Clinical Trial Protocol

Protocol Title:	A Phase 3, Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Efficacy and the Safety of Efgartigimod (ARGX-113) PH20 Subcutaneous in Adult Patients With Primary Immune Thrombocytopenia
Protocol Number:	ARGX-113-2004
Protocol Version:	6.0
Amendment Number:	5
Compound:	ARGX-113/Efgartigimod
Trial Phase:	3
Short Title:	Not applicable
Acronym:	ADVANCE^{SC}
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Confidentiality Statement

Sponsor Signatory:

See appended signature page

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Chief Medical Officer

Date

SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE:

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

PROTOCOL NO./ALIAS: ARGX-113-2004/ ADVANCE^{SC}

This protocol is a confidential document of argenx BV. 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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from argenx BV.

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: _____

_____

_____

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document history for global protocol	**Date**
v6.0 Amendment 5	06 Apr 2023
v5.0 Amendment 4	17 Feb 2023
v4.0 Amendment 3	15 Jul 2022
v3.0 Amendment 2	16 Jul 2021
v2.0 Amendment 1	12 Jan 2021
v1.0 Original Protocol	12 Sep 2020

Amendment 5 (06 Apr 2023)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for This Amendment

The primary reason for amendment 4 (v5.0, 17 Feb 2023) was to implement recommendations from the data safety monitoring board (DSMB) to modify the exclusion criterion regarding medical history of thromboembolic events and to require a mandatory discontinuation from trial intervention for participants who have an initial or recurrent malignancy. Editorial changes were included to help with readability.

The reason for amendment 5 (v6.0) is that the protocol is still under the Directive 2001/20/EC and it will not transition to the new Regulation (EU) No 536/2014 of the European Parliament and the Council of the European Union.

The protocol amendment Summary of Changes table for the previous amendments can be found in Section 10.12.

The major changes from protocol v4.0 to v5.0 and v5.0 to v6.0 are summarized in the following table. Refer to Section 10.11 for any undefined abbreviations.

Section	Description of change	Brief rationale
Version 6.0		
Protocol Amendment Summary of Changes	The substantiality assessment was revised from referring to Article 2 §2 (13) of the Regulation (EU) No 536/2014 of the European Parliament and the Council of the European Union to Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.	This protocol is still under the directive and it will not transition to the new regulations.
Version 5.0		
5.2, Exclusion Criteria, Criterion 12 10.4, Appendix 4: Washout Requirements Before First IMP Administration	The exclusion criterion and washout period for serious thromboembolic events was updated. The prohibited period for any major thrombotic or embolic event (eg, myocardial infarction, stroke, deep venous thrombosis, or pulmonary embolism) was revised from within 12 months to within 5 years before randomization. Exclusion criterion 12 was renumbered as 12a.	The DSMB monitoring the ARGX-113 ITP program recommended a revision to the washout period for the exclusion of participants with serious thromboembolic events.
7.1, Discontinuation of Trial Intervention	Language was added to clarify that any participant developing a new or recurrent malignancy except basal cell carcinoma will discontinue trial treatment regardless of the relationship to IMP.	The DSMB monitoring the ARGX-113 ITP program recommended a mandatory discontinuation from trial intervention for trial participants with an initial or recurrent malignancy.
1.3, Schedule of Activities, Table 1 10.9, Appendix 9, Table 5, Schedule of Activities 8.6, Pharmacokinetics	Footnote n regarding when PK/PD/ADA samples should be collected was revised from within 2 hours to within the same day, before IMP administration. Table 4 was renumbered as Table 5.	The revision allows additional flexibility for trial sites.
2.3.1, Risk Assessment	Table 2 of potential risks and mitigation strategies was added.	The table succinctly addresses the trial risks and mitigation strategies.
5.1, Inclusion Criteria, Criterion 8b 10.6.2, Contraception Guidance	The contraception requirement for male participants was removed. Inclusion criterion 8a was renumbered as 8b. Section 10.6.2.2 Male Contraception was deleted.	This global change was made to all ARGX-113 studies based on emerging nonclinical data indicating that efgartigimod has a low risk of teratogenicity/fetotoxicity.

3, Objectives and Endpoints 9.5.7, Other Secondary Endpoint Analyses Not Subject to Alpha Control	An efficacy objective was added to compare efgartigimod PH20 SC to placebo PH20 SC in IWG response and initial response, measuring the proportions of participants with an IWG response, an IWG complete response, and an initial response.	The revision was made to align with the SAP.
3, Objectives and Endpoints 8.12, Immunogenicity Assessments 10.3, Appendix 3, Table 4	Text reading "and titers of NAb against efgartigimod and/or rHuPH20 in the overall population" was revised to "and titers of NAb against rHuPH20 in the overall population." Table 3 was renumbered as Table 4.	The text was not correct. Titers are determined for only the PH20 NAb assay, not the efgartigimod NAb assay.
8.3.2, Vital Signs	Instructions for taking blood pressure were amended to include that participants should be seated and rested.	The updated instructions match site practices and prevent protocol deviations.
10.4, Appendix 4: Washout Requirements Before First IMP Administration	Anti-CD20 therapy (eg, rituximab) with a washout of 6 months before randomization was added.	This requirement was added to match inclusion criterion 7.
2.2, Background 1.1, Synopsis	ARGX-113-1801 was added to the list of sources of clinical history.	Additional data were available in ARGX-113-1801 to support product development.
2.3.2, Benefit Assessment	Lengthy description was replaced with language that directs the reader to the benefit/risk assessment in the current IB.	The IB is the primary repository for updated product data.
5.1, Inclusion Criteria, Criterion 2	The age of consent inclusion criterion was revised to state that participants should be at least the local legal age of consent for clinical trials when signing the ICF. Inclusion criterion 2 was renumbered as 2a.	The revision matches global requirements for the legal participation age.
8.3.5, Clinical Safety Laboratory Assessments 10.2, Appendix 2: Clinical Laboratory Tests	Language was added describing blinding of albumin and urine total protein (quantitative) values and noting that an alert system will notify the investigator to ensure appropriate safety follow up.	The DSMB monitoring the ARGX-113 ITP program advised that serum albumin and total protein results should remain blinded for the trial sites.
10.7, Appendix 7: Administrative Structure	The vendor name LGC was revised to DDS.	The change was made to reflect the legal name of the vendor.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

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

Short Title:

Not applicable

Indication:

Primary immune thrombocytopenia (ITP)

Trial Sites/Countries:

This 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, at the start of the trial taking concurrent ITP treatment(s) and having received at least 1 prior therapy for ITP in the past, or not taking treatment for ITP but having received at least 2 prior treatments for ITP.

Test Product, Dose, and Mode of Administration:

Test product:

Efgartigimod 180 mg/mL coformulated with 2000 U/mL recombinant human hyaluronidase PH20 (rHuPH20) for subcutaneous (SC) administration (efgartigimod PH20 SC)

Dose:

Each dose of efgartigimod PH20 SC will include 1000 mg efgartigimod per injection.

Mode of administration:

Subcutaneous injection

Comparator, Dose, and Mode of Administration:

Comparator:

Placebo PH20 SC

Dose:

Placebo with rHuPH20 for SC administration (placebo PH20 SC)

Mode of administration:

Subcutaneous injection

Rationale:

This phase 3 trial aims to evaluate the efficacy, safety, and effect on the quality of life (QoL) and patient-reported outcomes (PRO) of efgartigimod PH20 administered as SC injections in adult patients with primary ITP who have had an insufficient response or who are intolerant to existing ITP treatments, evidenced by an average platelet count that is below the clinically accepted level for intervention ($<30\times10^9$/L).

Participants classified as having persistent primary ITP (between 3 and 12 months since diagnosis) and chronic primary ITP (greater than 12 months since diagnosis) will be recruited. The diagnosis of primary ITP should be supported by a response to a prior ITP therapy other than thrombopoietin receptor agonists (TPO-RAs). At the start of the trial, the participants are either taking concurrent ITP treatment(s) and have received at least 1 prior therapy for ITP in the past, or the participants are not taking treatment for ITP but have received at least 2 prior treatments for ITP. If participants are receiving concurrent ITP therapies at baseline, these therapies should have been maintained at a stable dose and dosing frequency for 4 weeks before randomization.

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, participants with and without concurrent ITP therapy will be enrolled. Experience to date of efgartigimod treatment in combination with steroids and immunosuppressants in phase 2 and phase 3 trials in primary ITP and myasthenia gravis (MG) have not raised any safety concerns with these combinations of treatments.

Results of the phase 1 trials in healthy subjects (ARGX-113-1501, ARGX-113-1702), the phase 2 trials in participants with ITP (ARGX-113-1603) and MG (ARGX-113-1602), the phase 3 trials in participants with MG (ARGX-113-1704 and ARGX-113-1705) and ITP (ARGX-113-1801), as well as pharmacokinetic/pharmacodynamic (PK/PD) modeling analysis, indicate that a dose of 10 mg/kg efgartigimod, administered weekly (qw) through intravenous (IV) infusion achieved close to maximal immunoglobulin G (IgG) reduction (PD effect), resulted in a reduction of pathogenic autoantibodies, and was associated with clinical efficacy in both participants with ITP and participants with MG. Furthermore, this dose was safe and well-tolerated in all populations.

In order to allow for a convenient SC administration with efgartigimod to achieve the targeted exposure and PD effect, efgartigimod will be coformulated with rHuPH20. rHuPH20 is being used in coformulations with approved therapeutic antibodies to facilitate SC injection with volumes larger than 2 mL.

In designing the current phase 3 trial, a dose of 1000 mg efgartigimod administered as qw or every other week (q2w) SC injections coformulated with rHuPH20 was predicted to result in a comparable effect on IgG levels as with 10 mg/kg IV administered qw or q2w.

No significant safety findings have been identified to date with efgartigimod administered SC in combination with rHuPH20 in completed or ongoing trials.

Objectives and Endpoints

Objectives and Endpoints:	
Objectives	**Endpoints**
Primary	
• To evaluate the efficacy of efgartigimod PH20 SC compared to placebo PH20 SC in achieving a sustained platelet count response in patients with chronic primary ITP, with a sustained platelet count response defined as 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 Note: "week" instead of "visit" is 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)	• Proportion of patients with chronic 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
Secondary	
• To evaluate the efficacy of efgartigimod PH20 SC compared to placebo PH20 SC in overall platelet count response	• 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 (Key Secondary Endpoint 1) • 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 (Key Secondary Endpoint 2) • 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 (Key Secondary Endpoint 3) • Proportion of patients in the overall population 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 in the overall population • Proportion of patients in the overall population 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 in the overall population • Time to response defined as the time to achieve 2 consecutive platelet counts of $\geq 50\times10^9$/L in the overall population • The number of cumulative weeks over the planned 24-week treatment period with platelet counts of $\geq 30\times10^9$/L and $\geq 20\times10^9$/L above baseline in the overall population • 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 $\geq 20\times10^9$/L above baseline in the overall population
• To evaluate the incidence and severity of bleeding events while receiving treatment with efgartigimod PH20 SC compared to placebo PH20 SC	• Incidence and severity of the World Health Organization (WHO)-classified bleeding events in the overall population (Key Secondary Endpoint 4)
• To evaluate the efficacy of efgartigimod PH20 SC compared to placebo PH20 SC in International Working Group (IWG) response	• Proportion of patients with an IWG response • Proportion of patients with an IWG complete response

	• Proportion of patients with an initial response
• To evaluate the safety and tolerability of efgartigimod PH20 SC administered qw or q2w compared to placebo PH20 SC	• Incidence and severity of adverse events (AEs), AEs of special interest (AESIs), and serious AEs (SAEs) in the overall population • Vital signs, electrocardiogram (ECG), and laboratory assessments in the overall population
• To evaluate the use of rescue treatment and changes in concurrent ITP therapy while receiving treatment with efgartigimod PH20 SC compared to placebo PH20 SC	• Rate of receipt of rescue therapy (rescue per patient per month) in the overall population • Proportion of patients for whom dose and/or frequency of concurrent ITP therapies have increased at week 12 or later in the overall population
• To evaluate the effects of efgartigimod PH20 SC treatment on QoL measures and PRO compared to placebo PH20 SC	• Change from baseline in PRO (Functional Assessment of Chronic Illness Therapy Fatigue Scale [FACIT-Fatigue], Functional Assessment of Cancer Therapy questionnaire-Th6 [Fact-Th6]) and QoL (Short Form-36 [SF-36]) at planned visits in the overall population
• To assess the immunogenicity of efgartigimod and rHuPH20	• Incidence and prevalence of antibodies to efgartigimod and/or rHuPH20 in the overall population • Titers of antibodies to efgartigimod and/or rHuPH20 in the overall population • Presence of neutralizing antibodies (NAb) against efgartigimod and/or rHuPH20, and titers of NAb against rHuPH20 in the overall population
• To assess the PK of efgartigimod PH20 SC	• Serum efgartigimod concentration observed predose (C_{trough}) in the overall population
• To assess the PD effects of efgartigimod PH20 SC	• Pharmacodynamics markers: total IgG and antiplatelet antibody levels in the overall population

Exploratory	
• [redacted]	[redacted]
• [redacted]	[redacted]
• [redacted]	[redacted]
• [redacted]	[redacted]

Overall Design:

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

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

Disclosure Statement:

ARGX-113-2004 is a double-blinded, randomized, parallel-group trial to evaluate the efficacy, safety, and effect on QoL/PRO of fixed doses of efgartigimod PH20 SC, compared to placebo PH20 SC.

Number of Participants:

Approximately 180 participants with chronic ITP and up to 39 participants with persistent ITP will be randomized in a 2:1 ratio to receive efgartigimod PH20 SC or placebo PH20 SC, respectively. Recruitment will end when 180 participants with chronic ITP have been randomized.

Participants will be stratified according to the following factors:

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

Intervention Groups and Duration:

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

- Up to 2 weeks of screening
- 24 weeks treatment period
- End-of-treatment visit: 1 week after visit 24
- 8 weeks of follow-up

After confirmation of eligibility, the participants enter a 24-week treatment period and will be randomized to receive efgartigimod PH20 SC or placebo PH20 SC, qw from visits 1 to 4 and then from visits 5 to 16 either qw or q2w, adjusted according to their platelet counts. From visits 17 to 24, participants will be fixed on the dose schedule they were receiving at visit 16 or at the last visit at which the investigational medicinal product (IMP) was administered before visit 16 (ie, either qw or q2w).

All participants or their caregivers (as defined in Section 10.10) will be invited to receive training to (self-)administer the IMP while under supervision at least 4 times in the last 10 weeks, until they are capable of and comfortable with the (self-)administration ([self-]administration without supervision is foreseen only in the open-label extension trial ARGX-113-2005, not in ARGX-113-2004).

If the participant or his/her caregiver successfully completes the training to the satisfaction of the authorized staff, the participant or his/her caregiver, then the participant or his/her caregiver may administer the next injections at the trial site under the supervision of the authorized staff. The training must be documented in the participant's source documents and eCRF.

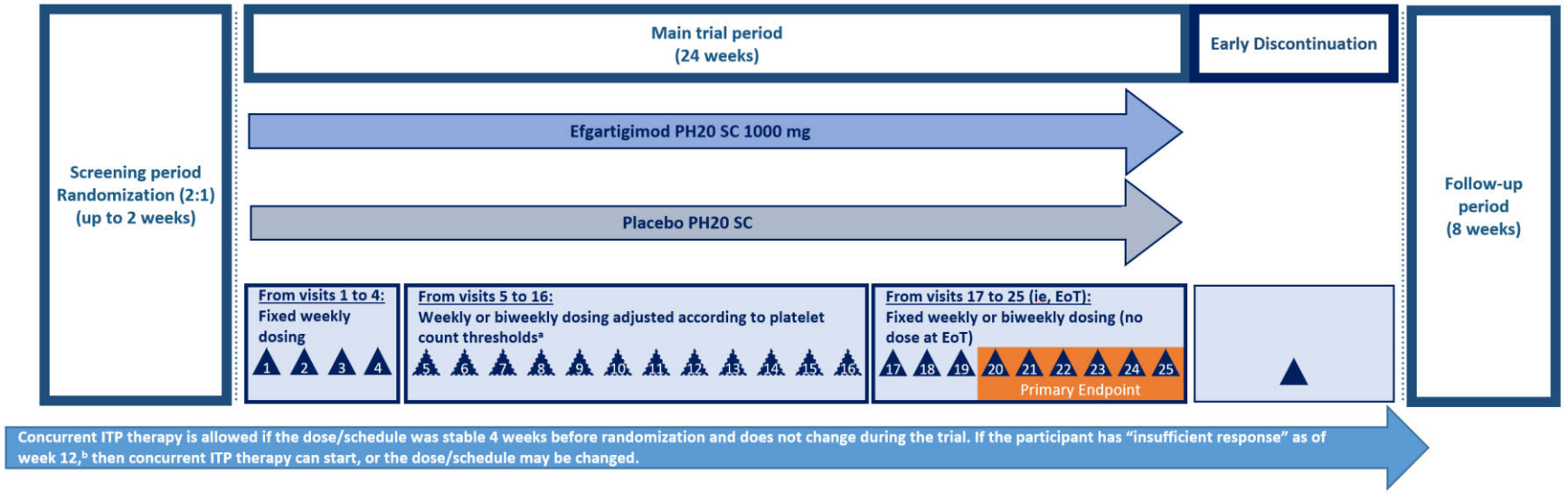
Participants who complete the 24-week randomized trial period will perform the end-of-treatment visit and can enter the open-label extension trial, ARGX-113-2005. If a participant has had an SAE during ARGX-113-2004, his/her eligibility for ARGX-113-2005 should be evaluated by the investigator. The platelet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

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

For participants who discontinue the trial early, all the assessments listed for the early discontinuation visit specified in the Schedule of Activities (Section 1.3), will be performed.

Data Monitoring Committee: yes (see Section 10.1.5.1)

1.2. Schema



Efgartigimod PH20 SC=efgartigimod coformulated with rHuPH20 for subcutaneous administration; EoT=end-of-treatment visit; ITP=immune thrombocytopenia; Placebo PH20 SC=placebo with rHuPH20 for subcutaneous administration; rHuPH20=recombinant human hyaluronidase PH20

[a] The dosing frequency can be changed from weekly to biweekly if the participant has platelet counts $\geq 100\times10^9$/L for 3 out of 4 consecutive visits (the fourth visit being the current visit) and has a platelet count of $\geq 100\times10^9$/L at the last of these 4 visits—OR—for 3 consecutive visits.

[b] As of week 12, the start or an increase in the dose and/or schedule of permitted concurrent ITP therapy is allowed for participants who have an "insufficient response" (ie, no platelet count of $\geq 30\times10^9$/L in any of the visits during the last 4 weeks). These participants will be considered "nonresponders" for the primary endpoint analysis.

1.3. Schedule of Activities

Table 1: Schedule of Activities

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

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

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

[a] **Trial Period:**

Screening Period: maximum 14 days

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

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

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

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

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

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

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

[d] Platelet count is measured locally and can be performed within 1 day (for postbaseline visits) of the next procedure as per schedule of activities (both dosing and nondosing visits). Eligible participants should have a mean platelet count of $<30\times10^9$/L from at least 3 documented, qualifying counts within the 3 preceding months where at least 2 of the qualifying counts must be taken during the screening period: 1 platelet count collected during the screening period

and the predose platelet count on the day of randomization (visit 1). If the third count is not available from the 3 preceding months, this third platelet count can be obtained during the screening period. [redacted]

[e] If available at baseline.

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

[g] If IMP is administered, the ECG will be performed after the IMP administration.

[h] Laboratory assessments include all parameters mentioned in Section 10.2. On days that IMP is administered, samples for laboratory assessments should be collected before dosing, unless otherwise requested.

[i] At the screening visit, if the investigator detects 1 or more screening laboratory abnormalities which are not aligned with the medical history and clinical evaluation of the participant, the result(s) should be confirmed if still within the screening window. For rescreening criteria see Section 5.4.

[j] Only for women of childbearing potential.

[k] At the screening visit, the total IgG level must be determined by the central laboratory (exclusion criterion 9).

[l] Only for women of non-childbearing potential.

[m] To maintain the blind, the IgG testing cannot be performed locally.

[n] To be collected predose, on the day of IMP administration.

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

[p] If the visit does not coincide with an IMP administration, then the assessment should **NOT** be performed.

[redacted].

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

[s] Participants or their caregivers will be invited to receive training to (self-)administer the IMP while under supervision at least 4 times in the last 10 weeks, until they are capable of and comfortable with the (self-)administration ([self-]administration without supervision is foreseen only in the open-label extension trial ARGX-113-2005, not in ARGX-113-2004).

[t] To be obtained before initiation of the IMP administration training.

[u] The IMP (efgartigimod PH20 SC or placebo PH20 SC) will be administered as an SC injection at each IMP administration visit. Participants will remain at the trial site for at least 30 minutes following the end of the injection for routine safety monitoring based on the participant's clinical status. Assessment of the dosing regimen as described in Section 6.5 will be applied.

[v] Adverse events, procedures, and intake of concomitant medication(s) will be monitored continuously from signing the ICF until the last trial-related activity, unless the participant withdraws consent. In case of early discontinuation, any adverse events/serious adverse events should be assessed until the participant has ended the trial or until satisfactory resolution or stabilization. All available vaccination history will be recorded as part of the participant's prior medication for vaccinations received in the past, or concomitant medication for vaccinations received during the trial.

2. INTRODUCTION

2.1. Trial Rationale

This phase 3 trial aims to evaluate the efficacy, safety, and effect on quality of life (QoL)/patient-reported outcomes (PRO) of efgartigimod coformulated with recombinant human hyaluronidase PH20 (rHuPH20) for subcutaneous (SC) administration (efgartigimod PH20 SC) in adult patients with primary immune thrombocytopenia (ITP) who have had an insufficient response or who are intolerant to existing ITP treatments, evidenced by an average platelet count that is below the clinically accepted level for intervention ($<30\times10^9$/L).

Participants classified as having persistent primary ITP (between 3 and 12 months since diagnosis) and chronic primary ITP (greater than 12 months since diagnosis) will be recruited. The diagnosis of primary ITP should be supported by a response to a prior ITP therapy other than thrombopoietin receptor agonists (TPO-RAs). At the start of the trial, the participants are either taking concurrent ITP treatment(s) and have received at least 1 prior therapy for ITP in the past, or the participants are not taking treatment for ITP but have received at least 2 prior treatments for ITP. If participants are receiving concurrent ITP therapies at baseline, these therapies should have been maintained at a stable dose and dosing frequency for 4 weeks before randomization.

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, participants with and without concurrent ITP therapy will be enrolled. Experience to date of efgartigimod treatment in combination with steroids and immunosuppressants in phase 2 and phase 3 trials in primary ITP and myasthenia gravis (MG) have not raised any safety concerns with these combinations of treatments.

This trial will utilize an SC dose schedule aiming to maximize the pharmacodynamic (PD) effect (ie, reduction in immunoglobulin G [IgG] levels, including autoantibody levels) and seeking to result in an improvement in platelet count. In participants who achieve a prespecified threshold of maintained platelet count, the frequency of efgartigimod PH20 SC 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 6.5 will be applied. The aim is to achieve the maximum possible proportion of participants with a platelet count improvement and then assess whether this can be sustained in the last 6 weeks of trial treatment.

To allow for a convenient SC administration, efgartigimod will be coformulated with rHuPH20. rHuPH20 is being used in coformulations with approved therapeutic antibodies to facilitate SC injection with volumes larger than 2 mL.

In clinical trials, efgartigimod in combination with rHuPH20 administered SC has been generally safe and well tolerated with no significant safety issues identified.

2.2. Background

Efgartigimod (ARGX-113) is a modified human IgG1-derived crystallized fragment (Fc) 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 antibody that enhances IgG degradation (ABDEG) technology[1] to increase its affinity for FcRn at both physiological and acidic pH, resulting in a blockage of FcRn-mediated recycling of IgGs.

Given the essential role of the FcRn 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.

Phase 2 trials in participants with primary ITP (ARGX-113-1603), generalized myasthenia gravis (gMG; ARGX-113-1602), and pemphigus (ARGX-113-1701), and phase 3 trials in participants with gMG (ARGX-113-1704 and ARGX-113-1705) and ITP (ARGX-113-1801) have indicated that efgartigimod formulation for IV administration (efgartigimod IV) 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 patients with primary ITP[2] and gMG (see Section 2.1).

A detailed description of the chemistry, pharmacology, efficacy, and safety of efgartigimod is provided in the Investigator's Brochure (IB).

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] The 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] Immune thrombocytopenia 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 clinical manifestations 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,[4] as well as with impaired 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 normal immunoglobulins given IV

(IVIg) and anti-D. Second-line treatments include broad immunosuppressants and TPO-RAs. There is limited evidence to guide the use of these treatments, as described in the American Society of Hematology guideline (ASH).[10] There is very limited 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 develops 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 given the central role of IgG antiplatelet 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.

In the current trial, efgartigimod is coformulated with the permeation enhancer rHuPH20 (efgartigimod PH20 SC). rHuPH20 acts as a spreading factor that increases the dispersion and absorption of other coadministered drugs and allows SC dosing of greater volumes than without rHuPH20. Subcutaneous injections of rHuPH20 with fluids, small molecules, peptides, and proteins (eg, IgG) were well-tolerated in all clinical trial populations studied to date.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits, risks, and reasonably expected adverse events (AEs) of efgartigimod may be found in the current efgartigimod IB.

2.3.1. Risk Assessment

Table 2: Potential Risks and Mitigation Strategies

Potential clinically significant risk	Summary of data/rationale for risk	Mitigation strategy
Serious infection	Efgartigimod reduces IgG levels, potentially hindering immune response and increasing the risk for infection.	Exclude participants with clinically significant active infection not sufficiently resolved in the investigator's opinion (Section 5.2). Infections are considered AESIs (Section 8.4.9). Monitor for infections and temporarily interrupt IMP dosing as specified in Section 7.1.
Injection-related reactions	All therapeutic proteins can elicit immune responses, potentially resulting in hypersensitivity or	Monitor participants during administration and for 30 minutes thereafter for clinical signs and

Potential clinically significant risk	Summary of data/rationale for risk	Mitigation strategy
	allergic reactions such as rash, urticaria, angioedema, serum sickness, and anaphylactoid or anaphylactic reactions.	symptoms of injection-related reactions. Injection-related reactions are considered AEs.
Injection-site reactions	Most AEs have been mild, transient injection-site reactions, including erythema, pain, bruising, pruritus, burning, tenderness, edema, induration, irritation, paresthesia, numbness, and rash. Moderate injection-site reactions occurring less include burning, erythema, pain, and numbness. Mild to moderate headache is commonly reported. Localized injection-site reactions are frequently observed in studies in which efgartigimod is comixed with PH20 and administered SC.	Continuously monitor participants for injection-site reactions. Injection-site reactions are considered AEs (Section 8.3.1).

AE=adverse event; AESI=adverse event of special interest; IgG=immunoglobulin G; IMP=investigational medicinal product; SC=subcutaneous

2.3.2. Benefit Assessment

More detailed information about the known and expected benefits and risks of efgartigimod and reasonably expected AEs can be found in the current version of the IB.

2.3.3. Overall Benefit: Risk Conclusion

The favorable balance between risks and anticipated efficacy/benefits supports the use of efgartigimod PH20 SC in clinical development.

3. OBJECTIVES AND ENDPOINTS

Objectives and Endpoints:	
Objectives	**Endpoints**
Primary	
• To evaluate the efficacy of efgartigimod PH20 SC compared to placebo PH20 SC in achieving a sustained platelet count response in patients with chronic primary ITP, with a sustained platelet count response defined as 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 Note: "week" instead of "visit" is 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)	• Proportion of patients with chronic 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
Secondary	
• To evaluate the efficacy of efgartigimod PH20 SC compared to placebo PH20 SC in overall platelet count response	• 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 (Key Secondary Endpoint 1) • 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 (Key Secondary Endpoint 2) • 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 (Key Secondary Endpoint 3) • Proportion of patients in the overall population 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 in the overall population • Proportion of patients in the overall population 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 in the overall population • Time to response defined as the time to achieve 2 consecutive platelet counts of $\geq 50\times10^9$/L in the overall population • The number of cumulative weeks over the planned 24-week treatment period with platelet counts of $\geq 30\times10^9$/L and $\geq 20\times10^9$/L above baseline in the overall population • 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 $\geq 20\times10^9$/L above baseline in the overall population
• To evaluate the incidence and severity of bleeding events while receiving treatment with efgartigimod PH20 SC compared to placebo PH20 SC	• Incidence and severity of the World Health Organization (WHO)-classified bleeding events in the overall population (Key Secondary Endpoint 4)
• To evaluate the efficacy of efgartigimod PH20 SC compared to	• Proportion of patients with an IWG response

placebo PH20 SC in International Working Group (IWG) response	• Proportion of patients with an IWG complete response • Proportion of patients with an initial response
• To evaluate the safety and tolerability of efgartigimod PH20 SC administered qw or every other week (q2w) compared to placebo PH20 SC	• Incidence and severity of AEs, AEs of special interest (AESIs), and SAEs in the overall population • Vital signs, ECG, and laboratory assessments in the overall population
• To evaluate the use of rescue treatment and changes in concurrent ITP therapy while receiving treatment with efgartigimod PH20 SC compared to placebo PH20 SC	• Rate of receipt of rescue therapy (rescue per patient per month) in the overall population • Proportion of patients for whom dose and/or frequency of concurrent ITP therapies have increased at week 12 or later in the overall population
• To evaluate the effects of efgartigimod PH20 SC treatment on QoL measures and PRO compared to placebo PH20 SC	• Change from baseline in PRO (Functional Assessment of Chronic Illness Therapy Fatigue Scale [FACIT-Fatigue], Functional Assessment of Cancer Therapy questionnaire-Th6 [Fact-Th6]) and QoL (Short Form-36 [SF-36]) at planned visits in the overall population
• To assess the immunogenicity of efgartigimod and rHuPH20	• Incidence and prevalence of antibodies to efgartigimod and/or rHuPH20 in the overall population • Titers of antibodies to efgartigimod and/or rHuPH20 in the overall population • Presence of neutralizing antibodies (NAb) against efgartigimod and/or rHuPH20, and titers of NAb against rHuPH20 in the overall population
• To assess the PK of efgartigimod PH20 SC	• Serum efgartigimod concentration observed predose (C_{trough}) in the overall population

• To assess the PD effects of efgartigimod PH20 SC	• Pharmacodynamics markers: total IgG and antiplatelet antibody levels in the overall population
Exploratory	
• [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
• [redacted]	[redacted]

4. TRIAL DESIGN

4.1. Overall Design

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

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

- Up to 2 weeks of screening
- 24 weeks treatment period
- End-of-treatment visit: 1 week after visit 24
- 8 weeks of follow-up

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

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

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

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

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

For participants who discontinue the trial early, all the assessments listed for the early discontinuation visit as specified in the Schedule of Activities (SoA, Section 1.3), will be performed.

All participants or their caregivers (as defined in Section 10.10) will be invited to receive training to (self-)administer the IMP while under supervision at least 4 times in the last 10 weeks, until they are capable of and comfortable with the (self-)administration ([self-]administration without supervision is foreseen only in the open-label extension trial ARGX-113-2005, not in ARGX-113-2004) as specified in the SoA in Section 1.3.

If the participant or his/her caregiver successfully completes the training to the satisfaction of the authorized staff, the participant or his/her caregiver, then the participant or his/her caregiver may administer the next injections at the trial site under the supervision of the authorized staff. The training must be documented in the participant's source documents and eCRF.

4.2. Scientific Rationale for Trial Design

In the current trial, efgartigimod PH20 SC or placebo PH20 SC will be administered in participants with primary ITP, with the aim to evaluate the efficacy, safety, and effect on QoL/PRO of efgartigimod PH20 SC versus placebo PH20 SC.

This trial is designed as a randomized, double-blinded trial to evaluate the effect of fixed doses of efgartigimod PH20 SC compared to placebo PH20 SC. The trial consists of a treatment period where all participants will initially receive qw SC injections from visits 1 to 4. From visits 5 to 16, the dosing frequency can be altered (ie, increased or decreased) according to specified rules.

[redacted] explored.

4.2.1. Participant Input into Design

Not applicable.

4.3. Justification for Dose

Results of the phase 1 studies in healthy subjects (ARGX-113-1501, ARGX-113-1702), the phase 2 trials in participants with primary ITP and participants with gMG, the phase 3 trials in MG, as well as PK/PD modeling analysis, indicate that a dose of 10 mg/kg efgartigimod, administered qw through IV infusion achieved close to maximal IgG reduction (PD effect), resulted in a reduction of pathogenic autoantibodies, and was associated with clinical efficacy in both participants with ITP and participants with gMG. Furthermore, this dose was safe and well-tolerated in all populations.

The selected SC dose targets a similar PD effect compared with the 10 mg/kg IV dose, anticipating a similar clinical response. PK/PD modeling indicated that qw or q2w doses of efgartigimod PH20 SC 1000 mg result in a comparable effect on IgG levels as with 10 mg/kg IV administered qw or q2w. No body weight effect was found to be statistically significant on either PK or PD parameters.

No significant safety findings have been identified to date with efgartigimod administered SC in combination with rHuPH20 in trials with healthy participants, participants with gMG,

participants with primary ITP, participants with CIDP, or participants with pemphigus (vulgaris or foliaceus).

4.4. End of Trial Definition

The end of trial is defined as the last participant's last visit in ARGX-113-2004.

5. TRIAL POPULATION

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

The criteria for screening and enrollment are to be followed explicitly. If it is noted that a participant who does not meet 1 or more of the inclusion criteria and/or meets 1 or more of the exclusion criteria was inadvertently enrolled and dosed, the sponsor's designated contract research organization (CRO) (medical) monitor and the sponsor's medical director must be contacted immediately. The decision to discontinue a participant from the trial will be taken on a case-by-case base.

5.1. Inclusion Criteria

Participants are eligible to be included in the trial only if all of the following criteria apply:

1. Ability to understand the requirements of the trial and provide written informed consent (including consent for the use and disclosure of research-related health information), willing and able to comply with the trial protocol procedures (including attending the required trial visits)

2a. Is at least the local legal age of consent for clinical studies when signing the ICF.

3. Confirmed diagnosis of primary ITP made at least 3 months before randomization and based on the American Society of Hematology Criteria, and no known 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 at least 3 documented, qualifying counts within the 3 preceding months where at least 2 of the qualifying counts must be taken during the screening period: 1 platelet count collected during the screening period and the predose platelet count on the day of randomization (visit 1). If the third count is not available from the 3 preceding months, this third platelet count can be obtained during the screening period.

6. A documented history of a platelet count of $<30\times10^9$/L before screening

7. At the start of the trial, the participant is either receiving concurrent ITP treatment(s) and has received at least 1 prior therapy for ITP in the past, or the participant does not take treatment for ITP (see note) but has received at least 2 prior treatments for ITP.

   Participants receiving permitted concurrent ITP treatment(s) at baseline must have been stable in dose and frequency for at least 4 weeks before randomization.

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

   Note: Participants not receiving concurrent ITP therapy are also eligible for the trial if they have not received prior ITP therapy for at least 4 weeks before baseline, and 6 months in case of prior ITP therapy with an anti-CD20 therapy (eg, rituximab).

8b. Agree to use contraceptive measures consistent with local regulations and the following:

Female participants of childbearing potential (defined in Section 10.6.1.1) must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline before receiving IMP. Contraceptive requirements are provided in Section 10.6.2.1.

5.2. Exclusion Criteria

Participants are excluded from the trial if any of the following criteria apply:

1. Secondary ITP/thrombocytopenia associated with another condition, eg, lymphoma, chronic lymphocytic leukemia, viral infection, hepatitis, induced or alloimmune thrombocytopenia, thrombocytopenia associated with myeloid dysplasia, or hematopoietic stem cell transplant
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) within 4 weeks prior to randomization
5. Use of romiplostim within 4 weeks prior to randomization
6. Undergone splenectomy less than 4 weeks prior to randomization
7. Use of an investigational product within 3 months or 5 half-lives (whichever is longer) before the first dose of the IMP
8. Use of any monoclonal antibody or Fc fusion proteins, other than those previously indicated, within 6 months before the first dose of the IMP (eg, anti-CD20)
9. At the screening visit, clinically significant laboratory abnormalities as follows:
   - Hemoglobin ≤9 g/dL

     – OR –
   - International normalized ratio >1.5 or activated partial thromboplastin time >1.5×upper limit of normal

     – OR –
   - total IgG level <6 g/L
10. History of malignancy unless deemed cured by adequate treatment with no evidence of recurrence for ≥3 years before the first administration of IMP. Participants with the following cancer can be included at any time:
    a. Adequately treated basal cell or squamous cell skin cancer
    b. Carcinoma in situ of the cervix
    c. Carcinoma in situ of the breast or
    d. Incidental histological finding of prostate cancer (TNM stage T1a or T1b)

11. Uncontrolled hypertension, defined as a repeated elevated blood pressure exceeding 160 mmHg (systolic) and/or 100 mmHg (diastolic) despite appropriate treatments

12a. History of any major thrombotic or embolic event (eg, myocardial infarction, stroke, deep venous thrombosis, or pulmonary embolism) within 5 years before randomization

13. History of coagulopathy or hereditary thrombocytopenia or a family history of thrombocytopenia

14. Evidence of an active clinically significant bleeding of an organ or internal mucosal bleeding, other than expected in ITP, that warrants emergent treatment or therapeutic procedure based on the investigator's judgment (eg, intracranial hemorrhage, pulmonary hemorrhage, bleeding with ongoing need for packed red blood cell transfusion)

15. Estimated high risk of a clinically significant bleeding of an organ or internal mucosal bleeding, other than expected in ITP, that warrants emergent treatment or therapeutic procedure according to the investigator's judgment

16. Clinical evidence of other significant serious diseases, have had a recent major surgery, or who have any other condition in the opinion of the investigator, that could confound the results of the trial or put the participant at undue risk

17. 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

18. Known hypersensitivity reaction to efgartigimod, rHuPH20, or 1 of its excipients

19. Previously participated in a clinical trial with efgartigimod and have received at least 1 administration of the IMP

20a. Pregnant or lactating or intends to become pregnant during the trial

21. Clinically significant uncontrolled active or chronic bacterial, viral, or fungal infection at screening

22. Any other known autoimmune disease that, in the opinion of the investigator, would interfere with an accurate assessment of clinical symptoms of ITP or put the participant at undue risk

23. 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 participant at undue risk

24. Current or history of (ie, within 12 months of screening) alcohol, drug, or medication abuse
25. Received a live/live-attenuated vaccine less than 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

5.3. Lifestyle Considerations

No lifestyle restrictions are required.

5.3.1. Meals and Dietary Restrictions

Not applicable.

5.3.2. Caffeine, Alcohol, and Tobacco

Participants with a current or history of alcohol abuse cannot participate in the trial (see exclusion criterion 24).

5.3.3. Activity

Not applicable.

5.4. Screen Failures, Retesting, and Rescreening

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

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

Retesting may be considered in the following case:

- A participant who has clinical laboratory test values meeting 1 or more exclusion criteria which are not aligned with the medical history and clinical evaluation of the participant, 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 participant should be rescreened (ie, redoing the full assessments as per SoA, Section 1.3). Refer to Section 8.3.5.

Rescreening is allowed as long as the participant has not received any IMP. Examples of conditions under which rescreening may be considered include participants who required treatment for an acute illness (eg, a urinary tract infection) or have a chronic medical problem (eg, uncontrolled hypertension); participants may be rescreened once the illness has resolved or the medical problem is stabilized.

The decision to rescreen participants, based on the clinical state of the participant 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 participant identification number (ID) will be generated.

6. TRIAL INTERVENTION

Trial intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a trial participant according to the trial protocol. Trial intervention is defined as IMP in this trial.

6.1. Trial Intervention(s) Administered

	Active Treatment	**Control**
Intervention Name	Efgartigimod PH20 SC	Placebo PH20 SC
Type	Biologic	Other: placebo
Dose Formulation	Efgartigimod + 2000 U/mL rHuPH20 solution for SC injection to be dosed at a fixed dose of 1000 mg per injection	Matching placebo + 2000 U/mL rHuPH20 solution for SC injection
Unit Dose Strength(s)	Efgartigimod 180 mg/mL Experimental	Placebo
Dosage Level(s)	1000 mg, qw or q2w	Matching SC administration, qw or q2w
Route of Administration	SC injection	SC injection
Use	Investigational	Placebo comparator
IMP	IMP	IMP
Sourcing	Provided by the sponsor to the trial site	Provided by the sponsor to the trial site
Packaging and Labeling	The IMP will be provided in glass vials. Each glass vial will be labeled as required per country requirement	The IMP will be provided in glass vials. Each glass vial will be labeled as required per country requirement

IMP=investigational medicinal product; qw=every week; q2w=every other week; SC=subcutaneous

Fixed doses of SC IMP will be administered as SC injections.

All IMP treatment administered SC will be fully blinded.

For each injection, the date, initiation and completion times (hour and minute), and details of any interruptions or premature discontinuation of injections will be recorded on the eCRF. The start will be marked as the moment of start pressing the plunger and the end will be marked as the completion time of administration of the total volume of IMP.

The IMP will be administered as 1 injection. The abdomen is the preferred injection site. Optional sites (ie, thighs or arms) may be chosen, eg, if the abdomen is affected by lesions, bleedings, or other injection site reactions. The injection site and the reason of using another site than the abdomen will be documented on the electronic CRF (eCRF).

After the administration of the IMP, the participants will be asked to remain at the investigative site for at least 30 minutes after the end of the injection as part of routine safety monitoring.

More details are available in the Pharmacy Manual.

6.2. Preparation/Handling/Storage/Accountability/Packaging

6.2.1. Preparation

Efgartigimod PH20 SC will be provided as a sterile, clear to opalescent, yellowish solution for SC injection in glass vials covered with a blinding shell.

Placebo PH20 SC will be provided as a sterile, colorless, clear solution for injection in glass vials covered with a blinding shell, with the same formulation as the efgartigimod PH20 SC solution for injection, but without the active ingredient (efgartigimod).

The IMP will be manufactured to ensure the blind and in accordance with Good Manufacturing Practice regulations. Detailed instructions for IMP management on-site (including preparation of the IMP) are included in the Pharmacy Manual.

6.2.2. Handling

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IMP received and any discrepancies are reported and resolved before use of the IMP.

Only participants enrolled in the trial may receive IMP and only authorized and trained site staff may dispense IMP. The IMP administration must be performed by authorized and trained site staff or by an adequately trained and supervised participant or his/her caregiver. All IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized site staff. Detailed instructions are included in the Pharmacy Manual.

6.2.3. Storage

The IMP (efgartigimod PH20 SC and placebo PH20 SC) will be supplied to the pharmacy or dedicated site location at the trial site 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.

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 investigative site.

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

Further requirements on temperature logging during storage and information on how to handle temperature excursions can be found in the Pharmacy Manual.

The investigator (or designee) is responsible for the correct and safe storage of the IMP assigned to the investigative 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.

Further guidance and information for the final disposition of used and unused IMP are provided in the Pharmacy Manual.

6.2.4. Accountability

The investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Detailed instructions on accountability of the IMP are included in the Pharmacy Manual.

6.2.5. Packaging and Labeling

The IMP will be labeled and secondary packed in accordance with local laws and regulatory requirements. Detailed instructions are included in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Once the participant has provided informed consent, the investigative site will enroll the participant and a screening number will be automatically allocated through interactive response technology (IRT).

Upon confirmation of eligibility at baseline (visit 1), the participant will be randomized through IRT.

Participants will be randomized in a 2:1 ratio to receive efgartigimod PH20 SC or placebo PH20 SC, respectively.

At randomization, participants will be stratified according to whether they underwent a splenectomy (yes versus no) and if they are receiving concurrent ITP therapies at baseline (yes versus no).

This is a randomized, double-blinded, placebo-controlled trial with limited access to the IMP treatment assigned (see also Section 10.10).

An independent unblinded data safety monitoring board (DSMB), including an independent statistician, will review all unblinded safety data as specified in Section 10.1.5.1.

6.3.1. 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 participant, unless there is a participant safety issue that via knowledge of the IMP treatment assignment would change participant management. If the investigator decides that unblinding is warranted, the investigator may contact the sponsor before unblinding a participant's IMP

unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours of this occurrence. If the blind is broken by the investigator, it may be broken only for the participant concerned, and the IMP treatment assignment should not be revealed to the Sponsor's trial team members, nor to the sponsor's designated CRO, pharmacy personnel, or other site staff.

Once unblinded, the participant will be discontinued from the trial and will be followed for 8 weeks for ongoing safety and efficacy monitoring. The follow-up period will consist of 2 visits every 4 weeks (q4w).

Pertinent information regarding the circumstances of unblinding of a participant's IMP treatment code must be documented in the participant's source documents and eCRF.

The sponsor and monitor at the sponsor's designated CRO must be notified immediately if a participant and/or investigator is unblinded during the course of the trial.

6.4. Trial Intervention Compliance

The participants are dosed by qualified approved personnel. Adequately trained participants or their caregivers are also allowed to administer the IMP on-site under supervision of the authorized site staff. They will receive IMP directly from the investigator or designee, under medical supervision. The date and time of each dose administered at the investigative site will be recorded in the source documents and recorded on the eCRF.

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

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

6.4.1. Handling Missed Doses of the Investigational Medicinal Product

All efforts will be made to ensure that the participant receives all administrations of IMP within the allowed visit windows. However, if a participant misses more than 2 consecutive scheduled doses, then he/she will be discontinued early from trial treatment (see Section 7.1). Withholding IMP as described in Section 6.7 and Section 7.1.1 is not considered a missed dose.

If a participant misses any dose of IMP, he/she should not make up the missed dose. A dose is only considered as missed in case of a missed visit. Other reasons for not administering the IMP are not considered as a missed dose.

6.4.2. Protocol Deviations

Prospective approval of protocol deviations to enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

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 participants, 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.

6.5. Screening and Treatment

After the informed consent has been obtained, the participant will be screened (screening period of maximum 14 days) at the investigative site for eligibility based on the inclusion and exclusion criteria defined in Section 5.1 and Section 5.2, respectively.

The assessments as specified in the SoA, Section 1.3 will be performed during screening.

All participants will initially receive qw SC injections from visit 1 to 4 (consecutive administrations of IMP should be at least 5 days apart).

Based on the platelet counts as of visit 2, the dosing frequency can be altered from visits 5 to 16 (consecutive administrations of IMP should be at least 5 or 12 days apart for the qw or q2w administration schedule, respectively) according to the following rules (the change in dosing frequency will occur at the current visit):

- Reduce from qw to q2w in participants having 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 –

  Reduce from qw to q2w in participants having platelet counts of $\geq 100\times10^9$/L for 3 consecutive visits

  Note: In this case, no IMP will be administered at the last visit confirming the qualifying platelet counts of $\geq 100\times10^9$/L.

- Increase from q2w to qw in participants whose platelet counts drop to $<100\times10^9$/L on 2 consecutive visits

  – OR –

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

  – OR –

in participants who receive rescue therapy (see Section 6.6.4)

- Postbaseline platelet count can be performed within 1 day of the next procedure as per SoA (both dosing and nondosing visit), allowing the results to be incorporated into the criteria above.

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

Exceptions to the fixed dosing frequency are:

- Continued qw dosing for participants requiring rescue therapy
- Continued q2w dosing for participants resuming IMP when the platelet count falls to $<150\times10^9$/L after having had platelet counts $>400\times10^9$/L

6.6. Prior and Concomitant Therapy

All prior ITP procedures and therapies received by the participant since diagnosis, before baseline, must be recorded on the eCRF, including the name, dose/schedule, duration (including start and stop dates), intolerance, whether the participant responded to them, details of platelet counts on prior ITP therapies (ie, supporting the participant's response), and the reason for discontinuation from prior therapies that are documented on the participant's source documents at the current trial site.

The washout periods as specified in the exclusion criteria must be followed. See also Section 10.4.

All available vaccination history should be recorded as part of the participant's prior medication for vaccinations received in the past, or concomitant medication for vaccinations received during the trial as described in the SoA (Section 1.3). Any vaccination information that the participant, his/her caregiver, or his/her legally authorized representative can remember should be recorded on the eCRF (with the brand name of the vaccine and date of vaccination, if possible).

All concomitant medications and procedures whether allowed or not must be recorded on the eCRF (including the name, indication [for use], dose/schedule, and start and stop dates).

6.6.1. Concurrent ITP Therapy

- Participants 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 corticosteroids, danazol, vinca alkaloids, oral immunosuppressants, dapsone, fostamatinib, and/or oral TPO-RAs (see inclusion criterion 7, Section 5.1).
- Dose and frequency of permitted concurrent ITP therapies should remain unchanged during the trial.

- Exceptions are participants who are receiving concurrent treatment with oral TPO-RAs in whom dose changes are permitted at label-defined platelet thresholds, and participants 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 participants 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 participants will be considered as "nonresponders" 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.
- Participants not receiving concurrent ITP therapy are also eligible for the trial (see inclusion criterion 7, Section 5.1). The washout periods as specified in exclusion criteria 2 to 8 must be followed. See also Section 10.4.
- Any change in concurrent ITP therapy should appropriately be recorded on the eCRF.
- The medical monitor at the sponsor's designated CRO should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.2. Prohibited Medications and Therapy Before Randomization

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

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

6.6.3. 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, Fc fusion proteins, or other investigational drug
- Live/live-attenuated vaccines

6.6.4. Rescue Therapy

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

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

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

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

The following rescue treatments 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 participants
- platelet transfusions

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 6.7 and Section 6.4.1)

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

- Administration of the IMP continues during rescue therapy

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

For participants 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 participant can transition to q2w treatment.

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

6.7. Dose Modification

The administration of IMP will be temporarily withheld if it could put the participant at undue risk in any of the following circumstances:

- Platelet count increases to $>400\times10^9$/L
  The IMP administration should be resumed at the visit where the platelet count falls to $<150\times10^9$/L, at the q2w dosing frequency.
- Occurrence of infection grade ≥3 according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)
- Occurrence of bleeding grade ≥3 according to the WHO bleeding scale
- Occurrence of a thromboembolic event grade >1 according to the NCI CTCAE

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

Even if the participant rolls over to the open-label extension trial (ARGX-113-2005), the IMP will be resumed when:

- The platelet count decreases to $<150\times10^9$/L at the q2w dosing frequency
- The AEs as listed previously are resolved according to the medical assessment of the investigator

6.8. Intervention After the End of the Trial

After a participant has completed the trial, has withdrawn/discontinued early, or has completed the 2 follow-up visits, 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 participant's individual needs.

Eligible participants who have completed the 24-week randomized trial period can enter the open-label extension trial ARGX-113-2005 to receive efgartigimod (see Section 4.1).

- Participants who are receiving a qw regimen:
  - The baseline visit (including the first dose of IMP) of ARGX-113-2005 will occur on the same day as the end-of-treatment visit of ARGX-113-2004. Assessments that were performed at the end-of-treatment visit of ARGX-113-2004 should not be repeated at visit 1 (baseline) of ARGX-113-2005.
- Participants who are receiving a q2w regimen:
  - If visit 24 of ARGX-113-2004 is a dosing visit, then the baseline visit of ARGX-113-2005 (including the first dose of IMP) will occur 7 days after the end-of-treatment visit of ARGX-113-2004.
  - If visit 24 of ARGX-113-2004 is a nondosing visit, then the baseline visit (including the first dose of IMP) of ARGX-113-2005 will occur on the same day as the end-of-treatment visit of ARGX-113-2004. Assessments that were

performed at the end-of-treatment visit of ARGX-113-2004 should not be repeated at visit 1 (baseline) of ARGX-113-2005.

- Participants who are receiving a qw regimen who meet the criteria (Section 6.5) to switch to a q2w regimen based on their platelet counts at the ARGX-113-2004 end-of-treatment visit:
  - The baseline visit of ARGX-113-2005 (including the first dose of IMP) will occur 7 days after the ARGX-113-2004 end-of-treatment visit.

7. DISCONTINUATION OF TRIAL INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Trial Intervention

- Early discontinuation from treatment means that the participant stops receiving the ongoing IMP treatment and does not restart IMP treatment; however, informed consent is not withdrawn. These participants will continue the qw trial visits as specified in the SoA (Section 1.3) without IMP-related assessments.
- Participants **must** be discontinued early from **treatment** in the following circumstances:
  - at the request of the sponsor (eg, following DSMB advice, see Section 10.1.5.1)
  - participant has missed more than 2 consecutive scheduled doses of IMP treatment
  - participant has received more than 3 occurrences of rescue therapy
  - participant develops a new or recurrent malignancy except for basal cell carcinoma of the skin, regardless of relationship

7.1.1. Temporary Discontinuation

See Section 6.7 for specifications regarding temporary withholding of IMP treatment.

7.1.2. Rechallenge

Not applicable.

7.2. Participant Discontinuation/Withdrawal From the Trial

- Early discontinuation from the trial is defined as the permanent cessation of further participation in the trial before its planned completion and without the possibility to roll over to the open-label extension trial ARGX-113-2005.
- The reason for early discontinuation from the trial will be clearly documented by the investigator.
- A participant may withdraw from the trial at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- At the time of discontinuing from the trial, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of trial discontinuation and follow-up, and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the IMP and from the trial at that time.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the trial, he/she may request destruction of any unused samples, and the investigator must document this in the site trial records and inform the sponsor accordingly. Trial information and samples collected, including their results, from before the participant decided to leave the trial, may still be included in the trial results.
- Participants **must** be discontinued early from the **trial**, and complete the early discontinuation visit as specified in the SoA (Section 1.3), if:
  - they withdraw their consent
    All participants 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. Before actual withdrawal of consent, an effort should be made to perform a final set of assessments as per the early discontinuation visit.

    Investigators will make and document all efforts made to contact those participants who do not return for such scheduled visits.
- Participants **must** be discontinued early from the **trial**, complete the early discontinuation visit as specified in the SoA (Section 1.3), and be followed for 8 weeks (2 visits q4w) for ongoing safety and efficacy monitoring if:
  - it is in the participant's best interest
  - unblinding occurred
  - prohibited medication is taken (see Section 6.6.2)
  - a severe hypersensitivity reaction to IMP occurs
  - the participant became pregnant
  - at the request of the sponsor (eg, following DSMB advice, see Section 10.1.5.1)

7.3. Completion of the Trial

Participants who complete the 24-week trial period but who do not enter the open-label extension trial ARGX-113-2005, or participants who discontinue the trial early, with the exception of participants who withdraw their consent, will be followed for 8 weeks for ongoing safety and efficacy monitoring.

7.4. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the investigative site (see Section 6.4.1).

The following actions must be taken if a participant fails to return to the investigative site for a required trial visit:

- The investigative site must attempt to contact the participant as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the trial.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, it will be considered that he/she does not want to continue participating in the trial. He/she will be considered as lost to follow-up.

Discontinuation of specific investigative sites or of the trial as a whole are handled as part of Appendix 1 (Section 10.1).

8. TRIAL ASSESSMENTS AND PROCEDURES

- Trial procedures and their timing are summarized in the SoA (Section 1.3).
- Adherence to the trial requirements, including those specified in the SoA (Section 1.3), is essential and required for trial conduct.
- 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. This will be considered a protocol deviation and will be recorded accordingly.
- At screening, all eligibility assessments should be performed after obtaining informed consent.
- All screening evaluations must be completed and reviewed to confirm that participants meet all eligibility criteria before randomization.
- The investigator will maintain a screening log to record details of all participants screened and confirm eligibility or record reasons for screening failure, as applicable.
- Each participant should attend each trial visit on the designated days. There is a permissible visit window of +2 days during the treatment period as well as the end-of-treatment visit and follow-up period. Every effort should be made to schedule every visit on the exact day (which is relative to baseline [visit 1]) as described in the SoA (Section 1.3).
- From the signature of informed consent until the last trial-related activity, all AEs that occur and all concomitant medications that are taken and procedures performed, whether allowed or not, during the trial are to be recorded on the appropriate pages on the eCRF.
- During the IMP treatment period, all assessments and procedures must be performed before the start of the IMP administration, except for ECG assessment and the continuous assessment of AEs and the recording of concomitant therapy and procedures.

8.1. Demography

Demographic characteristics comprise age, year of birth, gender, race, and ethnicity (per local regulations). Only if requested as per local regulations, no source data verification will be performed on race and ethnicity.

8.2. Efficacy Assessments

Procedures assessing the efficacy of efgartigimod will mainly focus on measures of response derived from platelet counts. These assessments will be performed at the qw visits predose on all IMP administration days, and at the unscheduled visits (if needed), as specified in the SoA (Section 1.3).

8.2.1. [redacted]

[redacted]

8.2.2. General Bleeding Assessment

- Signs and symptoms of bleeding are the predominant clinical manifestation of ITP and are typically related to 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 every visit using the WHO bleeding scale (Section 10.8) as specified in the SoA (Section 1.3). The WHO bleeding scale was originally developed to assess bleeding in participants undergoing treatment for cancer and has been used extensively.[11]
- The wide use of the scale and incorporation into the 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]

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.3.1. Physical Examinations

- Physical examination will be performed at the time points indicated in the SoA (Section 1.3).
- A physical examination will include at a minimum an assessment of general appearance, skin, lymph nodes, musculoskeletal/extremities, abdomen, cardiovascular, respiratory, and neurological system.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

- Clinically significant abnormalities in physical examination at screening will be reported as medical history on 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.
- Injection site reactions observed after SC administration will be reported as an AE.

8.3.2. Vital Signs

- The assessment of vital signs (supine blood pressure, heart rate, and body temperature) will be performed at the time points indicated in the SoA (Section 1.3).
- Supine blood pressure and heart rate will be measured using standard equipment after at least 10 minutes with the participant rested and seated.
- It is recommended that the method used to measure the body temperature (eg, orally, tympanic, rectal, axillary, skin, temporal) at screening is maintained throughout the trial for each participant.
- For the assessment of height and weight, participants will be required to remove their shoes and wear light indoor clothing.
- Height will be measured at screening only. Weight will be measured at screening and at the time points indicated in the SoA (Section 1.3).
- Clinically significant abnormalities in vital signs at screening will be reported as medical history on 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.

8.3.3. Electrocardiograms

- The assessment of ECG will be performed at the time points indicated in the SoA (Section 1.3).
- If IMP is administered, the ECG will be performed after the IMP administration.
- A single 12-lead ECG will be taken at a paper speed of 25 mm/sec in the supine position after the participant 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.
- Clinically significant abnormalities in ECG at screening will be reported as medical history on 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.

8.3.4. 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 participant 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 from coagulation disorder will be prespecified on the eCRF.
- Information should be provided on medical and surgical history and concomitant medical conditions, specifying those ongoing at screening.
- A history of a platelet count of $<30\times10^9$/L before screening should be documented for the determination of the participant's eligibility.

8.3.5. Clinical Safety Laboratory Assessments

- Blood and urine samples for determination of clinical chemistry, hematology, urinalysis, coagulation, thyroid, autoimmune antibody testing, follicle-stimulating hormone (FSH; only for women of non-childbearing potential), viral testing, and tuberculosis QuantiFERON test will be collected and analyzed at a central laboratory as indicated in the SoA (Section 1.3) and Section 10.2. The blood sample for platelet counts and the urine sample for the pregnancy test will be analyzed locally.
- For safety assessments during screening, participants may be rescreened (ie, redoing the full assessments as per SoA, Section 1.3) or retested once (ie, repeating 1 test, see Section 5.4) if still within the screening period.
- On days that IMP is administered, samples for laboratory assessments should be collected before dosing, unless otherwise requested.
- Additional safety samples may be collected if clinically indicated, at the discretion of the investigator.
- For all female participants 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 investigative site at the visits specified in the SoA (Section 1.3).
- Clinical laboratory tests will be reviewed for results of potential clinical significance at all time points throughout the trial, with the exception of albumin and urine total protein (quantitative) values. Albumin and urine total protein (quantitative) values will remain blinded for the trial site. An alert system will be implemented to notify the investigator if there are out-of-range albumin or urine total protein (quantitative) values to allow for appropriate safety follow-up.
- 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 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 participant's source documents and on the central laboratory assessment eCRF page. For urinalysis samples only the date of collection is to be entered.
- Refer to Section 10.7 for the addresses of the laboratories used for sample analyses.
- All laboratory tests with values considered clinically significantly abnormal during participation in the trial should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
  - All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

8.3.5.1. 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 after the end of the trial, in the laboratory or long-term storage designated by the sponsor or research partners worldwide, for future additional medical, academic, or scientific 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 participant would not have agreed. After this period of time, the samples will be destroyed.

In addition, serum or plasma samples may be used to validate methods to support the efgartigimod program. These samples may also be used for vaccination antibody testing and any other additional research interests linked to the development of efgartigimod.

8.3.6. Suicidal Ideation and Behavior Risk Monitoring

Not applicable.

8.3.7. Visit Reminder/Participant Identification Card

Participants must be provided with the address and telephone number of the main investigative site contact for information about the clinical trial. The investigator must therefore provide a "Visit Reminder/Participant ID Card" to each participant. In an emergency situation, this card serves to inform the responsible attending physician that the participant is in a clinical trial and that relevant information may be obtained by contacting

the investigator. Participants must be instructed to keep the card in their possession at all times.

8.4. Adverse Events and Serious Adverse Events

- Definitions of AE and SAE are provided in Section 10.5 as well as guidelines for assessing causality and relationship to IMP.
- AEs will be reported by the participant.
- The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to IMP or trial procedures, or that caused the participant to discontinue IMP and/or the trial (see Section 7).
- 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), 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.

8.4.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

- All AEs and SAEs will be collected from the signing of the ICF until the end-of-treatment or last follow-up visit at the time points specified in the SoA (Section 1.3).
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.5). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs after conclusion of the trial participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the trial, and he/she considers the event to be reasonably related to the IMP or trial participation, the investigator must promptly notify the sponsor.

8.4.2. Method of Detecting Adverse Events and Serious Adverse Events

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.5.
- Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. 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 "nonserious") 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 on 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). Further information on follow-up procedures is provided in Section 8.4.4 and Section 10.5.
- 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 for AEs.
- 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.

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

- After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts.
- Any AEs observed from signing the ICF to the last trial-related activity will be followed until resolution, until the participant is lost to follow-up, or until the participant withdraws consent (as defined in Section 7.4). Resolution means that the participant 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 participant is lost to follow-up, all AEs will be categorized based on the investigator's last assessment.
- For the duration the participant is in the trial, resolution of SAEs (with dates) should be documented on the AE page of the eCRF and in the participant'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. See Section 10.6.
- For SAEs, AESIs, 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.
- Further information on follow-up procedures is provided in Section 10.5.

8.4.5. Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of IMP under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of IMP under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and file it with the IB and notify the IRB/IEC, if appropriate, according to local requirements.
- The sponsor or designee will be responsible for reporting SUSARs to the relevant regulatory authorities and IEC/IRB, as per applicable regulatory requirements. The sponsor or designee will also be responsible for forwarding SUSAR reports to all trial investigators, who will be required to report these SUSARs to their respective IECs/IRBs per local regulatory requirements.

8.4.6. Pregnancy

- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.6.

- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.7. Cardiovascular and Death Events

See Section 8.4.3.

8.4.8. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as Reportable Adverse Events or Serious Adverse Events

Not applicable.

8.4.9. 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/potential immunosuppression). Further characterizing information will be collected on the eCRF. This event could be expected due to the natural progression of the underlying disease, disorder, or condition of the participant(s) and the participant's predisposing risk factor profile including concomitant medications (eg, bruising in participants 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 AESIs in this trial.
- Due to the nature of the underlying disease (ie, ITP), any occurrence of bleeding will also be considered an AESI.

8.5. Treatment of 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 an AE.
- An overdose is defined as a deliberate or accidental administration of IMP to a participant, at a dose greater than that which was assigned to that participant per the trial protocol.
- A medication error is any preventable incident that may cause or lead to inappropriate IMP use or participant harm while the IMP is in the control of health care professionals. Such incidents 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 participant 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 on the eCRF including the additional AE, if any.

- In the event of an overdose, the investigator should:
  - Contact the medical monitor immediately.
  - Closely monitor the participant for any AE/SAE and laboratory abnormalities.
  - Document the quantity of the excess dose as well as the duration of the overdose on the eCRF.
- Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.6. Pharmacokinetics

- Serum samples for PK will be collected from each participant as presented in the SoA (Section 1.3). Concentrations of efgartigimod will be determined using a validated assay.
- The date and time of each sample will be recorded.
- Samples will be analyzed by the designated laboratory.
- If no sample was taken, the reason will be recorded in the relevant section of the eCRF.
- The PK samples will be taken predose, on the day of IMP administration.

8.7. Pharmacodynamics

- Serum samples for the determination of the PD marker (total IgG) will be collected as indicated in the SoA (Section 1.3).
- The date and time of each sample will be recorded.
- The PD samples will be taken predose on IMP administration visits.
- Samples will be analyzed by the designated laboratory. To maintain the blind, the IgG testing cannot be performed locally.
- The PD marker will be determined using a validated assay.
- Additionally, presence, nature, and level of antiplatelet antibodies will be tested as indicated in the SoA (Section 1.3).
- If no sample was taken, the reason will be recorded in the relevant section of the eCRF.

8.8. [redacted]

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

8.9. Hospitalization for ITP Management

- In-patient hospitalization for the management of ITP during the current trial, for at least an overnight stay, will be recorded separately.
- The hospitalization date and time of admission and discharge will be entered on the eCRF.
- Hospitalization for the participant's convenience will not be taken into account.

8.10. Genetics

Genetics are not evaluated in this trial.

8.11. Biomarkers

Biomarkers are not evaluated in this trial.

8.12. Immunogenicity Assessments

- Serum samples to assess antidrug antibodies (ADA) against efgartigimod and plasma samples to assess antibodies against rHuPH20 will be collected as indicated in the SoA (Section 1.3).
- Samples will be analyzed by the designated laboratory.
- Sampling will be done predose on IMP administration visits.
- All samples will be analyzed in validated immunogenicity assays, where samples are first screened for a positive assay response. A titer will be determined in the confirmed positive samples. Additionally, these samples will be tested for the presence of NAb against efgartigimod and/or rHuPH20, and titers will be determined for NAb against rHuPH20 in the overall population.
- If no sample was taken, the reason will be recorded in the relevant section of the eCRF.

8.13. Health Economics/Medical Resource Utilization

Not applicable.

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

The participant will complete the QoL questionnaire (SF-36 v2.0 and ITP-PAQ) and the PRO (FACT-Th6 and FACIT-Fatigue Scale) as indicated in the SoA (Section 1.3).

FACT-Th6: The FACT-Th6 uses the Likert scale, with participants 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 his/her 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."

ITP-PAQ: The ITP-PAQ is a 44-item questionnaire to assess the health-related QoL in adults with ITP. It includes scales on a 0 (worst) to 100 continuum for physical health (symptoms, fatigue/sleep, bother, and activity), emotional health (psychological and fear), overall QoL, social activity, women's reproductive health, and work.

9. STATISTICAL CONSIDERATIONS

The statistical analyses will be performed by the sponsor's designated CRO using statistical analysis systems SAS (SAS Institute, Cary, NC, United States) 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.

A detailed and comprehensive Statistical Analysis Plan (SAP) will be written and signed-off before final analysis database lock. Minor changes to the statistical methods set out in this protocol do not require a protocol amendment but will be documented (as changes from the protocol) in the SAP and in the trial report(s). The following paragraphs contain the main general features of the statistical analysis. More details will be provided as needed in the SAP.

9.1. Statistical Methods

9.1.1. Summary Tables, Figures, and Listings

- Summary tables will summarize endpoints (outcomes) by treatment group and time point (eg, visit). For continuous variables, the number of participants (with nonmissing values), mean, standard deviation and/or standard error, median, quartiles, minimum and maximum will be presented. For categorical variables, for each category, the number of participants (count) and percentage will be presented for participants without missing values.
- All summary tables and figures will be supported by full participant listings.

9.1.2. Hypothesis Testing and Confidence Intervals

Unless otherwise stated, all statistical tests will be two-sided and will be conducted at a 5% significance level. Two-sided 95% confidence intervals (CIs) will be provided.

9.2. Statistical Hypotheses

The statistical hypothesis was derived from the primary trial objective as stated in Section 3.

- Null hypothesis: the proportion of participants achieving sustained platelet count response while receiving efgartigimod PH20 SC is equal to the proportion of participants achieving sustained platelet count response while receiving placebo PH20 SC
- Alternative hypothesis: the proportion of participants achieving sustained platelet count response while receiving efgartigimod PH20 SC is different from the proportion of participants achieving sustained platelet count response while receiving placebo PH20 SC

9.3. Sample Size Determination

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

The null and alternative hypotheses are defined as H0: $\pi 1 = \pi 2$ vs HA: $\pi 1 \neq \pi 2$, where $\pi 1$ and $\pi 2$ are the population probabilities to achieve a sustained platelet count response (primary efficacy endpoint) for participants with chronic ITP receiving placebo PH20 SC and for participants with chronic ITP receiving efgartigimod PH20 SC, respectively.

In the placebo PH20 SC group, the response rate of participants with chronic ITP who reach the primary endpoint is expected to be ≤5%, while the response rate of participants with chronic ITP in the efgartigimod PH20 SC group is expected to be 21.8% (ie, π_1=0.05 and π_2=0.218), based on the observed response rates in trial ARGX-113-1801. Given these assumptions, a total of N=180 randomized participants with chronic ITP will ensure a power of at least 80% to reject the null hypothesis at a 1-sided significance level α of 0.025, based on Fisher's exact test.

For the first key secondary endpoint "extent of disease control," assuming distributions for cumulative number of weeks of disease control over the planned 24-week treatment period with platelet counts of $\geq 50 \times 10^9$/L in the chronic ITP population similar to those observed in ARGX-113-1801, a total of N=180 participants will ensure a power of >99% (2-sided α of 0.05), conditionally on reaching the primary endpoint, to detect a significant difference between both treatment groups. For ensuring a power of at least 90%, a total number of N=75 participants would be needed, given these assumptions. Calculations are based on the Wilcoxon-Mann-Whitney test, where the O'Brien-Castelloe approach[14] was taken to compute the power, taking into account a 2:1 allocation ratio to receive efgartigimod PH20 SC versus placebo PH20 SC.

9.4. Populations for Analyses

The following populations are defined:

Population	Description
Full analysis set (FAS)	All randomized participants.
Per protocol analysis set (PP)	All participants in the FAS for whom no major protocol deviation is reported.
Safety analysis set (SAF)	All participants in the randomized population who have received at least 1 dose or part of a dose of IMP.
PK analysis set	All participants from the safety analysis set who have at least 1 serum postbaseline PK measurement

9.5. Statistical Analyses

The SAP will be finalized before database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a

summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.5.1. General Considerations

- The baseline value will be the last assessment before the first administration of IMP.
- All trial visits will be recalculated based on actual dates and will be referred to as "analysis visits" which will be used in the statistical analyses. The rules for calculating the analysis visits will be documented in the SAP. Rules for imputing partial dates or missing dates will also be documented in the SAP.

9.5.2. Participant Disposition

Participant disposition will be summarized in a table. It will include the number of participants screened, randomized, received IMP treatment, completed the trial, as well as the number of early discontinuations from IMP treatment and trial, with reasons for discontinuation from IMP or trial. Summaries will be provided by treatment group.

9.5.3. Analysis Sets and Protocol Deviations

- The number of participants for each analysis set, as described in Section 9.4, will be presented in a table and listing.
- Major protocol deviations, by treatment group, will be summarized in a table and presented in a listing.
- The efficacy analysis will be performed on the FAS or the subset of participants in the FAS with chronic ITP; supportive analyses will be conducted on the per protocol analysis set.
- The efficacy analysis will be analyzed with intent-to-treat principle (ie, participants will be analyzed according to their planned treatment irrespective of the treatment actually received).
- The safety analysis will be performed on the safety analysis set.

9.5.4. Demographic and Baseline Characteristics, and Concomitant Medication

Participant demographic and baseline characteristics data, including prior and concomitant therapies will be summarized using standard summary statistics (see Section 9.1.1) and listed.

9.5.5. Primary Endpoint

9.5.5.1. Definition of the Estimand for the Primary Endpoint

- Population: adult participants with chronic ITP, having an average platelet count of $<30\times10^9$/L, and, at the start of the trial, either receiving concurrent ITP treatment(s) and having received at least 1 prior therapy for ITP in the past, or not receiving treatment for ITP but having received at least 2 prior treatments for ITP.

- Variable: 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
- Main intercurrent events:
  - early discontinuation of treatment (before visit 24) due to lack of efficacy (eg, more than 3 occurrences of rescue therapy) or due to an AE
  - initiation of rescue therapy at week 12 or later
  - increase of dose and/or frequency of concurrent ITP therapies at week 12 or later
- Population-level summary: proportion of participants with sustained platelet count response

9.5.5.2. Handling of Main Intercurrent Events

A composite strategy approach will be taken to address the main intercurrent events described previously. This implies that participants who discontinue treatment before visit 24 due to lack of efficacy (eg, more than 3 occurrences of rescue therapy) or due to an AE, as well as participants who receive rescue therapy at week 12 or later, or for whom dose and/or frequency of concurrent ITP therapies have increased at week 12 or later, will be considered nonresponders for the primary endpoint analysis.

9.5.5.3. 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 2-sided p-value. In addition, an adjusted difference of the proportions with its 95% CI will be provided.

9.5.5.4. Handling of Missing Data

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

9.5.5.5. 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 “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.

9.5.6. 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 $\geq50\times10^9$/L. For each participant, 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 two-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 of $\alpha=0.05$. An estimate of the location shift will be provided, along with the associated 95% CI.

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 participants in the overall population with a sustained platelet count response and on proportion of participants 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 will be analyzed in the same manner as the primary endpoint.

The number of bleeding events per participant (assessed using the WHO Bleeding Scale, where WHO scale ≥1 at any visit is considered a new bleeding event) will be analyzed using a stratified Wilcoxon-Mann-Whitney test similar to that used to compare the extent of disease control between both treatment groups. The test will be conducted at a significance level of $\alpha=0.05$. An estimate of the location shift will be provided, along with the associated 95% CI. 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 predefined 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 participants 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. Proportion of participants 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
4. The incidence and severity of the WHO-classified bleeding events in the overall population

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.

9.5.7. Other Secondary Endpoint Analyses Not Subject to Alpha Control

The secondary endpoints on overall platelet count and IWG response[3] will be analyzed in the same manner as the primary endpoint. The secondary endpoint on extent of disease control will be 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/QoL 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/QoL, history of splenectomy (yes vs no), and receiving concurrent ITP therapies at baseline (yes vs no). Within-participant correlation will be modeled by assuming an unstructured covariance matrix for the error terms. Least square (LS) means for placebo PH20 SC and efgartigimod PH20 SC will be provided, along with the difference in LS means, 95% two-sided CI, and two-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 PH20 SC vs placebo PH20 SC will be provided, along with the associated 95% two-sided CI and two-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 $\geq 20\times10^9$/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 $\geq 20\times10^9$/L above baseline within the group of participants 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 participant (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.

9.5.8. Exploratory Endpoints

- [redacted]

[redacted]

9.5.9. Safety Analyses

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

9.5.10. Other Analyses

9.5.10.1. Pharmacodynamics, Pharmacokinetics, and Immunogenicity

Descriptive statistics will be provided for PD parameters (total IgG and antiplatelet antibodies), the presence of antibodies and neutralizing antibodies, and titers of antibodies against efgartigimod and/or rHuPH20. Efgartigimod serum concentration data will be summarized.

A population PK/PD analysis may be performed and will be reported in a separate report.

9.6. Interim Analyses

Not applicable.

9.7. Data Monitoring Committee

See Section 10.1.5.1.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This trial will be conducted and the informed consent will be obtained in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
  - The applicable drug and data protection laws and regulations of the countries where the trial will be conducted
- Before the start of the trial, approval of regulatory authorities should be obtained (if applicable).
- To comply with the Declaration of Helsinki (2013), the sponsor is currently assessing the appropriateness and possibility of making the trial drug available for clinical trial participants posttrial.
- The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure (IB), and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board/Independent Ethics Committee (IRB/IEC) by the investigator, and reviewed and approved by the IRB/IEC before the trial is initiated.
- Any amendments to the protocol will require IRB/IEC and regulatory authority (if applicable) approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the trial to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures

- Providing oversight of the conduct of the trial at the investigative site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- Providing 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.
- Supplying 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.
- Promptly reporting to the IRB/IEC any new information that may adversely affect the safety of participants or the conduct of the trial.
- Upon completion of the trial, the investigator will provide the IRB/IEC with a brief report of the outcome of the trial, if required.

10.1.2. Financial Disclosure

- 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 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.

10.1.3. Informed Consent Process

- Before signing the ICF, the trial participants 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. If a participant's caregiver will be trained to administer the IMP, he/she will also have to sign an ICF.
- If the IMP will be administered by the participant's caregiver at the trial site, he/she will have to sign a separate ICF in which he/she agrees to share personal data and to be trained by the investigator or designee to administer the SC injections of efgartigimod PH20.
- The participant will sign the caregiver's ICF to indicate that he/she agrees that this person will be his/her caregiver.
- The investigator needs to confirm that the caregiver is competent to administer the IMP.
- The caregiver's training will be documented. The investigator will sign and save this documentation in the participant's file.

- Any participant who provides informed consent will be assigned a unique participant ID via the IRT system.
- The investigator or his/her representative will explain the following to the participant and answer all questions regarding the trial: 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 participant's records.
- The investigator or his/her representative will explain the following to the caregiver and answer all questions regarding his/her role as a caregiver: the purpose of the trial, the purpose of his/her role as a caregiver, the expected duration, and the extent to which confidentiality of his/her personal data will be maintained.
- Participants must be informed that their participation is voluntary, that they may withdraw from the trial at any time, and that withdrawal of consent will not affect their subsequent medical treatment or relationship with the treating physician.
- Caregivers must also be informed that taking on the role of caregiver is voluntary and that they may withdraw at any time.
- Participants will be required to sign a statement of informed consent, after receipt of detailed information on the trial, that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or trial center.
- Caregivers will also be required to sign an ICF, after receipt of detailed information on their role as a caregiver in this trial.
- The ICF will be used to explain the potential risks and benefits of trial participation to the participant in simple terms before the participant is screened.
- The caregiver ICF will be used to explain, in simple terms, the potential risks and disadvantages of taking on the role of caregiver.
- A separate ICF will be issued in case of pregnancy of a female partner of a male participant.
- The ICF and the caregiver ICF contain a statement that the consent is freely given.
- All participant information and ICFs must be available in the local and vernacular languages required at the investigative site and include participant information sheets/brochures that outline the trial procedures. All ICF(s) must be signed and dated by the participant.
- The caregiver ICF must be available in the local and vernacular languages required at the investigative site. All caregiver ICF(s) must be signed and dated by the caregiver and the participant.
- Confirmation of a participant's informed consent must also be documented in the participant's medical record before any trial-related procedure under this protocol,

including screening tests and assessments. The authorized person obtaining the informed consent must also sign the ICF.

- Confirmation of a caregiver's informed consent must also be documented in the participant's medical records before any administration of IMP by the caregiver occurs. The authorized person obtaining the informed consent must also sign the caregiver ICF.
- The investigator is responsible for ensuring that the informed consent is obtained from each participant and for obtaining the appropriate signatures and dates on the informed consent document before the performance of any protocol procedures and before the administration of investigational medicinal product (IMP).
- The investigator is responsible for ensuring that the informed consent is obtained from the caregiver, including the appropriate signatures and dates on the caregiver ICF, before any administration of IMP by the caregiver occurs.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the trial.
- If a new version of the caregiver ICF is issued, the participant and his/her caregiver must both reconsent.
- A signed and dated copy of the ICF(s) must be provided to the participant.
- A signed and dated copy of the caregiver ICF must also be provided to the participant and his/her caregiver.
- Participants may be rescreened (ie, redoing the full assessments as per Schedule of Activities [SoA], Section 1.3) or retested once (ie, redoing 1 test) if still within the screening period. See Section 5.4.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant and his/her caregiver must be informed that his/her personal trial-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant and his/her caregiver, who will be required to give consent for their data to be used as described in the respective informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

- The ICF and the caregiver ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.
- The caregiver must be informed that his/her personal data may be examined by clinical quality assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

10.1.5.1. Data Safety Monitoring Board

- The sponsor will appoint an independent Data Safety Monitoring Board (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 participants treated up to that point, rates, and participant-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).

10.1.6. Dissemination of Clinical Trial Data

- The sponsor or designee, and auditor may access participant 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 participant's chart and electronic case report form (eCRF) records. Such information must be kept confidential in 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 participant enrolled into the trial.
- The investigator is responsible for maintaining source documents. These will be made available for verification by the sponsor's designated contract research organization (CRO) monitor at each monitoring visit. The investigator must submit an eCRF for each participant, regardless of duration of participation or administration of IMP (ie, an eCRF must be submitted for screen failures as well). All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the trial and participant number.

Any personal information, including participant name, should be removed or rendered illegible to preserve data privacy.

10.1.7. Data Quality Assurance

- All participant data relating to the trial will be recorded on eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this trial including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Trial monitors will perform ongoing source data verification to confirm that data entered onto the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements. Only if not allowed as per local regulations, no source data verification will occur for data regarding race and ethnicity since the eCRF will serve as the source.

10.1.7.1. 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 participant 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. Participant identification codes (participant 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 before changing the location or status of any essential clinical trial documents. The investigator must contact the sponsor before disposing of any trial records.
- No records should be disposed without the written approval of argenx BV.
- 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.

10.1.7.2. 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.

10.1.7.3. 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 the sponsor or its 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 clinical trial report (CTR)
- to avoid interobserver 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 World Health Organization (WHO) bleeding scale.

In addition, periodic audits can be performed as specified in Section 10.1.7.2.

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.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Paper quality-of-life (QoL) questionnaires and patient-reported outcome (PRO) are part of the source documents and must be transcribed onto the eCRF.
- Data entered on the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial. Also, current medical records must be available.

10.1.9. 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 standard operating procedures (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 participants 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 (wherever allowed as per local regulations), and source document review.
- The source documentation agreement form describes the source data for the different data on 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 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 of the trial, the sponsor's designated CRO monitor will conduct investigative site closure activities with the investigator and site staff as appropriate, in accordance with applicable regulations, ICH GCP guidelines, and CRO/sponsor procedures.

10.1.10. 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 participant in electronic format (ie, eCRF). Data will be transcribed by the trial site staff from the source documents onto the eCRF, as per local regulations. 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 before the trial is initiated, and any data are entered into the system for any trial participant 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. Only if requested as per local regulations, no data collection or source data verification will be performed on race and ethnicity. Source documents are all documents used by the investigator or hospital that relate to the participant's medical history, that verify the existence of the participant and the inclusion and exclusion criteria, and all records covering the participant's participation in the trial. They can include laboratory notes, electrocardiogram (ECG) results, memoranda, pharmacy dispensing records, participant 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. Before 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 on the eCRFs has been reviewed by the investigator and is true and accurate. The investigator will be required to electronically sign the eCRF.

- The data will be verified for completeness, 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 electronic data capture 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, etc. These data will need to be reconciled with the data recorded on 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 procedures, and medical history terms will be assigned to a lowest level term and a preferred term (PT), and will be classified by high level term, high level group term, and primary system organ class (SOC) 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 and procedures.

10.1.11. Trial and Site Start and Closure

- The trial start date is the date of the first ICF signature.
- The sponsor or designee reserve the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of the sponsor. Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial site closure visit has been performed.
- The investigator may initiate trial site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.
- Reasons for the early closure of a trial site by the sponsor may include but are not limited to:
  - Safety concerns as recommended by the DSMB
  - Inability to achieve the recruitment target within a reasonable time
  - In the sponsor’s judgment there are no further benefits to be expected from the trial

  - Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
  - Discontinuation of further trial medication development

- If the trial is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the trial of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.
- 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 participants.

10.1.12. Investigator Obligations

- This trial will be conducted by qualified investigators under the sponsorship of argenx BV (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 investigative site.
- The investigator is responsible for ensuring that all trial site personnel, including subinvestigators, 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.
- The investigator will comply with the protocol which has been approved/given favorable opinion by the IRB/IEC, according to ICH 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. Subinvestigators or other designated site staff are eligible to sign for the investigator, except where the investigator's signature is specifically required.

10.1.13. Sponsor 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.

10.1.14. 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 results have been analyzed and reported and must be submitted to the sponsor for review and comment before submission for publication or presentation. Trial participant identifiers will not be used in the publication of results.
- The sponsor will comply with the requirements for publication of trial results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual investigative site data.
- Authorship will be determined by mutual agreement and aligned with International Committee of Medical Journal Editors criteria[15] authorship requirements, 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.

10.2. Appendix 2: Clinical Laboratory Tests

Table 3: Protocol-Required Laboratory Assessments

Hematology	Hemoglobin, white blood cell (WBC) count with WBC differential
Coagulation	Activated partial thromboplastin time (aPTT), prothrombin time
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[a], potassium, sodium, calcium, hemoglobin A1c (HbA1c), cholesterol (total cholesterol, high density lipoprotein [HDL], low density lipoprotein [LDL]), triglycerides, serum levels of total IgG[b]
Urinalysis	Color, clarity/appearance, specific gravity, pH, protein[a], glucose, ketones, blood, bilirubin, urobilinogen, nitrite, leukocyte esterase, and microscopic examination including red blood cell (RBC) count, WBC, casts, crystals, bacteria
Serology	HIV antibodies (1 and 2), HBV surface antigen (HBsAg), antibodies to the surface and core antigens of the HBV (anti-HBs and anti-HBc), HBV DNA, hepatitis C virus antibody (HCV-Ab), HCV RNA
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, thyroid peroxidase antibody, thyroglobulin antibody, TSH receptor antibody
Local evaluations	[redacted] urine pregnancy
Other exploratory	[redacted]

[a] Albumin and urine total protein (if result is quantitative) will not be reported to the site to maintain the blind, and an alert system will be implemented for appropriate communication to the investigator, as necessary.
[b] This will be assessed at screening only, to maintain the blind.

10.3. Appendix 3: Pharmacokinetic, Pharmacodynamic, and Immunogenicity Assessments

Table 4: Protocol-Required Pharmacokinetic, Pharmacodynamic, and Immunogenicity Assessments

Pharmacokinetics	Serum levels of efgartigimod
Pharmacodynamic markers	Serum levels of total IgG
Antiplatelet antibodies	Presence, nature, and level of antiplatelet antibodies
Immunogenicity	Serum levels of anti-efgartigimod and plasma levels of anti-rHuPH20 binding antibodies, neutralizing antibodies (NAb) against efgartigimod and rHuPH20, and titers of NAb against rHuPH20 in the overall population

10.4. Appendix 4: Washout Requirements Before First IMP Administration

Drug/Intervention/Event	Prohibited Period (from Last Dose of Agent)
Major thrombotic or embolic event (eg, myocardial infarction, stroke, deep venous thrombosis, or pulmonary embolism)	5 years
Any monoclonal antibody or Fc fusion protein	6 months
Investigational drug, Fc-containing biologics, like soluble receptors	3 months or 5 half-lives, whichever is longer
Anticoagulants (eg, vitamin K antagonist, direct oral anticoagulant)	4 weeks
Transfusion (blood, platelets, plasma)	4 weeks
Ig (IV, SC, or intramuscular) or PLEX	4 weeks
Romiplostim (contains Fc fragment)[a]	4 weeks
Splenectomy	4 weeks
Live/live-attenuated vaccines	4 weeks before screening
Anti-CD20 therapy (eg, rituximab)	6 months before randomization

[a] Binds to FcRn to extend half-life; efgartigimod might interfere with disposition.

10.5. Appendix 5: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.5.1. Definition of Adverse Event

Adverse Event Definition
• An adverse event (AE) is any untoward medical occurrence in a clinical trial participant, temporally associated with the use of trial intervention, whether or not considered related to the trial intervention. • 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 trial intervention.

Events to be Collected as Adverse Events
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram [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 trial intervention administration even though it may have been present before the start of the trial. • Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either trial intervention or a concomitant medication. Overdose per se will not be reported as an AE/serious adverse event (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 an AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT to be Collected as Adverse Events
• 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 participant'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 participant's condition. Note: Except for any occurrence of bleeding which will be considered an AESI as per Section 8.4.9. • 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 trial that do not worsen.

10.5.2. Definition of Serious Adverse Event

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

1. Results in death

2. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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 were more severe.

3. Requires in-patient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant 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.

4. Results in persistent disability/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.

5. Is a congenital anomaly/birth defect

6. 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 participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
  - 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.

10.5.3. Recording and Follow-up of Adverse Events and/or Serious Adverse Events

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Severity

The investigator will make an assessment of intensity for each AE and SAE reported during the trial.

All AEs observed will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

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, using 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 (ADL) (eg, preparing meals, shopping for groceries or clothes, using the telephone).
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4: Life-threatening consequences or urgent intervention indicated.
- Grade 5: Death related to AE.

NOTE: An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between trial intervention and each occurrence of each AE/SAE, using 1 of the following categories:
  - Not related: events can be classified as "not related" if there is not a reasonable possibility that the investigational medicinal product (IMP) caused the AE.
  - Unlikely related: 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.
  - Possibly related: 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.
  - Probably related: 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.
  - Related: 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 participant's clinical state.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to trial intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.
- In the final evaluation for reporting, the assigned relationship, as per the CIOMS will be converted into a "binary determination," as follows: Events with an assigned relationship of "unrelated" and "unlikely" will be grouped into the "unrelated" category. Events with an assigned relationship of "related," "possibly related," or "probably related" will be grouped into the "related" category.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the trial or during a recognized follow-up period, the investigator will provide a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally submitted documents. • The investigator will submit any updated SAE data within 24 hours of receipt of the information.

10.5.4. Reporting of Serious Adverse Events

SAE Reporting via Paper Report Form
• All SAEs will be recorded (within 24 hours) on the paper SAE report form and the AE form on the electronic case report form (eCRF). • The investigator or delegated site staff should check that all entered data are consistent. • An alert email for the SAE report on the eCRF will then automatically be sent by email to the sponsor's designated contract research organization (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).

10.6. Appendix 6: Contraceptive Guidance and Collection of Pregnancy Information

10.6.1. Definitions

10.6.1.1. Woman of Childbearing Potential

A female is considered a woman of childbearing potential (WOCBP) unless she is either:

a. Postmenopausal:
A postmenopausal state is defined by continuous amenorrhea for at least 1 year without an alternative medical cause with a follicle-stimulating hormone (FSH) measurement of >40 IU/L. If a postmenopausal woman is using hormonal therapy, such as hormone replacement therapy or hormonal contraceptives, FSH levels might be suppressed and therefore an FSH test to confirm a postmenopausal state is not considered valid. In this case, the postmenopausal state will need to be assessed by the investigator.
b. Surgically sterilized:
Women who have had a documented permanent sterilization procedure (eg, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).

10.6.2. Contraception Guidance

10.6.2.1. Female Contraception For Women of Childbearing Potential

WOCBP must use 1 of the following contraception methods from signing the ICF until the date of the last dose of IMP.

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with the inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner

- Sexual abstinence: A highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the IMP. The reliability of sexual abstinence needs to be evaluated relative to the duration of the trial and the preferred and usual lifestyle of the participant.
- Progestogen-only hormonal contraception in which inhibition of ovulation is not the primary mode of action:
  - Oral
  - Injectable
  - Implantable
- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide

10.6.3. Collection of Pregnancy Information

10.6.3.1. Male Participants With Partners Who Become Pregnant

- Male participants will be instructed through the ICF to immediately inform the investigator if their partner becomes pregnant during the trial.
- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this trial.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy and submitted via email or fax (see the Safety Mailbox/Fax details on the title page of this protocol).
- The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- An investigator, who is contacted by the male participant 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.

10.6.3.2. Female Participants Who Become Pregnant

- 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 Schedule of Activities (SoA) (Section 1.3).

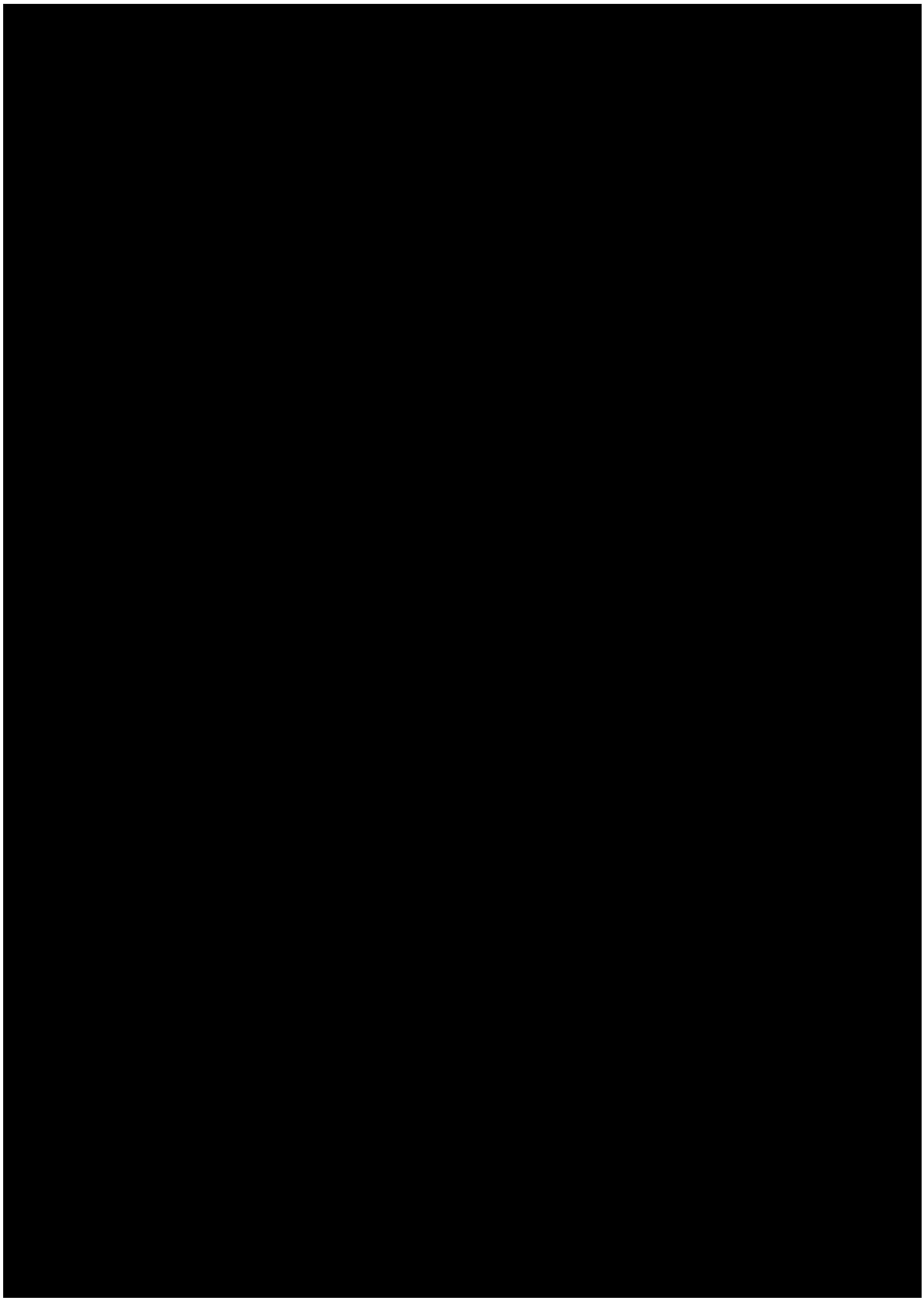
- The investigator will collect pregnancy information on any female participant who becomes pregnant during the trial until their last dose of IMP. The initial information will be recorded on the appropriate form and submitted to the sponsor and/or sponsor's designee within 24 hours of learning of a participant's pregnancy. The following actions will be performed:
  - The participant should immediately be discontinued from IMP treatment.
  - The participant should have the early discontinuation assessments and enter the 8-week follow-up period.
  - All assessments for early discontinuation (see Section 7) must be performed unless contraindicated by pregnancy (harmful to fetus) or unless the participant withdraws informed consent.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an adverse event (AE) or serious adverse event (SAE), any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such. Any posttrial pregnancy-related SAE considered reasonably related to the IMP by the investigator will be reported to the sponsor as described in Section 8.4.5. While the investigator is not obligated to actively seek this information in former trial participants, he or she may learn of an SAE through spontaneous reporting.
- The investigator must update the participant with information currently known about potential risks and available treatment alternatives.
- 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.

10.7. Appendix 7: Administrative Structure

Central Laboratories
Cerba Research NV Industriepark Zwijnaarde 3 9052 Gent Belgium
Analysis of Pharmacokinetics, Anti-Drug Antibodies, and Neutralizing Antibodies Against Efgartigimod
DDS (formerly known as 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
Binding Antibodies and Neutralizing Antibodies Against rHuPH20
LabCorp Bioanalytical Services, LLC 8211 SciCor Drive, Suite B Indianapolis, IN 46214 USA
Antiplatelet Antibodies
Sanquin Diagnostic Services Plesmanlaan 125 1066 CX Amsterdam The Netherlands
Long-Term Storage of Pharmacokinetics-Pharmacodynamics, Anti-Drug Antibodies, Antiplatelet Antibodies Samples
Azenta Life Science (previously known as Brooks Life Science, BioStorage Technologies GmbH) Im Leuschnerpark 1B 64347 Griesheim Germany
[redacted]
[redacted]

Central ECG Reading
Clario 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 (an ICON company) 700 Deerpath Drive Vernon Hills, IL 60061-1802 USA
Clinical Trial Supply Management
Trial-specific packaging and labeling, shipment to non-EU trial centers: Fisher Clinical Services GmbH Steinbühlweg 69 4123 Allschwil Switzerland Final EU batch release: Fisher Clinical Services GmbH Im Woerth 3 79576 Weil am Rhein Germany Trial-specific packaging and labeling, shipment to EU and non-EU trial centers: Fisher Clinical Services GmbH Marie-Curie-Str. 16 D-79618 Rheinfelden (Baden) Germany
Data Management, Biostatistics, and Medical Data Review
SGS Life Sciences (SGS LS), a division of SGS Belgium NV Generaal de Wittelaan 19A b5 B-2800 Mechelen Belgium
Drug Safety Reporting
Parexel International 1 Federal Street Billerica, MA 01821 USA

10.8. Appendix 8: World Health Organization Bleeding Scale



10.9. Appendix 9: Possible Adaptations of Trial Protocol During COVID-19 Pandemic

The aim of trial ARGX-113-2004 is to evaluate the efficacy and safety of efgartigimod PH20 SC in adult participants 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 Schedule of Activities [SoA], Table 5). 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 AEs reported during argenx clinical trials.

Based on this risk/benefit assessment, ARGX-113-2004 can continue during the COVID-19 pandemic. However, it may not always be possible to perform all visits at the trial site during the pandemic.

To allow participants with ITP to receive treatment with the investigational medicinal product (IMP) during the COVID-19 pandemic, this appendix to the protocol has been developed. If a visit to the trial site is not possible, a home visit or a visit at an alternative convenient location can be allowed, as per local regulations. 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 participants to attend the trial visits at the trial site. As soon as the situation returns to normal, the measures specified here will no longer apply.

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

Permission and Duration to Use the "Updated" Protocol Version

This appendix to the protocol is intended for countries and/or investigative 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 written approval from the sponsor or the contract research organization (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 on the electronic case report form (eCRF) for the applicable visit.

Testing for COVID-19

Additional testing for COVID-19 beyond that mandated by relevant local authorities for the participant's screening and randomization is not required. However, argenx recommends participants who develop symptoms of COVID-19 during the trial to be tested. See also Figure 1.

Based on exclusion criterion 23 "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 participant at undue risk," participants 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, as well as qualified personnel from an alternative convenient location, should apply appropriate social distancing and use personal protective equipment as directed by the local guidelines.

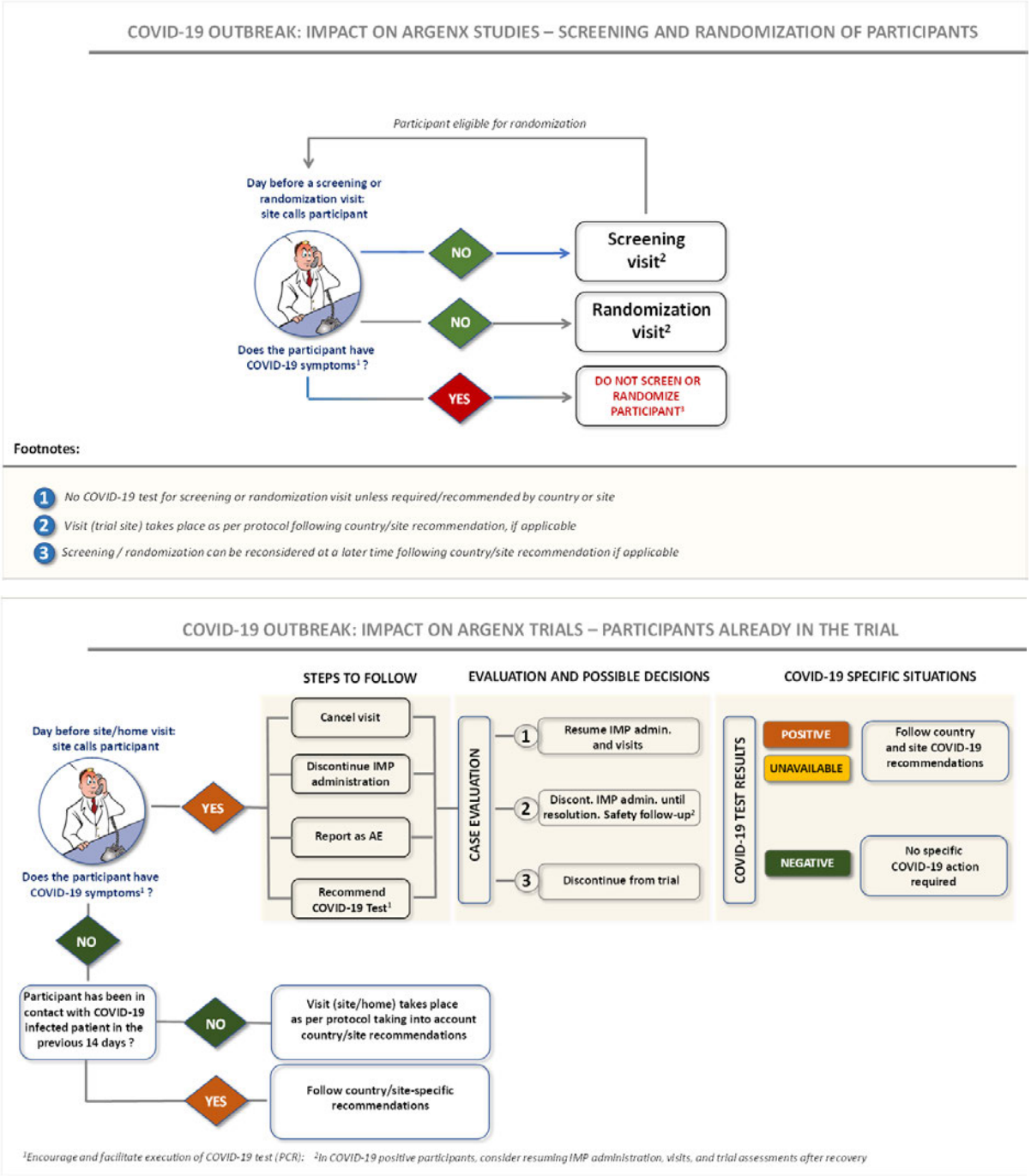
Participants With COVID-19 (Either a Positive Test or With Symptoms)

The instructions to manage infections in the main protocol are also applicable in case of COVID-19 (ie, it will be considered an adverse event of special interest [AESI]). The administration of IMP may be temporarily withheld if it could put the participant at undue risk due to clinically significant disease, including evidence of infection (see Section 6.7).

During the pandemic, site staff or the home nurse should call participants before each visit to inquire 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 that follow. If the participant is placed in quarantine and is not able to receive IMP, the investigator can specify on 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 on the eCRF.

Figure 1: Decision Tree for the Treatment of Participants



In case of (suspected) COVID-19, the participant will be treated as guided by the local health care system. Participants 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. If the participant must 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 participant can remain in the trial.

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

Forms completed at the participant's home must be taken back to the site for data entry. If the trial site is closed due to the COVID-19 situation, the completed forms must 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. If the trial site is closed due to the COVID-19 situation, an alternative convenient location considered appropriate by the investigator and the participant (and confirmed and approved by the sponsor) can be used (eg, an infusion center, local clinic).

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

Please note that prospective protocol waivers remain unacceptable and that participants 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. If the trial site is closed due to the COVID-19 situation, an alternative convenient location considered appropriate by the investigator and the participant (and confirmed and approved by the sponsor) can be used (eg, an infusion center, local clinic).

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 participant's home (or an alternative convenient location) to conduct the visit(s). The investigator will talk to the participant via an audio or video interview to elicit AEs, concomitant medications, and the general well-being of the participant. The investigator will perform the World Health Organization (WHO) bleeding assessments using a video interview with the participant. 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 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 and should be aligned with applicable local regulations.

Scheme for Home Visits[a]		
Assessment	**Performed by**	**Place/Method of Assessment**[a]
• Participant eligibility	Trained qualified physician	Preferably at the trial site
• Quality-of-life and patient-reported outcomes	Participant	At participant's home
• Weight • Electrocardiogram • Urinalysis • Urine pregnancy test • Blood sample (platelet count, hematology, chemistry, serum pregnancy, viral tests, pharmacodynamics, antiplatelet antibodies, immunogenicity, pharmacokinetics) • IMP injection	Trained qualified nurse	In person at participant's home
• Vital signs • Physical examination	Trained qualified nurse/trained qualified physician	In person at participant's home
• General bleeding assessment (WHO)	Trained qualified physician	In person at participant'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 take the blood sample at the participant'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 from the day before, or all can be done on the day in 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, ITP-PAQ, FACT-Th6, and FACIT-Fatigue can be completed at home (or an alternative convenient location) by the participant.

Weight

Calibrated scales can be provided to the home nurse or the participant.

Vital Signs

Vital signs can be performed at home (or an alternative convenient location) by a trained qualified nurse or physician. 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 laboratory. 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 laboratory. 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 laboratory. 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 laboratory. 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 laboratory. The testing should be done by the initially appointed designated 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 laboratory. The testing should be done by the initially appointed laboratory.

Immunogenicity

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 laboratory. 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) using the laboratory kits/requisition forms supplied by the central laboratory. The testing should be done by the initially appointed laboratory.

IMP Injections

A trained qualified nurse can administer the IMP at the participant's home (or an alternative convenient location). Detailed instructions on IMP management can be found in the Home Guide for Preparation and Administration. After the administration of the IMP, the participant must be observed for injection-related reactions by the trained qualified nurse for at least 30 minutes following the end of the injection for routine safety monitoring based on the participant'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 AEs can be performed at home (or an alternative convenient location) through a phone/video call with the investigator.

Schedule of Activities

In the following SoA, the assessments preferably performed at the trial site are indicated with a solid dot "●"(ie, mandatory). The assessments that can be omitted if 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 5: Schedule of Activities

Trial Period[a]		**Treatment Period**																											
Visit	Screening[b]	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	End-of-Treatment	Early Discontinuation	Follow-up 1	Follow-up 2	Unscheduled
Trial day	*-14 to -1*	*1*	*8*	*15*	*22*	*29*	*36*	*43*	*50*	*57*	*64*	*71*	*78*	*85*	*92*	*99*	*106*	*113*	*120*	*127*	*134*	*141*	*148*	*155*	*162*	*169*				
Visit window, days			+2																											
Informed consent form[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	Δ
			Can be performed within 1 day of the next procedure																											
SF-36(v2)		●								Δ								Δ								Δ	Δ			
ITP-PAQ[f]		●												Δ												Δ	Δ			
FACT-Th6/FACIT-fatigue scale		●				Δ				Δ				Δ				Δ				Δ				Δ	Δ			
Weight	●									Δ								Δ							Δ	Δ	Δ			
Vital signs, including height[g]	●	●	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	Δ
Physical examination	●	●				Δ				Δ								Δ							Δ	Δ	Δ			Δ
Electrocardiogram	●	●[h]				Δ[h]				Δ[h]				Δ[h]				Δ[h]				Δ[h]			Δ[h]	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	Δ
Urinalysis[i]	●[j]	●	Δ	Δ	Δ		Δ		Δ		Δ		Δ		Δ		Δ		Δ		Δ		Δ		Δ	Δ	Δ	Δ	Δ	Δ
Urine pregnancy test[k]		●				Δ				Δ				Δ				Δ				Δ				Δ	Δ	Δ	Δ	Δ
Hematology and chemistry test[i]	●[j,l]	●	Δ	Δ	Δ		Δ		Δ		Δ		Δ		Δ		Δ		Δ		Δ		Δ		Δ	Δ	Δ	Δ	Δ	Δ
Serum pregnancy test[i,k]	●[j]																													
Follicle-stimulating hormone[i,m]	●[j]																													
Coagulation, thyroid, and autoimmune antibody testing[i]	●[j]																													
Viral tests[i]	●[j]																													
Tuberculosis QuantiFERON test[i]		●[n]																												
Pharmacodynamics[i,o,p]		●	Δ	Δ	Δ		Δ[q]		Δ[q]		Δ[q]		Δ[q]		Δ[q]		Δ[q]		Δ[q]		Δ[q]		Δ[q]		Δ[r]	Δ	Δ	Δ	Δ	Δ
Antiplatelet antibodies[i,p]		●							Δ[q]								Δ[q]								Δ[r]	Δ	Δ			Δ
Immunogenicity[i,p]	●	●			Δ				Δ[q]				Δ[q]				Δ[q]				Δ[q]				Δ[r]	Δ	Δ	Δ	Δ	Δ
[redacted]																														
Pharmacokinetics[i,p]		●	Δ	Δ	Δ		Δ[q]		Δ[q]		Δ[q]		Δ[q]		Δ[q]		Δ[q]		Δ[q]		Δ[q]		Δ[q]		Δ[r]	Δ	Δ	Δ	Δ	Δ
Randomization[t]		●																												

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

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

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

[a] **Trial Period:**

Screening Period: maximum 14 days

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

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

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

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

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

[b] 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 informed consent form (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.

[e] Platelet count is measured locally and can be performed within 1 day (for postbaseline visits) of the next procedure as per schedule of activities (both dosing and nondosing visits). Eligible participants should have a mean platelet count of $<30\times10^9$/L from at least 3 documented, qualifying counts within the 3 preceding months where at least 2 of the qualifying counts must be taken during the screening period: 1 platelet count collected during the screening period and the predose platelet count on the day of randomization (visit 1). If the third count is not available from the 3 preceding months, this third platelet count can

be obtained during the screening period. [redacted].

[f] If available at baseline.

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

[h] If IMP is administered, the ECG will be performed after the IMP administration.

[i] Laboratory assessments include all parameters mentioned in Section 10.2. On days that IMP is administered, samples for laboratory assessments should be collected before dosing, unless otherwise requested.

[j] At the screening visit, if the investigator detects 1 or more screening laboratory abnormalities which are not aligned with the medical history and clinical evaluation of the participant, the result(s) should be confirmed if still within the screening window. For rescreening criteria see Section 5.4.

[k] Only for women of childbearing potential.

[l] At the screening visit, the total IgG level must be determined by the central laboratory (exclusion criterion 9).

[m] Only for women of non-childbearing potential.

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

[o] To maintain the blind, the IgG testing cannot be performed locally.

[p] To be collected predose, on the day of IMP administration.

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

[r] If the visit does not coincide with an IMP administration, then the assessment should **NOT** be performed.

[s] [redacted]

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

[u] The IMP (efgartigimod PH20 SC or placebo PH20 SC) will be administered as an SC injection at each IMP administration visit. Participants will be observed for at least 30 minutes following the end of the injection for routine safety monitoring based on the participant's clinical status. Assessment of the dosing regimen as described in Section 6.5 will be applied.

[v] Adverse events, procedures, and intake of concomitant medication(s) will be monitored continuously from signing the ICF until the last trial-related activity, unless the participant withdraws consent. In case of early discontinuation, any adverse events/serious adverse events should be assessed until the participant has ended the trial until satisfactory resolution or stabilization. All available vaccination history will be recorded as part of the participant's prior medication for vaccinations received in the past, or concomitant medication for vaccinations received during the trial.

10.10. Appendix 10: Definition of Terms

Blinding:

A procedure in which 1 or more parties to the trial are kept unaware of the treatment assignment 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 an adverse event (AE) or serious adverse event (SAE). In a double-blinded trial, the participant, the investigator, site staff, and sponsor staff who are involved in the treatment or clinical evaluation of the participants and the review or analysis of data are all unaware of the treatment assignment.

Council for International Organizations of Medical Sciences:

- The 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 BV, assume(s) 1 or more obligations of argenx BV, eg, development of a protocol, selection and/or monitoring of investigators, evaluation of reports, or 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 recommendations 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 participants are protected (ICH E6 [R2]).

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), the 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 ICF.

International Council for Harmonisation:

The ICH is a project that brings together the regulatory authorities of Europe, Japan, and the 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 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 trial participant.

Caregiver:

A caregiver is a person of legal age from the participant's social network (eg, family, relatives, friends), chosen by the participant. Once he/she receives the necessary training and is found competent by the authorized site staff to perform IMP administration, the caregiver can administer SC injections to the participant.

10.11. Appendix 11: Abbreviations

ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ASH	American Society of Hematology
CI	confidence interval
CIDP	chronic inflammatory demyelinating polyneuropathy
CIOMS	Council for International Organizations of Medical Sciences
CRO	contract research organization
CTCAE	common terminology criteria for adverse events
CTR	clinical trial report
C_{trough}	serum concentration observed predose
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
FACIT	Functional Assessment of Chronic Illness Therapy
FACT	Functional Assessment of Cancer Therapy
FAS	full analysis set
Fc	crystallized fragment
FcRn	neonatal crystallized fragment receptor
FSH	follicle-stimulating hormone
GCP	good clinical practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
Ig	immunoglobulin
IMP	investigational medicinal product
IND	investigational new drug
[redacted]	[redacted]
[redacted]	[redacted]
IRB	Institutional Review Board

IRT	interactive response technology
ITP	immune thrombocytopenia
ITP-PAQ	ITP-Patient Assessment Questionnaire
IV	intravenous
IVIg	immunoglobulins given intravenously
IWG	International Working Group
LS	least square
MG	myasthenia gravis
NAb	neutralizing antibodies
NCI	National Cancer Institute
OR	odds ratio
PD	pharmacodynamic
PK	pharmacokinetics
PLEX	plasmapheresis
PRO	patient-reported outcomes
QoL	quality-of-life
qw	every week/weekly
q2w	every other week
q4w	every 4 weeks
rHuPH20	recombinant human hyaluronidase PH20
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SF-36	Short Form-36
SoA	schedule of activities
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TPO-RA	thrombopoietin receptor agonist
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

10.12. Appendix 12: Protocol Amendment History

Amendment 4 (17 Feb 2023)

This amendment is considered to be substantial based on the definition in Article 2 §2 (13) of the Regulation (EU) No 536/2014 of the European Parliament and the Council of the European Union.

Overall Rationale for This Amendment

The primary reason for this amendment is to implement recommendations from the data safety monitoring board (DSMB) to modify the exclusion criterion regarding medical history of thromboembolic events and to require a mandatory discontinuation from trial intervention for participants who have an initial or recurrent malignancy. Editorial changes are included to help with readability.

The protocol amendment Summary of Changes table for the previous amendment can be found in Section 10.12.

The major changes from protocol v4.0 to v5.0 are summarized in the following table. Refer to Section 10.11 for any undefined abbreviations.

Section	Description of change	Brief rationale
5.2, Exclusion Criteria, Criterion 12 10.4, Appendix 4: Washout Requirements Before First IMP Administration	The exclusion criterion and washout period for serious thromboembolic events was updated. The prohibited period for any major thrombotic or embolic event (eg, myocardial infarction, stroke, deep venous thrombosis, or pulmonary embolism) was revised from within 12 months to within 5 years before randomization. Exclusion criterion 12 was renumbered as 12a.	The DSMB monitoring the ARGX-113 ITP program recommended a revision to the washout period for the exclusion of participants with serious thromboembolic events.
7.1, Discontinuation of Trial Intervention	Language was added to clarify that any participant developing a new or recurrent malignancy except basal cell carcinoma will discontinue trial treatment regardless of the relationship to IMP.	The DSMB monitoring the ARGX-113 ITP program recommended a mandatory discontinuation from trial intervention for trial participants with an initial or recurrent malignancy.
1.3, Schedule of Activities, Table 1 10.9, Appendix 9, Table 5, Schedule of Activities 8.6, Pharmacokinetics	Footnote n regarding when PK/PD/ADA samples should be collected was revised from within 2 hours to within the same day, before IMP administration. Table 4 was renumbered as Table 5.	The revision allows additional flexibility for trial sites.

Section	Description of change	Brief rationale
2.3.1, Risk Assessment	Table 2 of potential risks and mitigation strategies was added.	The table succinctly addresses the trial risks and mitigation strategies.
5.1, Inclusion Criteria, Criterion 8b 10.6.2, Contraception Guidance	The contraception requirement for male participants was removed. Inclusion criterion 8a was renumbered as 8b. Section 10.6.2.2 Male Contraception was deleted.	This global change was made to all ARGX-113 studies based on emerging nonclinical data indicating that efgartigimod has a low risk of teratogenicity/fetotoxicity.
3, Objectives and Endpoints 9.5.7, Other Secondary Endpoint Analyses Not Subject to Alpha Control	An efficacy objective was added to compare efgartigimod PH20 SC to placebo PH20 SC in IWG response and initial response, measuring the proportions of participants with an IWG response, an IWG complete response, and an initial response.	The revision was made to align with the SAP.
3, Objectives and Endpoints 8.12, Immunogenicity Assessments 10.3, Appendix 3, Table 4	Text reading “and titers of NAb against efgartigimod and/or rHuPH20 in the overall population” was revised to “and titers of NAb against rHuPH20 in the overall population.” Table 3 was renumbered as Table 4.	The text was not correct. Titers are determined for only the PH20 NAb assay, not the efgartigimod NAb assay.
8.3.2, Vital Signs	Instructions for taking blood pressure were amended to include that participants should be seated and rested.	The updated instructions match site practices and prevent protocol deviations.
10.4, Appendix 4: Washout Requirements Before First IMP Administration	Anti-CD20 therapy (eg, rituximab) with a washout of 6 months before randomization was added.	This requirement was added to match inclusion criterion 7.
2.2, Background 1.1, Synopsis	ARGX-113-1801 was added to the list of sources of clinical history.	Additional data were available in ARGX-113-1801 to support product development.
2.3.2, Benefit Assessment	Lengthy description was replaced with language that directs the reader to the benefit/risk assessment in the current IB.	The IB is the primary repository for updated product data.

Section	Description of change	Brief rationale
5.1, Inclusion Criteria, Criterion 2	The age of consent inclusion criterion was revised to state that participants should be at least the local legal age of consent for clinical trials when signing the ICF. Inclusion criterion 2 was renumbered as 2a.	The revision matches global requirements for the legal participation age.
8.3.5, Clinical Safety Laboratory Assessments 10.2, Appendix 2: Clinical Laboratory Tests	Language was added describing blinding of albumin and urine total protein (quantitative) values and noting that an alert system will notify the investigator to ensure appropriate safety follow up.	The DSMB monitoring the ARGX-113 ITP program advised that serum albumin and total protein results should remain blinded for the trial sites.
10.7, Appendix 7: Administrative Structure	The vendor name LGC was revised to DDS.	The change was made to reflect the legal name of the vendor.

Amendment 3 (15 Jul 2022)

This amendment was considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The primary reason for this amendment was to increase the sample size, to change the hierarchical order for testing the key secondary endpoints based on the top-line results of trial ARGX-113-1801, and to revise contraception requirements based on emerging nonclinical data that indicated that efgartigimod has a low risk of teratogenicity/fetotoxicity.

The major changes from protocol v3.0 to v4.0 are summarized below. Refer to Section 10.11 of the protocol for any undefined abbreviations.

Section	Description of change	Brief rationale
Section 9.3. Sample Size Determination Section 1.1 Synopsis	Changed the sample size to approximately 180 participants with chronic ITP	Adjusted the sample size using suitably modified assumptions of the treatment effect size based on the top-line results of trial ARGX-113-1801
Section 9.5.6. Key Secondary Endpoint Analyses Subject to Alpha Control	Changed the hierarchical order for testing the third and fourth key secondary endpoints	Modified based on the top-line results of ARGX-113-1801
Section 9.5.6. Key Secondary Endpoint Analyses Subject to Alpha Control	Modified the statistical method for analysis of the key secondary endpoint “incidence and severity of the World Health Organization (WHO)-classified bleeding events in the overall population”	Modified based on the top-line results of ARGX-113-1801

Section	Description of change	Brief rationale
Section 10.6.2. Contraception Guidance Section 10.6.1.1. Woman of Childbearing Potential Section 5.1. Inclusion Criteria Section 5.2. Exclusion Criteria	Updated contraception requirements to: • change the period for contraceptive use by male and female participants from 90 days after last dose of IMP to the date of the last dose of IMP • remove the restriction on donating sperm during the trial • specify that male participants are subject to contraception rules if they are not sterilized • change the criteria for determining postmenopausal status	Updated to align with previous nonclinical study results that indicate that efgartigimod has a low risk of teratogenicity/ fetotoxicity
Section 10.6.2. Contraception Guidance Section 5.1. Inclusion Criteria	Instruction on contraception requirements moved to Section 10.6.2	Moved from eligibility criteria to Appendix 6: Contraceptive Guidance and Collection of Pregnancy Information
Section 10.6.3. Collection of Pregnancy Information	Changed the time period for collecting pregnancy information during the trial from 90 days after the last dose of IMP to the date of the last dose of IMP	Updated to align with previous nonclinical study results that indicate that efgartigimod has a low risk of teratogenicity/ fetotoxicity
Section 1.1. Synopsis Section 4.1. Overall Design Section 6.3.1. Emergency Unblinding Section 6.6.4. Rescue Therapy Section 8. Trial Assessments and Procedures Section 10.1.7.3. Quality Control	Removed mandatory requirements for the investigator to consult the sponsor (or its designee) in decisions to: • Confirm a participant's eligibility before randomization • Enroll a participant who had a serious adverse event during ARGX-113-2004 in the open-label extension trial ARGX-113-2005 • Unblind a participant's treatment assignment • Discontinue a participant from IMP or the trial • Initiate rescue therapy • Determine whether an abnormal laboratory value is considered clinically significant	Updated because the investigator has sole responsibility for decisions concerning an individual participant's enrollment and medical care at their site. The sponsor retains its consultative role and its monitoring and auditing responsibilities.

Section	Description of change	Brief rationale
Section 1.1. Synopsis Section 2.2. Background Section 2.3. Benefit/Risk Assessment Section 4.3. Justification for Dose	Revised to reflect emerging data and to refer to the current IB for detailed information	Updated to refer to the IB for a summary of contemporaneous data
Section 6.8. Intervention After the End of the Trial	Specified that for ARGX-113-2004 participants who meet the criteria to switch to a q2w IMP regimen based on their platelet counts at the end-of-treatment visit, the baseline visit in ARGX-113-2005 will occur 7 days after the ARGX-113-2004 end-of-treatment visit	Clarified the timing of the baseline visit/first dose of IMP for participants who are eligible to switch to a q2w IMP regimen when entering ARGX-113-2005
Section 8.4.5. Regulatory Reporting Requirements for Serious Adverse Events	Updated the reporting requirements for serious adverse events	Updated safety reporting processes to align with the sponsor's current practices
Section 10.2. Appendix 2: Clinical Laboratory Tests Table 1 and Table 4	Removed the clinical chemistry parameters apoliprotein B (apoB), lipoprotein A, fibrinogen, von Willebrand factor, D-dimer, and proprotein convertase subtilisin/kexin type 9 (PCSK9)	Removed because efgartigimod does not reduce albumin levels and has had no observed effect on cholesterol, HDL, or LDL levels
Sponsor Signatory	Updated the sponsor signatory to [redacted], MD, PhD	Updated to reflect the sponsor's current chief medical officer (effective 01 Apr 2022)
Section 10.7. Appendix 7: Administrative Structure	• Replaced vendor for central ECG reading • Updated the business name of the vendor for long-term storage of pharmacokinetics-pharmacodynamics, antidrug antibodies, and antiplatelet antibodies samples • Updated vendor locations for clinical trial supply management	Updated to reflect new vendors/vendor information

Amendment 2 (16 Jul 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The overall rationale for the changes implemented in the protocol amendment is to make clarifications and corrections.

The major changes from protocol version 2.0 compared to protocol version 3.0 are summarized below. A strikethrough font is used to indicate deleted text and a bold font to indicate added text. Minor editorial changes and document formatting revisions have not been summarized.

Section	Description of Change	Brief 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.
Section 1.1. Synopsis Section 4.1. Overall Design	All participants or their caregivers **(as defined in Section 10.10)** will be invited to receive training to **(**self-**)**administer the IMP **while** under supervision at least 4 times in the last 10 weeks**, until they are capable of and comfortable with the (self-)administration ([**self-**]**administration without supervision is foreseen only in the open-label extension trial ARGX-113-2005, not in the current ARGX-113-2004 trial). If the participant or his/her caregiver successfully completes the training to the satisfaction of the authorized staff**,** ~~as well as~~ the participant **or his/her caregiver**, **then** the participant or his/her caregiver may administer the next injections at the trial site under the supervision of the authorized staff. The training must be documented in the participant's source documents and eCRF.	To clarify caregiver-related requirements.

Section	Description of Change	Brief Rationale
Table 1: Schedule of Activities	**Caregiver informed consent form** Footnote: **To be obtained before initiation of the IMP administration training.**	To clarify caregiver-related requirements.
	IMP **(**self-**)**administration training Footnote s: Participants or their caregivers will be invited to receive training to **(**self-**)**administer the IMP **while** under supervision at least 4 times in the last 10 weeks**, until they are capable of and comfortable with the (self-)administration** (**[**self-**]**administration without supervision is foreseen only in the open-label extension trial ARGX-113-2005, not in the current ARGX-113-2004 trial).	

Section	Description of Change	Brief Rationale
Section 10.1.3. Informed Consent Process	• Before signing the ICF, the trial participants 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. **If a participant's caregiver will be trained to administer the IMP, he/she will also have to sign an ICF.** • **If the IMP will be administered by the participant's caregiver at the trial site, he/she will have to sign a separate ICF in which he/she agrees to share personal data and to be trained by the investigator or his/her designee to administer the SC injections of efgartigimod PH20.** • **The participant will sign the caregiver's ICF to indicate that he/she agrees that this person will be his/her caregiver.** • **The investigator needs to confirm that the caregiver is competent to administer the IMP.** • **The caregiver's training will be documented. The investigator will sign and save this documentation in the participant's file.** • **The investigator or his/her representative will explain the following to the caregiver and answer all questions regarding his/her role as a caregiver: the purpose of the trial, the purpose of his/her role as a caregiver, the expected duration, and the extent to which confidentiality of his/her personal data will be maintained.** • **Caregivers must also be informed that taking on the role of caregiver is voluntary and that they may withdraw at any time.** • **Caregivers will also be required to sign an ICF, after receipt of detailed information on their role as a caregiver in this trial.** • **The caregiver ICF will be used to explain, in simple terms, the potential risks and disadvantages of taking on the role of caregiver.** • The ICF **and the caregiver ICF** contain~~s~~ a statement that the consent is freely given. • **The caregiver ICF must be available in the local and vernacular languages required at the investigative site. All caregiver ICF(s) must be signed and dated by the caregiver and the participant.**	To clarify caregiver-related requirements.

Section	Description of Change	Brief Rationale
Section 10.1.3. Informed Consent Process	• **Confirmation of a caregiver's informed consent must also be documented in the participant's medical records before any administration of IMP by the caregiver occurs. The authorized person obtaining the informed consent must also sign the caregiver ICF.** • **The investigator is responsible for ensuring that the informed consent is obtained from the caregiver, including the appropriate signatures and dates on the caregiver ICF, before any administration of IMP by the caregiver occurs.** • **If a new version of the caregiver ICF is issued, the participant and his/her caregiver must both reconsent.** • **A signed and dated copy of the caregiver ICF must also be provided to the participant and his/her caregiver.**	To clarify caregiver-related requirements.
Section 10.1.4. Data Protection	• The participant **and his/her caregiver** must be informed that his/her personal trial-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant **and his/her caregiver** who will be required to give consent for their data to be used as described in the **respective** informed consent. • The ICF **and the caregiver ICF** will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. • **The caregiver must be informed that his/her personal data may be examined by clinical quality assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.**	
Section 10.10. Appendix 10: Definition of Terms	**Caregiver:** **A caregiver is a person of legal age from the participant's social network (eg, family, relatives, friends), chosen by the participant. Once he/she receives the necessary training and is found competent by the authorized site staff to perform IMP administration, the caregiver can administer SC injections to the participant.**	

Section	Description of Change	Brief Rationale
Section 1.1. Synopsis Section 4.1. Overall Trial Design	**If a participant has had an SAE during the ARGX-113-2004 trial, his/her eligibility for the ARGX-113-2005 trial should be evaluated by the investigator and the sponsor's trial physician. The decision to enroll the participant will be made case by case.**	Additional safety measure.
Section 1.1. Synopsis Section 3. Objectives and Endpoints	[redacted]	Clarification.
Section 1.1. Synopsis Section 3. Objectives and Endpoints	[redacted]	Inclusion of a disease-specific measure of health-related quality-of-life for use in adults with ITP.
Table 1: Schedule of Activities Table 4: Schedule of Activities	**ITP-PAQ** To be assessed at the following timepoints: Baseline, visit 13, end-of-treatment, and early discontinuation Footnote: **If available at baseline.**	
Table 1: Schedule of Activities Table 4: Schedule of Activities	Hematology and chemistry test: Footnote added at baseline and visit 14: **The following parameters should be tested at baseline and visit 14: apoB, lipoprotein A, fibrinogen, von Willebrand factor, D-dimer, PCSK9**	For safety purposes.

Section	Description of Change	Brief Rationale
Section 8.14. Quality-of-Life and Patient-Reported Outcomes	The participant will complete the QoL questionnaire (SF-36 v2.0 **and ITP-PAQ**) and the PRO (FACT-Th6 and FACIT-Fatigue Scale) as indicated in the SoA (Section 1.3). **ITP-PAQ: The ITP-PAQ is a 44-item questionnaire to assess the health-related QoL in adults with ITP. It includes scales on a 0 (worst) to 100 continuum for physical health (symptoms, fatigue/sleep, bother, and activity), emotional health (psychological and fear), overall QoL, social activity, women's reproductive health, and work.**	Inclusion of a disease-specific measure of health-related quality-of-life for use in adults with ITP.
Section 10.9. Appendix 9: Possible Adaptations of Trial Protocol During COVID 19 Pandemic	Quality-of-Life and Patient-Reported Outcomes: SF-36**, ITP-PAQ**, FACT-Th6, and FACIT-Fatigue can be completed at home (or an alternative convenient location) by the participant.	
Table 1: Schedule of Activities Table 4: Schedule of Activities	Footnote k and l (Table 1 and Table 4, respectively) "At the screening visit, the total IgG level must be determined by the central laboratory (exclusion criterion 9)." added to the screening assessment "Hematology and chemistry test" and removed from "Pharmacodynamics"	Clarification.
Table 1: Schedule of Activities Section 8.3.5. Clinical Safety Laboratory Assessments Table 4: Schedule of Activities	On days that IMP is administered, ~~blood~~ **samples** for laboratory assessments should be collected before dosing**, unless otherwise requested**.	To allow urine samples as well.
Section 5.1. Inclusion Criteria	2. Male or female, aged ≥18 years at the time the informed consent form (ICF) is signed. **Exceptions are made for The Republic of South Korea and Taiwan where, according to local regulatory requirements, legal age is reached at 19 years and 20 years, respectively.**	To comply with local regulatory requirements.

Section	Description of Change	Brief Rationale
Section 5.2. Exclusion Criteria	**14. Evidence of an active clinically significant bleeding of an organ or internal mucosal bleeding, other than expected in ITP, that warrants emergent treatment or therapeutic procedure based on the investigator's judgment (eg, intracranial hemorrhage, pulmonary hemorrhage, bleeding with ongoing need for packed red blood cell transfusion)** **15. Estimated high risk of a clinically significant bleeding of an organ or internal mucosal bleeding, other than expected in ITP, that warrants emergent treatment or therapeutic procedure according to the investigator's judgment**	To increase the safety of the selected population.
	17. 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 ≤~~<~~200 cells/mm^3	Clarification on the allowed test for HBV detection.
Section 6.4. Trial Intervention Compliance	The participants are dosed by qualified approved personnel. **Adequately-trained participants or their caregivers are also allowed to administer the IMP on-site under supervision of the authorized site staff.**	Clarification.
Section 6.6.4. 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 participants**	Clarification upon request of the German competent authorities.
Section 6.7. Dose Modification	The administration of IMP will be temporarily withheld if it could put the participant at undue risk in any of the following circumstances: • Platelet count increases to >400×10^9/L The IMP **administration** should be resumed ~~at the q2w dosing frequency when~~ **at the visit where** the platelet count falls to <150×10^9/L**, at the q2w dosing frequency**.	Clarification.

Section	Description of Change	Brief Rationale
Section 6.8. Intervention After the End of the Trial	• For participants on a q2w dosing regimen, the baseline visit including the first IMP dose administration in the ARGX-113-2005 trial will be done 7 days after the end-of-treatment visit in the current trial **if visit 24 of the ARGX-113-2004 trial was a dosing visit**. **If visit 24 of the ARGX-113-2004 trial was a nondosing visit, the end-of-treatment visit will coincide with visit 1 of the ARGX-113-2005 trial.**	Clarification.
Section 8.3.5. Clinical Safety Laboratory Assessments	• Blood and urine samples for determination of clinical chemistry, hematology, urinalysis, coagulation, thyroid, autoimmune antibody testing, follicle-stimulating hormone (FSH; only for women of non-childbearing potential), ~~PK, PD, antiplatelet antibodies,~~ viral testing, **and** tuberculosis QuantiFERON test,~~ and anti-drug antibodies (ADA)~~ will be collected and analyzed at a central laboratory as indicated in the SoA (Section 1.3) and Section 10.2. The blood sample for platelet counts and the urine sample for the pregnancy test will be analyzed locally.	PK, PD, antiplatelet antibodies, and ADA are not safety assessments.
	~~The estimated total maximum blood volume needed for a participant during the trial (when completing the trial) is approximately526 mL.~~	Not required as per protocol template.
Section 8.4. Adverse Events and Serious Adverse Events	• Adverse events will be reported by the participant ~~(or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative)~~.	Only the participant should report AEs.
	• 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.
Section 8.4.9. Adverse Events of Special Interest	• Due to the nature of the underlying disease (ie, ITP), any ~~AE~~ **occurrence** of bleeding will also be ~~treated~~ **considered** ~~as~~ an AESI.	Clarification.
Section 8.6. Pharmacokinetics Section 8.12.1. Anti-Drug Antibodies	• **Samples will be analyzed by the designated laboratory.**	
Section 8.7. Pharmacodynamics	• Samples will be analyzed by the ~~specialty~~ **designated** laboratory. To maintain the blind, the IgG testing cannot be performed locally.	

Section	Description of Change	Brief Rationale
Section 8.8. Platelet Functionality	• The sample will be used for an exploratory endpoint and will be analyzed in a ~~specialty~~ **designated** laboratory.	Clarification.
Section 9.5.6. Key Secondary Endpoint Analyses 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).
	When 1 of the **main** intercurrent events ~~described in Section 9.5.5~~ 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.
	The model will **consist of**~~have~~ 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.
Section 9.5.10.1. Pharmacodynamics, Pharmacokinetics, and Immunogenicity	Descriptive statistics will be provided for PD parameters (total IgG ~~and subtypes,~~ and antiplatelet antibodies), the presence of antibodies, and titers of antibodies against efgartigimod and/or rHuPH20.	Correction; subtype levels are not required for PD evaluations.
Section 10.2. Protocol-Required ~~Safety~~ Laboratory Assessments **Section 10.3. Appendix 3: Pharmacokinetic, Pharmacodynamic, and Immunogenicity Assessments**	"Table 2: Protocol-Required ~~Safety~~ Laboratory Assessments" has been split into "Table 2: Protocol-Required ~~Safety~~ Laboratory Assessments" and "**Table 3: Protocol-Required Pharmacokinetic, Pharmacodynamic, and Immunogenicity Assessments**"	To make a distinction with the assessments related to PK, PD, and immunogenicity.

Section	Description of Change	Brief Rationale
Table 2: Protocol-Required ~~Safety~~ Laboratory Assessments	Clinical chemistry: **, hemoglobin A1c (HbA1c)[a], cholesterol[a] (total cholesterol, high density lipoprotein [HDL], low density lipoprotein [LDL]), triglycerides, apoB[a], lipoprotein A[a], fibrinogen[a], von Willebrand factor[a], D-dimer[a], PCSK9[a]** Footnote a: **Parameter to be tested at baseline and at visit 14.**	For safety purposes.
	Clinical chemistry: …**, serum levels of total IgG[b]** Footnote b: **At screening only, to maintain the blind.**	Clarification.
	Serology: Human immunodeficiency virus (HIV) antibodies (1 and 2), ~~hepatitis B~~ **HBV** surface antigen (HbsAg), antibodies to the surface and core antigens of the ~~hepatitis B virus~~ **HBV** (anti-HBs and anti-HBc), hepatitis C virus antibody (HCV Ab)**, HCV RNA**	
Section 10.5.1. Definition of Adverse Event	Events NOT to be Collected as Adverse Events • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. **Note: Except for any occurrence of bleeding, which will be considered an AESI as per Section 8.4.9.**	
Section 10.5.2. Definition of Serious Adverse Event	Definition of Serious Adverse Event 3. Requires in-patient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant 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.	To clarify the term "hospitalization" in the definition of SAE.
	6. 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).

Section	Description of Change	Brief Rationale
Section 10.6.2.1. Female Contraception For Women of Childbearing Potential	Progest~~erone~~**ogen**-only hormonal contraception …	Correction.
Section 10.6.3.1. Male Participants With Partners Who become Pregnant	• Male participants will be instructed through the informed consent form (ICF) to immediately inform the investigator if their partner becomes pregnant during the trial ~~or up to 90 days after they received the last investigational medicinal product (IMP)~~.	
Section 10.7. Appendix 7: Administrative Structure	Home Care Vendor: ~~Symphony Clinical Research~~**Accellacare In-Home Services** (an ICON company)	Administrative change.
	Analysis of Pharmacokinetics~~ Pharmacodynamics~~, Anti-Drug Antibodies, and Neutralizing Antibodies Against Efgartigimod LGC	
	Analysis of Total IgG **PPD Laboratories - US** **2 Tesseneer Road** **Highland Heights, KY 41076** **United States**	
	Antibodies and Neutralizing Antibodies Against rHuPH20 ~~Covance~~ **LabCorp** Bioanalytical Services, LLC	
Section 10.9. Appendix 9: Possible Adaptations of Trial Protocol During COVID 19 Pandemic	To allow patients with ITP to receive treatment with the investigational medicinal product (IMP) during the COVID 19 pandemic, this appendix to the protocol has been developed. If a visit to the trial site is not possible, a home visit or a visit at an alternative convenient location can be allowed**, as per local regulations**. … **If allowed per local regulations, i**~~I~~t remains at the investigator's discretion to assess if it is in the best interest of the participant to start/continue in the trial. …	Clarification.
	Pharmacodynamics: The testing should be done by the initially appointed ~~central~~ **designated** laboratory.	

Section	Description of Change	Brief Rationale
Section 10.9. Appendix 9: Possible Adaptations of Trial Protocol During COVID-19 Pandemic Table 4: Schedule of Activities	~~IMP self-administration training~~[u] Footnote: ~~Participants or their caregivers will be invited to receive training to self-administer the IMP under supervision at least 4 times in the last 10 weeks (self administration without supervision is foreseen only in the open-label extension trial ARGX-113-2005, not in the current ARGX-113-2004 trial).~~	Self-administration training is not applicable for the protocol adaptations during the COVID-19 pandemic.
Section 11. References	12. Recombinant human hyaluronidase PH20 (rHuPH20) Investigator's Brochure. Version **9**~~8~~.0. January 202**1**~~0~~.	Update.

Amendment 1 (12 Jan 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The overall rationale for the changes implemented in the protocol amendment is to align the protocol with the responses to the US FDA comments in IND 152588 and make clarifications and corrections.

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 editorial changes and document formatting revisions have not been summarized.

Summary of Changes Between Protocol Version 1.0 and Protocol Version 2.0

Section	Description of Change	Brief Rationale
Section 1.1. Synopsis Section 3. Objectives and Endpoints	Secondary Endpoints: • Incidence and prevalence of ~~anti-drug antibodies (ADA)~~ **antibodies** to efgartigimod and/or rHuPH20 in the overall population • Titers of ~~ADA~~ **antibodies** to efgartigimod and/or rHuPH20 in the overall population	Correction
	Secondary Endpoints: • Pharmacodynamics markers: total IgG~~, IgG isotypes (IgG1, IgG2, IgG3, and IgG4),~~ **and** antiplatelet antibody levels in the overall population	Subtype levels are not required for PD evaluations
	Exploratory Objectives: • **To evaluate the competency of participants or their caregivers to administer efgartigimod PH20 SC**	To assess the participants self-administration performance during the supported administration training
	Exploratory Endpoints: • **Number and percentage of participants or caregivers completing the self-administration/caregiver-supported administration training** • **Number and percentage of participants or caregivers determined by the site staff to be sufficiently competent to administer efgartigimod PH20 SC** • **Number and percentage of participants or caregivers that administer efgartigimod PH20 SC under site staff supervision**	

Section	Description of Change	Brief Rationale
Section 1.1. Synopsis	All participants or their caregivers will be **invited to receive** train**inged** ~~ed~~ to self-administer the IMP **under supervision at least 4 times in the last 10 weeks** (self-administration **without supervision** is foreseen **only** in the open-label extension trial ARGX-113-2005, not in the current ARGX-113-2004 trial). **If the participant or his/her caregiver successfully completes the training to the satisfaction of the authorized staff as well as the participant, the participant or his/her caregiver may administer the next injections at the trial site under the supervision of the authorized staff. The training must be documented in the participant's source documents and eCRF.**	Clarification
Section 1.2. Schema	Schema has been updated	Administrative change for consistency and clarification
Section 1.3. Schedule of Activities Table 2: Protocol-Required Safety Laboratory Assessments Section 10.8. Appendix 8: Possible Adaptations of Trial Protocol During COVID 19 Pandemic Table 3: Schedule of Activities	~~Anti-drug antibodies~~**Immunogenicity**	Sampling is done for antibodies against the drug and the formulation
Section 1.3. Schedule of Activities Section 10.8. Appendix 8: Possible Adaptations of Trial Protocol During COVID 19 Pandemic Table 3: Schedule of Activities	End-of-Treatment: This visit should be performed on trial day 169 (+2 days) (ie, 7 days [+2 days] after the last dosing visit) for all participants who have completed the 24-week treatment period ~~and who want to roll over to the open-label extension trial~~, whether they were still receiving IMP or not. Every effort should be made to schedule every visit on the exact day (which is relative to baseline randomization [visit 1]).	Correction

Section	Description of Change	Brief Rationale
Section 1.3. Schedule of Activities	Footnote d: Platelet count is measured locally and can be performed within 1 day (for postbaseline visits) of the next procedure as per schedule of activities (both dosing and non-dosing visits). Eligible participants should have a mean platelet count of $<30\times10^9$/L from ~~2~~ **at least 3 documented, qualifying** counts **within the 3 preceding months where at least 2 of the qualifying counts must be taken during the screening period**: 1 platelet count collected during the screening period and the predose platelet count on the day of randomization (visit 1). **If the third count is not available from the 3 preceding months, this third platelet count can be obtained during the screening period.**	As per request from the FDA
Section 1.3. Schedule of Activities	Footnote e: ~~Patient-reported outcomes and quality-of-life (QoL) assessments will preferably be performed after the platelet count assessment.~~	Correction
	Footnote f: ~~Electrocardiogram will be assessed after the end of the IMP administration, if any.~~ **If IMP is administered, the ECG will be performed after the IMP administration.**	Clarification
	Footnote h: At the screening visit, if the investigator detects 1 or more screening laboratory abnormalities **which are not aligned with the medical history and clinical evaluation of the participant**, the result(s) should be confirmed if still within the screening window. For rescreening criteria see Section 5.4.	
	Footnote o: ~~Samples demonstrating a positive anti-drug antibodies (ADA) titer will be tested for neutralizing ADAs.~~	Correction

Section	Description of Change	Brief Rationale
Section 1.3. Schedule of Activities	Footnote q: Participants or their caregivers will be **invited to receive** train**inged** ~~ed~~ to self-administer the IMP **under supervision at least 4 times in the last 10 weeks** (self-administration **without supervision** is foreseen **only** in the open-label extension trial ARGX-113-2005~~;~~, not in the current ARGX-113-2004 trial) ~~at least 4 times in the last 10 weeks~~.	Clarification
	Footnote r: The IMP (efgartigimod PH20 SC or placebo PH20 SC) will be administered as an SC injection at each IMP administration visit. Participants will remain at ~~home~~ **the trial site** for at least 15 minutes following the end of the injection for routine safety monitoring based on the participant's clinical status.	Correction
Section 1.3. Schedule of Activities	Footnote s: Adverse events, procedures, and intake of concomitant medication(s) will be monitored continuously from signing the ICF until the last trial-related activity, unless the participant withdraws consent. In case of early discontinuation, any adverse events/serious adverse events should be assessed **until the participant has ended the trial** ~~for 30 days following the early discontinuation visit~~ or until satisfactory resolution or stabilization. **All available vaccination history will be captured as part of the participant's prior medication for vaccinations received in the past, or concomitant medication for vaccinations received during the trial.**	Clarification
Section 2.2. Background	The 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~~.	Correction
Section 2.3. Benefit/Risk Assessment	Please refer to the current Investigator's Brochure (IB) for more information regarding preclinical and clinical trials, and the potential risks and benefits of efgartigimod[3] and rHuPH20,[12] **respectively**.	Clarification

Section	Description of Change	Brief Rationale
Section 2.3.1. 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 the reporting phase.~~	As per results of reproductive toxicology studies
Section 4.1. Overall Design	All participants or their caregivers will be **invited to receive** train**inged** ~~ed~~ to self-administer the IMP **under supervision at least 4 times in the last 10 weeks** (self-administration **without supervision** is foreseen **only** in the open-label extension trial ARGX-113-2005, not in the current ARGX-113-2004 trial) as specified in the SoA in Section 1.3. **If the participant or his/her caregiver successfully completes the training to the satisfaction of the authorized staff as well as the participant, the participant or his/her caregiver may administer the next injections at the trial site under the supervision of the authorized staff. The training must be documented in the participant's source documents and eCRF.**	Clarification
Section 5.1. Inclusion Criteria	5. Mean platelet count of $<30\times10^9$/L from ~~2~~ **at least 3 documented, qualifying** counts **within the 3 preceding months where at least 2 of the qualifying counts must be taken during the screening period**: 1 platelet count collected during the screening period and the predose platelet count on the day of randomization (visit 1). **If the third count is not available from the 3 preceding months, this third platelet count can be obtained during the screening period.**	As per request from the FDA

Section	Description of Change	Brief Rationale
Section 5.1. Inclusion Criteria	8. Must be on a stable regimen for at least 1 month of a~~t least 1~~ highly effective **or acceptable** method of contraception (~~ie, failure rate of less than 1% per year;~~ see Highly Effective Methods of Female Contraception) during the trial and for 90 days after the last administration of IMP	Final results from reproductive toxicity studies became recently available and did not indicate a risk to male or female fertility or embryo-fetal developmental toxicity
	9. Non-sterilized male participants who are sexually active with a female partner of childbearing potential must use ~~effective~~ **an acceptable method of** contraception**, ie, a condom** (see Male Contraception) from signing the ICF through ~~90 days after~~ the last administration of the IMP. ~~Male participants practicing true sexual abstinence (as consistent with preferred and usual lifestyle) can be included. Sterilized male participants who have had a vasectomy and with documented absence of sperm post-procedure can be included.~~ Male participants are **also** not allowed to donate sperm **during this time** ~~from signing the ICF through 90 days after the last dose of the IMP~~.	
Section 5.2. Exclusion Criteria	8. Use of any monoclonal antibody **or Fc fusion proteins, other than those previously indicated,** within 6 months before the first dose of the IMP (eg, anti-CD20)	Clarification
	15. b. Hepatitis C virus (HCV) based on HCV-antibody assay **(unless associated with a negative HCV RNA test)**	
	23. Received a **live/**live-attenuated vaccine less than 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.	

Section	Description of Change	Brief Rationale
Section 6.1. Trial Intervention(s) Administered	**For each injection, the initiation and completion times (hour and minute), and details of any interruptions or premature discontinuation of injections will be recorded on the eCRF. The start will be marked as the moment of start pressing the plunger and the end will be marked as the completion time of administration of the total volume of IMP.**	Paragraph moved from Section 8.10. IMP Administration in order to group all information regarding the administration of IMP in the same section
Section 6.2.1. Preparation	Efgartigimod PH20 SC will be provided as a sterile**, clear to opalescent,** ~~colorless to~~ yellowish~~, clear~~ solution for **SC** injection in glass vials covered with a blinding shell.	Clarification
Section 6.2.2. Handling	Only participants enrolled in the trial may receive IMP and only **authorized and** trained ~~personnel~~ **site staff** may **dispense** ~~supply or administer~~ IMP. **The IMP administration must be performed by authorized and trained site staff or by an adequately trained and supervised participant or his/her caregiver.**	
Section 6.2.3. Storage	The IMP (efgartigimod PH20 SC and placebo PH20 SC) will be supplied to the pharmacy **or dedicated site location** at the ~~investigative~~ **trial** site by and under the responsibility of the sponsor's designated IMP supply vendor.	
Section 6.4.1. Handling Missed Doses of the Investigational Medicinal Product	However, if a participant misses more than 2 consecutive scheduled doses, then he/she will be discontinued early from ~~the~~ trial **treatment** (see Section 7.1).	Correction
Section 6.5. Screening and Treatment	**Note: in this case, no IMP will be administered at the last visit confirming the qualifying platelet counts of ≥100×10⁹/L.**	Clarification

Section	Description of Change	Brief Rationale
Section 6.6. Prior and Concomitant Therapy	All prior ITP procedures and therapies received by the participant since diagnosis, before baseline, must be recorded on the eCRF, including the name, dose/schedule, duration (including start and stop dates), intolerance, ~~and~~ whether the participant responded to them**, details of platelet counts on prior ITP therapies (ie, supporting the participant's response), and the reason for discontinuation from prior therapies that are documented on the participant's source documents at the current trial site**.	As per request from the FDA
	~~All vaccinations received by the participant in the 6 months before baseline should be recorded.~~ **All available vaccination history will be captured as part of the participant's prior medication for vaccinations received in the past, or concomitant medication for vaccinations received during the trial as described in the SoA (Section 1.3). Any vaccination information the participant, his/her caregiver, or his/her legally authorized representative can remember should be recorded on the eCRF (with the brand name of the vaccine and date of vaccination, if possible).**	To evaluate the impact of efgatigimod on antibody response to vaccines
Section 6.6.4. Rescue Therapy	If a participant needs rescue therapy according to the investigator, it is encouraged to inform the medical monitor at the sponsor's designated CRO **and the sponsor's medical monitor**, whenever possible before actual implementation of the rescue therapy.	Clarification
Section 8.3.3. Electrocardiograms	• **If IMP is administered, the ECG will be performed after the IMP administration.** • A single 12-lead ECG will be taken ~~postdose~~ at a paper speed of 25 mm/sec in the supine position after the participant has rested in this position for at least 10 minutes.	

Section	Description of Change	Brief Rationale
Section 8.3.5. Clinical Safety Laboratory Assessments	• The estimated total maximum blood volume needed for a participant during the trial (when completing the trial) is approximately ~~568.5~~**5526 mL**. • The actual sample collection date and time must be entered in the participant's source documents and on the central laboratory assessment eCRF page**. For urinalysis samples only the date of collection is to be entered**.	Correction
Section 8.3.5.1. Storage of Blood Samples in the Trial	**After this period of time, the samples will be destroyed.** In addition, serum or plasma samples may be used to validate methods to support the efgartigimod program**. These samples may also be used for vaccination antibody testing and any other additional research interests linked to the development of efgartigimod**.	Clarification
Section 8.7. Pharmacodynamics	• Serum samples for the determination of the PD marker~~s~~ (total IgG~~, IgG subtypes [IgG1, IgG2, IgG3, and IgG4]~~) will be collected as indicated in the SoA (Section 1.3).	Subtype levels are not required for PD evaluations
Section 8.10. IMP Administration	~~For each injection, the initiation and completion times (hour and minute), and details of any interruptions or premature discontinuation of injections will be recorded and will be transferred to the eCRF. The start will be marked as the moment of start pressing the plunger and the end will be marked as the completion time of administration of the total volume of IMP.~~ ~~Each participant or his/her caregivers will be trained to self-administer the IMP (self-administration is foreseen in the open-label extension trial ARGX-113-2005, not in the current ARGX-113-2004 trial). The participant will receive a manual on preparation, handling, storage and administration of the IMP.~~ ~~More details are available in the Pharmacy Manual.~~	This section was deleted in order to avoid repetition

Section	Description of Change	Brief Rationale
Section 8.12.1. Anti-Drug Antibodies	• Serum samples to assess ~~ADA~~ **antibodies** against efgartigimod and plasma samples to assess ~~ADA~~ **immunogenicity** against rHuPH20 will be collected as indicated in the SoA (Section 1.3).	Correction
Section 9.4. Population for Analyses	Full analysis set (FAS) All randomized patients ~~who have a baseline efficacy observation~~.	As per FDA recommendations
Section 9.5.5.3. Estimation of Treatment Effect and Statistical Interference	The primary endpoint will be **analyzed using a Cochran-Mantel-Haenszel statistic test stratified for the stratification factors history** ~~tested by means~~ 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**~~exact logistic regression, also known~~ as **the odds ratio together with its 95% confidence interval (CI) and 2-sided p-value. In addition, an adjusted difference of the proportions with its 95% CI will be provided**~~exact conditional logistic regression.[18] 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.[17] 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.[19] 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	Description of Change	Brief Rationale
Section 9.5.5.5. 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.**	As per FDA recommendations
Section 9.5.7. Other Secondary Endpoint Analyses Not Subject to Alpha Control	~~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 previously.~~	Correction
Section 9.5.8.	• Descriptive statistics will be presented for immature platelet fraction**,** ~~and~~ the incidence and duration of hospitalizations related to ITP management**, and the endpoint related to self-administration/caregiver-supported administration of efgartigimod PH20 SC**.	
Section 9.5.10.1. Pharmacodynamics, Pharmacokinetics, and Immunogenicity	Descriptive statistics will be provided for PD parameters (total IgG and subtypes, and antiplatelet antibodies), the presence of ~~ADA~~**antibodies**, and titers of ~~ADA~~ **antibodies** against efgartigimod and/or rHuPH20.	
Section 10.2. Appendix 2: Clinical Laboratory Tests	Pharmacodynamic markers Serum levels of total IgG ~~and IgG subtypes (IgG1, IgG2, IgG3, and IgG4)~~	Subtype levels are not required for PD evaluations
	~~Anti-drug antibodies~~**Immunogenicity**	Correction
Section 10.3. Appendix 3: Washout Requirements Before First IMP Administration	Live/live-attenuated vaccines: 4 weeks **before screening**	
Section 10.4.3. Recording and Follow-up of Adverse Events and/or Serious Adverse Events	Assessment of Causality • **In the final evaluation for reporting, the assigned relationship, as per the CIOMS will be converted into a "binary determination," as follows: Events with an assigned relationship of "unrelated" and "unlikely" will be grouped into the "unrelated" category. Events with an assigned relationship of "related," "possibly related," or "probably related" will be grouped into the "related" category.**	Clarification

Section	Description of Change	Brief Rationale
Section 10.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information	~~Highly Effective Methods of~~ Female Contraception~~:~~ **For Women of Childbearing Potential** **Women of childbearing potential must use a**~~The following methods are considered~~ highly effective **or acceptable** method~~s~~ of contraception**, which should be maintained at a minimum until 90 days after the last dose of IMP** ~~(ie, failure rate of <1% per year):~~. **The same type of hormonal contraception must have been received for at least 1 month before starting the trial. Hormonal contraception can be administered orally (the pill), by injection, patch, implant, or vaginal ring.** **The following methods are considered highly effective methods of contraception:** 1. Combined (~~contains~~ estrogen- and progest**ogen**~~erone~~ **-containing**) hormonal contraception associated with inhibition of ovulation: … 6. Vasectomized partner~~: if the partner is the sole sexual partner of the trial participant and the absence of sperm has been documented after the procedure~~ 7. Sexual abstinence~~: defined as continuous abstinence from heterosexual contact. Sexual abstinence is only allowed if it is the preferred and usual lifestyle of the participant. Periodic abstinence (eg, calendar, symptothermal, or postovulation methods) is not an acceptable method of contraception.~~	Final results from reproductive toxicity studies became recently available and did not indicate a risk to male or female fertility or embryo-fetal developmental toxicity

Section	Description of Change	Brief Rationale
Section 10.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information	**The following methods are considered acceptable methods of contraception:** **1. Progesterone-only hormonal contraception associated with the inhibition of ovulation:** – **Oral** – **Injectable** – **Implantable** **2. Male or female condom with or without spermicide** **3. Cap, diaphragm, or sponge with spermicide** Male Contraception: ~~Effective~~ **An acceptable** method~~s~~ of contraception **is a**~~include~~ condom ~~for the male participants combined with a highly effective method of contraception for the female partner who is a woman of childbearing potential~~.	Final results from reproductive toxicity studies became recently available and did not indicate a risk to male or female fertility or embryo-fetal developmental toxicity
Section 10.6. Appendix 6: Administrative Structure	~~Anti-Drug~~ Antibodies and Neutralizing Antibodies Against rHuPH20	Correction
	~~Project Management and Clinical Research Organization for Georgia~~ ~~EastHORN~~ ~~Panska 73 Str./804~~ ~~00-834 Warsaw~~ ~~Poland~~	Administrative update
	Home Care Vendor **Symphony Clinical Research (an ICON company)** **700 Deerpath Drive** **Vernon Hills, IL 60061-1802** **Illinois** **USA**	

Section	Description of Change	Brief Rationale
Section 10.8. Possible Adaptations of Trial Protocol During COVID-19 Pandemic	Possible Home Visits/Home Assessments The investigator will perform the World Health Organization (WHO) bleeding assessments using a video interview with the participant. ~~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
	~~anti-drug antibodies~~**immunogenicity**	
Section 10.8. Possible Adaptations of Trial Protocol During COVID-19 Pandemic Table 3: Schedule of Activities	Footnote e: Eligible participants should have a mean platelet count of $<30\times10^9$/L from ~~2~~**at least 3 documented, qualifying** counts **within the 3 preceding months where at least 2 of the qualifying counts must be taken during the screening period**: 1 platelet count collected during the screening period and the predose platelet count on the day of randomization (visit 1). **If the third count is not available from the 3 preceding months, this third platelet count can be obtained during the screening period.**	As per request from the FDA
	Footnote e: ~~Patient-reported outcomes and quality-of-life (QoL) assessments will preferably be performed after the platelet count assessment.~~	Correction
	Footnote g: ~~Electrocardiogram will be assessed after the end of the IMP administration, if any.~~ **If IMP is administered, the ECG will be performed after the IMP administration.**	Clarification
	Footnote i: At the screening visit, if the investigator detects 1 or more screening laboratory abnormalities **which are not aligned with the medical history and clinical evaluation of the participant**, the result(s) should be confirmed if still within the screening window. For rescreening criteria see Section 5.4.	

Section	Description of Change	Brief Rationale
Section 10.8. Possible Adaptations of Trial Protocol During COVID-19 Pandemic Table 3: Schedule of Activities	Footnote q: ~~Samples demonstrating a positive anti-drug antibodies (ADA) titer will be tested for neutralizing ADAs.~~	Correction
	Footnote s: The IMP (efgartigimod PH20 SC or placebo PH20 SC) will be administered as an SC injection at each IMP administration visit. Participants will **be observed** ~~remain at home~~ for at least 15 minutes following the end of the injection for routine safety monitoring based on the participant's clinical status. Assessment of the dosing regimen as described in Section 6.5 will be applied.	
	Footnote t: Participants or their caregivers will be **invited to receive** train**inged** to self-administer the IMP **under supervision at least 4 times in the last 10 weeks** (self-administration **without supervision** is foreseen **only** in the open-label extension trial ARGX-113-2005~~;~~, not in the current ARGX-113-2004 trial) ~~at least 4 times in the last 10 weeks~~.	Clarification
	Footnote u: In case of early discontinuation, any adverse events/serious adverse events should be assessed ~~for 30 days following the early discontinuation visit~~ **until the participant has ended the trial** or until satisfactory resolution or stabilization. **All available vaccination history will be captured as part of the participant's prior medication for vaccinations received in the past, or concomitant medication for vaccinations received during the trial.**	

Section	Description of Change	Brief Rationale
Section 11. References	3. Efgartigimod, *ARGX-113 Investigator's Brochure*. Version **9**~~8~~.0.	Update
	12. Recombinant human hyaluronidase PH20 (rHuPH20) *Investigator's Brochure.* Version ~~7~~**8**.0. January ~~2019~~**2020**.	
	~~18. Cox D, Snell E. Analysis of Binary Data. New York: Chapman & Hall; 1970.~~ ~~19. Agresti A. Categorical Data Analysis. Second Edition. New York: John Wiley & Sons. 2002.~~	

11. REFERENCES

1. Vaccaro C, Zhou J, Ober RJ, Ward ES. Engineering the Fc region of immunoglobulin G to modulate in vivo antibody levels. *Nature Biotechnol*. 2005;23(10):1283-1288.
2. Newland AC, Sanchez-Gonzalez B, Rejtő L, et al. Phase 2 study of efgartigimod, a novel FcRn antagonist, in adult patients with primary immune thrombocytopenia. *Am J Hematol.* 2020;95(2):178-187.
3. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood*. 2009;113(11):2386-2393.
4. Terrell DR, Beebe LA, Veseley SK, Neas BR, Segal JB, George JN. The incidence of immune thrombocytopenic purpura in children and adults: A critical review of published reports. *Am J Hematol.* 2010;85(3):174-180.
5. Fogarty PF, Segal JB. The epidemiology of immune thrombocytopenic purpura. *Curr Opin Hematol*. 2007:14(5):515-519.
6. Kistangari G, McCrae KR. Immune thrombocytopenia. *Hematol Oncol Clin North Am*. 2013:27(3):495-520.
7. Zufferey A, Kapur R, Semple JW. Pathogenesis and Therapeutic Mechanisms in Immune Thrombocytopenia (ITP). *J Clin Med*. 2017;6(2):16.
8. Cohen YC, Djulbegovic B, Shamai-Lubovitz O, Mozes B. The bleeding risk and natural history of idiopathic thrombocytopenic purpura in patients with persistent low platelet counts. *Arch Intern Med*. 2000;160(11): 1630-1638.
9. Norgaard M, Cetin K, Maegbaek ML, et al. Risk of arterial thrombotic and venous thromboembolic events in patients with primary chronic immune thrombocytopenia: a Scandinavian population-based cohort study. *Br J Haematol*. 2016;174(4):639-642.
10. Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. *Blood Adv*. 2019;3(23):3829-3866.
11. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer*. 1981;47(1):207-214.
12. Josephson CD, Granger S, Assmann SF, et al. Bleeding risks are higher in children versus adults given prophylactic platelet transfusions for treatment-induced hypoproliferative thrombocytopenia. *Blood*. 2012;120(4).
13. Signorovitch J, Brainsky A, Grotzinger KM. Validation of the FACIT-fatigue subscale, selected items from FACT-thrombocytopenia, and the SF-36v2 in patients with chronic immune thrombocytopenia. *Qual Life Res*. 2011;20(10):1737-1744.
14. O'Brien RG, Castelloe J. Exploiting the link between the Wilcoxon-Mann-Whitney Test and a simple odds statistic. In: *Proceedings of the Thirty-first Annual SAS Users Group International Conference*. San Francisco, CA: SAS Institute Inc; 2006. Paper 209-231.
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. Accessed 04 Feb 2020.

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