008-302984.~~ **Neunert C, Terrell D, Arnold D, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. *Blood Adv.* 2019;3(23):3829-3866.**	Administrative change.
	O'Brien RG, Castelloe JM. Exploiting the Link between the Wilcoxon-Mann-Whitney Test and a Simple Odds Statistic. *Proceedings of the Thirty-First Annual SAS Users Group International Conference.* 2006:209-231.	Citation in new wording in Section 8.1.
• Appendix 1 laboratory Evaluations	Coagulation ~~International normalized ratio (INR),~~ activated partial thromboplastin time (aPTT), prothrombin time (PT **INR**)	Wording updated as per information of the central laboratory
	Urinalysis …, casts**,** crystals, bacteria	Casts and crystals are separate laboratory evaluations
	Other exploratory [redacted]	To investigate whether (1) efgartigimod can [redacted] s and (2) if [redacted]

Section(s)	Change	Rationale
• Appendix 2 Administrative Structure	Central Laboratories **Cerba Research NV** ~~**BARC NV**~~ Industriepark Zwijnaarde 3 B-9052 Gent Belgium	Administrative change.
	Central ECG Reading **ERT Clinical** **Peterborough Business Park** **Lync Wood** **Peterborough** **PE2 6FZ** **United Kingdom**	
	Data Management, Biostatistics, Drug Safety Reporting, Medical **Data** Review	
	[redacted]	To investigate whether (1) efgartigimod can [redacted] and (2) if [redacted]
• **Appendix 4 Possible Adaptations of Trial Protocol During COVID-19 Pandemic**	Addition of COVID-19 appendix.	To allow patients to receive/continue receiving IMP during the COVID-19 pandemic.
• **Appendix 5 Protocol Amendment History**	The protocol amendment history for the previous amendments has been moved to Appendix 5.	Administrative change.

The major change from Protocol Version 2.0 compared to Protocol Version 3.0 is summarized below.

A bold font is used to indicate added text. Minor administrative editorial changes are not summarized in the following table:

Summary of Changes Between Protocol Version 2.0 and Protocol Version 3.0

Section(s)	Change	Rationale
• Section 7.3.1 Adverse Events	A bullet was added to the definition of serious AE: • **other: medically significant events, which do not meet any of the criteria above, but may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the other serious outcomes listed in the definition above. Examples of such events are blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in inpatient hospitalization.**	Alignment of the protocol with ICH E2A guidelines and the categories of seriousness in the SAE form.

The major changes from Protocol Version 1.0 compared to Protocol Version 2.0 are summarized below.

A strikethrough font is used to indicate deleted text and a bold font to indicate added text. Minor administrative changes involving document formatting and renumbering of sections, grammar, syntax, punctuation, updating of the list of abbreviations, updating abbreviations in the body of the document, updating of cited references, and other editorial changes are not summarized in the following table:

Summary of Changes Between Protocol Version 1.0 and Protocol Version 2.0

Section(s)	Change	Rationale
SIGNATURE OF SPONSOR	**Version 2.0**: [redacted]	Change in the individual fulfilling the role of Chief Medical Officer
• Synopsis • Section 4.1 Summary of Trial Design	The total maximum trial duration per patient is up to ~~30~~ **31** weeks: - Up to 2 weeks of screening - 24 weeks treatment period - **End-of-Treatment visit 1 week after visit 24** - 4 weeks of follow-up	Clarified timing of the end-of-treatment visit and updated the total trial duration accordingly.
Synopsis	**The number of planned sites changed** **Version 2.0:** approximately ~~80~~ **95** sites	As a result from the trial feasibility assessment, the number of sites will be increased.
	Version 2.0: Planned Countries: **This trial is a global, multicenter trial** ~~United States, Europe, and Japan (European countries to be determined) (this list is not exhaustive)~~	

Section(s)	Change	Rationale
• Synopsis • Section 1.3 Trial Rationale • Section 4.1 Summary of Trial Design • Section 4.3.1 Inclusion Criteria • Section 8.4.1 Primary Endpoint Analysis	**Eligibility criteria changed from 1 prior therapy to 2 prior therapies:** **Version 2.0: At the start of the trial, the patient is either on concurrent ITP treatment(s) and has received** ~~Patients have previously received at least 1 typical ITP therapy~~**at least 1 prior therapy for ITP in the past, or the patient is not on treatment for ITP but has received at least 2 prior treatments for ITP** ~~and are continuing at least 1 concurrent therapy while on the study~~. Patients receiving permitted concurrent ITP treatment**(**s**)** at baseline, must have been stable in dose and frequency for at least 4 weeks prior to randomization. (The following sentence was also deleted in Section 1.3 Trial Rationale: The trial requires patients to have had previous exposure to an ITP treatment.)	Change in eligibility criteria implemented at the request of the FDA.
• Synopsis • Section 4.3.1 Inclusion Criteria	**Version 2.0:** Non-sterilized male patients who are sexually active with a female partner of childbearing potential must use effective double contraception, ~~of which 1 method must be a barrier method and the other another barrier method or~~ **being a condom for male patients and a** highly effective form of contraception ~~as described above~~ for **the female partner** ~~women~~ of childbearing potential **(same as for female patients described in inclusion criterion 8)** ~~(eg, condom with spermicidal cream or jelly, 1 hormonal plus 1 barrier method, IUD plus 1 barrier method, or 2 simultaneous barrier methods)~~. Male patients practicing true sexual abstinence (when this is in line with the preferred and usual lifestyle of the participant) can be included. Sterilized male patients who have had vasectomy with documented aspermia post procedure can be included. In addition, male patients are not allowed to donate sperm during this period from signing of ICF, throughout the duration of the trial, and for 90 days after the last administration of IMP.	To align with the CTFG recommendations.

Section(s)	Change	Rationale
• Synopsis • Schedule of Assessments • Section 4.3.1 Inclusion Criteria	**Removed Inclusion Criterion 3**: For Japanese patients enrolled in sites in Japan only: A Japanese patient is defined as a patient 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.	A separate region-specific protocol amendment for Japan will be prepared.
• Synopsis • Section 4.1 Summary of Trial Design	**Version 2.0:** ~~Non-Japanese patients with chronic ITP will be stratified according to the following factors:~~ **Patients will be stratified according to the following factors:** • History of splenectomy (yes vs. no) • Receiving concurrent ITP therapies at baseline (yes vs. no) ~~For Japanese patients enrolled in sites in Japan (inclusion criterion n°3), there will be no stratification ie, randomization will be performed within the full set of Japanese patients. For non-Japanese patients with persistent ITP, there will also be no stratification.~~	
• Synopsis • Section 4.3.1 Inclusion Criteria	**Version 2.0:** Male or female patient aged ≥18 years ~~(for Japan only, patients aged ≥20 years)~~.	
• Synopsis • Schedule of Assessments • Section 4.3.2 Exclusion Criteria	**Removed Exclusion Criterion 12**: For patients enrolled in sites in Japan only: positive Helicobacter pylori test at the screening visit.	

Section(s)	Change	Rationale
• Synopsis • Definition of Terms • Section 4.3.1 Inclusion Criteria	**Removed that the FSH value must be within the postmenopausal range per the laboratory.** **Version 2.0:** Women of childbearing potential (see DEFINITION OF TERMS) must have a negative serum pregnancy test at the screening visit and a negative urine pregnancy test at baseline **before ~~study~~ trial medication ~~prior to~~ (**infusion**) can be administered**. Women **are considered** of childbearing potential ~~are defined as all female patients~~ unless they are postmenopausal (defined by continuous amenorrhea) for at least 1 year with a follicle-stimulating hormone (FSH) of >40 IU/L or are surgically steril**ize**d (ie, women who had a hysterectomy, both ovaries surgically removed, or have **a** documented ~~tubal ligation or any other documented~~ permanent female sterilization procedure **including tubal ligation**). Follicle-stimulating hormone can be used to confirm postmenopausal status in amenorrheic patients not on hormonal replacement therapy ~~if the value is within the postmenopausal range per the laboratory~~.	FSH testing is done at the central lab and an FSH of >40 IU/L will be considered for assessing postmenopausal status.

Section(s)	Change	Rationale
• Synopsis • Section 4.3.1 Inclusion Criteria	**Version 2.0:** Women of childbearing potential should use a highly effective method of contraception (ie, pregnancy rate of less than 1% per year) during the trial and for 90 days after the last administration of the IMP. They must be on a stable regimen, for at least 1 month, of**:** • combined **(**estrogen and progestogen **containing)** hormonal contraception **associated** with inhibition of ovulation**:** o **oral** o **intravaginal** o **transdermal** • progestogen-only hormonal contraception associated with inhibition of ovulation o **oral** o **injectable** o **implantable** • intrauterine device (IUD) • intrauterine hormone-releasing system • bilateral tubal occlusion • vasectomized partner **(provided that the partner is the sole sexual partner of the trial participant and documented aspermia post procedure)** • ~~, or agree upon~~ continuous abstinence from heterosexual sexual contact. Sexual abstinence is only allowable if it is the preferred and usual lifestyle of the patient. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is not acceptable.	Clarification on the need to have a highly effective method of contraception and clarifying the highly effective methods of contraception.
• Section 4.4.1 Early Discontinuation from Trial	**Version 2.0**: Early discontinuation from the trial is defined as the permanent cessation of further participation in the trial prior to its planned completion **and without the possibility to roll-over to the open-label extension trial (ARGX-113-1803)**. ~~Any patient prematurely discontinuing the trial should perform the assessments listed for the Early Discontinuation visit as specified in the SoA (Table 1).~~	Definition for early discontinuation clarified.

Section(s)	Change	Rationale
• Section 4.4.1 Early Discontinuation from Trial	**Version 2.0:** **The reason for early discontinuation from the trial will be clearly documented by the investigator.** - Patients must be discontinued early from the trial and complete the Early Discontinuation visit **as specified in the SoA (Table 1)** if: • they withdraw their consent • ~~in the patient's best interest, discussion with the sponsor's medical director is encouraged prior to discontinuation~~ • ~~the IMP treatment code is unblinded~~ All patients are free to withdraw consent from participation in the trial at any time, for any reason, specified or unspecified, and without prejudice to further treatment. Prior to actual withdrawal of consent, an effort should be made to perform a final set of assessments as per Early Discontinuation visit ~~in the SoA (Table 1)~~. Investigators will make and document all efforts made to contact those patients who do not return for scheduled visits. ~~The reason for early discontinuation from the trial will be clearly documented by the investigator.~~ ~~Patients who discontinue the current trial early and do not wish to roll-over into the ARGX-113-1803 trial, will perform all the assessments listed for the Early Discontinuation visit as mentioned in the SoA (Table 1). These patients will be followed-up for 4 weeks (2 biweekly visits) for ongoing safety and efficacy monitoring.~~ ~~Patients who complete the current trial treatment but who do not wish to roll-over into the ARGX-113-1803 trial will be followed-up for 4 weeks (2 biweekly visits) for ongoing safety and efficacy monitoring.~~ - **Patients must be discontinued early from the trial, complete the Early Discontinuation visit as specified in the SoA (Table 1), and have to be followed-up for 4 weeks (2 biweekly visits) for ongoing safety and efficacy monitoring if:** • **it is in the patient's best interest, discussion with the sponsor's medical director is encouraged prior to discontinuation** • **the IMP treatment code is broken** • **prohibited medication is taken (see Section 6.8.1)** • **a severe hypersensitivity reaction to IMP occurs** • **the patient became pregnant**	Differentiate the reasons for early discontinuation from trial, move the prohibited medications and pregnancy from "early discontinuation from treatment" to "early discontinuation from trial", and add hypersensitivity reaction as a new bullet at the request of the FDA (stopping rule for immunogenicity).

Section(s)	Change	Rationale
• Section 4.4.2 Early Discontinuation from Treatment	**Version 2.0:** These patients will ~~complete all the procedures listed for the Early Discontinuation visit as mentioned~~ **continue the weekly trial visits as specified** in **the** SoA (Table 1) **without IMP-related assessments.** ~~If a patient discontinues trial treatment early, he/she will enter a 4-week follow-up period (2 biweekly visits).~~ Patients must be discontinued early from treatment in the following circumstances: ~~• pregnancy~~ • on the request of the sponsor (eg, following data safety monitoring board [DSMB] advice, see Section 7.3.5) ~~• prohibited medication is taken (see Section 6.8.1)~~ • patient has missed more than 2 consecutive **scheduled** doses of IMP treatment • **patient has received rescue therapy more than 3 times** ~~The administration of IMP may be withheld if, in the opinion of the investigator, it could put the patient at undue risk or confound the results of the trial, in the following circumstances:~~ ~~• clinical evidence of bacterial, viral, or fungal disease~~ ~~• other significant disease~~ ~~Rescue therapy (pulse steroids, IVIg, anti-D, or platelet transfusions) may be administered during the 24-week trial treatment period.~~ **Patients who complete the 24-week trial period but who do not enter the open-label extension trial ARGX-113-1803, or patients who discontinue the trial early, with the exception of patients who withdraw their consent, will be followed for 4 weeks for ongoing safety and efficacy monitoring.**	Differentiate the reasons for early discontinuation from trial, move the prohibited medications and pregnancy from "early discontinuation from treatment" to "early discontinuation from trial", and add hypersensitivity reaction as a new bullet at the request of the FDA (stopping rule for immunogenicity).

Section(s)	Change	Rationale
• Synopsis • New Section 4.5 Temporary Withholding Treatment • Section 5.4 Treatment Period	**Individual stopping rules, reasons for early discontinuation from treatment and for temporary withholding treatment have been added or clarified.** **Version 2.0:** - The administration of IMP may be **temporary** withheld if, in the opinion of the investigator, it could put the patient at undue risk ~~or confound the results of the trial,~~ in the following circumstances: • ~~clinical evidence of bacterial, viral, or fungal disease~~ • ~~other~~ **clinically** significant disease, **including evidence of infection** • **severe bleeding, grade 3 or 4 on the WHO bleeding scale, requiring urgent medical and/or surgical intervention** • **thrombosis** If the IMP is being withheld, it **can** ~~should~~ be reintroduced once the investigator considers the undue risk to the patient~~or trial~~ has passed. ~~However, if a patient misses more than 2 consecutive doses, he/she will be discontinued early from further IMP treatment, and will enter the 4-week follow-up period according to the SoA (Table 1) without the possibility to roll-over to the open-label extension trial (ARGX-113-1803).~~ - **The administration of IMP must be temporary withheld from patients with platelet counts greater than 400×10^9/L, IMP should be resumed at the 10 mg/kg every other week dose when the platelet count falls to fewer than 150×10^9/L.**	Text added at the request of the FDA.
• Synopsis • Section 4.1 Summary of Trial Design • New Section 4.5 Temporary Withholding Treatment • Section 5.4.1 Screening and Treatment	**Version 2.0:** • **Temporary withholding treatment:** ○ **for reasons described in Section 4.5, IMP should be reintroduced once the investigator considers the undue risk to the patient~~or trial~~ has passed** ○ **in patients with platelet counts greater than 400×10^9/L, IMP should be resumed at the 10 mg/kg every other week dose when the platelet count falls to fewer than 150×10^9/L**	Individual rules for temporary withholding treatment have been added at the request of the FDA.
• Section 5.3 Randomization	**Version 2.0:** If a patient meets all the eligibility criteria and after approval from the sponsor, he/she will be ~~stratified~~ **randomized** via IRT.	Correction

Section(s)	Change	Rationale
• Synopsis • Table 1 Schedule of Assessments • Section 5.4.1 Screening and Treatment • Section 6.1 Treatment Administered	**Version 2.0**: From visits 17 to 24, the dosing frequency is fixed for each individual patient (ie, either weekly or biweekly regimen), based on the regimen the patient was receiving at visit 16 **or at the last visit at which IMP was administered.**	Clarification on the visit used as reference for the fixed dosing period and of the exceptions to the fixed dosing frequency.
• Section 4.1 Summary of Trial Design • Section 5 Trial Procedures • Section 6.4 Treatment Administered	**Version 2.0:** 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 biweekly)**. Assessment of the dosing regimen as described in Section 5.4.1 will be applied.**	
• Synopsis • Section 4.1 Summary of Trial Design • Section 5.4.1 Screening and Treatment	**Version 2.0:** From visits 17 to 24, the dosing frequency is fixed for each individual patient (ie, either the weekly or biweekly regimen), based on the regimen the patient was receiving at visit 16 **or at the last visit at which IMP was administered. Exceptions to the fixed dosing frequency are**: • **Continued weekly dosing for patients requiring rescue therapy unless deemed medically inappropriate by the investigator.** • **Continued biweekly dosing for patients resuming IMP when the platelet count falls to fewer than 150×10^9/L after having had platelet counts greater than 400×10^9/L.**	
• Synopsis • Section 4.1 Summary of Trial Design • 6.8.4 Rescue Therapy	**Version 2.0:** Patients requiring rescue therapy ~~beyond visit 12 will be considered non-responders for the primary endpoint analysis~~ **more than 3 times will discontinue from IMP.**	Text updated at the request of the FDA.

Section(s)	Change	Rationale
• Section 1.3 Trial Rationale	**Removed paragraph:** The IV infusions of trial treatment will be administered weekly from visits 1 to 4. As from visits 5 to 16, in patients who achieve a platelet count of ≥100×10⁹/L for 3 out of 4 consecutive visits (the fourth visit being the current visit) and have a platelet count of ≥100×10⁹/L at the last of these visits, or 3 consecutive visits, the frequency will be reduced to biweekly administration. Trial treatment will be increased from biweekly to weekly administration in patients whose platelet counts drop below 100×10⁹/L on 2 consecutive visits, or <30×10⁹/L at 1 visit, or in patients who receive rescue therapy. From visits 17 to 24, the dosing frequency is fixed for each individual patient (ie, either weekly or biweekly regimen), based on the regimen the patient was receiving at visit 16.	Paragraph removed due to redundancy. Dosing and frequency regimen are specified in Section 4.1 Summary of Trial Design (SCREENING AND TREATMENT)
• Section 4.1 Summary of Trial Design • Section 5.4.2 Roll-Over to the Open-Label Extension Trial (ARGX-113-1803)	**Version 2.0:** ~~Patients who consent to roll-over into the open-label extension trial ARGX-113-1803 should complete the End-of-Treatment visit of the current trial, on the same day as the signature of the ICF and the baseline visit/first IMP dose administration of the ARGX-113-1803 trial.~~ Patients who complete the 24-week ~~treatment~~ **trial** period have the possibility ~~to consent~~ to enter the open-label extension trial (ARGX-113-1803) to receive efgartigimod 10 mg/kg IV ~~according to the frequency they were receiving at the time of leaving the ARGX-113-1801 trial (ie, weekly or biweekly)~~. **The platelet counts from the ARGX-113-1801 trial will be taken into account to assess the dosing frequency in ARGX-113-1803.**	Text updated to clarify the assessment of the dosing frequency in ARGX-113-1803.

Section(s)	Change	Rationale
• Section 5.4.2 Roll-Over to the Open-Label Extension Trial (ARGX-113-1803)	**Eligible patients who consent to roll-over into the open-label extension trial ARGX-113-1803** should complete the End-of-Treatment visit of the current trial~~, on the same day as the signature of the ICF and the baseline visit/first IMP dose administration of the ARGX-113-1803 trial. Patients who complete the 24-week treatment period have the possibility to consent to enter the open-label extension trial (ARGX-113-1803) to receive efgartigimod 10 mg/kg IV according to the frequency they were receiving at the time of leaving the ARGX-113-1801 trial (ie, weekly or biweekly)~~. • **For patients on a weekly dosing regimen, the baseline visit including first IMP dose administration of the ARGX-113-1803 trial will be done on the same day.** • **For patients on a biweekly dosing regimen, the baseline visit including first IMP dose administration of the ARGX-113-1803 trial will be done 7 days after the End-of-Treatment visit of the current trial.** Patients who do not enter the open-label extension trial (ARGX-113-1803) will remain in ~~this~~ **the current** trial to be followed for 4 weeks (2 biweekly visits).	Text updated to clarify the assessments done at the End-of-Treatment visit for patients eligible and willing to roll-over to ARGX-113-1803.
• Table 1 Schedule of Assessments	**Version 2.0:** End-of-Treatment~~/Early Discontinuation~~: This visit should be ~~completed for all patients, whether they discontinue the trial early, or complete the 24-week treatment period~~ **performed 7 days (+2 days) after visit 24 for all patients who have completed the 24-week trial period, whether they were still on IMP or not**. **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 ~~treatment~~ 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 biweekly visits (ie, 4 weeks). [h] Lab**oratory** assessments include all parameters mentioned in Appendix 1 of the protocol ~~and should be done predose~~.	Text updated/added for clarification purposes.
• Table 1 Schedule of Assessment • Section 1.3 Trial Rationale	**Version 2.0: Assessment of the dosing regimen as described in Section 5.4.1 will be applied.**	

Section(s)	Change	Rationale
• Section 6.11 Handling Missed Doses of the Investigational Medicinal Product • Section 4.4.3 Missed Doses • Section 5.4 Treatment Period	**Version 2.0:** All efforts will be ~~done~~ **made** to ensure that the patient receives all administrations of IMP within the allowed visit windows. However, if a patient misses more than 2 consecutive **scheduled** doses, **then** he/she will be discontinued early from further IMP treatment~~, and will enter the 4-week follow-up period according to the SoA (Table 1) without the possibility to roll-over to the open-label extension trial (ARGX-113-1803)~~ **(see Section 4.4.2)**. Removed Section 4.4.3 Missed Doses: If a patient misses 1 or 2 consecutive doses of IMP, he/she can stay in the trial and will follow the assessments as per SoA (Table 1). If a patient has missed more than 2 consecutive doses he/she will be discontinued early from IMP treatment and will enter the 4-week follow-up period according to the SoA (Table 1) without the possibility to roll-over to the open-label extension trial (ARGX-113-1803).	Procedure for patients who miss more than 2 consecutive IMP doses clarified.
• Synopsis • Section 4.1 Summary of Trial Design • Section 6.8.1 Concurrent ITP Therapy	**Version 2.0:** As of week 12, ~~an increase in dose and/or schedule of permitted concurrent ITP therapy is allowed for the~~ **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" (ie, no platelet count of $\geq 30\times10^9$/L in any of the visits during the last 4 weeks) ~~can start or increase the dose and/or schedule of permitted concurrent ITP therapy~~. These patients will be considered as "non responders" for the primary endpoint analysis.	Text updated/added for clarification purposes.
• Synopsis • Section 4.1 Summary of Trial Design • Section 6.8.1 Concurrent ITP Therapy	**Version 2.0**: Patients receiving **at least 1** permitted concurrent ITP therapy are eligible for the trial, if the dose and schedule have remained unchanged in the last 4 weeks before randomization (ie, visit 1). Permitted concurrent ITP medications include oral corticosteroids, oral immunosuppressants, dapsone/danazol, and/or eltrombopag (inclusion criterion n°~~7~~**6, Section 4.3.1).**	
• Synopsis • Section 3.1 Primary Endpoint • Section 4.2 Discussion of Trial Design • Section 8.4.1 Primary Endpoint Analysis	**Version 2.0:** Patients who discontinue treatment prior to visit 24 due to lack of efficacy **(eg, need rescue therapy more than 3 times)** or due to an AE, and who have not achieved sustained platelet count response between visits 19 and 24, are considered non responders**.**	Text added per request of the FDA.

Section(s)	Change	Rationale
• Synopsis • Section 4.1 Summary of Trial Design • Section 4.4.2 Early Discontinuation from Treatment • Section 5.5 Follow-up Period	**Version 2.0:** Patients who complete the **24-week** trial ~~treatment~~period but who do not enter the open-label extension trial **ARGX-113-1803** ~~will complete all the assessments as listed for the End of Treatment/Early Discontinuation visit and~~**, or patients who discontinue the trial** ~~treatment~~ **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 trial early, all the assessments listed for the ~~End of Treatment~~/Early Discontinuation visit as specified in the schedule of assessments (SoA, Table 1), will be performed ~~at the termination visit. These patients will be followed up for 4 weeks (2 biweekly visits) for ongoing safety and efficacy monitoring~~.	Clarified that patients who withdraw their consent cannot be asked to return for further follow-up visits.
• Section 7.3.1.1 Adverse Events of Special Interest	**Version 2.0:** ~~Efgartigimod treatment induces hypogammaglobulinemia, and there is a potential risk for infections caused by the hypogammaglobulinemia. As such, infections are considered AE(S)I in this trial.~~ **Efgartigimod treatment induces reductions in IgG levels, and there is a potential risk for infections associated with low IgG levels. As such, infections are considered AESI in this trial.** Any bleeding or infection will be considered as AESI. (Section moved from 7.3.2 to 7.3.1.1)	Clarified the reason for risk of infection.
• Section 7.3.1.2 Reporting of Adverse Events and Serious Adverse Events • Section 7.3.1.4 Follow-up of Adverse Events and Serious Adverse Events	**Version 2.0:** ~~The investigator shall report within 24 hours any SAE he/she becomes aware of after a patient's last visit if a causal relationship with the investigational product is suspected. Such a serious adverse reaction is to be collected and reported as previously described for SAEs.~~ **All SAEs that are spontaneously reported within 30 days after the last ~~study~~ trial visit are to be collected and reported as previously described and all efforts should be made to follow-up until resolution.** (This paragraph was moved from Section 7.3.1.4 Follow-up of Adverse Events and Serious Adverse Events to Section 7.3.1.2 Reporting of Adverse Events and Serious Adverse Events)	Text updated/added with a reporting timeframe for clarification purposes.

Section(s)	Change	Rationale
• Section 7.3.1.5.1 Pregnancies in Female Patients	**Version 2.0:** • The patient should have the **Early Discontinuation** ~~End of Treatment~~ assessments and enter the 4-week follow-up period. • All assessments for **Early Discontinuation** ~~End of Treatment~~ (see Section 4.4.1) must be performed unless contraindicated by pregnancy (harmful to fetus) or unless the patient withdraws informed consent.	Correction
• Section 7.3.2 Clinical Laboratory Evaluations	**Version 2.0:** **On days that IMP is administered, blood for laboratory assessments should be collected before dosing.** For all female patients of childbearing potential, a serum pregnancy test will be performed centrally at screening (on the samples taken for clinical laboratory tests), and a urine pregnancy test will be conducted and analyzed locally at the site ~~(on the urine samples taken for urinalysis)~~ at the visits specified in the SoA (Table 1).	Text updated for clarification purposes.
• Section 8.1 Determination of Sample Size	**Version 2.0**: **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 ≥50×10^9/L in the chronic ITP population of 14 weeks for patients receiving efgartigimod and 3 weeks for patients receiving placebo, a total of N=117 patients will ensure a power of >99.9% (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=27 patients would be needed, given these assumptions. Calculations are based on the log-rank test.**	Text added at the request of the FDA.
• Section 8.3 Patient Disposition, Characteristics, and Concomitant Medication	**Version 2.0**: Patient characteristics will be listed and summarized (**by treatment group and overall**). ~~Overall s~~**S**ummaries will include descriptive statistics for continuous measures (number of observations, mean, standard deviation, median, 1st quartile, 3rd quartile, minimum, and maximum) and for categorical measures (frequency and percentage). Use of concomitant medication will be summarized **by treatment group** with frequency and percentage. **Separate summaries of concurrent ITP therapies and rescue therapy by treatment group will be provided.** All concomitant medications used will be listed.	Text added at the request of the FDA.

Section(s)	Change	Rationale
• Section 8.4.1 Primary Endpoint Analysis	**Version 2.0**: Definition of the ~~primary~~ estimand **for the primary endpoint** • Population: adult patients with chronic ITP, having an average platelet count of $<30\times10^9$/L**,** and**, at the start of the trial, either being on concurrent ITP treatment(s) and** having ~~previously~~received at least 1 **prior** ~~ITP~~ therapy **for ITP in the past, or not being on treatment for ITP but having received at least 2 prior treatments for ITP**. • Variable: sustained platelet count response defined as achieving platelet counts of at least 50×10^9/L for at least 4 of the 6 visits between visits 19 and 24 of the trial • Main intercurrent events: ▪ early discontinuation **of treatment** (prior to visit 24) due to lack of efficacy **(eg,, need for rescue therapy more than 3 times)** or due to an AE ▪ initiation of rescue therapy at visit 12 or later ▪ increase of dose and/or frequency of concurrent ITP therapies at visit 12 or later • Population-level summary: proportion of patients with sustained platelet count response Handling of main intercurrent events A composite strategy approach will be taken to address the main intercurrent events described above. This implies that patients who discontinue treatment prior to visit 24 due to lack of efficacy **(eg, need rescue therapy more than 3 times)** or due to an AE, as well as patients who receive rescue therapy at visit 12 or later, or for whom dose and/or frequency of concurrent ITP therapies have increased at visit 12 or later, will be considered non-responders for the primary endpoint analysis. Estimation of treatment effect and statistical inference The primary endpoint will be tested by means of exact logistic regression ~~with~~, **also known as exact conditional logistic regression.[14] The model will contain** fixed effect terms for randomized treatment and baseline platelet count level~~. The model~~ **and** will be stratified by history of splenectomy (yes vs. no) and receiving concurrent ITP therapies at baseline (yes vs. no), at randomization. **Parameter estimation and hypothesis testing will be performed on ~~I~~ log** odds ratio **(OR)** of a sustained platelet count response on placebo and efgartigimod ~~will be provided, along with the 95% 2-sided confidence interval (CI) and 2-sided p-value~~ **. Using the Newton-Raphson**	Text updated/added at the request of the FDA regarding testing strategy of the primary endpoint.

Section(s)	Change	Rationale
	algorithm, a maximum exact conditional likelihood estimate of the log OR will be obtained. In the event the algorithm does not converge, the median unbiased estimate will be used.[15] 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.[16] The OR (by exponentiating the log OR) will be provided, along with the 95% 2-sided confidence interval (CI) and 2-sided p-value. Complementary analyses To facilitate interpretation of the estimated treatment effect in the primary analysis, complementary analyses **will** ~~may~~ be conducted where the main intercurrent events are handled differently, eg, by using the hypothetical and/or "treatment policy" strategy. Details will be provided in the SAP.	
• Synopsis • Section 3.2 Secondary Endpoints	**Version 2.0:** 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 $\geq 50\times10^9$/L in the chronic ITP population. • Proportion of patients in the overall population (chronic and persistent ITP) with a sustained platelet count response defined as achieving platelet counts of at least 50×10^9/L for at least 4 of the 6 visits between visits 19 and 24 of the trial. • Incidence and severity of the WHO-classified bleeding events. • **Proportion of patients in the overall population achieving platelet counts of at least 50×10^9/L for at least 6 of the 8 visits between visits 17 and 24 of the trial.**	Key secondary efficacy endpoint subject to alpha control added.
• Figure 1	**Version 2.0:** The figure has been updated.	For consistency and clarification purposes.

Section(s)	Change	Rationale
• Section 8.2 Analysis Populations	**Version 2.0:** The full analysis set (FAS) consists of all randomized patients who have a baseline efficacy observation. **In general, the**~~The~~ FAS will be used for ~~the main~~ efficacy analyses. **For the primary and first key secondary endpoint the subset of all patients in the FAS with chronic ITP will be used.** The analysis will follow the intent-to-treat principle, ie, patients will be analyzed according to their randomized treatment, irrespective of the treatment they actually received. The per protocol (PP) population is a subset of the FAS, ie, all patients from the FAS without a major protocol deviation ~~deemed to influence the efficacy evaluation~~. The PP population will be used for sensitivity analyses for the primary and key secondary endpoints.	Clarification and more general definition of PP population, as analysis for initial, more specific, definition will be covered by other sensitivity analyses where the intercurrent events will be handled differently than for primary analysis.
• Synopsis • Section 8.4 Statistical Methods	**Version 2.0:** The efficacy analysis will be performed on the FAS **or the subset of patients in the FAS with chronic ITP,** and analyzed with intent-to-treat principle (ie, patients will be analyzed according to their planned treatment irrespective of the treatment actually received).	Text added for clarification purposes.
• Synopsis • Section 8.4.2 Key Secondary Endpoint Analyses Subject to Alpha Control	**Version 2.0:** Extent of disease control defined as the number of cumulative weeks over the planned 24-week treatment period with platelet counts of $\geq 50\times10^9$/L, will be analyzed using Cox regression methodology. ~~In this analysis patients with no cumulative weeks of disease controlled well be assumed to have reached the event (ie, loss of disease control) at zero weeks~~. The 2 treatment groups will be compared using a Cox proportional hazards regression model with fixed effect terms for randomized treatment and baseline platelet level. The model will be stratified by history of splenectomy (yes vs. no) and receiving concurrent ITP therapies at baseline (yes vs. no), at randomization. **A Wald test will be used to test the null hypothesis that the log of the hazard ratio on placebo and efgartigimod is equal to zero (or, equivalently, that the hazard ratio is equal to 1) against the alternative that it is different from zero (or, equivalently, that the hazard ratio is different from 1).** From the model, the hazard ratio for efgartigimod vs. placebo will be provided, along with the associated 95% 2 sided **Wald-type** CI and 2-sided p-value. ~~This will estimate the relative probability of disease control with efgartigimod as compared to placebo.~~ **The hazard ratio will estimate the relative probability of disease control with efgartigimod as compared to placebo.** The data will also be displayed using Kaplan-Meier curves and the median length of disease control will be displayed by randomized treatment arm.	Text added/updated at the request of the FDA.

Section(s)	Change	Rationale
	~~Missing platelet counts for reason of one of the main intercurrent events will be handled as "no disease control" (<50x10^9/L) in case of early discontinuation (prior to visit 24). In case of initiation of rescue therapy, or increase of dose and/or frequency of concurrent ITP therapies, platelet counts will be censored as of the corresponding start date.~~ The key secondary endpoint**s** on proportion of patients in the overall population with a sustained platelet count response **and on proportion of patients in the overall population achieving platelet counts of at least 50×10^9/L for at least 6 of the 8 visits between visits 17 and 24 of the trial** will be analyzed in the same manner as the primary endpoint. The number of bleeding events per patient (assessed using the WHO Bleeding Scale; **where WHO scale ≥1 at any visit is considered a new bleeding event**) will be analyzed using a zero-inflated negative binomial model. This model will account for the large expected number of patients with zero bleeding events. ~~The model will be stratified by history of splenectomy (yes vs. no) and receiving concurrent ITP therapies at baseline (yes vs. no), at randomization.~~ **It is a mixture model consisting of 2 components: a negative binomial count model and a binary model for predicting excess zeros. It will have the number of events as the dependent variable and both randomized treatment and the stratification variables (history of splenectomy; receiving concurrent ITP therapies at baseline) as factors in the model.** An offset term will be used to allow for patient exposure. **Both the count model, using the log link, and the binary model, using the logit link, will contain the same independent variables**. The probability of no bleeding will be estimated for each randomized treatment group. **A Wald test will be used to test the null hypothesis that the log of the bleeding rate ratio on placebo and efgartigimod is equal to zero against the alternative that it is different from zero.** The rate of bleeding over 24 weeks on placebo and efgartigimod will be provided, along with the rate ratio, 95% 2-sided **Wald-type** CI, and 2-sided p value. If the primary endpoint is met, the key secondary endpoints will be analyzed using a ~~closed test~~ **fixed-sequence testing** procedure~~, for example Hochberg or Holm~~, to maintain the overall type I error rate at 5%. **The type I error rate of each individual test will be 5%, but the test will only be conducted if the analysis for all previous endpoints in the pre-defined hierarchy resulted in a p-value <0.05. The order in the testing hierarchy is as follows:**	

Section(s)	Change	Rationale
	1. The proportion of patients with chronic ITP with a sustained platelet count response defined as achieving platelet counts of at least 50×10^9/L for at least 4 of the 6 visits between visits 19 and 24 of the trial (primary endpoint). **2. 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 population with chronic ITP.** **3. The proportion of patients in the overall population (chronic and persistent ITP) with a sustained platelet count response defined as achieving platelet counts of at least 50×10^9/L for at least 4 of the 6 visits between visits 19 and 24 of the trial.** **4. The incidence and severity of the WHO-classified bleeding events.** **5. Proportion of patients in the overall population achieving platelet counts of at least 50×10^9/L for at least 6 of the 8 visits between visits 17 and 24 of the trial.**	

<table>
<tr><th>Section(s)</th><th>Change</th><th>Rationale</th></tr>
<tr><td>• Section 8.4.2 Key Secondary Endpoint Analyses Subject to Alpha Control</td><td>Version 2.0: The main event and censoring rules are as follows, where event is defined as “loss of disease control”:
<table>
<tr><th>Situation</th><th>Date of event or censoring</th><th>Outcome</th></tr>
<tr><td>No occurrence of platelet count of ≥50×10^9/L throughout 24-week treatment period</td><td>Date of baseline</td><td>Event</td></tr>
<tr><td>Early discontinuation of treatment (prior to W24)</td><td>Date of treatment discontinuation</td><td>Event</td></tr>
<tr><td>Rescue therapy started</td><td>Date of initiation of rescue therapy</td><td>Event</td></tr>
<tr><td>Dose and/or frequency of concurrent ITP therapy increased</td><td>Start date of increase</td><td>Event</td></tr>
<tr><td>Disease control at end of 24-week treatment period</td><td>Date of last assessment (analysis visit)</td><td>Censored</td></tr>
</table>
Missing platelet counts for other reasons ~~of one of the main intercurrent events will be handled as “no disease control” (<50x10^9/L) in case of early discontinuation (prior to visit 24). In case of initiation of rescue therapy, or increase of dose and/or frequency of concurrent ITP therapies, platelet counts will be censored as of the corresponding start date. Missing platelet counts for other reasons will be imputed by multiple imputation~~ than those mentioned in the final event and censoring rules table (as detailed in the SAP) will be imputed by multiple imputation. Sensitivity analyses will be conducted to assess the robustness of the analysis results to the applied imputation method.</td><td>Text added/updated at the request of the FDA.</td></tr>
<tr><td>• Section 11.3.3 Publication Policy</td><td>Version 2.0: Any manuscript, abstract or other publication, presentation of results, or information arising in connection with the trial must be prepared in conjunction with the sponsor after the trial has been analyzed and reported and must be submitted to the sponsor for review and comment prior to submission for publication or presentation.
Authorship will be granted according to the International Committee of Medical Journal Editors criteria(–17), based on scientific input and recruitment efforts~~, and will be granted upon decision of a publication committee. This committee will include among others the coordinating investigator and the sponsor~~.</td><td>Wording “after the trial has been analyzed and reported” added for clarification purposes. As there is no publication committee at argenx, the reference has been deleted and the reference to the International Committee of Medical Journal Editors has been corrected.</td></tr>
</table>

Section(s)	Change	Rationale
• Appendix 1	Version 2.0: Pharmacodynamic markers Serum levels of total IgG and IgG subtypes (IgG1, IgG2, IgG3, and IgG4). ~~Presence, nature, and level of antiplatelet antibodies.~~	Specification of the antiplatelet antibodies on a separate line for clarification because these samples are to be taken at a different time point.
	Version 2.0: **Antiplatelet antibodies Presence, nature, and level of antiplatelet antibodies**	
• Table 1 Schedule of Assessments • List of abbreviations • Section 7.2.1 Platelet Count • Appendix 1	**Version 2.0:** [redacted]	Correction.