CLINICAL STUDY PROTOCOL

Protocol Title:	A phase 2 randomized, double-blinded, placebo-controlled study to evaluate the efficacy and safety of efgartigimod IV in adult patients with post–COVID-19 postural orthostatic tachycardia syndrome (POTS)
Protocol Number:	ARGX-113-2104
Version Number:	3.0 (Amendment 2)
Compound:	Efgartigimod (ARGX-113)
Study Phase:	2
Sponsor Name:	argenx BV
Legal Registered Address:	Industriepark Zwijnaarde 7 9052 Zwijnaarde (Ghent) Belgium Phone: +32 9 310 34 00 Fax: +32 9 310 34 99
Regulatory Agency Identifier Number(s):	[redacted]
Approval Date:	25 Jul 2023

Sponsor's Medical Contact:	[redacted] Global Clinical Trial Physician argenx BV 33 Arch St Boston, MA United States Email: [redacted]
Sponsor's Designee:	IQVIA
24-Hour Urgent Medical Helpline:	IQVIA's Medical Emergency Contact Center can be accessed 24/7 by calling the relevant telephone number(s) Americas: +1 (973) 659-6677 (main) or +1 (512) 652-0191 (backup)
Serious Adverse Event Reporting:	Email Address: safety@argenx.com Fax: +1 833 874 7325

The information contained in this medium is the property of argenx BV and/or its subsidiaries (jointly "argenx") and is confidential and proprietary. Without prior authorization from argenx, information contained herein may not be used, reproduced, divulged, published, or otherwise disclosed to anyone.

SIGNATURE OF SPONSOR

Protocol Title:	A phase 2 randomized, double-blinded, placebo-controlled study to evaluate the efficacy and safety of efgartigimod IV in adult patients with post–COVID-19 postural orthostatic tachycardia syndrome (POTS)
Protocol Number:	ARGX-113-2104

Sponsor Signatory:

See appended signature page

[redacted], MD, PhD
Chief Medical Officer, argenx BV

Date

SIGNATURE OF THE INVESTIGATOR

Investigator's Acknowledgment

I have read the protocol for study ARGX-113-2104.

Title: A phase 2 randomized, double-blinded, placebo-controlled study to evaluate the efficacy and safety of efgartigimod IV in adult patients with post–COVID-19 postural orthostatic tachycardia syndrome (POTS)

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a participant in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the sponsor.

Investigator Name _____
Institution _____
Address _____
(please print or type) _____

Signature _____

Date _____

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	25 Jul 2023
Amendment 1	11 Dec 2022
Original Protocol v1.0	25 Mar 2022

Amendment 2 (25 Jul 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 the Amendment:
The rationale for this amendment is to update Section 3, Inclusion Criterion 3a to allow for diagnosis of post-COVID-19 POTS based on a history of COVID-19, per previous positive test result from either laboratory-confirmed COVID-19 test (eg, a PCR test) or non-laboratory-confirmed COVID-19 test (eg, rapid antigen test); this positive result may be either documented or patient-reported.

Section # and Name	Description of Change	Brief Rationale
Cover page	Sponsor's Medical Contact details updated from [redacted], MD to [redacted] MD.	To reflect change in personnel for this study role.
Section 1.1, Synopsis Section 4.1, Overall design	Corrected follow-up period from 7 weeks (56 days ± 3 days) to 8 weeks (56 days ± 3 days).	Minor error in original protocol wording required update.
Section 2.3.1, Risk Assessment	Infusion-related reactions mitigation strategy changed from: "Monitor participants for 1 hour at the site after IMP administration. IMP will be administered by a healthcare professional." to "Monitor participants during administration and for 30 minutes thereafter for clinical signs and symptoms of infusion/injection-related reactions. Infusion/injection-related reactions are considered AEs of clinical interest (Section 8.4.7)."	Monitoring requirements updated and reference to AEs of clinical interest section added for consistency across the efgartigimod program.
	New row added for Infusion /injection-site reactions, including summary of data and mitigation strategy.	Updated per current safety requirements for efgartigimod.
Section 5.1, Inclusion criteria	Update of inclusion criterion 3a to allow documented or patient-reported confirmation of a previous positive	To allow patients who are unable to provide documentation of a prior PCR test to be included in

Section # and Name	Description of Change	Brief Rationale
	laboratory or non-laboratory test for COVID-19.	the study.
Section 5.4, Screen Failures Section 6.4, Blinding Section 7, IMP Discontinuation and Participant Discontinuation/Withdrawal	Updated wording throughout for consistency with current template language.	Updated per current CSP template for consistency across the efgartigimod program.
Section 7.1.1, Permanent Discontinuation	Removal of sentence: "Blood samples for participants remaining in the study following IMP discontinuation will be collected for PK analyses as per the SoA (Section 1.3) for up to 3 weeks post IMP discontinuation."	Not required in this section; PK sampling requirements are captured in Section 8.5, Pharmacokinetics.
	Added allowance for participants who have discontinued IMP but remained in the study to attend previously scheduled visits via telephone or web teleconferencing.	To encourage participants who have discontinued IMP to continue with previously scheduled visits.
	Clarified that if the participant cannot attend the previously scheduled visits for any reason, the study site will minimally perform an EDV and the SFV on-site.	Wording updated to clarify the intended process.
	Updated requirement for EDV from within the 7 days after the participant's final IMP administration to within 7 days after of last contact with the participant.	Updated per current CSP template for consistency across the efgartigimod program.
	Added the following to the list of circumstances which will result in permanent discontinuation of IMP: "Participant develops a new or recurrent malignancy except for basal cell carcinoma of the skin, regardless of relationship".	Updated per current safety requirements for efgartigimod.
Section 7.2, Participant Discontinuation/Withdrawal from the Study	Updated to clarify that if a participant withdraws consent to participate in future research, data collected up to that point may be retained and used for the results of the study.	Wording updated to clarify the intended process.
	Change of process from "participants withdrawing from the study can request the destruction of collected untested samples" to "samples collected from participants who have withdrawn from the study will be used for the study results but not for future research".	Updated for clarity around what use of samples are permitted or disallowed following patient withdrawal from the study.
	Removal of the following line: "Before withdrawing from the study, the participant will attend the EDV within 7	Removed as visit attendance is not mandated following participant discontinuation or

Section # and Name	Description of Change	Brief Rationale
	days after their final IMP dose. The data collected at the EDV are specified in the Schedule of Activities (SoA) (Section 1.3). The SFV will occur within 56 days (± 3 days) of the participant's final IMP dose."	study withdrawal; EDV attendance following IMP discontinuation is captured in Section 7.1.
Section 7.3, Lost to Follow-up	Clarified that lost to follow-up items must be completed if a participant fails to complete a required study visit, rather than if a participant fails to attend a required study visit.	Updated per current CSP template for consistency across the efgartigimod program.
	Added statement that participants who continue to be unreachable after attempts to regain contact will be recorded as lost to follow-up.	Wording updated to clarify the intended process.
Section 8.2, Efficacy Assessments	Replaced "study manual" with "Investigator Site File".	The study does not use a formal study manual; instead, the information is included in Investigator Site File.
Section 8.3, Safety Assessments	Clarified that new abnormal or worsened pre-existing conditions that the investigator considers clinically significant will be reported as an AE where observed after signing the informed consent form, rather than where observed after screening.	Updated per current CSP template for consistency across the efgartigimod program.
Section 8.4, Adverse Events, Serious Adverse Events, and Other Safety Reporting	Text updated with the following changes: • Added "An AESI is an AE of scientific and medical concern specific to the sponsor's product or program and described in Section 8.4.6." • Removed "or the participant's legally authorized representative" from the list of individuals who may report an AE on behalf of the patient. • Clarified that the investigator and qualified designees are responsible for monitoring all reported events, including those reported by the participant.	Updated per current CSP template for consistency across the efgartigimod program.
Section 8.4.5, Pregnancy	Clarified that the pregnant female partner of a participant will be followed to determine the outcome of the pregnancy only where the pregnant female partner has consented to this.	Wording updated to clarify the intended process.
Section 8.4.6, Adverse Events of Special Interest	Specified that AESIs will be reported according to the same timeframe as that for SAEs specified in Section 8.4.1 and Section 10.3.4.	Wording added to clarify the intended process.

Section # and Name	Description of Change	Brief Rationale
Section 8.4.7, AEs of Clinical Interest	Addition of new section detailing AEs of clinical interest (infusion/injection-related reactions and injection site reaction).	Updated per current CSP template for consistency across the efgartigimod program.
Section 1.3, Schedule of activities	References to "plasma" samples are removed throughout the protocol.	Corrected as no plasma samples will be taken.
Section [redacted]		
Section 8.8.1.2, [redacted]		
Section 10.4.2.2, Male Contraception	Updated to remove male contraception requirements.	Updated per current safety requirements for efgartigimod.
Section 10.7, Appendix 7: Protocol Amendment History	Addition of appendix to capture fprotocol amendment history prior to the current amendment.	Added per CSP template requirements.

No other changes were made during this protocol amendment.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Expansion
[redacted]	[redacted]
ADA	antidrug antibody(ies)
AE	adverse events
COMPASS 31	Composite Autonomic Symptom Score
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
EDC	electronic data capture
EDV	early discontinuation visit
FcRn	neonatal Fc receptor
IgG	immunoglobulin G
NCI	National Cancer Institute
MaPS	Malmö POTS symptom score
OLE	open-label extension
PD	pharmacodynamic(s)
PGI-C	Patient Global Impression – Change
PGI-S	Patient Global Impression – Severity
PK	pharmacokinetic(s)
PLEX	plasma exchange
POTS	postural orthostatic tachycardia syndrome
PROMIS	Patient-Reported Outcomes Measurement Information System
[redacted]	[redacted]
SC	subcutaneous
SFV	safety follow-up visit
SoA	schedule of activities
WOCBP	women of childbearing potential

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A phase 2 randomized, double-blinded, placebo-controlled study to evaluate the efficacy and safety of efgartigimod IV in adult patients with post–COVID-19 postural orthostatic tachycardia syndrome (POTS) (ARGX-113-2104)

Rationale:

Efgartigimod is a neonatal Fc receptor (FcRn) antagonist in clinical development for treating autoimmune diseases mediated by immunoglobulin G (IgG) autoantibodies. POTS arising in patients after infection with the SARS-CoV-2 virus (COVID-19) may be caused by pathogenic IgG autoantibodies that lead to autonomic dysfunction. This phase 2 study will evaluate the efficacy and safety of efgartigimod in participants with post–COVID-19 POTS.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
• Evaluate the efficacy of efgartigimod in reducing the severity of post-COVID-19 POTS symptoms • Evaluate the safety and tolerability of efgartigimod in patients with post-COVID-19 POTS	• Change from baseline to week 24 in the Composite Autonomic Symptom Score 31 (COMPASS 31) (2-week recall version) • Change from baseline to week 24 in the Malmö POTS Symptom Score (MaPS) • Incidence and severity of adverse events (AEs), incidence of SAEs, changes in laboratory test results, vital signs, and electrocardiogram (ECG) results
Secondary	
• Evaluate the efficacy of efgartigimod on patient global assessment of disease activity and fatigue	• Change from baseline to week 24 in the Patient Global Impression of Severity (PGI-S) • Patient Global Impression of Change (PGI-C) at week 24 • Change from baseline to week 24 in the Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form 8a • Change from baseline to week 24 in the PROMIS Cognitive Function Short Form 6a

• Assess the pharmacodynamic (PD) effect of efgartigimod	• Absolute values, changes from baseline, and percent reduction from baseline in total IgG levels
• Assess the pharmacokinetic (PK) profile of efgartigimod	• Efgartigimod serum concentration-time profile
• Assess the immunogenicity of efgartigimod	• Incidence and prevalence of antidrug antibodies (ADA) against efgartigimod

Overall Design Synopsis:

This phase 2 study is a randomized, double-blinded, placebo-controlled, parallel-group study in participants with post–COVID-19 POTS.

The sponsor/designee, investigator, and participant are blinded to investigational medicinal product (IMP) treatment assignment.

Brief Summary:

This study aims to evaluate the efficacy and safety of weekly infusions of efgartigimod IV 10 mg/kg compared to matched-placebo IV in adult participants with post–COVID-19 POTS.

After an up to 28-day screening period, eligible participants will be randomized to efgartigimod IV 10 mg/kg or placebo in a 2:1 ratio, respectively, at baseline. IMP will be administered weekly during the 24-week randomized treatment period. At the end of the randomized treatment period, eligible participants may roll over into an open-label extension (OLE) study ARGX-113-2105 or remain in this study through the end of the 56-day follow-up period.

Number of Participants:

Approximately 42 participants will be randomized to IMP (efgartigimod IV 10 mg/kg or placebo).

Note: Enrolled means the participant agrees to participate in the clinical study after completing the informed consent process.

Study Arms and Duration:

Each participant will participate in the following study periods:

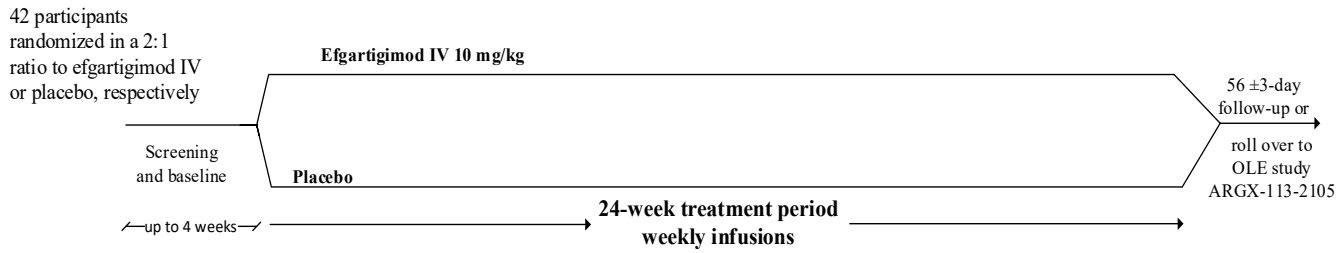
- Screening period of approximately 4 weeks
- Treatment period of 24 weeks
- Follow-up period of approximately 8 weeks (56 days ± 3 days) for participants who do not roll over to the OLE study ARGX-113-2105

Participants will receive IMP weekly during the 24-week treatment period, with the final weekly dose administered at week 23.

Data Monitoring/Other Committee: No

1.2. Schema

Figure 1: ARGX-113-2104 Study Overview



IV=intravenous; OLE=open-label extension

1.3. Schedule of Activities

	SCN	Study week															SFV	Applicable protocol section(s)
		BL	1	2	3	4	5-7	8	9-11	12	13-17	18	19-23	24	IDV[a]	EDV[b]		
Study day (±2)	**-28 to -1**	**1**[c]	**8**	**15**	**22**	**29**	**36-50**	**57**	**64-78**	**85**	**92-120**	**127**	**134-162**	**169**			**218**[d]	
All activities (safety and efficacy assessments, predose blood sampling) will be completed before administering the IMP infusion. Visits that must be attended on-site are SCN, BL, W1, W2, W4, W12, W24, IDV, EDV, and SFV																		
Eligibility/BL only																		
Informed consent	X																	Section 10.1.3
SARS-CoV-2	X[e]																	Section 5.2
HIV/HBV/HCV	X																	Section 5.2
FSH test [f]	X																	Section 10.4.1
Medical history	X																	
Demography	X																	
Active stand test (HR on 10-minute stand)	X																	Section 8.1.1
Eligibility check	X	X																Section 5.1 Section 5.2
Randomization		X																Section 6.3
Questionnaires																		
COMPASS 31 (original)	X																	Section 8.2.1
COMPASS 31 (modified)		X		X		X				X				X	X	X		Section 8.2.1
MaPS		X		X		X		X		X		X		X	X	X		Section 8.2.1.2
PGI-S, PGI-C		X[g]		X		X				X		X		X	X	X		Section 8.2.1.3

	SCN	Study week															SFV	Applicable protocol section(s)
		BL	1	2	3	4	5-7	8	9-11	12	13-17	18	19-23	24	IDV[a]	EDV[b]		
Study day (±2)	**-28 to -1**	**1[c]**	**8**	**15**	**22**	**29**	**36-50**	**57**	**64-78**	**85**	**92-120**	**127**	**134-162**	**169**			**218[d]**	
All activities (safety and efficacy assessments, predose blood sampling) will be completed before administering the IMP infusion. Visits that must be attended on-site are SCN, BL, W1, W2, W4, W12, W24, IDV, EDV, and SFV																		
PROMIS Fatigue		X		X		X				X				X	X	X		Section 8.2.1.4
[redacted]	[redacted]																	
PROMIS Cognition		X				X				X				X	X	X		Section 8.2.1.4
[redacted]	[redacted]																	
Exit interview														X[h]				Section 8.2.1.5
Efficacy tests[i]																		
[redacted]	[redacted]																	
[redacted]	[redacted]																	
[redacted]	[redacted]																	
[redacted]	[redacted]																	
Safety except reviews																		
Physical examination[k]	X	X				X				X				X	X	X	X	Section 8.3.1
Weight/height[l]	X	X				X				X				X				Section 6.1 Section 8.3.1
Vital sign measurements[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.3.2
ECG[n]	X	X								X				X	X	X		Section 8.3.3

	SCN	Study week															SFV	Applicable protocol section(s)
		BL	1	2	3	4	5-7	8	9-11	12	13-17	18	19-23	24	IDV[a]	EDV[b]		
Study day (±2)	**-28 to -1**	**1[c]**	**8**	**15**	**22**	**29**	**36-50**	**57**	**64-78**	**85**	**92-120**	**127**	**134-162**	**169**			**218[d]**	
All activities (safety and efficacy assessments, predose blood sampling) will be completed before administering the IMP infusion. Visits that must be attended on-site are SCN, BL, W1, W2, W4, W12, W24, IDV, EDV, and SFV																		
TSH/CRP/ESR		X												X				Table 2
Serum chemistry and hematology	X	X				X				X				X	X	X		Section 8.3.4 Table 2
Urinalysis	X	X								X				X	X	X		Table 2
Pregnancy test[o]	X	X				X		X		X	W16		W20	X	X	X	X	Section 8.3.5 Section 8.4.5
Blood sampling																		Section 8.1.2
PK profile[p]		X	X			X				X				X	X	X		Section 8.5
PD profile[q]	X	X	X			X				X				X	X	X	X	Section 8.6
[redacted]																		
AE review	Continuous monitoring																	Section 8.4
Conmed review	Continuous monitoring																	Section 6.9
IMP infusion		X[c]	X	X	X	X	X	X	X	X	X	X	X					Section 6

[redacted] ADA=antidrug antibodies; AE=adverse event; BL=baseline; COMPASS=composite autonomic symptom score; Conmed=concomitant medications; CRP=C-reactive protein; ECG=electrocardiogram; EDV=early discontinuation visit; ESR=erythrocyte sedimentation rate; FSH=follicle-stimulating hormone; [redacted]; HBV=hepatitis B virus; HCV=hepatitis C virus; HR=heart rate; IDV=IMP discontinuation visit; IMP=investigational medicinal product; PCR=polymerase chain reaction; PD=pharmacodynamics; PGI-C=Patient Global Impression–Change; PGI-S=Patient Global Impression–Severity; PK=pharmacokinetics; POTS=postural orthostatic tachycardia syndrome; PROMIS=Patient-Reported Outcomes Measurement Information System; SCN=screening; SFV=safety follow-up visit; TSH=thyroid stimulating hormone; WOCBP=women of childbearing potential

[a] The IDV will be performed at the next scheduled visit after permanent IMP discontinuation and applies for participants who discontinue IMP but remain in the study. Participants who permanently discontinue IMP will perform the IDV and then be asked to proceed with their regularly scheduled visits (Section 7.1).
[b] Within 7 days after last dose of IMP. The EDV applies for participants who discontinue the study.
[c] The first infusion of IMP will occur only once all BL assessments have been completed.
[d] Participants will attend an SFV unless rolling over into the OLE study ARGX-113-2105. For participants who discontinue IMP but remain in the study attending on-site visits, safety assessments will occur on the previously scheduled visit closer to 56 days (±3 days) from the last IMP dose.
[e] A positive PCR test for SARS-CoV-2 during screening is exclusionary for study participation (Section 5.2, exclusion criterion 6).
[f] FSH will be measured in postmenopausal women during screening to confirm their postmenopausal state. The investigator will assess the postmenopausal state in postmenopausal women receiving hormonal therapy. Tests may be analyzed at a local or a central laboratory.
[g] The participant will complete only the PGI-S and not the PGI-C at BL.
[h] The participant's perspective on the questionnaires administered during the study will be captured in an optional exit interview. The interview can be conducted after EDV for participants who prematurely discontinue the study.
[i] These assessments may be performed on the day before the scheduled time point.
[j] Eligibility is based on a change in orthostatic HR with either active stand testing or head-up tilt testing, consistent with consensus criteria (Section 5.1, inclusion criterion 3.a). Participants who do not meet this criterion with active stand testing may be reevaluated using the head-up tilt test to confirm eligibility during the screening period.
[k] The physical examination will comprise a full assessment of systems at screening and a brief assessment at all other time points. See Section 8.3.1 for specific parameters.
[l] Height will be measured only at screening. The 10 mg/kg efgartigimod dose is based on body weight, and the maximum total dose per efgartigimod infusion is 1200 mg for participants who weigh ≥120 kg. The dose level will be recalculated if a participant's weight has changed (increased or decreased) by more than 10% from baseline.
[m] Vital signs will be measured before collecting any blood sample or administering IMP infusions. Vital sign parameters are listed in Section 8.3.2.
[n] On days when ECGs are performed, this will be the first assessment of the day.
[o] WOCBP will be tested for pregnancy by serum at screening and urine on day 1 (BL) and during the study, including the follow-up period.
[p] At IMP administration visits, blood for PK analyses will be collected predose (within 2 hours before the infusion) and postdose (within 30 minutes after the end of the infusion). At other visits, blood samples may be collected at any time during that visit. Blood samples for participants remaining in the study following IMP discontinuation will be collected for up to 3 weeks post IMP discontinuation for PK analysis.
[q] At IMP administration visits, blood for PD, immunogenicity, and biomarker analyses will be collected predose (within the 2 hours before IMP infusion). At other visits, blood samples may be collected at any time during that visit.

[redacted]

2. INTRODUCTION

The study aims to investigate the safety, tolerability, efficacy, pharmacodynamics (PD), pharmacokinetics (PK), and immunogenicity of efgartigimod compared to placebo in participants with post–COVID-19 postural orthostatic tachycardia syndrome (POTS) (post–COVID-19 POTS).

2.1. Study Rationale

Efgartigimod is a first-in-class antibody fragment that binds to the neonatal Fc receptor (FcRn). This binding prevents FcRn from recycling immunoglobulin G (IgG) and leads to a reduction in circulating disease-causing autoantibodies. Approved by the Food and Drug Administration (FDA) in the US for use in adult patients with acetylcholine receptor (AChR) antibody-positive generalized myasthenia gravis (gMG) efgartigimod is being clinically developed in other autoimmune diseases mediated by pathogenic IgG autoantibodies.

Efgartigimod may be a viable treatment option for individuals diagnosed with post–COVID-19 POTS because it has been shown to reduce IgG levels, including IgG autoantibodies, which may underlie some of the autonomic disease manifestations in these patients.

2.2. Background

The novel SARS-CoV-2 and resulting COVID-19 emerged in late 2019, becoming an ongoing global pandemic in 2022.[1] Because of COVID-19, many patients develop chronic, debilitating symptoms after recovery from the acute infection.[2] Multiple terms have been used to describe the constellation of symptoms, including long-COVID, long-haul COVID, and post-acute sequelae of SARS-CoV-2 syndrome. Typical symptoms of long-COVID include breathlessness, fatigue, cognitive impairment (eg, brain fog), orthostatic intolerance, and palpitations.[2] These symptoms are often debilitating, and most patients receive disability or modified independence.[3] Evidence is emerging that autonomic dysfunction underlies the symptoms that persist after the acute SARS-CoV-2 infection resolves.[4]

POTS in patients who continue to have long-lasting symptoms after recovery from the initial SARS-CoV-2 infection has been identified in several case reports.[5,6] A POTS diagnosis is based on evaluations for excessive orthostatic tachycardia (sustained heart rate [HR] increment of not less than 30 beats/minute [bpm] within 10 minutes of standing or head-up tilt [≥40 bpm in 12 to 19 years old]); absence of orthostatic hypotension; frequent symptoms of orthostatic intolerance during standing, with rapid improvement upon return to a supine position; duration of symptoms for ≥3 months; and absence of other conditions explaining sinus tachycardia.[7] Patients who develop POTS after COVID-19 are designated in this study as having post–COVID-19 POTS.

Currently, the underlying pathophysiology and effective treatments are unknown for post–COVID-19 POTS. Pharmacologic therapy mainly focuses on orthostatic symptoms, targeting blood volume expansion and stabilizing HR and blood pressure; however, POTS may be related to immune dysfunction and autoimmunity preceded by infection.[7] Several infectious pathogens may be associated with the development of POTS, including SARS-CoV-2.[8,9,10] Patients with POTS have a higher prevalence of autoantibodies, including ganglionic AChR antibody G-protein coupled receptor (GPCR) antibodies, which could increase sympathetic tone by

activating adrenergic receptors.[11] Patients with POTS have been shown to have higher levels of these autoantibodies than healthy subjects.[12] The binding of these autoantibodies to adrenergic receptors has been hypothesized to cause tachycardia in some patients.[13,14] These autoantibodies, acting as partial agonists, are thought to decrease the effectiveness of peripheral norepinephrine leading to an increased sympathetic response to posture resulting in postural tachycardia in the absence of hypotension.[15]

Collectively, these data suggest that post–COVID-19 POTS could be caused by IgG autoantibodies that induce autonomic dysfunction. The aim of this phase 2 study is to evaluate if efgartigimod is safe and efficacious in treating the autonomic symptoms and clinical manifestations of autonomic dysfunction in patients diagnosed with POTS after COVID-19.

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

2.3. Benefit/Risk Assessment

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

2.3.1. Risk Assessment

Overall, available data confirm that efgartigimod IV has been well-tolerated across studies in different indications and has an acceptable safety profile.

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 infection risk.	Exclude participants with clinically significant uncontrolled infections, malignancies, or certain viral infections (Section 5.2). Monitor for infections, considered an AE of special interest (AESI) (Section 8.4.6), and temporarily interrupt IMP dosing as specified in Section 7.1.2.
Infusion-related reactions (IRR)	All therapeutic proteins can elicit immune responses, potentially resulting in hypersensitivity or allergic reactions such as rash, urticaria, angioedema, serum sickness, and anaphylactoid or anaphylactic reactions.	Monitor participants during administration and for 30 minutes thereafter for clinical signs and symptoms of infusion/injection-related reactions. Infusion/injection-related reactions are considered AEs of clinical interest (Section 8.4.7).
Infusion/injection-site reactions	Most AEs have been mild, transient injection site reactions, including erythema, pain, bruising, pruritus, burning, tenderness, edema, induration,	Continuously monitor participants for injection site reactions.

Potential clinically significant risk	Summary of data/rationale for risk	Mitigation strategy
	irritation, paresthesia, numbness, and rash. Moderate injection site reactions occurring less frequently include burning, erythema, pain, and numbness. Mild to moderate headache is commonly reported.	Infusion/injection-site reactions are considered AEs of clinical interest (Section 8.4.7).

2.3.2. Benefit Assessment

Efgartigimod has been investigated in nonclinical studies, phase 1 clinical pharmacology studies in healthy subjects, and phase 2-3 clinical studies in patients with IgG-driven autoimmune diseases, including gMG, primary immune thrombocytopenia (ITP), chronic inflammatory demyelinating polyneuropathy, myositis, and pemphigus.

In clinical studies, efgartigimod effectively reduces IgG antibody levels, including pathogenic autoantibodies. The efficacy of efgartigimod to improve clinical outcomes in gMG and reduce pathogenic autoantibodies was confirmed in a pivotal phase 3 study in participants with gMG (ARGX-113-1704). In addition, clinical benefit was observed in phase 2 studies in primary ITP (ARGX-113-1603) and pemphigus (ARGX-113-1701), in which pathogenic autoantibodies underlie the disease pathology (see current efgartigimod IB). The available clinical data support the clinical benefit of efgartigimod for reducing pathogenic IgG autoantibodies, which may mitigate autonomic dysfunction and improve symptoms and the ability to function in patients with post–COVID-19 POTS.

2.3.3. Overall Benefit-Risk Conclusion

The potential risks associated with efgartigimod are justified by the anticipated benefits possibly afforded to participants with post–COVID-19 POTS in this study and considering the measures implemented to minimize risks. The favorable balance between risks and anticipated efficacy/benefit supports the use of efgartigimod in the clinical development for post–COVID-19 POTS.

Detailed information is provided in the efgartigimod IB on the known and expected benefits and risks and reasonably expected AEs from efgartigimod clinical studies.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints
Primary	
• Evaluate the efficacy of efgartigimod in reducing the severity of post-COVID-19 POTS symptoms • Evaluate the safety and tolerability of efgartigimod in patients with post-COVID-19 POTS	• Change from baseline to week 24 in the Composite Autonomic Symptom Score 31 (COMPASS 31) (2-week recall version) • Change from baseline to week 24 in the Malmö POTS Symptom Score (MaPS) • Incidence and severity of AEs, incidence of serious adverse events (SAEs), changes in laboratory test results, vital sign measurements, and electrocardiogram (ECG) results
Secondary	
• Evaluate the efficacy of efgartigimod on patient global assessment of disease activity and fatigue	• Change from baseline to week 24 in the Patient Global Impression of Severity (PGI-S) • Patient Global Impression of Change (PGI-C) at week 24 • Change from baseline to week 24 in the Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form 8a • Change from baseline to week 24 in the PROMIS Cognitive Function Short Form 6a
• Assess the PD effect of efgartigimod	• Absolute values, changes from baseline, and percent reduction from baseline in total IgG levels
• Assess the PK profile of efgartigimod	• Efgartigimod serum concentration-time profile
• Assess the immunogenicity of efgartigimod	• Incidence and prevalence of antidrug antibodies (ADA) against efgartigimod

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

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blinded, placebo-controlled, parallel-group, phase 2 study.

The total study duration is approximately 36 weeks comprising:

- Screening period of approximately 4 weeks
- Treatment period of 24 weeks
- Follow-up period of approximately 8 weeks (56 days ± 3 days) for participants who do not roll over to the open-label extension (OLE) study ARGX-113-2105

The study population is adult patients with new-onset POTS post–COVID-19.

Participants will be randomized to receive efgartigimod IV 10 mg/kg or matching placebo in a 2:1 ratio, respectively.

IMP (efgartigimod or matching placebo) will be administered during the treatment period in an approximately 1-hour IV infusion once weekly by site staff or a home nurse. The final dose will be administered at week 23.

At week 24, eligible participants may roll over into a single-arm OLE ARGX-113-2105.

4.2. Scientific Rationale for Study Design

This study aims to evaluate the efficacy and safety of weekly infusions of efgartigimod IV 10 mg/kg compared to matched-placebo IV in adult participants with post–COVID-19 POTS.

The study design is randomized, double-blinded, and placebo-controlled to evaluate the effect of efgartigimod administered as an IV infusion compared to placebo. The study consists of a treatment period when all participants will receive weekly IV infusions for 24 weeks. As there are no standardized approved therapies for post–COVID-19 POTS, the comparison to placebo is justified.

The primary endpoints are the safety and tolerability of efgartigimod in participants with post-COVID-19 POTS and efficacy as assessed by change from baseline to week 24 in COMPASS 31 (2-week recall version) and the MaPS. Safety and tolerability are included as a primary endpoint as efgartigimod has not been previously administered in this patient population.

COMPASS 31 is a quantitative measure of autonomic symptoms developed for use in autonomic research and clinical practice.[16] It is a self-rated questionnaire with 31 questions in 6 domains (orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor) (Section 8.2.1).

The MaPS score, recently reported by Fedorowski and colleagues, is a dedicated POTS symptom scoring questionnaire.[17] The score consists of 12 questions that assess symptom burden related and unrelated to orthostatic intolerance (related: tachycardia, palpitations, dizziness, presyncope; unrelated: gastrointestinal (GI) symptoms, insomnia, concentration difficulties) (Section 8.2.1.2).

The COMPASS 31 and MaPS questionnaires were chosen to provide a comprehensive assessment of autonomic (COMPASS 31) and POTS-specific symptoms (MaPS). COMPASS 31 is a validated measure of autonomic symptoms in a common disease of dysautonomia, small fiber polyneuropathy.[18] Prior studies in patients with POTS support the ability of this assessment to measure autonomic symptom burden in patients relative to controls and over time.[19,20] Elevations in COMPASS 31 have also been found in patients post–COVID-19 with evidence of POTS and other forms of dysautonomia.[21,22] The MaPS questionnaire was developed specifically for patients with POTS by investigators at the Skåne University Hospital, Lund University in Malmö, Sweden. The 12-item evaluation score is being evaluated in a case-control study in patients with POTS compared to healthy controls (A. Fedorowski, unpublished data, 2022). MaPS is expected to provide an accurate assessment of POTS symptoms over time. Further validation of the score will be accomplished by its comparison to COMPASS 31 and the other measures included in this study.

All secondary endpoints complement the primary efficacy endpoints and provide additional information on efficacy, including measures of patients' assessment of disease severity and change over time (PGI-S and PGI-C) and an established assessment of fatigue (PROMIS Fatigue), which is a common symptom among patients with POTS.[15]

4.3. Justification for Dose

Weekly doses of efgartigimod IV 10 mg/kg will be administered to achieve a maximal total IgG reduction (PD effect), thereby ensuring maximal clinical response on the efficacy outcomes.

As the hypothesis for treating post–COVID-19 POTS with efgartigimod is to reduce the pathogenic autoreactive IgG, the selected dose and dose regimen target a nearly maximal PD effect (ie, reduction of pathogenic IgGs). Considering the chronic nature of post–COVID-19 POTS, the dosing regimen of weekly IV administration reflects the need for chronic treatment to maintain pathogenic IgG autoantibody suppression and symptom reduction.

The cumulative data from a phase 1 study in healthy adult subjects; phase 2 studies in participants with gMG, ITP, and pemphigus; phase 3 studies in gMG; and PK/PD modeling results demonstrate that a 10 mg/kg efgartigimod dose administered weekly (q7d) through IV infusion achieved approximately 70% IgG reduction, including pathogenic autoantibodies. Maximal IgG reduction was associated with clinical efficacy observed in gMG, ITP, and pemphigus studies. Furthermore, this dose has been safe and well-tolerated in all study populations and has demonstrated similar PK and PD profiles across indications. Accordingly, the 10 mg/kg weekly IV dose regimen was selected for this study.

4.4. End-of-Study Definition

The end of study is defined as the date of the last participant's last visit.

A participant will have completed the study if the treatment period (or follow-up period, if applicable) has been completed.

Participants rolling over to the OLE study ARGX-113-2105 will have completed this study at week 24.

Participants not rolling over to the OLE study ARGX-113-2105 will have completed this study after the safety follow-up visit (SFV) or early discontinuation visit (EDV). If a participant continues in the study after discontinuing IMP, this will be week 23 or at the SFV (if permanent IMP discontinuation is <56 days from week 23).

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

1. Reached the age of consent when signing the informed consent form
2. Capable of providing signed informed consent, as described in Section 10.1.3, and complying with protocol requirements
3. Diagnosed with new-onset POTS post–COVID-19 established by the following:
   a. History of COVID-19 based on a previous positive test result from either laboratory-confirmed COVID-19 test (eg, a PCR test) or non-laboratory-confirmed COVID-19 test (eg, rapid antigen test); this positive result may be either documented or patient-reported
   b. Tilt table or orthostatic vital sign measurements during screening consistent with consensus criteria: sustained HR increase of ≥30 bpm within 10 min of standing or head-up tilt (≥40 bpm for individuals aged 18 to 19 years) and/or HR reaching >120 bpm within 10 min; absence of sustained 20 mmHg decrease in systolic blood pressure (SBP)
   c. Ongoing symptoms of POTS confirmed by the investigator with at least 3 symptoms in each of the following areas lasting longer than 12 weeks after either diagnosis of COVID-19 or after hospital discharge for COVID-19:
      i. Vasomotor symptoms: fatigue, orthostatic intolerance, brain fog, exertional dyspnea, difficulty with concentration, venous pooling, and exercise intolerance
      ii. Sympathetic over-compensation symptoms: palpitation, heat intolerance, nausea with or without vomiting, insomnia, anxiety, lack of appetite, chest pain, and diaphoresis
4. COMPASS 31 ≥35 at screening
5. Agree to use contraceptives consistent with local regulations regarding the methods of contraception for those participating in clinical studies and the following:

   Male participants: see Section 10.4.2.2

   Female participants of childbearing potential (defined in Section 10.4.1) 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 10.4.2.1.
6. Body mass index (BMI) <35 kg/m^2

5.2. Exclusion Criteria

Participants will be excluded from the study if any of the following criteria apply:

1. Diagnosis of or receiving treatment for the following conditions before COVID-19: peripheral neuropathy, POTS, myalgic encephalomyelitis encephalitis/chronic fatigue syndrome, Ehlers Danlos syndrome confirmed by genetic testing, autonomic neuropathy, multiple sclerosis, stroke, spinal cord injury, or any known lesions in the central nervous system by imaging or neurological exam
2. History of or currently being treated for clinically significant ongoing cardiac arrythmia, heart failure, myocarditis, pulmonary embolism requiring anticoagulation, pulmonary fibrosis, or critical illness-related polyneuropathy or myopathy
3. Known autoimmune disease that, in the investigator's judgment, would interfere with an accurate assessment of clinical symptoms of post–COVID-19 POTS or puts the participant at undue risk
4. Known HIV disease or common variable immunodeficiency
5. History of malignancy unless considered cured by adequate treatment with no evidence of recurrence for ≥3 years before the first administration of IMP. Adequately-treated participants with the following cancers may be included at any time:
    a. Basal cell or squamous cell skin cancer
    b. Carcinoma in situ of the cervix
    c. Carcinoma in situ of the breast
    d. Incidental histological finding of prostate cancer (TNM stage T1a or T1b)
6. Clinically significant uncontrolled active or chronic bacterial, viral, or fungal infection or positive SARS-CoV-2 PCR test at screening
7. Positive serum test at screening for an active infection with any of the following:
    a. Hepatitis B virus (HBV) that is indicative of an acute or chronic infection, unless associated with a negative HB surface antigen (HBsAg) or negative HBV DNA test
    b. Hepatitis C virus (HCV) based on HCV antibody assay unless a negative RNA test is available
    c. HIV
8. A medical condition that could confound the results of the study or put the participant at undue risk in the investigator's judgment
9. Clinically significant disease, recent major surgery (within 3 months of screening), or intends to have surgery during the study; or any other condition that in the opinion of the investigator could confound the results of the study or put the participant at undue risk
10. Total IgG <4 g/L at screening
11. Received within 12 weeks or 5 half-lives (whichever is longer) before screening an investigational product
12. Received within 12 weeks before screening either intravenous immunoglobulin (Ig) IV or SC or plasma exchange (PLEX)

13. Received a live or live-attenuated vaccine less than 4 weeks before screening
14. Known hypersensitivity to IMP or 1 of its excipients
15. Previously participated in an efgartigimod clinical study and received at least 1 dose of IMP
16. Currently participating in another interventional clinical study
17. History (within 12 months of screening) of or current alcohol, drug, or medication abuse
18. Pregnant or lactating or intends to become pregnant during the study
19. Unwilling to remain on a stable regimen of medications during the study
20. Unwilling to avoid initiation of new physical rehabilitation or other physician-prescribed exercise programs during the 24-week treatment period

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

No restrictions apply.

5.3.2. Caffeine, Alcohol, and Tobacco

No restrictions apply except for those described in the exclusion criteria (Section 5.2, exclusion criterion 17).

5.3.3. Activity

Participants will not initiate a new physical rehabilitation or other physician-prescribed exercise programs during the 24-week treatment period (See Section 5.2, exclusion criterion 20).

5.4. Screen Failures

A screen failure occurs when a participant who has signed the ICF is not assigned to IMP. A minimal set of screen failure information (demography, screen failure details, eligibility criteria, SAE reports) is required to ensure transparent reporting of screen failure participants and address regulatory authority queries.

- Retesting: Participants with exclusionary clinical laboratory results, ECGs, vital sign measurements, etc that are inconsistent with their medical history or clinical evaluation, can be retested once within the remaining screening period to confirm the test value(s).
- Rescreening: Participants who do not initially meet this study's eligibility criteria can be rescreened once. For example, a participant who does not meet eligibility criteria because of an acute illness ongoing during screening (considering the illness itself does not violate inclusion/exclusion criteria), they can be rescreened once the illness is resolved or the medical issue stabilized. Rescreened participants will be reconsented and assigned a new participant number for each rescreening event.

5.5. Criteria for Temporarily Delaying Enrollment

Not applicable.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

IMP includes efgartigimod and placebo. All IMPs are manufactured according to Good Manufacturing Practice regulations.

6.1. Study Intervention(s) Administered

Table 1: Study Intervention(s) Administered

Intervention label	**Efgartigimod IV**	**Placebo**
Intervention name	Efgartigimod IV	Placebo
Intervention description	Sterile, colorless, clear concentrate solution for intravenous infusion efgartigimod 20 mg/mL, administered IV	Sterile, colorless, clear concentrate solution for infusion, with the same excipients as efgartigimod IV, but without the active ingredient (efgartigimod)
Type	Biologic	Placebo
Dose formulation	Infusion	Infusion
Unit dose strength(s)	20 mg/mL	Not applicable
Dosage level(s)	10 mg/kg qw ×24 weeks	Not applicable
Route of administration	IV infusion	IV infusion
Use	Experimental	Placebo-comparator
IMP and NIMP/AxMP	IMP	IMP
Sourcing	Centrally by the sponsor/designee	Centrally by the sponsor/designee
Packaging and labeling	IMP will be provided in glass vials. Each vial will be labeled as required per country requirements.	IMP will be provided in glass vials. Each vial will be labeled as required per country requirements.
Former name	ARGX-113	Not applicable

The 10 mg/kg efgartigimod dose is based on body weight, and the maximum total dose per efgartigimod infusion is 1200 mg for participants who weigh ≥120 kg. The dose level will be recalculated if a participant's weight has changed (increased or decreased) by more than 10% from baseline.

6.2. Preparation, Handling, Storage, and Accountability

The IMP will be supplied to the investigational site by the sponsor/designees' designated IMP supply vendor.

Appropriate dilutions in a 0.9% saline solution in an infusion bag will be prepared before administration with an IV pump.

The pharmacy manual and home guide provide detailed instructions on the preparation, handling, storage, and accountability.

The investigator or designee is responsible for the correct and safe storage of the IMP. All IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated)

area following the labeled storage conditions, with access limited to the investigator and authorized site staff.

The investigator or designee must confirm that appropriate temperature conditions have been maintained for all IMP received during transit. Any discrepancies are reported and resolved before using the IMP. The home nurse will be trained to evaluate the maintenance of appropriate temperature conditions during IMP transit.

Only participants enrolled in the study may receive IMP, and only authorized site staff or designee may supply or administer IMP.

At a minimum, the first 3 doses of IMP must be administered on-site. These doses are scheduled to be administered at the baseline visit and the week 1 and 2 visits, but if doses are missed at 1 or more of these visits, then dosing at subsequent visits will also be on-site. IMP administration at home will not commence until after 3 doses have been administered on-site.

Participants will be observed for at least 30 minutes after the end of the infusion for routine safety monitoring.

The pharmacy manual and home guide provide further guidance and information for the final disposition of unused IMP.

Accountability of home-administered IMP will be documented as instructed in the home guide.

6.3. Assignment to Study Intervention

Participants whose eligibility has been confirmed will be randomized using interactive response technology (IRT) in a 2:1 ratio to efgartigimod or placebo, respectively. The preplanned randomization list will be produced using permuted blocks.

6.4. Blinding

This is a double-blinded study. The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator is solely responsible for determining if unblinding of the IMP assignment is necessary. Participant safety must always be the first consideration in making such a determination.

If the investigator decides that unblinding is warranted, the investigator can contact the sponsor before unblinding a participant's IMP unless this could delay emergency treatment for the participant. If a participant's IMP assignment has been unblinded, the sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded in the source documents.

6.5. Study Compliance

Under medical supervision, participants will receive IMP directly from the site staff or delegate. The infusion start date/time and infusion end date/time of each dose administered will be recorded in the source documents, as well as the total dose administered at each visit.

Any participant who misses a scheduled dose (±2 days) will wait to receive the next scheduled dose (see Section 1.3).

6.6. Dose Modification

The maximum total efgartigimod dose per efgartigimod infusion is 1200 mg for participants weighing ≥120 kg. The IMP weight-based dose will be recalculated if a participant's weight has changed (increased or decreased) by more than 10% from baseline. Otherwise, dose modifications are not permitted.

6.7. Continued Access to IMP After the End of the Study

At the end of the study, eligible participants may enroll in the OLE study ARGX-113-2105 and receive open-label efgartigimod.

6.8. Treatment of Overdose

An overdose is defined as a deliberate or accidental administration of IMP to a study participant at a dose greater than that assigned to that participant under the study protocol.

For this study, a variation of more than 10% of the intended weekly amount of IMP will be considered an overdose.

The sponsor/designee does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator will:

- Contact the medical monitor (MM) immediately
- Evaluate the participant to determine if IMP should be interrupted in consultation with the MM
- Closely monitor the participant for any AE/SAE and laboratory abnormalities

Document the quantity of the excess dose and the overdose duration and report any AE/SAE that occurred in association with the overdose.

6.9. Prior and Concomitant Therapy

Participants should maintain a stable regimen of medications throughout the study. Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements [including Chinese traditional medicine]) or other specific categories of interest that the participant is receiving at the time of screening or receives during the study must be recorded and include the following information:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information (ie, dose and frequency)

All available vaccination history should be recorded as part of the participant's prior medications or as concomitant medication for vaccinations received during the study.

6.9.1. Prohibited Medication

The following medications or treatments are not permitted while the participant receives IMP:

- Subcutaneous or intravenous immunoglobulin
- PLEX
- Live or live-attenuated vaccines (this restriction also applies for up to 28 days after the final dose of IMP)
- IV saline bolus treatments for volume expansion for treating POTS symptoms

7. IMP DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or the entire study is described in Appendix 1 (Section 10.1).

7.1. IMP Discontinuation

7.1.1. Permanent Discontinuation

Permanent discontinuation of IMP occurs when the participant stops receiving IMP before the end of the study and does not resume receiving IMP. The participant also must not have withdrawn informed consent.

The investigator will document the primary reason for early discontinuation of IMP.

Participants who permanently discontinue IMP will be encouraged to remain in the study and attend any previously scheduled visits, even if only by telephone. Participants unwilling to participate in on-site visits for AE and concomitant medication monitoring will be offered the option to attend these visits by web teleconferencing or telephone. If the participant cannot attend the previously scheduled visits for any reason, the study site will minimally perform the EDV and the SFV on-site.

Unless consent from the study has been withdrawn, the participant will attend an EDV and an SFV. Study sites will attempt to perform the EDV within 7 days of last contact with the participant. The SFV will occur 56 ±3 days after the participant's final IMP administration.

The following circumstances will result in the permanent discontinuation of IMP:

- Participant becomes pregnant or intends to become pregnant (refer to Section 8.3.5)
- Investigator decides that discontinuing IMP is in the participant's best interest (the sponsor will be informed)
- Participant develops an SAE or AE that contraindicates further administration of IMP in the investigator's opinion or an AE of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade 4 that is considered related to IMP by the sponsor
- Participant develops a new or recurrent malignancy except for basal cell carcinoma of the skin, regardless of relationship
- The participant receives a prohibited medication or substance (Section 6.9.1)

Participants permanently discontinuing IMP will be ineligible to roll over into the OLE study.

7.1.2. Temporary Discontinuation

Temporary discontinuation of IMP occurs when the participant discontinues receiving IMP before the end of the study and resumes once the cause for the discontinuation has been resolved.

Reasons for temporary discontinuation may include an AE that meets the following criteria :

- Any SAE considered related to IMP by the sponsor

- Clinically significant active infection considered related to the IMP by the sponsor

7.2. Participant Discontinuation/Withdrawal from the Study

Study withdrawal is defined as the permanent cessation of further participation in any study assessment before its planned completion.

The primary reason for permanent study withdrawal will be recorded.

The following circumstances will result in permanent discontinuation and withdrawal from the study:

- Participant withdrawal of consent
- Sponsor request

If the participant also withdraws consent to participate in future research, the sponsor can retain and continue to use any data collected before such consent was withdrawn.

- Samples collected from participants who have withdrawn from the study will be used for the study results but not for future research.

Participants withdrawn from the study will be ineligible to roll over into the OLE study.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be completed if a participant fails to complete a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to continue in the study.
- Before a participant is considered lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (when possible, 3 phone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record.
  - Participants who continue to be unreachable will be considered to have withdrawn from the study, and will be recorded as lost to follow-up.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.

Visits that must be attended on-site are SCN, BL, W1, W2, W4, W12, W24, IMP discontinuation visit, EDV, and SFV. All other visits may occur at the participant's home (Appendix 6, Section 10.6)

All screening evaluations must be completed and reviewed to confirm that potential 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.

Operational considerations due to the COVID-19 pandemic are provided in Section 10.5. Per local health authority/ethics requirements, the sponsor/designee or the investigator may implement alternate strategies for participant visits, assessments, medication distribution, and monitoring.

8.1. Administrative and General/Baseline Procedures

All significant findings, surgeries, and pre-existing conditions (including allergies) present at screening will be reported. Complete information will be collected on medical and surgical history and concomitant medical conditions and specifying those ongoing at screening.

Details collected as a part of the medical history must include but are not limited to all previous treatment/therapy for COVID-19 and post–COVID-19 POTS.

Questionnaires will be administered before any other assessment, if applicable for that visit. If applicable, all other assessments will be completed after the questionnaires and before the infusion except the postdose PK blood sample.

All assessments will be completed before administering the IMP infusion.

8.1.1. Screening

Eligibility is based on a change in orthostatic HR with either active stand testing or head-up tilt testing, consistent with consensus criteria (Section 5.1, criterion 3.a) (Shelton).[15,23] Participants who do not meet this criterion with active stand testing may be evaluated using the head-up tilt test to confirm eligibility during the screening period. In this case, investigators may direct the participant to withhold medications based on clinical judgment that could confound the head-up tilt test interpretation. The screening head-up tilt testing may occur on the same day as other screening assessments or another day during the screening period.

Blood samples collected at the screening visit may be used to validate methods to measure efgartigimod, antibodies, and biomarkers. Participants must consent to their samples being used before such procedures are performed.

8.1.2. Use and Storage of Blood Samples

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 study, in the laboratory or long term storage worldwide designated by the sponsor/designee or research partners for future additional medical, academic, or scientific research to address any scientific questions related to efgartigimod, FcRn biology, or POTS, unless this would not be allowed according to local regulations or the participant would not have agreed.

8.2. Efficacy Assessments

Time points for all efficacy assessments are provided in the SoA (Section 1.3).

Questionnaires should be administered before any other study assessment and may be completed up to 1 day before the visit.

Please see the Investigator Site File for instructions on administering these assessments.

8.2.1. Questionnaires

8.2.1.1. COMPASS 31

COMPASS 31 is an easily scored questionnaire to evaluate the severity and distribution of autonomic symptoms in various autonomic nerve disorders, providing clinically relevant scores of autonomic symptom severity. The questionnaire is based on the well-established 169-item Autonomic Symptom Profile (ASP) and the validated 84-question scoring instrument, the Composite Autonomic Symptom Score (COMPASS).[16] The COMPASS 31 questionnaire has been previously used to assess patients with POTS.[19,20]

The 31-item questionnaire requires approximately 10 minutes to administer and addresses 6 domains: orthostatic intolerance, vasomotor, secretomotor, bladder, pupillomotor, and gastrointestinal-mixed upper and diarrhea.

The original version of COMPASS 31 (longer recall) will be administered at screening and the modified version (2-week recall) will be administered at baseline and all other time points.

Higher scores indicate a more severe degree of autonomic symptoms.

8.2.1.2. MaPS

The MaPS has been developed to assess the severity of the most common symptoms found in patients with POTS based on clinical experience and literature (A. Fedorowski, unpublished data, 2022). The score consists of 12 questions that assess symptom burden related (tachycardia, palpitations, dizziness, presyncope) and unrelated to orthostatic intolerance (GI symptoms, insomnia, concentration difficulties).

Participants will grade their symptoms for the past 7 days using a visual analog scale (VAS) ranging from 0 (no symptoms) to 10 (worst possible). The maximum score is 120 points, with higher scores indicating more severe symptoms. In general, patients with POTS score >40 points, whereas healthy controls have lower values. A score >90 points indicates debilitating/severe symptoms.

8.2.1.3. PGI-S and PGI-C

The PGI-S and PGI-C questionnaires are simple, participant-rated, single-item global measures of their perceived condition.

- PGI-S: Severity of symptoms over the past week and overall experience of symptoms over the past 2 weeks (2 week recall) are both rated on a 4-point Likert scale, with scores ranging from 1 (none) to 4 (severe)
- PGI-C: Overall change in symptoms from the start of IMP to time point is rated on a 7-point Likert scale, with scores ranging from 1 (much better) to 7 (much worse)

8.2.1.4. PROMIS

PROMIS is a publicly available system of highly reliable, precise patient-reported health status measures of physical, mental, and social well-being. PROMIS instruments measure concepts including pain, fatigue, and physical function.

- PROMIS Fatigue Short Form 8a: assesses the impact and perceived fatigue during the last 7 days. This validated 8-question scale has 5 response options, with scores ranging from 1 to 5. Scores are converted to a T-score, and higher scores indicate higher fatigue levels. A decrease in score (negative change from baseline) indicates improvement in fatigue.
- [redacted]

8.2.1.5. Exit Interview

Trained independent moderators will interview approximately 15 to 20 participants over the telephone within 14 days after the week 24 visit. Participants will respond to open-ended questions on their experience with post–COVID-19 POTS and provide their perspectives on the relevance, completeness, and comprehensibility of questionnaires implemented during the study. For participants who prematurely discontinue the study, the interview can be conducted after their EDV.

Participation in the interview is optional.

Further details will be provided in a separate interview manual.

8.2.2. [redacted]

[redacted]

8.2.3. [redacted]

[redacted]

8.2.4. [redacted]

[redacted]

8.3. Safety Assessments

Time points for all safety assessments are provided in the SoA (Section 1.3). Safety measures will be assessed before IMP infusion unless otherwise stated.

At screening, clinically significant abnormalities in any safety assessment will be reported as medical history. New abnormal or worsened pre-existing conditions observed after signing the informed consent form that the investigator considers clinically significant will be reported as an AE.

8.3.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the musculoskeletal, gastrointestinal, pulmonary, cardiovascular, respiratory, and neurological systems and general appearance, skin, and lymph nodes. Height and weight will also be measured without shoes, attired in light clothing, and recorded using calibrated instruments.

Brief physical examination will include assessments of gastrointestinal, pulmonary, cardiovascular, and respiratory systems and general appearance.

8.3.2. Vital Signs

Oral temperature, pulse rate, respiratory rate, and blood pressure will be recorded before blood collection for laboratory tests.

Blood pressure and pulse will be assessed with the participant rested and seated.

8.3.3. Electrocardiograms

Single 12-lead ECG(s) will be obtained using an ECG machine. On days when ECGs are performed, this will be the first assessment of the day.

8.3.4. Clinical Safety Laboratory Tests

Blood and urine samples will be analyzed at a laboratory for serum chemistry and hematology, coagulation, urinalysis, serology (eg, viral marker testing), and specialty laboratory parameters.

See Appendix 2 (Table 2) for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.

The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.

8.3.5. Pregnancy Testing

WOCBP will be tested for pregnancy by serum at screening. Urine tests for pregnancy will occur at the time points specified in the SoA (Section 1.3).

Pregnancy testing in WOCBP will be conducted at the end of relevant systemic exposure (ie, at the SFV).

Additional pregnancy testing may be performed as necessary by the investigator or required by local regulations to establish the absence of pregnancy at any time during the study.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AE and SAE are provided in Appendix 3 (Section 10.3). An AESI is an AE of scientific and medical concern specific to the sponsor's product or program and described in Section 8.4.6.

AEs (including SAEs, AESIs, and AEs of clinical interest) will be reported by the participant (or, if appropriate, by the caregiver or surrogate).

The investigator and qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and monitoring all reported events, including those reported by the participant.

The method of recording, evaluating, and assessing the causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs will be collected from the signing of the ICF until the SFV, as specified in the SoA (Section 1.3).

All SAEs and AESIs will be recorded and reported to the sponsor or designee immediately, and under no circumstance will this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). 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 information on AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including death, at any time after a participant has been discharged from the study, and they consider the event to be reasonably related to IMP or study participation, the investigator must promptly notify the sponsor.

8.4.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and SAEs. Open-ended and nonleading verbal questioning of the participant is preferred to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator must proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs (defined in Section 8.4.6) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a 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 a 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 suspected unexpected serious adverse reactions (SUSARs) to the relevant regulatory authorities and IEC/IRB, per applicable regulatory requirements. The sponsor or designee will also be responsible for forwarding SUSAR reports to all study investigators, who will be required to report these SUSARs to their respective IECs/IRBs per local regulatory requirements.

8.4.5. Pregnancy

- If pregnancy is reported, the investigator will record the pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the pregnancy in the female participant or the female partner of the male participant. Contact details are provided in Serious Adverse Event Reporting.
- The participant (and, if consented, the pregnant female partner of a participant), will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate and forward it to the sponsor.
- While pregnancy itself is not considered an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported accordingly.
- Any poststudy pregnancy-related SAE considered reasonably related by the investigator to IMP will be reported to the sponsor as described in Section 8.4.4.
- Any female participant who becomes pregnant during the study will discontinue IMP.

8.4.6. Adverse Events of Special Interest

An AESI is an AE of scientific and medical concern specific to the sponsor's product or program. An AESI can be serious or nonserious, related or unrelated to the IMP or study procedures. These events will be reported according to the same timeframe as that for SAEs specified in Section 8.4.1 and Section 10.3.4.

Efgartigimod treatment leads to reduced IgG levels. As low IgG levels can be associated with increased infection risks, events under the MedDRA SOC *Infections and infestations* are considered AESIs in this study. These events will be reported according to the timeframe specified in Section 8.4.1 and Section 10.3.4, with the following information provided:

- Causal pathogen
- Location of infection
- Relationship to an underlying medical condition, medical history, and concomitant medications
- Reoccurrence of a previous infection
- Any confirmatory procedure, culture, or urgent medical intervention, if applicable

Participants for whom an AESI has been reported may be temporary interrupted from IMP treatment, as specified in Section 7.1.2.

8.4.7. AEs of Clinical Interest

8.4.7.1. Infusion/Injection-Related Reactions

All therapeutic proteins can elicit immune responses, potentially resulting in hypersensitivity or allergic reactions such as rash, urticaria, angioedema, serum sickness, and anaphylactoid or anaphylactic reactions. As with any SC or IV injection, injection- or infusion-related reactions can occur during or after administration.

Overall, the frequency of injection-related reactions in clinical studies has been low.

The efgartigimod IB provides more information on infusion-/injection related reactions.

8.4.7.2. Injection Site Reaction

An injection site reaction is any AE developing at the site of the injection. Localized injection site reactions were frequently observed in studies in which efgartigimod and PH20 were administered SC. The most frequently reported injection site reaction AEs were *Injection site erythema*, *Injection site pain*, and *Injection site swelling*.

Any injection site reaction will be reported as an AE (Section 8.4). Certain types of local reactions may be photographed and shared with the sponsor for review and assessment.

As a routine precaution, participants will be trained or observed closely by a trained health care professional for any potential injection-site reaction.

Refer to the current IB for more information on injection site reactions.

8.5. Pharmacokinetics

Blood samples for PK analysis will be collected at the time points specified in the SoA (Section 1.3). At IMP administration visits, PK blood samples will be collected predose (within the 2 hours before IMP infusion) and postdose (within the 30 minutes after the end of the infusion). Samples collected after the end of infusion should be collected in the opposite arm from the arm used for IMP infusion. On other visits, a single blood sample will be collected as described in the SoA. Blood samples for participants remaining in the study following IMP discontinuation will be collected as per the SoA for up to 3 weeks post IMP discontinuation. Efgartigimod serum concentrations will be determined using a validated method.

8.6. Pharmacodynamics

Blood samples for PD analysis will be collected at the time points specified in the SoA (Section 1.3). At IMP administration visits, PD blood samples will be collected predose (within the 2 hours before IMP infusion). At other visits, blood samples may be collected at any time during that visit.

Total IgG concentrations will be quantified using validated methods at a central laboratory. Results will not be reported to investigative sites or other study personnel to maintain the study blind.

8.7. Genetics

Genetics will not be evaluated in this study.

8.8. Biomarkers

Serum and whole blood will be collected at the time points specified in the SoA (Section 1.3) to identify [redacted] At IMP administration visits, samples will be collected predose (within the 2 hours before IMP infusion). At other visits, blood samples may be collected at any time during that visit. [redacted]

8.8.1. [redacted]

The impact of efgartigimod treatment on [redacted] will confirm the [redacted]

Specific analyses may include:

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

Procedures for collecting and shipping these samples are in the laboratory manual.

8.8.1.1. [redacted]

[redacted] will be performed to determine changes in [redacted] These [redacted] may include, but are not limited to, [redacted] Such [redacted] provide a [redacted] appropriate for [redacted]. The serum [redacted] may be reported in the final CSR or separately.

8.8.1.2. [redacted]s

[redacted] who have [redacted][27] [redacted]

includes but may not be limited to [redacted] These analyses may be reported in the final CSR or separately.

8.8.1.3. [redacted]

[redacted] cells will be collected and isolated from whole blood, and a decision will be made at the end of the study as to whether these samples will be analyzed with [redacted]. This will be done only if both [redacted] (Section 2.1). If so, results of [redacted] will be reported (separately from the final CSR). If they are not analyzed for this purpose, the samples will be retained for potential future research, per Section 8.1.2.

[redacted] will be used to assess changes in [redacted]. These analyses will help characterize the cellular pathological mechanism by investigating [redacted] Further, such markers may eventually aid in designing innovative patient-centric, molecular pathology-driven clinical studies.

8.9. Immunogenicity Assessments

Blood samples to evaluate serum levels of ADAs to efgartigimod will be collected at the time points specified in the SoA (Section 1.3). At IMP administration visits, blood samples will be collected predose (within the 2 hours before IMP infusion). At other visits, blood samples may be collected at any time during that visit.

Samples will be analyzed by the designated laboratory in a tiered approach using validated immunogenicity assays. Initially, samples will be screened for a positive assay response (tier 1). Screened positive samples will then be tested in a confirmation assay (tier 2). Finally, a titration of the ADA response will be performed on positive tier 2 samples to characterize the magnitude of the antibody response (tier 3).

8.10. Health Economics or Medical Resource Utilization and Health Economics

8.10.1. [redacted]

[redacted]

8.10.2. [redacted]

[redacted]

9. STATISTICAL CONSIDERATIONS

The statistical analysis plan (SAP) will be completed before database lock and includes a more technical and detailed description of the statistical analyses described in this section.

9.1. Statistical Hypothesis

No formal hypothesis will be tested in this phase 2 study. Primary endpoints COMPASS 31 and Malmö POTS will be analyzed using longitudinal mixed model repeated measures using the change from baseline as the response value. Prognostic variables are baseline and visit by treatment interaction using an unstructured variance covariance matrix. The treatment effect and 95% CIs will be estimated at week 24 using an appropriate contrast. Inference will be based on the precision of the estimation rather than hypothesis testing.

9.2. Analysis Sets

The following analysis sets are defined:

Participant Analysis Set	Description
Full analysis set	All randomized participants
Safety analysis set	All participants exposed to IMP

The full analysis set will be used to analyze endpoints related to the efficacy objectives, and the safety analysis set will be used to analyze the endpoints and assessments related to safety.

Participants will be included in the efficacy analyses according to the intended IMP assignment and included in the safety analyses according to the IMP actually received.

9.3. Statistical Analyses

9.3.1. General Considerations

- Data collected will be listed with derived variables. Descriptive statistical methods will be used to analyze safety and efficacy data.
- Summaries will be provided by treatment assignment and overall.
- Summaries will include the number of observations (n), mean, SE, 95% CI, median, minimum, and maximum for continuous measures.
- Summaries will include sample size, frequencies, and percentages for categorical variables.
- The baseline value will be the last assessment before the first administration of IMP.
- All study visits will be recalculated based on actual dates. The rules for calculating the analysis visits will be documented in the SAP.
- Rules for imputing partial dates or missing dates will be provided in the SAP.

- Exposure to IMP will be summarized by treatment group.
- TEAEs, AESIs, SAEs, and other safety parameters will be summarized by treatment group.
- AEs will be classified using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) classification system.
- AEs, AESIs, and SAEs will be listed corresponding to MedDRA system organ class (SOC) and preferred term (PT).
- Multiple occurrences of a single PT in a participant will be counted only once at the maximum severity/grade.
- AEs with missing severity or relationship to IMP will be classified as severe and treatment-related, respectively. All AEs will be summarized by relatedness to IMP.
- Any AEs leading to death or discontinuation of IMP will also be summarized.
- Population PK/PD analysis may be performed based on the PK and PD data and reported separately.
- Laboratory parameters, physical examinations, vital sign measurements, ECG data, and PK, PD, immunogenicity, and biomarker results will be analyzed descriptively.

9.4. Interim Analysis

An unblinded interim analysis may be conducted mid-course at the sponsor/designee's discretion. Results will be available to senior sponsor/designee staff only while maintaining the clinical study team members' blind to IMP assignment.

9.5. Sample Size Determination

The anticipated width of the 95% CI of the treatment difference on changes from baseline in COMPASS 31 is estimated as follows:

The SD of COMPASS 31 at a single time point in subjects living with POTS is assumed to be approximately 15, with mean score of 50.[20] As the COMPASS 31 scale has favorable test-retest reliability, the Pearson correlation between 2 measurements is assumed to be a minimum of 0.8.[18]

From this, it is estimated that the within-subject SD on COMPASS 31 is approximately [redacted], from which the SD on the change from baseline is derived to be approximately [redacted]

Therefore, the anticipated width (half-width) of the 95% CI is approximately [redacted] assuming complete data, which could increase to [redacted] when applying a conservative dropout rate of [redacted]%. With an anticipated 95% CI half-width [redacted], COMPASS 31 data from approximately 42 participants will provide sufficient precision to estimate the treatment effect at week 24.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

This study will be conducted according to the protocol and 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 (ICH) Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementing changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval before initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently according to 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 study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor/designee with sufficient, accurate financial information as requested to allow the sponsor/designee to submit a complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing changes in financial interests during the study through 1 year after the study completes.

10.1.3. Informed Consent Process

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

The investigator or their representative will explain the following to the participant and answer all questions regarding the study: the nature of the study, 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 the confidentiality of the participant's records.

The investigator or their representative will explain the nature of the study—including the risks and benefits—to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or site.

The medical record must include a statement that written informed consent was obtained before any study related activity was performed and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

The sponsor/designee will assign participants a unique identifier. Any participant records or datasets transferred to the sponsor/designee will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that the sponsor/designee will use their personal study-related data following local data protection laws. The extent of disclosure must also be explained to the participant, who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor/designee, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

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

10.1.5. Data Safety Monitoring Board

Not applicable.

10.1.6. Dissemination of Clinical Study Data

The sponsor/designee and auditor may access participant records to monitor this study, auditing and managing progress details. The investigator must be fully aware that the sponsor/designee and auditor can inspect documents to verify the accuracy and completeness of a participant's chart and 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 in the study.

The investigator is responsible for maintaining source documents. These will be made available for verification by the sponsor/designee's monitor at each monitoring visit. The investigator must submit an eCRF for each participant, regardless of the duration of participation or administration of IMP (ie, an eCRF has to be submitted for screen failures). All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study 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 study will be recorded on eCRFs unless electronically transmitted to the sponsor/designee (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

The eCRF Completion Guidelines document will provide instructions for completing eCRFs.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and direct access to source data documents.

Monitoring details describing strategy, including definition of study critical data items and processes (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/designee is responsible for the data management of this study, including quality checking of the data.

The sponsor/designee assumes accountability for actions delegated to other individuals (eg, contract research organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into 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 study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.7.1. Data Handling and Record-Keeping

It is the investigator's responsibility to maintain essential study documents (records and documents pertaining to the conduct of this study 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 study site will retain these documents for 25 years minimally after study completion. The study 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/designee 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 study is being conducted. Participant identification codes (ie, participant names and corresponding study numbers) will be retained for this same period of time. These documents may be transferred to another responsible party, acceptable to the sponsor/designee, who agrees to abide by the retention policies. The investigator is required to notify the sponsor/designee (or an authorized representative) in writing before changing the location or status of any essential clinical study documents. The investigator must contact the sponsor/designee before disposing of any study records.

No records should be disposed of without the written approval of the sponsor/designee.

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

10.1.7.2. Quality Assurance Audit

Study processes, study sites (including, but not limited to site visits, central laboratories, vendors), the study database, and study documentation may be subject to quality assurance audit during the study by the sponsor/designee. 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 study.

10.1.7.3. Quality Control

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

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

- Investigator meetings
- Central laboratories for clinical laboratory parameters
- Site initiation visit
- Routine site monitoring
- Ongoing site communication and training
- Ongoing oversight by sponsor/designee of safety parameters and adherence to selection criteria
- Eligibility review by sponsor/designee and medical monitors

- Data management quality control checks
- Continuous data acquisition and cleaning
- Quality control check of the CSR
- 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.

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 study-related documents, including medical history and concomitant medication documentation to the authorized sponsor/designee'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.

Data entered on the eCRF 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 study. Also, current medical records must be available.

The investigator must maintain accurate documentation (source data) that supports the information entered on the eCRF.

Study monitors will perform ongoing source data verification to confirm that data entered into 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 study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Monitoring

The sponsor/designee has engaged the services of a designee to perform all clinical study monitoring functions within this clinical study. The sponsor/designee's designee monitors will work following its SOPs.

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 study is conducted following the currently approved protocol, other study agreements, and all applicable regulatory requirements.

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

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

The sponsor/designee will perform an eCRF review, source document verification (wherever allowed 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/designee and the investigator and filed in the investigator's study file. Any data item for which the eCRF will serve as the source must be identified, agreed upon, and documented in the source documentation agreement form.

Upon completion or premature discontinuation from the study, the sponsor/designee will conduct site closure activities with the investigator and site staff as appropriate, following applicable regulations, ICH GCP guidelines, and sponsor/designee procedures.

10.1.10. Data Management

Data generated within this clinical study will be processed according to the SOPs of the sponsor/designee's data management and biostatistics departments.

Case report forms are provided for each participant in electronic format (ie, eCRF). Data will be transcribed by the study site staff from the source documents onto the eCRF, per local regulations. Data must be entered in English. The sponsor/designee will provide guidelines for eCRF completion, including collecting the investigator's e-signature, which will be provided by the sponsor/designee. Appropriate training and security measures will be completed by the investigator and all designated site staff before the study is initiated. Any data will be entered into the system for any study 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. Source documents are those used by the investigator or hospital and relate to the participant's medical history, verify the existence of the participant, the inclusion and exclusion criteria, and all records covering the participant's participation in the study. Source documents can include laboratory notes, ECG results, memoranda, pharmacy dispensing records, participant files, etc. The eCRFs will be completed by the investigator or the site's qualified designee once 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 confirms that the information contained on the eCRFs has been reviewed by the investigator and is true and accurate. The investigator will be required to sign off the eCRF electronically.

The data will be verified for completeness, missing data, inconsistencies, and necessary medical clarifications. Queries arising from these checks will be flagged to the study site, and the study site staff will correct data, confirm, or clarify data as appropriate. The sponsor/designee will describe 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 (EDC)

system, meaning the name of the person, time and date stamp, and the reason for change are captured.

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 sponsor/designee will provide a data management plan describing this reconciliation.

AEs, concomitant diseases, and medical history terms will be assigned to a lowest level term and a PT, and will be classified by high level term, high level group term, and primary SOC according to the MedDRA thesaurus.

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

The anatomical therapeutic chemical classes will be assigned to prior and concomitant medications. Prior and concomitant procedures will be coded according to the MedDRA thesaurus.

10.1.11. Study and Site Start and Closure

The study start date is the date when the clinical study will be open for recruitment of participants upon the availability of mandatory approvals.

The sponsor/designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor/designee. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and enough advanced notice provided of the intended termination.

Reasons for the early closure of a study site by the sponsor/designee may include but are not limited to:

- Inability to achieve the recruitment target within a reasonable time
- Determination that no further benefits are expected from the study (in the sponsor/designee's judgment)
- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor/designee's procedures, or GCP guidelines
- Discontinuation of further study medication development

If the study is prematurely terminated or suspended, the sponsor/designee will promptly inform the investigators, the IECs/IRBs, the regulatory authorities, designee, and any vendors used in the study of the reason for termination or suspension as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and assure appropriate participant therapy and/or follow up.

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

10.1.12. Investigator Obligations

Qualified investigators will conduct this study under the sponsorship of argenx BV and IQVIA (the sponsor's designee).

The name and telephone/fax numbers of the sponsor/designee's contact personnel are listed in the investigator study file provided to each site.

The investigator is responsible for ensuring that all study site personnel, including subinvestigators, adhere to all applicable regulations and guidelines, including local laws and regulations, regarding the study, both during and after study completion. The investigator is responsible for informing the IRB/IEC of the study's progress and obtaining annual IRB/IEC renewal. The investigator is responsible for informing the IRB/IEC of the study's completion and providing the IRB/IEC with a summary of the study results.

The investigator will comply with the protocol that has been approved/given favorable opinion by the IRB/IEC, according to ICH GCP and applicable regulatory requirements. The investigator is ultimately responsible for conducting all aspects of the study at the study site and verifying the integrity of all data transmitted to the sponsor/designee by signature. The term "investigator," used in this protocol and other study documents, refers to the investigator or site staff that the investigator has designated to perform specific duties. Subinvestigators or other designated site staff can sign for the investigator, except where the investigator's signature is specifically required.

10.1.13. Protocol Signatures

After reading the protocol, each site's principal investigator will sign the protocol signature page and send a copy of the signed page to the sponsor/designee). By signing the protocol, the principal investigator confirms in writing that they have read, understand, and will strictly adhere to the study protocol and will conduct the study following ICH tripartite guidelines for GCP and applicable regulatory requirements. The study will not be initiated at any site where its principal investigator has not signed the protocol.

10.1.14. Publication Policy

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

The CSR will be ICH E3 compliant and submitted following local regulations.

The results of this study may be published or presented at scientific meetings. Any manuscript, abstract or other publication, presentation of results, or information associated with the study must be prepared with the sponsor/designee after the study results have been analyzed and reported and submitted to the sponsor/designee for review and comment before submission for publication or presentation. Study participant identifiers will not be used in the publication of results.

The sponsor/designee will comply with the requirements for the publication of study results. Following standard editorial and ethical practice, the sponsor/designee will generally support the publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Based on scientific input and recruitment efforts, the authorship will be determined by mutual agreement and consistent with the International Committee of Medical Journal Editors criteria.

The sponsor/designee will register and disclose the results of clinical studies as required by law.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests listed in Table 2 will be performed as described in the Laboratory Manual.
- Protocol-specific requirements for the inclusion and exclusion of participants are detailed in Section 5.1 and Section 5.2, respectively.
- Additional tests may be performed during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Table 2: Protocol-Required Laboratory Tests

Laboratory Test	Parameters		
Hematology	RBC count platelet count hemoglobin hematocrit	RBC indices: MCV MCH	WBC count with differential: neutrophils eosinophils lymphocytes basophils monocytes
Serum chemistry	ALT AST albumin[a] BUN	creatinine glucose potassium chloride bicarbonate	sodium total protein[a] calcium bilirubin (total and direct)
Routine urinalysis	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase Microscopic examination (if blood or protein is abnormal)		
Pregnancy testing	Highly sensitive serum hCG pregnancy serum test at screening and urine test at other time points (as needed for WOCBP potential, defined in Appendix 4 Section 10.4.1) A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (See Appendix 4 Section 10.4.1)		
Specialty laboratory tests	C-reactive protein	ESR	TSH
Other screening tests	SARS-CoV-2 nasopharyngeal swab test Serology for HBV, HCV, HIV (see exclusion criterion 7 and Sections 10.2.1.2, 10.2.1.3, and Section 10.2.1.4, respectively)		

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; ESR=erythrocyte sedimentation rate; FSH=follicle-stimulating hormone; hCG=human chorionic gonadotropin; HBV=hepatitis B virus; HCV=hepatitis C virus; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; TSH=thyroid stimulating hormone; WBC=white blood cell; WOCBP=women of childbearing potential
[a] Results will be blinded.

10.2.1. Other Screening Tests

10.2.1.1. SARS-CoV-2

A SARS-CoV-2 nasopharyngeal swab test will be performed on all participants at screening; individuals with positive test results are excluded from participating in the study (Section 5.2, exclusion criterion 6).

Additional COVID-19 testing recommendations/guidelines are presented in Section 10.5.

10.2.1.2. Hepatitis B Virus

Participants with an active acute or chronic hepatitis B viral infection at screening will be excluded from randomization in the study.

The following combinations of serologic markers will be used to identify an active HBV infection (https://www.cdc.gov/hepatitis/HBV/PDFs/SerologicChartv8.pdf):

Table 3: Interpretation of Hepatitis B Serological Test Results

Test result			Interpretation
HBsAg	Anti-HBc	Anti-HBs	
Positive	Positive	Negative	The patient cannot be randomized in the study because the test results indicate an active HBV infection.
Negative	Positive	Negative	The patient cannot be randomized in the study because the test results indicate a low-level chronic HBV infection with impaired liver function.[a]

anti-HBc=total hepatitis B core antibody; anti-HBs=hepatitis B surface antibody

[a] This decision will be made by a medical physician with enough experience in hepatology or infectious disease. Additional tests (eg, HBV viral load) could be required to determine the patient's status.

10.2.1.3. Hepatitis C Virus

Participants with an active acute or chronic hepatitis C viral infection at screening cannot be randomized in the study. The hepatitis C virus antibody serologic test will identify an active hepatitis C viral infection as indicated in Table 4.

Table 4: Interpretation of the Hepatitis C Antibody Test

HCV antibody test result	Interpretation
Positive	The patient cannot be randomized in the study because the test results indicate an active acute or chronic HCV infection unless associated with a negative HCV RNA test

HCV=hepatitis C virus

10.2.1.4. Human Immunodeficiency Virus

Individuals who are HIV positive are not eligible for this study.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of IMP, whether or not considered related to the IMP. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of IMP.

Events to be Collected as AEs
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign 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 condition detected or diagnosed after IMP administration even though it may have been present before the start of the study • Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction • Signs, symptoms, or the clinical sequelae of a suspected overdose of either IMP or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae • Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE

Events <u>NOT</u> to be Collected as AEs
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that 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 • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital) • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

10.3.2. Definition of SAE

An SAE is Defined as Any Untoward Medical Occurrence That, at Any Dose:

a. Results in death

b. 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 that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to 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 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 screening will not be collected as an AE.

d. Results in persistent or significant 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 events of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. 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 one 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.

10.3.3. Recording and Follow Up of AE and/or SAE

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 assess intensity for each AE and SAE reported during the study.

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 used for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between IMP and each occurrence of each AE/SAE as **related** or **not related**. The investigator will use clinical judgment to determine whether there is reasonable possibility that the IMP caused the AE.
- 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.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IMP administration, will be considered and investigated.
- **Related** means that the AE cannot be explained by the participant's medical condition, other therapies, or an accident. The temporal relationship between the AE and IMP administration is compelling and/or follows a known or suspected response pattern concerning that IMP.
- **Not related** means that the AE can be readily explained by other factors such as the participant's underlying medical condition, concomitant therapy, or accident. No plausible temporal or biologic relationship exists between the IMP and the AE.
- 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 they have 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. However, it is very important that the investigator always assess causality for every event before the initial transmission of the SAE data.
- 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 one of the criteria used when determining regulatory reporting requirements.

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 study or during a recognized follow-up period, the investigator will provide a copy of any postmortem findings including histopathology.
- The investigator will submit any updated SAE data within 24 hours of receiving the information.

10.3.4. Reporting of SAEs and AESIs

SAE and AESI Reporting

- All SAEs and AESIs will be recorded on the AE form of the eCRF. SAEs will also be recorded on the paper SAE report form.
- The investigator or designated site staff will ensure all entered data are consistent.
- An alert email for the SAE and AESI reports on the eCRF will automatically be sent by email to the sponsor/designee's safety mailbox via the EDC system.
- The paper SAE report form will be faxed or emailed to the sponsor/designee (see Serious Adverse Event Reporting on page 2 of this protocol).

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Women of Childbearing Potential Definition

A woman is considered to be of childbearing potential (WOCBP) unless she is either:

- Postmenopausal:
  - continuous amenorrhea for ≥1 year without an alternative medical cause
  - FSH >40 IU/L

  If a postmenopausal woman is using hormonal therapy, such as hormone replacement therapy or hormonal contraceptives, FSH levels could be suppressed and therefore an FSH test to confirm a postmenopausal state is not considered valid. In this case the postmenopausal state will be assessed by the investigator.
- Surgically sterilized: documented permanent sterilization procedure (eg, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy)

10.4.2. Contraception Guidance

10.4.2.1. Female Contraception for Women of Childbearing Potential

WOCBP must use one of the following contraception methods from signing the ICF until 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 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 concerning the duration of the study 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

10.4.2.2. Male Contraception

No male contraception is required.

10.5. Appendix 5: Operational Considerations for COVID-19 Risk Mitigation

During the study, the sites will implement all recommendations issued by the local government regarding the spread of COVID-19, including specific guidelines related to clinical research performed in clinical research centers.

This appendix is intended to be used only if unforeseen changes in the COVID-19 pandemic result in new restrictions at the site or new risks for participants or site staff from attending visits at the site. The sponsor/designee and the clinical site must agree to the duration of these changes.

10.5.1. Testing for COVID-19

Additional testing for COVID-19 beyond what is listed in the SoA (Section 1.3) is not required during the study. However, it is recommended that participants who develop COVID-19 symptoms be tested, and results reported for the study.

10.5.2. Critical Parameters to Be Collected During the Study

All assessments should be performed as indicated in the SoA (Section 1.3). If assessments cannot be performed because of the COVID-19 pandemic, the following critical parameters must be collected: all AE reporting, administration site reactions, IMP administration, questionnaires, and safety laboratory assessments from the first visit through the end of study.

Analyses may be performed at a local laboratory if the central laboratory is unavailable because of the pandemic.

10.5.3. Mandatory Site Visits

All visits designated as mandatory on-site visits must occur at the site. If adaptations are required because of the COVID-19 pandemic, the following visits must still be attended at the site:

- Screening visits
- Baseline/day 1
  - Participants cannot be randomly assigned to IMP unless this visit occurs on-site.
- W1, W2, W4, W12, W24, IMP discontinuation visit, EDV, and SFV

10.6. Appendix 6 Home Study Visits

During the study, a home nurse may travel to the participant's home to conduct visits (or the participant may go to a convenient alternate location). For each home visit, the investigator or designee will confer with the participant via an audio or video interview to elicit AEs and concomitant medications and the participant's general well-being. The investigator or designee will also ensure the participant has completed all required efficacy assessments that can be done at home (eg, questionnaires). Any scheduled assessments will be conducted before the home nurse administers IMP.

10.7. Appendix 7: Protocol Amendment History

Amendment 1 (11 Dec 2022)

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 primary rationale for this amendment is to correct the time point at which the final dose of IMP will be administered. Other clarifications and corrections have been made and are summarized below.

The major changes from protocol version 1.0 to protocol version 2.0 are summarized in the following table. Minor editorial changes, including the correction of typographical errors and formatting inconsistencies, are not summarized in the table. Refer to the List of Abbreviations for any undefined abbreviations.

Section # and Name	Description of Change	Brief Rationale
SIGNATURE OF SPONSOR	[redacted], MD, PhD is now the sponsor signatory for this protocol.	Effective 01 Apr 2022, Dr. [redacted] became the sponsor's chief medical officer.
Title Page	argenx telephone numbers for 24-hour urgent medical helpline have been replaced with IQVIA telephone numbers.	IQVIA is responsible for the 24-hour urgent medical helpline.
1.3. Schedule of Activities	An IMP discontinuation visit has been added to the study.	The protocol has been updated in several places to make consistent with current argenx standards/guidance.
1.3. Schedule of Activities 8. STUDY ASSESSMENTS AND PROCEDURES 10.5.3. Mandatory Site Visits	Week 1, week 2, and the IMP discontinuation visit were added to the list of visits that must be on-site.	The first 3 doses should be administered on-site for participant safety reasons. The language has been updated to designate week 1 and week 2 as on-site visits.
1.1 Synopsis 1.2. Schema 1.3. Schedule of Activities 4.1. Overall Design 7.2. Participant Discontinuation/Withdrawal from the Study	The time between last IMP dose and the follow-up visit has been amended from 60 days to 56 days (±3 days) dose.	The protocol has been updated in several places to make consistent with current argenx standards/guidance.
1.3. Schedule of Activities	A footnote has been added	The protocol has been updated in

Section # and Name	Description of Change	Brief Rationale
	to clarify that the EDV will be within 7 days of the last dose of IMP, and that the visit applies for participants who discontinue the study.	several places to make consistent with current argenx standards/guidance.
4.4. End-of-Study Definition	A clarification has been added to note that if a participant continues in the study after discontinuing IMP, this will be week 23 or at the SFV (if permanent IMP discontinuation is <56 days from week 23)	The protocol has been updated in several places to make consistent with current argenx standards/guidance.
7.1. Discontinuation of IMP	The text regarding discontinuation of IMP has been substantially updated.	The protocol has been updated in several places to make consistent with current argenx standards/guidance.
7.2. Participant Discontinuation/Withdrawal from the Study	The text regarding discontinuation of IMP has been substantially updated.	The protocol has been updated in several places to make consistent with current argenx standards/guidance.
7.3. Lost to Follow-up	A minor change has been made to the wording in this section.	The protocol has been updated in several places to make consistent with current argenx standards/guidance.
1.3. Schedule of Activities 6.1. Study Intervention(s) Administered	Wording modified to clarify that dose level will be recalculated for if a participant's weight has changed (increased or decreased) by more than 10% from baseline.	This text has been updated to more accurately describe the criteria for redosing.
6.6. Dose Modification	Wording added about recalculation of weight-based dose.	This text has been updated in line with the sponsor's current standards.
6.2. Preparation, Handling, Storage, and Accountability	Language was added to note that, at a minimum, the first 3 doses of IMP must be administered on-site.	This text was updated to align with changes to Sections 1.3, 8, and 10.5.3.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3. Schedule of Activities 4.1. Overall Design	The week 24 dose has been removed.	This was a correction; there will be no dosing at this time point.
1.3. Schedule of Activities 8.3.3. Electrocardiograms	Language was added to note that ECGs will be the first assessment of the day on days when they are performed.	ECGs should be performed first because heart rate may increase after certain other assessments are performed.
8.2.3. [redacted]	Language was added that the tilt test will be the first of these tests to be performed.	POTS symptoms are more likely to be reproduced by testing in the morning.
1.3. Schedule of Activities 3. Objectives, Endpoints, and Estimands 8.2.3. [redacted]	[redacted]	The original frequency of testing was considered burdensome on the participant, and was unnecessary because the active stand test and tilt test both measure increase in heart rate on standing.
1.3. Schedule of Activities 8.2.2. [redacted] 8.2.3. [redacted] 8.2.4. [redacted]	Language was added to note that efficacy assessments may be performed on the day before the scheduled time point.	This update was made to relieve the burden of testing for the participant.

Section # and Name	Description of Change	Brief Rationale
8.5. Pharmacokinetics	Language was added that pharmacokinetic samples collected after the end of infusion should be collected in the opposite arm from the arm used for IMP infusion.	This instruction was added in to clarify best practice for collection of pharmacokinetic samples.
1.3. Schedule of Activities	The study day for SFV was changed from 230 to 218.	SFV was recalculated to occur 56 days after the dose at week 23.
1.3. Schedule of Activities	In footnote b, the detail that the SFV would be 60 days after final IMP dose was removed.	Corrected because for participants who remain on study despite discontinuing IMP, the SFV will not be 60 days (now amended to 56 days) after final IMP dose.
1.3. Schedule of Activities	The study days for visits during weeks 19-23 were updated from 134-161 to 134-162, and the study day for week 24 was updated from 170 to 169.	These were corrections due to miscalculations in the original Schedule of Activities.
1.3. Schedule of Activities 8.5. Pharmacokinetics 8.6. Pharmacodynamics 8.8. Biomarkers 8.9. Immunogenicity Assessments	Text added to note that blood samples on days other than IMP administration visits can be taken at any point during that visit.	This clarification was added as previously the protocol had suggested sampling predose for all visits, which was not appropriate for visits where no dosing will be performed.
1.3. Schedule of Activities 8.5. Pharmacokinetics	Blood samples for participants remaining in the study following IMP discontinuation will be collected as per the SoA for up to 3 weeks post IMP discontinuation for PK analysis.	These samples have been added because IMP is expected to still be detectable in blood for this period of time following permanent discontinuation.

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities 8.2.1.5. Exit Interview	Language was added to note that for participants who prematurely discontinue the study, the exit interview can be conducted after their EDV.	This was a clarification because the original protocol only described this interview relative to the week 24 visit.
2.3.1 Risk Assessment	The potential risk to teratogenicity/fetotoxicity has been removed, the risk 'immune modulation leading to increased infection' has been reworded to 'serious infection,' and the mitigation strategy for IRRs has been updated.	The language was updated to reflect the sponsor's current risks and mitigation strategy for efgartigimod IV.
1.1 Synopsis 3. Objectives, Endpoints, and Estimands	The reference to change from baseline for PGI-C removed from the secondary endpoint.	Baseline assessment is not applicable for this assessment.
8.8.1.1. Serum Autoantibodies and SARS-CoV-2 Antibodies	The description of the analyses has been updated.	The language was updated to be more specific.
8.8.1.3. [redacted]	Language was added to note that a decision will be made at the end of the study as to whether the samples will be analyzed; if not, the samples will be retained for potential future research.	[redacted]
10.3.3. Recording and Follow Up of AE and/or SAE	The bullet "New or updated information will be recorded in the originally submitted documents" was deleted.	The language was removed because per the current process this is not done.
10.2. Appendix 2: Clinical Laboratory Tests	Language was added to note that results for albumin and total protein will be blinded.	This clarification was added because results for these serum chemistry parameters may give an indication of treatment received.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3. Schedule of Activities 3. Objectives, Endpoints, and Estimands 4.2. Scientific Rationale for Study Design 8.2.1.1. COMPASS 31	COMPASS 31 was separated into 2 versions: the original used at screening and the modified used at other time points.	This language was updated to clarify that different versions will be used.
6.5. Study Compliance	Noted that the infusion start date/time and infusion end date/time of each dose administered will be recorded in the source documents, as well as the total dose administered at each visit.	More appropriate wording has been added for capturing information for infusions.
1.3. Schedule of Activities	[redacted]	[redacted]
1.3. Schedule of Activities	In the table, footnote "j" has been removed from the row "IMP infusion."	This footnote was only directly applicable to "vital signs measurements."
8.2.1.3. PGI-S and PGI-C	The word "valid" was removed from the description of these questionnaires.	There is not sufficient evidence to support the validity of the questionnaires.
8.2.1.3. PGI-S and PGI-C	The definitions of both scales have been amended.	The language has been updated to more accurately represent the wording from the scales.
8.2.4. [redacted]	The language was updated to note that the analyses may be reported in the final CSR or separately.	The language was updated for clarity.

Section # and Name	Description of Change	Brief Rationale
8.8.1.2. [redacted]	Language was added to note that the analyses may be reported in the final CSR or separately, and that the analyses will be performed using [redacted]	The language was updated for clarity.
8.10.1. [redacted]	The description of the scoring was updated to include the [redacted].	This language was updated for completeness/clarity.
6.9.1. Prohibited Medication	Noted that the prohibition of live or live-attenuated vaccines also applies for up to 28 days after the final dose of IMP.	This text has been updated in line with the sponsor's current standards.
10.1.10 Data Management	The sentence "No data collection or source data verification will be performed on race and ethnicity unless requested by local regulations" was deleted.	These data will be captured in the eCRF

11. REFERENCES

1. Centers for Disease Control and Prevention (2021) COVID-19 Cases, Data and Surveillance. CDC.gov (website). Accessed: 16 Mar 2022. Available at: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/index.html
2. Raj SR, Arnold AC, Barboi A, et al. Long-COVID postural tachycardia syndrome: an American Autonomic Society statement. *Clin Auton Res.* 2021 Jun;31(3):365-368.
3. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 syndrome. *Nat Med.* 2021;27(4):601-615.
4. Dani M, Dirksen A, Taraborrelli P, et al. Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies. *Clin Med (Lond).* 2021;21(1):e63-e67.
5. Blitshteyn S, Whitelaw S. Correction to: Postural orthostatic tachycardia syndrome (POTS) and other autonomic disorders after COVID-19 infection: a case series of 20 patients. *Immunol Res.* 2021;69(2):212.
6. Blitshteyn S, Whitelaw S. Postural orthostatic tachycardia syndrome (POTS) and other autonomic disorders after COVID-19 infection: a case series of 20 patients [published correction appears in *Immunol Res*. 2021;69(2):212]. *Immunol Res.* 2021;69(2):205-211.
7. Vernino S, Bourne KM, Stiles LE, et al. Postural orthostatic tachycardia syndrome (POTS): State of the science and clinical care from a 2019 National Institutes of Health Expert Consensus Meeting - Part 1. *Auton Neurosci. 2021*;235:102828.
8. Goldstein DS. The possible association between COVID-19 and postural tachycardia syndrome. *Heart Rhythm.* 2021;18(4):508-509.
9. Kanjwal K, Jamal S, Kichloo A, Grubb BP. New-onset postural orthostatic tachycardia syndrome following coronavirus disease 2019 infection. *J Innov Card Rhythm Manag.* 2020;11(11):4302-4304.
10. Miglis MG, Prieto T, Shaik R, Muppidi S, Sinn DI, Jaradeh S. A case report of postural tachycardia syndrome after COVID-19. *Clin Auton Res.* 2020;30(5):449-451.
11. Bisaccia G, Ricci F, Recce V, et al. Post-acute Sequelae of COVID-19 and cardiovascular autonomic dysfunction: what do we know? *J Cardiovasc Dev Dis.* 2021;8(11):156.
12. Wallukat G, Hohberger B, Wenzel K, et al. Functional autoantibodies against G-protein coupled receptors in patients with persistent long-COVID-19 symptoms. *J Transl Autoimmun.* 2021;4:100100.
13. Li H, Yu X, Liles C, et al. Autoimmune basis for postural tachycardia syndrome. *J Am Heart Assoc.* 2014;3(1):e000755.
14. Kharraziha I, Axelsson J, Ricci F, et al. Serum activity against G protein-coupled receptors and severity of orthostatic symptoms in postural orthostatic tachycardia syndrome. *J Am Heart Assoc.* 2020;9(15):e015989.
15. Vernino S, Stiles LE. Autoimmunity in postural orthostatic tachycardia syndrome: current understanding. *Auton Neurosci.* 2018;215:78-82.

16. Sletten DM, Suarez GA, Low PA, Mandrekar J, Singer W. COMPASS 31: a refined and abbreviated Composite Autonomic Symptom Score. *Mayo Clin Proc.* 2012;87(12):1196-1201.

17. Johansson M, Ståhlberg M, Runold M, et al. Long-haul post-COVID-19 symptoms presenting as a variant of postural orthostatic tachycardia syndrome: the Swedish experience. *JACC Case Rep.* 2021;3(4):573-580.

18. Treister R, O'Neil K, Downs HM, Oaklander AL. Validation of the composite autonomic symptom scale 31 (COMPASS 31) in patients with and without small fiber polyneuropathy. *Eur J Neurol.* 2015;22(7):1124-1130.

19. Rea NA, Campbell CL, Cortez MM. Quantitative assessment of autonomic symptom burden in postural tachycardia syndrome (POTS). *J Neurol Sci.* 2017;377:35-41.

20. Dipaola F, Barberi C, Castelnuovo E, et al. Time course of autonomic symptoms in postural orthostatic tachycardia syndrome (POTS) patients: two-year follow-up results. *Int J Environ Res Public Health*. 2020;17(16):5872.

21. Buoite Stella A, Furlanis G, Frezza NA, Valentinotti R, Ajcevic M, Manganotti P. Autonomic dysfunction in post-COVID patients with and witfhout neurological symptoms: a prospective multidomain observational study. *J Neurol.* 2022;269(2):587-596.

22. Kedor C, Freitag H, Meyer-Arndt L-A, et al. Chronic COVID-19 Syndrome and Chronic Fatigue Syndrome (ME/CFS) following the first pandemic wave in Germany – a first analysis of a prospective observational study. *medRxiv*. 2021.02.06.21249256.

23. Sheldon RS, Grubb BP II, Olshansky B, et al. 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. *Heart Rhythm*. 2015;12(6):e41-e63.

24. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test [published correction appears in Am J Respir Crit Care Med. 2016 May 15;193(10):1185]. *Am J Respir Crit Care Med.* 2002;166(1):111-117.

25. Novak P. Quantitative autonomic testing. *J Vis Exp.* 2011;(53):2502.

26. [redacted]

27. [redacted]

Signature Page for VV-TMF-90521 v2.0

Reason for signing: Approved (eSignature)	Name: [redacted] Role: A Date of signature: [redacted]

Signature Page for VV-TMF-90521 v2.0