TITLE PAGE

Protocol Title:	Open-Label Extension Study to Evaluate the Long-term Safety and Efficacy of Efgartigimod in Adult Patients with Post-COVID-19 Postural Orthostatic Tachycardia Syndrome (PC-POTS) who Completed Study ARGX-113-2104
Protocol Number:	ARGX-113-2105
Version Number:	2.0 (Amendment 1)
Compound:	Efgartigimod (ARGX-113)
Study Phase:	2
Sponsor Name:	argenx BV
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Approval Date:	23 Feb 2024

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SIGNATURE OF SPONSOR

Protocol Title:	Open-Label Extension Study to Evaluate the Long-term Safety and Efficacy of Efgartigimod in Adult Patients with Post-COVID-19 Postural Orthostatic Tachycardia Syndrome (PC-POTS) who completed Study ARGX-113-2104
Protocol Number:	ARGX-113-2105

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-113-2105.

Title: Open-Label Extension Study to Evaluate the Long-term Safety and Efficacy of Efgartigimod in Adult Patients with Post-COVID-19 Postural Orthostatic Tachycardia Syndrome (PC-POTS) who completed Study ARGX-113-2104

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 will not be disclosed, except 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 can lead to the termination of my participation as an investigator for this study.

I understand that the sponsor can 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, if 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 handprint or type) _____

Signature _____

Date _____

Protocol Amendment Summary of Changes

Global protocol document history	Date
Amendment 1 v2.0	23 Feb 2024
Original v1.0	11 Dec 2022

Amendment 1 (23 Feb 2024)

This amendment is considered 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 align the study with the current safety requirements for efgartigimod, including moving information on Infusion/injection related reactions and Infusion site reactions to AEs of Clinical Interest (previously included under AESIs, in error), as well as to align the contraception requirements between Study ARGX-113-2104 and this open-label extension study ARGX-113-2105.

Section	Description of change	Brief rationale
Throughout	Changed all references to "sponsor/designee" to "sponsor"	To be consistent across the efgartigimod program.
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	Updated study duration from: "The maximum length of time a participant can be in the study is approximately 56 weeks (48 weeks treatment plus 56 days follow-up)." to: "The maximum length of time a participant can be in the study is approximately 55 weeks. This includes 46 weeks of treatment (Q2W dosing) or 47 weeks of treatment (QW dosing) plus the safety follow-up period, with a safety follow-up visit approximately 56 days after the last dose of IMP administration)."	Updated to clarify the intended process, with safety follow-period starting from date of last dose rather than from end of treatment visit. Total study duration updated accordingly: end of treatment visit occurs during safety follow-up period rather than after it.

Section	Description of change	Brief rationale
Section 1.2, Schema; Section 1.3, Schedule of Activities	Study day removed for Safety Follow-up Visit.	Updated for clarity as the appropriate study day for this visit varies depending on multiple factors, including dosing and discontinuation of IMP.
Section 2.3.1, Risk Assessment	Updated Infusion/injection-related reactions mitigation strategy text to reflect that infusion/ injection-related reactions are considered AEs of Clinical Interest, instead of AESIs.	Correction of error in original protocol.
	Removal of list of AEs associated with infusion/injection-related reactions as these are now listed under infusion/injection-site reactions.	To be consistent across the efgartigimod program.
	Added separate row for Infusion/injection-related site reactions, including summary of data/rationale for risk and mitigation strategy.	
Section 1.1, Synopsis, Section 1.2, Schema, Section 1.3, Schedule of Activities, Section 4.1, Overall design.	Clarified that: - The treatment period is 48 weeks in duration; - The maintenance dosing period is 42 weeks in duration (weeks 4 to 46); - The end of treatment visit on week 48 (day 337) marks the end of the treatment period; - The safety follow-up period is from the final IMP dose to the safety follow-up visit.	Updated to reflect that IMP will only be received for a maximum of 47 weeks, but the treatment period includes end of treatment visit and is therefore 48 weeks long. Updated to clarify the intended process, with safety follow-period starting from date of last dose rather than from end of treatment visit.

Section	Description of change	Brief rationale
	Updated from: "Participants will return for a follow-up visit approximately 56 days after the week 48 visit. The total planned duration of the study is 393 days." to: "Participants will return for a safety follow-up visit approximately 56 days after the last dose of IMP administration. The total planned duration of the study is 386 days."	Updated to clarify the intended process, with safety follow-period starting from date of last dose rather than from end of treatment visit.
	56-day time period for Safety Follow-Up period removed, as time window may vary depending on when last IMP dose is given.	Updated to clarify the intended process.
Section 7.1.1, Permanent Discontinuation	Updated requirements to clarify that attendance at scheduled study visits is encouraged but not mandatory for participants who permanently discontinue IMP.	Updated for consistency across the efgartigimod program.
	Included options for teleconferencing or telephone visits for participants who have discontinued IMP.	
	Removed requirement that participants who permanently discontinue IMP will complete the IMP discontinuation visit and will be encouraged to remain in the study.	Not applicable for open-label extension studies.
	Removed requirement that any SAE of infection that are considered related to IMP will result in permanent discontinuation of IMP.	Updated as SAEs of infection are only considered a reason for permanent discontinuation when life-threatening and considered related to IMP by the sponsor.
	Added to circumstances which will result in permanent discontinuation of IMP: "The participant develops a new or recurrent malignancy except for basal cell carcinoma of the skin, regardless of relationship to IMP."	To ensure study participants' safety.

Section	Description of change	Brief rationale
Section 1.3, Schedule of Activities, Section 7.1.1, Permanent Discontinuation	Updated requirements for date of EDV from within 7 days after the participant's final IMP administration to within 7 days of last contact with the participant.	Updated for consistency across the efgartigimod program.
Section 7.2, Participant Discontinuation/Withdrawal from the Study	Removed statement that participants withdrawing from the study can request the destruction of collected untested samples.	Updated for clarity around what use of samples are permitted or disallowed following participant withdrawal from the study.
	Change of process from "participants withdrawing from the study can request the destruction of collected untested samples" to "If the participant withdraws consent to participate in the study, the sponsor can retain and continue to use any data collected before such consent was withdrawn. Future research on samples collected from participants who have withdrawn consent from the study is not impacted unless the participant also withdraws the consent for future research."	Updated for clarity around what use of samples are permitted or disallowed following participant withdrawal from the study.
Section 8.1, Administrative and General/Baseline Procedures	Removal of statement "except the postdose PK blood sample".	Updated to align with PK blood sampling schedule; PK blood samples are not taken postdose in this study.
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 1.3, Schedule of Activities Section 8.3.5, Pregnancy testing	Added following statement on timing of pregnancy testing: "On visits where both pregnancy testing and IMP administration will be performed, all pregnancy testing must be performed predose. Dosing should not begin until a negative pregnancy test result has been confirmed."	Updated to clarify the intended process.

Section	Description of change	Brief rationale
Section 8.3.5, Pregnancy testing	Addition of the following requirement: Any pregnancy reported during a clinical research study, including the safety follow up period, is routinely monitored as standard practice. The pregnancy could have arisen from a female clinical study participant or a male participant's female partner. In either situation, consent will be requested to collect medical information about the pregnancy and the baby's health for up to 12 months after the baby's birth.	Updated for consistency across the efgartigimod program.
Section 8.4, Adverse Events, Serious Adverse Events, and Other Safety Reporting	Added in definition of AESI: An AESI is an AE of scientific and medical concern specific to the sponsor's product or program. Clarified that SAEs, AESIs, and AEs of clinical interest will be reported by the participant, as types of AE.	Updated for consistency across the efgartigimod program.
Section 8.4.6, AESIs	Removal of Section 8.4.6.1 (Infections) and Section 8.4.6.2 (Infusion/Injection Related Reactions), as these are now categorized as AEs of Clinical Interest for efgartigimod rather than AESIs. Addition of detail that events under the MedDRA SOC *Infections and Infestations* are considered AESIs in this study.	Updated for consistency across the efgartigimod program.
Section 8.4.7, AEs of Clinical Interest	Addition of new section on AEs of Clinical Interest for the study, including "Infusion/ Injection-Related Reactions".	Updated based on the current safety profile of efgartigimod and for consistency across the efgartigimod program.
Section 1.3, Schedule of Activities, Table 1 and Table 2; Section 8.8, Biomarkers	References to "plasma" samples are removed throughout the protocol.	Corrected as no plasma samples will be taken.
Section 9, Statistical Considerations	Clarified that the SAP will be finalized before the first interim analysis database lock.	Updated to clarify the intended process.

Section	Description of change	Brief rationale
Section 9.3.3.3, Pharmacokinetics	Addition of the following information: "Efgartigimod serum trough concentrations will be calculated, in line with the secondary endpoint assessing exposure to efgartigimod. Details will be provided in SAP."	Updated to clarify the intended process, as serum trough concentrations are calculated values, whereas other serum concentrations are summarized data.
Section 10.4.2.2, Male Contraception	Requirements for male contraception removed.	Updated due to non-clinical studies results showing no effect on reproduction or fertility. Efgartigimod falls in the "unlikely" risk category and therefore does not require contraception measures in males or nonpregnant WOCBP partners.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

List of Abbreviations

Abbreviation	Expansion
[redacted]	[redacted]
AChR	acetylcholine receptor
ADA	antidrug antibody(ies)
AE	adverse events
AESI(s)	adverse event(s) of special interest
COMPASS 31	Composite Autonomic Symptom Score
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
eCRF	electronic case report form
EDV	early discontinuation visit
FcRn	neonatal Fc receptor
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
gMG	generalized myasthenia gravis
GPCR	G-protein coupled receptor
[redacted]	[redacted]
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC/IRB	independent ethics committee/institutional review board
Ig	immunoglobulin
IL	interleukin
IMP	investigational medicinal product
IRR	infusion/injection related reaction
ITP	immune thrombocytopenia
IV	intravenous
MaPS	Malmö POTS symptom score
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Expansion
OLE	open-label extension
PC-POTS	post-COVID-19 postural orthostatic tachycardia syndrome
PD	pharmacodynamic(s)
PGI-C	Patient Global Impression – Change
PGI-S	Patient Global Impression – Severity
PK	pharmacokinetic(s)
POTS	postural orthostatic tachycardia syndrome
PROMIS	Patient-Reported Outcomes Measurement Information System
Q2W	every 2 weeks
QW	once weekly
SAE	serious adverse event
SAP	statistical analysis plan
SFV	safety follow-up visit
SoA	schedule of activities
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
WOCBP	women of childbearing potential

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

Open-Label Extension Study to Evaluate the Long-term Safety and Efficacy of Efgartigimod in Adult Patients with Post-COVID-19 Postural Orthostatic Tachycardia Syndrome (PC-POTS) who Completed Study ARGX-113-2104

Regulatory Agency Identifier Number(s): IND[redacted]

Rationale:

Efgartigimod is a first-in-class antibody fragment that binds to FcRn. This binding prevents FcRn from recycling IgG and leads to a reduction in circulating disease-causing autoantibodies. This open-label extension study will evaluate the long-term safety of efgartigimod in participants with PC-POTS who have completed the 24-week treatment period of the parent study ARGX-113-2104.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
• Evaluate the long-term safety of efgartigimod in patients with PC-POTS	• Incidence and severity of AEs and AESIs, incidence of SAEs, changes in clinically significant laboratory test results (per investigator judgment), vital signs, and ECG results
Secondary	
• Evaluate the long-term efficacy of efgartigimod in reducing the severity of PC-POTS symptoms	• Change from baseline to week 24 and week 48 in COMPASS 31 (modified) • Change from baseline to week 24 and week 48 in MaPS
• Evaluate the long-term efficacy of efgartigimod on patient global assessment of symptom experience, fatigue, and cognitive function	• Change from baseline to week 24 and week 48 in PGI-S • PGI-C at week 24 and week 48 • Change from baseline to week 24 and 48 in the PROMIS Fatigue Short Form 8a • Change from baseline to week 24 and 48 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 over the 48-week treatment period
• Assess the exposure to efgartigimod	• Efgartigimod serum trough concentrations over the 48-week treatment period
• Assess the immunogenicity of efgartigimod	• Incidence and prevalence of ADA against efgartigimod over the 48-week treatment period

ADA=antidrug antibodies; AE=adverse event; AESI=adverse events of special interest; COMPASS=Composite Autonomic Symptom Score; ECG=electrocardiogram; IgG=immunoglobulin G; MaPS=Malmö POTS Symptom

Score; PC-POTS=post-COVID-19 postural orthostatic tachycardia syndrome; PD=pharmacodynamic; PGI-C=Patient Global Impression of Change; PGI-S=Patient Global Impression of Severity; PROMIS=Patient-Reported Outcomes Measurement Information System; SAE=serious adverse event

No estimands have been defined for this study.

Overall Design:

Study ARGX-113-2105 is a long-term, single-arm, open-label, multicenter extension of the ARGX-113-2104 study, designed to evaluate the long-term safety of efgartigimod IV in adult patients with PC-POTS. Participants will be enrolled from both active and placebo arms of the ARGX-113-2104 study and will receive efgartigimod IV 10 mg/kg in the extension study without knowledge of their prior treatment arm. To be eligible to enroll in this study, participants must have completed the 24-week treatment period of the ARGX-113-2104 study and must not have permanently discontinued the IMP in that study.

Brief Summary:

The treatment period of this study is 48 weeks. Participants will receive efgartigimod (10 mg/kg) by IV infusion QW for the first 4 weeks (induction dosing period), and then Q2W for 42 weeks (maintenance dosing period). Participants will return for a safety follow-up visit approximately 56 days after the last dose of IMP administration. The total planned duration of the study is 386 days.

Efgartigimod will be administered during the treatment period in an approximately 1-hour IV infusion by site staff or a home nurse. If clinically indicated, the participant and investigator (based on the participant-reported reason for the request and physical examination) can jointly decide to return the participant to QW dosing during the maintenance dosing period.

IMP infusions must occur at the site for a minimum of 3 consecutive visits (baseline visit and the week 1 and 2 visits) before home infusions are allowed. 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.

The study's primary objective is to assess the long-term safety of efgartigimod in participants with PC-POTS. Additional assessments will be conducted, and blood samples collected to assess the effectiveness of efgartigimod at treating PC-POTS, the PD effect of efgartigimod, and the immunogenicity of efgartigimod. Blood samples will also be collected to monitor the concentration of efgartigimod in blood over time.

A minimum of 8 study site visits over the 48-week treatment period and safety follow-up period is planned; all other visits may be conducted by a home health care service, or a telemedicine visit.

Health Measurement/Outcome:

The primary outcome of this study will be the incidence and severity of AEs and AESIs, the incidence of SAEs, changes in laboratory test results, vital signs, and ECG results.

Study Intervention and Intervention Form: Efgartigimod IV.

Condition/Disease: PC-POTS.

Study Duration:

The maximum length of time a participant can be in the study is approximately 55 weeks. This includes the 48-week treatment period plus the safety follow-up period, with a safety follow-up visit approximately 56 days after the last dose of IMP administration).

Treatment Duration:

Total treatment duration will be 46 weeks (Q2W dosing) or 47 weeks (QW dosing), with the end of treatment visit on week 48 (total treatment period of 48 weeks).

Visit Frequency:

A minimum of 8 study site visits over the 48-week treatment period and safety follow-up period is planned (baseline, weeks 1, 2, 4, 12, 24, 48, and the SFV); all other visits may be conducted by a home health care service, or a telemedicine visit.

Number of Participants:

Approximately 38 participants are expected to roll over to this OLE study and receive efgartigimod IV 10 mg/kg, assuming approximately 90% of participants in the parent study (ARGX-113-2104) will be eligible to enroll in the OLE study.

Note: Enrolled means the participant agrees to participate in the clinical study by completing the informed consent process, and having fully completed the parent study (ARGX-113-2104).

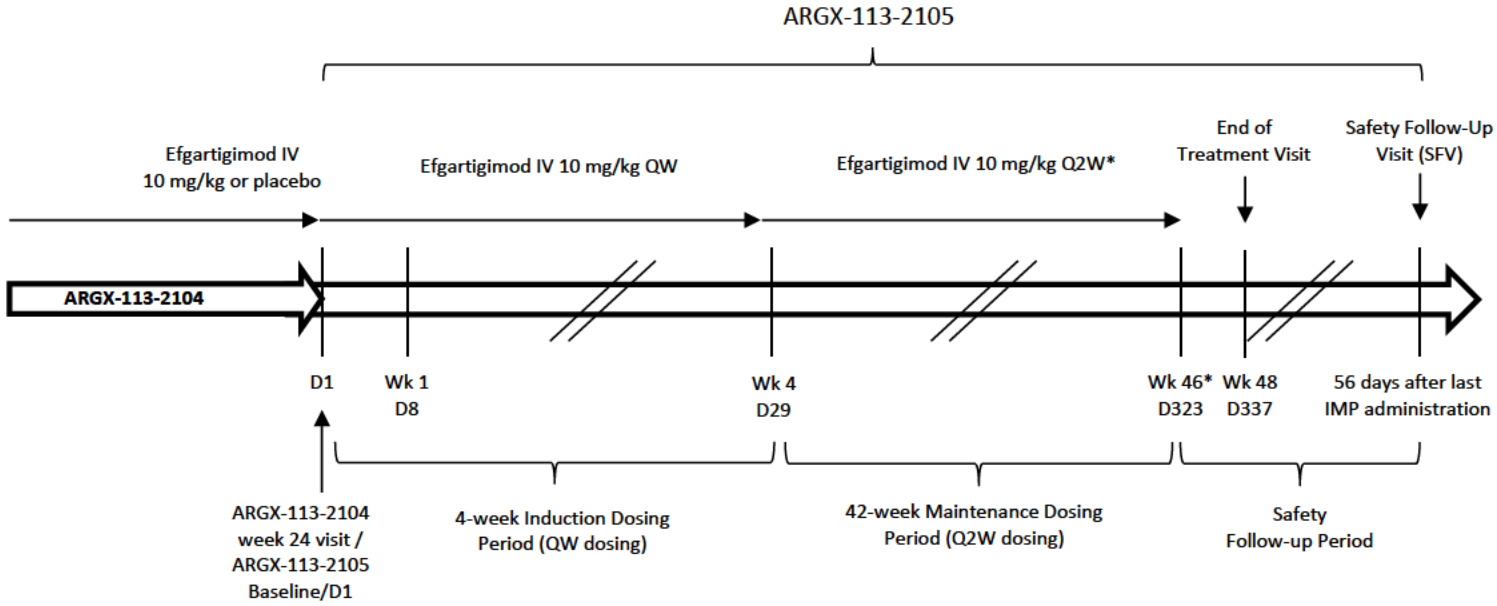
Study Arms and Duration:

Each participant will participate in the following study periods:

- Treatment period of 48 weeks:
  - Induction dosing period: 4-week period of QW efgartigimod IV dosing from day 1 (baseline) to day 22 (week 3)
  - Maintenance dosing period: 42-week period from day 29 (week 4) to day 323 (week 46) Q2W. Participants will receive efgartigimod IV doses Q2W, with the first dose of this period administered on day 29 (week 4). If clinically indicated (eg, the participant loses PC-POTS symptom control), the participant and investigator, based on the participant-reported reason for the request and physical examination, can jointly decide to return to QW dosing. Participants who switch back to QW dosing will not be allowed to switch back to Q2W dosing during the study. Participants who switch must attend an unscheduled visit. The decision to switch to QW dosing and the date of the switch should be recorded in the eCRF.
  - End of treatment visit on week 48.
- Safety follow-up period starting after last dose of IMP, with a safety follow-up visit approximately 56 days after the last dose of IMP administration.

Data Monitoring/Other Committee: No

1.2. Schema



Abbreviations: D = day; IV = intravenous; QW = once weekly; Q2W = every 2 weeks; Wk = week.
* During the maintenance dosing period, the participant and investigator (based on the participant-reported reason for the request and physical examination) can jointly decide to return the participant from Q2W to QW dosing. The final dose for participants who remain on Q2W dosing will be administered at week 46 (day 323). The final dose for participants who switch back to QW dosing during the maintenance dosing period will be administered at week 47 (day 330).

1.3. Schedule of Activities

Table 1: Schedule of Activities: Baseline to Week 48 (Treatment Period)

		Study week																Applicable Protocol Section(s)
	BL[a]	1	2	3	4	5-7	8	9-11	12	13-17	18	19-23	24	25-35	36	37-47	48	
Study day (±2)	1	8	15	22	29	36-50	57	64-78	85	92-120	127	134-162	169	176-246	253	260-330	337	
Note: All activities (safety and efficacy assessments, predose blood sampling) will be completed before administering the IMP infusion.																		
Visits that must be attended at the site are BL, W1, W2, W4, W12, W24, W48, IDV, EDV, and SFV; all other visits may be conducted by home health care service, or telemedicine visit																		
Eligibility																		
Informed consent	X																	10.1.3
Eligibility check	X																	5.1, 5.2
Questionnaires[b]																		
COMPASS 31 (modified)	X[c]		X		X		X		X				X		X		X	8.2.1.1
MaPS	X[c]		X		X	W6	X	W10	X	W16		W20	X		X		X	8.2.1.2
PGI-S, PGI-C	X[c]		X		X				X				X				X	8.2.1.3
PROMIS Fatigue	X[c]		X		X				X				X				X	8.2.1.4
PROMIS Cognition	X[c]				X				X				X				X	8.2.1.4
Efficacy tests[d]																		
[redacted]	[redacted]																	
Safety																		
Physical examination[e]	X[c]				X				X				X				X	8.3.1
Weight[f]	X[c]				X				X				X				X	8.3.1

	BL[a]	Study week																Applicable Protocol Section(s)
		1	2	3	4	5-7	8	9-11	12	13-17	18	19-23	24	25-35	36	37-47	48	
Study day (±2)	1	8	15	22	29	36-50	57	64-78	85	92-120	127	134-162	169	176-246	253	260-330	337	
Vital sign measurements[g]	X[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.3.2
Electrocardiogram	X[c]								X				X				X	8.3.3
TSH/CRP/ESR	X[c]												X				X	8.3.4
Serum chemistry and hematology	X[c]				X				X				X				X	8.3.4
Urinalysis	X[c]								X				X				X	8.3.4
Pregnancy test[h]	X[c]				X		X		X	W16		W20	X	W28 W32	X	W40 W44	X	8.3.5
Blood sampling																		
PK assessments[i]	X[c]	X			X				X				X				X	8.5
PD profile[i]	X[c]	X			X				X				X				X	8.6
Immunogenicity[i]	X[c]	X			X				X				X				X	8.9
Biomarkers[i]																		8.8
serum	X[c]				X				X				X				X	8.8.1, 8.8.2
whole blood	X[c]												X				X	8.8.3
AE review		Continuous monitoring																8.4
Conmed review		Continuous monitoring																6.9
IMP infusion[f,j]	X[k]	X	X	X	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]		6

[redacted]; AE=adverse event; BL=baseline; COMPASS=composite autonomic symptom scale; Conmed=concomitant medications; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; [redacted] IMP=investigational medicinal product; MaPS=Malmö POTS Symptom Score; 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; QW = once weekly; Q2W = every 2 weeks; TSH=thyroid stimulating hormone; W=week; WOCBP=women of childbearing potential.

[a] With the exception of informed consent, eligibility check, and IMP infusion, assessments at BL are conducted as part of the ARGX-113-2104 study.

[b] Questionnaires will be administered in the following order: MaPS, PGI-S past week recall, PROMIS Fatigue, PROMIS Cognitive Function, COMPASS 31, PGI-S 2-week recall, PGI-C.
[c] Procedure performed as part of the ARGX-113-2104 study week 24 assessments
[d] These assessments may be performed over 1 to 2 days at each time point, as long as all testing is completed prior to dosing scheduled for that time point.
[e] The physical examination will comprise a full assessment of systems at baseline and a brief assessment at all other time points.
[f] 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.
[g] Vital signs will be measured before collecting any blood sample or administering IMP infusions.
[h] A urine pregnancy test will be conducted for WOCBP at baseline and during the study, including during the follow-up period. On visits where both pregnancy testing and IMP administration will be performed, all pregnancy testing must be performed predose. Dosing should not begin until a negative pregnancy test result has been confirmed.
[i] Blood samples to be collected predose (except for week 48, where no IMP is administered and the sample can be taken at any time during the visit).
[j] If participants switch from Q2W to QW dosing during the maintenance phase, they must attend an unscheduled visit (see Table 2). The decision to switch to QW dosing and the date of the switch should be recorded in the electronic case report form.
[k] Day 1 IMP infusion to occur following eligibility and baseline assessments.
[l] During the maintenance dosing phase, IMP infusions will be administered Q2W (weeks 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46). If clinically indicated, the participant and investigator (based on the participant-reported reason for the request and physical examination) can jointly decide to return the participant to QW dosing during the maintenance dosing period, with the final QW dose administered on day 330 (week 47).

Table 2: Schedule of Activities: Unscheduled, IMP Discontinuation, Early Discontinuation, and Safety Follow-up Visits

	Unscheduled Visit for Dosing Frequency Switch[a]	IMP Discontinuation Visit[b]	EDV[c]	SFV[d]	Applicable Protocol Section (s)
Study day	**NA**	**NA**	**NA**	**NA**	
Questionnaires[e]					
COMPASS 31 (modified)		X	X		8.2.1.1
MaPS		X	X		8.2.1.2
PGI-S, PGI-C		X	X		8.2.1.3
PROMIS Fatigue		X	X		8.2.1.4
PROMIS Cognition		X	X		8.2.1.4
Efficacy tests[f]					
[redacted]	[redacted]				
Safety					
Physical examination[g]	X	X	X	X	8.3.1
Vital sign measurements[h]		X	X	X	8.3.2
Electrocardiogram		X	X		8.3.3
Serum chemistry and hematology		X	X		8.3.4
Urinalysis		X	X		8.3.4
Pregnancy test[i]		X	X	X	8.3.5
Blood sampling					
PK assessments[j]	X	X[k]	X		8.5
PD profile	X				8.6
Immunogenicity	X	X	X	X[l]	8.9
Biomarkers: serum		X	X		8.8.1, 8.8.2
AE review	X	X	X	X	8.4
Concomitant medication review	X	X	X	X	6.9

[redacted]; ADA=antidrug antibodies; AE=adverse event; COMPASS=composite autonomic symptom scale; EDV=early discontinuation visit; [redacted] IMP=investigational medicinal product; MaPS=Malmö POTS Symptom Score; NA=not applicable; PD=pharmacodynamics; PGI-C=Patient Global Impression – Change; PGI-S=Patient Global Impression – Severity; PK=pharmacokinetics; PROMIS=Patient-Reported Outcomes Measurement Information System; QW = once weekly; Q2W = every 2 weeks; SFV=safety follow-up visit; WOCBP=women of childbearing potential.

[a] If participants switch from Q2W to QW dosing during the maintenance phase, they must attend an unscheduled visit. The decision to switch to QW dosing and the date of the switch should be recorded in the electronic case report form.

[b] The IMP Discontinuation Visit will be performed at the earliest opportunity (within 7 days) after permanent IMP discontinuation and applies for participants who discontinue IMP but remain in the study.

[c] Within 7 days of last contact with participant. The EDV applies for participants who discontinue the study.

[d] Participants will attend a safety follow-up visit 56 ±3 days after their final IMP dose.

[e] Questionnaires will be administered in the following order: MaPS, PGI-S past week recall, PROMIS Fatigue, PROMIS Cognitive Function, COMPASS 31, PGI-S 2-week recall, PGI-C.

[f] These assessments may be performed over 1 to 2 days at each time point, as long as all testing is completed prior to dosing scheduled for that time point.

[g] The physical examination will comprise a full assessment of systems at baseline and a brief assessment at all other time points.

[h] Vital signs will be measured before collecting any blood sample or administering IMP infusions.

[i] A urine pregnancy test will be conducted for WOCBP at baseline and during the study, including during the follow-up period.

[j] Blood for PK analyses will be collected at the same time of the immunogenicity sample.

[k] Blood sample for PK analysis will not be collected if the IMP Discontinuation Visit is more than 4 weeks since the last dose of efgartigimod.

[l] In participants that discontinue study treatment, ADA will be assessed 56 days after the last dose administered.

2. INTRODUCTION

In Study ARGX-113-2104, the efficacy and safety of efgartigimod IV in adult patients with PC-POTS is evaluated using a randomized, double-blinded, placebo-controlled study design. Participants are randomized to receive efgartigimod IV 10 mg/kg or matching placebo in a 2:1 ratio. The IMP (efgartigimod or matching placebo) is administered during the treatment period in an approximately 1-hour IV infusion QW by site staff or a home nurse. The final dose is administered at week 23. At week 24, eligible participants from ARGX-113-2104 may roll over into the present single-arm OLE study: ARGX-113-2105.

2.1. Study Rationale

Efgartigimod is a first-in-class antibody fragment that binds to FcRn. This binding prevents FcRn from recycling IgG and leads to a reduction in circulating disease-causing autoantibodies.

Efgartigimod may be a viable treatment option for individuals diagnosed with PC-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.

This open-label extension study will evaluate the long-term safety of efgartigimod in participants with PC-POTS who have completed the 24-week treatment period of the parent study ARGX-113-2104.

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 HR increment of ≥30 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; 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 PC-POTS.

Currently, the underlying pathophysiology and effective treatments are unknown for PC-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 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 PC-POTS could be caused by IgG autoantibodies that induce autonomic dysfunction. The aim of this phase 2 study is to evaluate the long-term safety of efgartigimod in participants with PC-POTS who have completed the 24-week treatment period of the parent study ARGX-113-2104.

A detailed description of the chemistry, pharmacology, efficacy, and safety of efgartigimod is provided in the IB.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks of efgartigimod is provided 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 risk for infection.	Exclude participants with clinically significant active infection not sufficiently resolved in the investigator's opinion (Section 5.2). Infections are considered AESIs (Section 8.4.6). Monitor for infections and temporarily interrupt IMP dosing as specified in Section 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.	Monitor participants during administration and for 30 minutes thereafter for clinical signs and symptoms of infusion reactions. Infusion/injection-related reactions are considered AEs of clinical interest (Section 8.4.7). If an infusion reaction occurs, interrupt the infusion and institute appropriate supportive measures. Once resolved, the infusion can be resumed and at a slower rate, if necessary.

Potential clinically significant risk	Summary of data/rationale for risk	Mitigation strategy
Infusion/injection-site reactions	Most AEs have been mild, transient injection site reactions, including erythema, pain, bruising, pruritus, burning, tenderness, edema, induration, irritation, paresthesia, numbness, and rash. Moderate injection site reactions occurring less frequently include burning, erythema, pain, and numbness. Mild to moderate headache is commonly reported.	Continuously monitor participants for injection site reactions. Infusion/injection-site reactions are AEs of clinical interest (Section 8.4.7).

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

2.3.2. Benefit Assessment

Efgartigimod has been investigated in nonclinical studies, phase 1 clinical pharmacology studies in healthy subjects, and phase 2 to 3 clinical studies in patients with IgG-driven autoimmune diseases, including gMG, primary 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 PC-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 PC-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 PC-POTS.

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

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3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 3: Study ARGX-113-2105 Objectives and Endpoints

Objectives	Endpoints
Primary	
• Evaluate the long-term safety of efgartigimod in patients with PC-POTS	• Incidence and severity of AEs and AESIs, incidence of SAEs, changes in clinically significant laboratory test results (per investigator judgment), vital signs, and ECG results
Secondary	
• Evaluate the long-term efficacy of efgartigimod in reducing the severity of PC-POTS symptoms	• Change from baseline to week 24 and week 48 in COMPASS 31 (modified) • Change from baseline to week 24 and week 48 in MaPS
• Evaluate the long-term efficacy of efgartigimod on patient global assessment of symptom experience, fatigue, and cognitive function	• Change from baseline to week 24 and week 48 in PGI-S • PGI-C at week 24 and week 48 • Change from baseline to week 24 and 48 in the PROMIS Fatigue Short Form 8a • Change from baseline to week 24 and 48 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 over the 48-week treatment period
• Assess the exposure to efgartigimod	• Efgartigimod serum trough concentrations over the 48-week treatment period
• Assess the immunogenicity of efgartigimod	• Incidence and prevalence of ADA against efgartigimod over the 48-week treatment period
Exploratory	
• [redacted]	• [redacted]
• [redacted]	• [redacted] ○ [redacted] ○ [redacted] ○ [redacted]

[redacted] ADA=antidrug antibodies; AE=adverse event; AESI=adverse events of special interest; COMPASS=Composite Autonomic Symptom Score; ECG=electrocardiogram; [redacted];

IgG=immunoglobulin G; MaPS=Malmö POTS Symptom Score; PC-POTS=post-COVID-19 postural orthostatic tachycardia syndrome; PD=pharmacodynamic; PGI-C=Patient Global Impression of Change; PGI-S=Patient Global Impression of Severity; PROMIS=Patient-Reported Outcomes Measurement Information System; [redacted]; SAE=serious adverse event

No estimands have been defined for this study.

4. STUDY DESIGN

4.1. Overall Design

Study ARGX-113-2105 is a long-term, single-arm, open-label, multicenter extension of the ARGX-113-2104 study, designed to evaluate the long-term safety of efgartigimod IV in adult patients with PC-POTS. Participants will be enrolled from both active and placebo arms of the ARGX-113-2104 study and will receive efgartigimod IV 10 mg/kg in the extension study without knowledge of their prior treatment arm. To be eligible to enroll in this study, participants must have completed the 24-week treatment period of the ARGX-113-2104 study and must not have permanently discontinued the IMP in that study.

The treatment period of this study is 48 weeks. Participants will receive efgartigimod (10 mg/kg) by IV infusion QW for the first 4 weeks (induction dosing period), and then Q2W for 42 weeks (maintenance dosing period). Efgartigimod will be administered during the treatment period in an approximately 1-hour IV infusion by site staff or a home nurse. If clinically indicated (eg, the participant loses PC-POTS symptom control), the participant and investigator, based on the participant-reported reason for the request and physical examination, can jointly decide to return the participant to QW dosing during the maintenance dosing period. Participants who switch back to QW dosing will not be allowed to switch back to Q2W dosing during the study. Participants who switch must attend an unscheduled visit (see Table 2). The decision to switch to QW dosing and the date of the switch should be recorded in the eCRF. The final dose for participants who remain on Q2W dosing will be administered at week 46 (day 323). The final dose for participants who switch back to QW dosing during the maintenance dosing period will be administered at week 47 (day 330). The end of treatment visit occurs on week 48 (day 337).

Participants will return for a safety follow-up visit approximately 56 days after the last dose of IMP administration. The total planned duration of the study is 386 days.

IMP infusions must occur at the site for a minimum of 3 consecutive visits (baseline visit and the week 1 and 2 visits) before home infusions are allowed. 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.

The study's primary objective is to assess the long-term safety of efgartigimod in participants with PC-POTS. The primary outcome of this study will be the incidence and severity of AEs and AESIs, the incidence of SAEs, changes in clinically significant laboratory test results (per investigator judgment), vital signs, and ECG results. Additional assessments will be conducted, and blood samples collected to assess the effectiveness of efgartigimod at treating PC-POTS, the PD effect of efgartigimod, and the immunogenicity of efgartigimod. Blood samples will also be collected to monitor the concentration of efgartigimod in blood over time.

A minimum of 8 study site visits over the 48-week treatment period and safety follow-up period is planned (baseline, weeks 1, 2, 4, 12, 24, 48, and the SFV); all other visits may be conducted by a home health care service, or a telemedicine visit.

4.2. Scientific Rationale for Study Design

In the present OLE study (ARGX-113-2105), the long-term safety, efficacy, PD, and PK of efgartigimod IV will be evaluated in participants with PC-POTS.

The study includes a 48-week treatment period in which all patients will initially receive QW doses of efgartigimod (10 mg/kg) by IV infusion, ie, at the same dose, mode, and frequency of administration as in the preceding parent study ARGX-113-2104. After 4 weeks of this induction dosing period, participants will be switched to a less frequent dosing regimen (Q2W), for the maintenance dosing period, although if clinically indicated the participant can be returned to QW dosing.

The blinded treatment allocation (efgartigimod or placebo) from Study ARGX-113-2104 will be maintained.

The primary outcome measure is the ongoing safety of efgartigimod IV for approximately 1 year after completing Study ARGX-113-2104. The endpoints aim to demonstrate that efgartigimod IV is a safe long-term treatment option for PC-POTS. The safety endpoints selected for this study are those considered to be standard for any clinical study evaluating the safety of an IMP.

Efficacy is assessed as a secondary objective as assessed by change from baseline to weeks 24 and 48 in the modified version of COMPASS 31 (2-week recall) and the MaPS.

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 8.2.1.1).

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.[23] 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 other secondary efficacy 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

Doses of efgartigimod IV 10 mg/kg (QW) will be administered to achieve a maximal total IgG reduction (PD effect), thereby ensuring maximal clinical response on the efficacy outcomes. The dosing frequency will be reduced to Q2W (but the dose level will not be reduced) after 4 weeks, and this dosing frequency will be maintained for the remainder of the study unless a return to QW dosing is clinically indicated.

As the hypothesis for treating PC-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). The chronic nature of PC-POTS 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 QW through IV infusion achieved approximately 70% IgG reduction, including pathogenic autoantibodies. Data furthermore demonstrated that once maximum IgG reduction was achieved following weekly IV administration, a 45% or greater IgG reduction was maintained for at least 2 weeks following the last efgartigimod dose. 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 IV dose regimen (QW then Q2W) 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 SFV has been completed.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

1. The participant has completed the ARGX-113-2104 study without permanent discontinuation of IMP and agrees to directly roll over into the extension study without discontinuation of IMP.
2. The participant signs the informed consent form, as described in Section 10.1.3, and can comply with OLE study (ARGX-113-2105) protocol requirements.
3. The participant agrees to use contraceptives consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Contraceptive requirements are provided in Section 10.4.2.
4. Female participants of childbearing potential (defined in Section 10.4.1) must have a negative urine pregnancy test at baseline before receiving IMP.

5.2. Exclusion Criteria

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

1. The participant has a clinically significant condition, based on the judgement of the Study Investigator, eg, laboratory abnormalities, 12-lead ECG readings, concomitant medical disease(s), etc., which may place them at undue risk or confound interpretation of study data.
2. The participant intends to become pregnant or start breastfeeding during the study.

5.3. Lifestyle Considerations

Not applicable.

5.4. Screen Failures

Eligibility to roll over must be verified at the last visit of the preceding study ARGX-113-2104.

Participants who consent to participate in the clinical study but fail to meet the inclusion and exclusion criteria before IMP administration will be considered screen failures and will be captured as “enrollment failures.”

Individuals who do not meet the criteria for participation in this study (screen failures), based on the results from assessments in the preceding study, may not be rescreened.

5.5. Criteria for Temporarily Delaying Enrollment

Not applicable.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Efgartigimod is the IMP in this OLE study and is manufactured according to Good Manufacturing Practice regulations.

6.1. Investigational Medicinal Product Administered

Table 4: Study Intervention(s) Administered

Intervention label	Efgartigimod IV
Intervention name	Efgartigimod IV
Intervention description	Sterile, colorless, clear concentrate solution for IV infusion. Efgartigimod 20 mg/mL, administered IV
Type	Biologic
Dose formulation	Infusion
Unit dose strength(s)	20 mg/mL
Dosage level(s)	10 mg/kg QW or Q2W[a]
Route of administration	IV infusion
Use	Experimental
IMP and NIMP/AxMP	IMP
Sourcing	Centrally by the sponsor
Packaging and labeling	IMP will be provided in glass vials. Each vial will be labeled per country requirements.
Former name	ARGX-113

AxMP=auxiliary medicinal product; IMP=investigational medicinal product; IV=intravenous; NIMP= noninvestigational medicinal product; Q2W=every 2 weeks; QW=once weekly
[a] QW dosing during the induction dosing period followed by Q2W dosing during the maintenance dosing period.

6.2. Preparation, Handling, Storage, and Accountability

- The IMP will be supplied to the investigational site by the sponsors' designated IMP supply vendor.
- 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 are permitted to receive IMP, and only authorized site staff or designee are allowed to supply IMP.
- Appropriate dilutions in a 0.9% saline solution in an infusion bag will be prepared before administration with an IV pump.
- IMP must be stored refrigerated (2°C to 8°C) and protected from direct sunlight in secondary packaging. Do not shake IMP or expose it to freezing temperatures.
- Participants will be observed for at least 30 minutes after the end of IMP 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

All participants will receive efgartigimod (10 mg/kg) by IV infusion.

6.4. Blinding

ARGX-113-2105 is an open-label study. The blinded treatment allocation (efgartigimod or placebo) from the double-blind Study ARGX-113-2104 will be maintained until the database lock of that antecedent study.

6.5. Study Compliance

For some visits, participants will receive IMP under medical supervision at the site. 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.

IMP may be administered at home (by a health care professional [nurse]) for other visits. Participant compliance with IMP administration at home will be assessed by direct questioning during the site visit and documented in the source documents and relevant forms. The date and time of each dose administered will be recorded. Deviation(s) from the prescribed dosage regimen will be recorded.

IMP infusions must occur at the site for a minimum of 3 consecutive visits (baseline visit and the week 1 and 2 visits) before home infusions are allowed. 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.

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

Not applicable.

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 does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator will:

- Evaluate the participant to determine if IMP will be interrupted.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities (as medically appropriate and at least until the next scheduled follow-up).
- Immediately report the overdose and the quantity of the excess dose as well as the duration of the overdose.

6.9. Prior and Concomitant Therapy

Participants must 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 enrolment 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 IV Ig
- Plasma exchange/plasma electrophoresis
- 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. DISCONTINUATION OF IMP AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

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

7.1. Discontinuation of IMP

7.1.1. Permanent Discontinuation

Permanent discontinuation of IMP occurs when the participant stops receiving the IMP before the end of the study, does not resume receiving IMP, and does not withdraw informed consent.

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

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:

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

7.1.2. Temporary Discontinuation

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

Reasons requiring temporary interruption 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

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

The primary reason for permanent withdrawal from the study will be recorded.

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

- The participant withdraws consent
- At the request of the sponsor

The participant will be permanently discontinued from IMP and the study.

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

- If the participant withdraws consent to participate in the study, the sponsor can retain and continue to use any data collected before such consent was withdrawn.
- Future research on samples collected from participants who have withdrawn consent from the study is not impacted unless the participant also withdraws the consent for future research.

Attempts will be made to determine vital status (as a minimum) for participants who withdraw consent to participate in the 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.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoAs (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoAs, is required for study conduct.
- Visits that must be attended on-site are baseline, weeks 1, 2, 4, 12, 24, 48, IMP discontinuation visit, EDV, and SFV. All other visits may occur at the participant's home (Appendix 6, Section 10.6)
- All baseline evaluations must be completed and reviewed to confirm that participants meet all eligibility criteria before first dose. The investigator will maintain a log to record details of all participants who performed a baseline visit and confirm eligibility or record reasons for not being eligible, as applicable.
- Operational considerations due to the COVID-19 pandemic are provided in Section 10.5.

8.1. Administrative and General/Baseline Procedures

The baseline visit for Study ARGX-113-2105 will be conducted after the participant has completed Study ARGX-113-2104. All baseline assessments will be performed before first administration of efgartigimod IV in ARGX-113-2105, if applicable. Assessments do not need to be repeated if they are performed as part of ARGX-113-2104.

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.

All assessments will be completed before administering the IMP infusion.

8.1.1. Use and Storage of Biological Samples

Any samples remaining after the laboratory analyses as defined in the protocol have been completed can be stored for up to 15 years after the end of the study, in the laboratory or long term storage designated by the sponsor or research partners worldwide for future additional medical, academic, or scientific research to address any scientific questions related to efgartigimod, FcRn biology, or POTS, unless prohibited by local regulations or the participant.

As stated in Section 7.2, participants withdrawing from the study are allowed to request the destruction of collected, untested samples.

8.2. Efficacy Assessments

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

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

Instructions on completing these assessments are provided in the Investigator Site File.

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 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 modified version of COMPASS 31 (2-week recall) will be used throughout the study.

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.[23] The score consists of 12 questions that assess symptoms burden related (tachycardia, palpitations, dizziness, presyncope) and unrelated to orthostatic intolerance (gastrointestinal symptoms, insomnia, concentration difficulties).

Participants will grade their symptoms for the past 7 days using a numerical rating scale ranging from 0 (no symptoms) to 10 (very pronounced symptoms). 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 (1 week recall) 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.
- PROMIS Cognitive Function Short Form 6a: assesses the frequency of cognitive difficulties experienced in the past 7 days. The questionnaire comprises 6 questions on subjective cognitive difficulties regarding a patient's concentration, memory, language, mental acuity, and perceived changes in cognitive functioning. The participant marks their response on a 5-point Likert scale, with lower scores indicating worse perceived cognitive functioning.

8.2.2. [redacted]

[redacted]

8.2.3. [redacted]

[redacted]

8.3. Safety Assessments

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

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 validated 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. Protocol-Required 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 5) for the list of protocol-required laboratory tests to be performed and the SoAs (Section 1.3) for the timing.
- 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. Urine tests for pregnancy will occur at the time points specified in the SoAs (Section 1.3). On visits where both pregnancy testing and IMP administration will be performed, all pregnancy testing must be performed predose. Dosing should not begin until a negative pregnancy test result has been confirmed.
- Pregnancy testing in WOCBP will be conducted at the end of relevant systemic exposure (ie, at the SFV).

- Additional pregnancy testing could be performed, as necessary by the investigator or required by local regulations, to establish the absence of pregnancy at any time during the study.
- Any pregnancy reported during a clinical research study, including the safety follow-up period, is routinely monitored as standard practice. The pregnancy could have arisen from a female clinical study participant or a male participant's female partner. In either situation, consent will be requested to collect medical information about the pregnancy and the baby's health for up to 12 months after the baby's birth.

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

The definitions of AEs and SAEs 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 SoAs (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 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 towards the safety of participants and the safety of IMP under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of IMP under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.
- An investigator who receives a safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and file it with the IB and notify the IRB/IEC, if appropriate, according to local requirements.
- The sponsor or designee will be responsible for reporting SUSARs to the relevant regulatory authorities and IEC/IRB, as per applicable regulatory requirements. The sponsor or designee will also be responsible for forwarding SUSAR reports to all 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 pregnant female partner, if consented (Section 10.1.3), 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. AESIs

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 temporarily 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.

8.5. Pharmacokinetics

Blood samples for PK analysis will be collected predose on IMP administration visits (at the same time as the blood sample for immunogenicity assessments) as described in the SoAs (Section 1.3). At visits where IMP is not administered, blood samples may be collected at any time during that visit.

Efgartigimod serum concentrations will be determined using a validated method.

8.6. Pharmacodynamics

Blood samples for PD analysis will be collected predose on IMP administration visits (at the same time as the blood sample for immunogenicity assessments) as described in the SoAs

(Section 1.3). At visits where IMP is not administered, 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 parent study blind.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Serum and whole blood will be collected predose at the time points specified in the SoAs (Section 1.3) to identify putative biomarkers and explore their relationship with clinical effects. At visits where IMP is not administered, blood samples may be collected at any time during that visit. These analyses are exploratory as no biomarker has been validated for PC-POTS.

[redacted]

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

8.8.1. [redacted]

[redacted]

8.8.2. [redacted]

[redacted]

8.8.3. [redacted]

[redacted]

[redacted]

8.9. Immunogenicity Assessments

Blood samples will be collected at the time points indicated in the SoAs (Section 1.3), predose on IMP administration visits (within ≤2 hours before infusion), to evaluate serum levels of ADAs to efgartigimod. At visits where IMP is not administered, 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.[27] 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

Health economics and/or medical resource utilizations are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

The SAP will be finalized before the first interim analysis 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 OLE study. The primary objective of the study is to evaluate the long-term safety of efgartigimod in patients with PC-POTS.

9.2. Analysis Sets

The following analysis sets are defined:

Analysis set	**Description**
Full analysis set (FAS)	All enrolled participants
Safety analysis set	All participants exposed to study intervention.

All listings, including those for safety data, will be based on the FAS.

9.3. Statistical Analyses

9.3.1. General Considerations

The results of this study will not be used inferentially. No formal sample size calculation is presented.

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. For categorical variables, participants with missing data will be counted as a separate category; proportions will be calculated using as denominator all enrolled participants.

All study visits will be recalculated based on actual dates. The rules for calculating the analysis visits and for imputing partial dates or missing dates will be documented in the SAP.

Summaries will be provided both for the overall study population as well as grouped according to treatment received in Study ARGX-113-2104 (efgartigimod or placebo).

9.3.1.1. Estimands

No treatment effect will be estimated; the outcomes that will be summarized will be presented as descriptive and as pertaining to participants having efgartigimod as administered in the OLE, with in addition any treatments administered subsequent to efgartigimod, up to the end of scheduled follow-up.

9.3.2. Primary Endpoint Analysis

The primary endpoint is the incidence and severity of AEs and AESIs, incidence of SAEs, changes in laboratory test results, vital signs, and ECG results.

AEs will be coded using the latest version of the MedDRA classification system.

All AEs starting on or after the first infusion will be categorized as TEAEs.

TEAEs will be presented by SOC and PT, and will include the percentage of participants reporting at least one TEAE by SOC and PT and overall.

Multiple occurrences of a single PT in a participant will be counted only once at the maximum severity/grade.

The number and percentage of participants with most common AEs will be presented.

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.

All AE data will be listed.

The other safety endpoints will be summarized using descriptive statistics.

9.3.3. Secondary Endpoint Analysis

9.3.3.1. Efficacy

For analyses of change from baseline, the baseline is defined as the latest measurement prior to enrollment in the OLE study.

Summary statistics will be presented for the efficacy endpoints in Table 3 at baseline and at each scheduled visit for Study ARGX-113-2105.

In addition to change from the primary OLE baseline, summaries of absolute values at each visit will be similarly presented.

Plots of mean changes from the primary OLE baseline by visit will be presented, together with their 90% CI. Plots by visit of median change from the primary OLE baseline and its interquartile range will also be presented, represented by a boxplot at each visit.

For the two endpoints measuring reduction in severity of PC-POTS symptoms (COMPASS 31 and MaPS), summary statistics and plots for change from the parent study baseline will also be presented.

9.3.3.2. Pharmacodynamics

Absolute values, changes from baseline, and percent reduction from baseline in total IgG levels will be summarized using descriptive statistics. Two analyses will be presented, one using the baseline of the parent study (ARGX-113-2104); and the other using the baseline of the present OLE study (ARGX-113-2104 week 24 visit/ARGX-113-2105 baseline/day 1.

9.3.3.3. Pharmacokinetics

Efgartigimod serum concentrations will be summarized using descriptive statistics.

Efgartigimod serum trough concentrations will be calculated, in line with the secondary endpoint assessing exposure to efgartigimod. Details will be provided in SAP.

9.3.3.4. Population Pharmacokinetic/Pharmacodynamic Analysis

A population PK/PD analysis may be performed and may be reported separately from the final CSR.

9.3.3.5. Immunogenicity

Incidence and prevalence of ADAs will be summarized using descriptive statistics.

9.3.3.6. Change of Dosing Regimen and Analysis

Counts by visit will be presented of numbers and proportions on Q2W and QW dosing.

The temporal relationship between dosing regimen and both efficacy and safety will be explored and displayed visually.

COMPASS 31 efficacy score will be presented by visit for 2 subgroups, where the subgroups are defined as changing back at any time from Q2W to QW dosing regimen (Y/N).

Further exploratory analysis by dosing regimen may be performed.

Time from first infusion to switch back to QW dosing will be analyzed and a Kaplan-Meier plot of probability of staying on Q2W will be presented.

9.3.4. Exploratory Endpoint Analysis

[redacted]

9.4. Interim Analysis

Interim analyses in support of regulatory interactions may be performed for this study.

9.5. Sample Size Determination

The results of this study will not be used inferentially, and no formal sample size calculation was performed. Approximately 38 participants are expected to roll over to this OLE study and receive efgartigimod IV 10 mg/kg, assuming approximately 90% of participants in the parent study (ARGX-113-2104) will be eligible to enroll in the OLE study.

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 international ethical guidelines
  - Applicable ICH 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 is responsible for providing 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 with sufficient, accurate financial information as requested to allow the sponsor to submit a complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

The following information will be collected: any significant payments from the sponsor such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria, proprietary interest in IMP, significant equity interest in the sponsor as defined in 21 CFR 54 2(b) (1998).

10.1.3. Informed Consent Process

- The investigator or representative will explain the nature of the study, including risks and benefits to the potential participant and answer all questions before the participant completes the informed consent process by signing the informed consent form.
- Potential participants must be informed that their participation is voluntary. A statement of informed consent must be signed that meets the requirements of the IRB/IEC or study center, ICH guidelines, 21 CFR 50, local regulations, and, where applicable, privacy and data protection requirements.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study 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 if the changes to the ICF impact participant participation
- A copy of the ICF(s) must be provided to the participant (or their legally authorized representative).
- A copy of the ICF(s) must be provided to the participant.
- Participants who are rescreened are required to sign a new ICF (Section 5.4).

10.1.4. Recruitment Strategy

Not applicable.

10.1.5. Data Protection

- The sponsor will assign participants a unique identifier. Any participant records or datasets transferred to the sponsor 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, sponsor representatives, competent authorities, etc., can review source data containing identifiers and will use their personal study-related data per local data protection law. The level 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 contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.

- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.6. Committees Structure

Not applicable.

10.1.7. Dissemination of Clinical Study Data

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

10.1.8. Data Quality Assurance

- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- All participant data relating to the study will be recorded on eCRFs unless transmitted to the sponsor (or its designee) electronically (eg, laboratory data) or paper SAE forms. The investigator is responsible for verifying data entries are complete, accurate, and verifiable by electronically signing the eCRF.
- Guidance on completing eCRFs is provided in the eCRF completion document.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and direct access to source data documents.
- Study processes, study sites (including but not limited to site visits, central laboratories, vendors), the study database, and study documentation can be subject to quality assurance audit during the study by the sponsor or sponsor's designee on behalf of the sponsor. In addition, inspections could be conducted by foreign or domestic regulatory bodies at their discretion. Such audits/inspections can occur during or after the completion of the study.
- Records and documents, including signed ICFs, on the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a more extended retention period. Without the sponsor's written approval, no records will be destroyed during the retention period. No records are allowed to be transferred to another location or party without the sponsor's written notification.
- Monitoring details describing strategy and activities are described in a monitoring plan
  - 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 following the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. 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 in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data, and its origin can be found in the monitoring plan.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The sponsor or designee will perform monitoring 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.

10.1.10. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the first participant completes ARGX-113-2104 and rolls over to ARGX-113-2105.

Study/Site Termination

The sponsor or 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. 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 could initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator could include but are not limited to:

- For study termination:
  - Discontinuation of further compound development
- For site termination:
  - Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
  - Inadequate or lack of recruitment (evaluated after a reasonable amount of time) of participants by the investigator

- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator will promptly inform the participant and ensure appropriate therapy and/or follow-up for the participant, as necessary.

10.1.11. Publication Policy

- The results of this study can be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and consistent with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests listed in Table 5 will be performed as described in the Laboratory Manual.
- Additional tests can be performed during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory test result.

Table 5: Protocol-Required Laboratory Tests

Laboratory Test	Parameters		
Hematology	RBC count platelet count hemoglobin hematocrit	RBC indices: MCV MCH %reticulocytes	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	Urine test (as needed for WOCBP potential, defined in Section 10.4.1)		
Specialty laboratory tests	CRP, ESR, TSH		

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; 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 up to and including the week 4 (day 29) visit.

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 could 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 will 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 NOT 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:

Results in death

Is life threatening

The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event will be considered serious. When in doubt as to whether hospitalization occurred or was necessary, the AE is considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from screening will not be collected as an AE.

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 can interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect

Other situations:

- Medical or scientific judgment will be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that could jeopardize the participant or require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events are usually 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 considered 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 can 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 NCI CTCAE (version 5.0) definitions.

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 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 may not necessarily meet the criteria for 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. Grade 4 and 5 AEs are always assessed as serious (ie, SAE).

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 could 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 could 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 could 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 updated SAE data within 24 hours of receipt of 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 or designee's safety mailbox via the EDC system.
- The paper SAE report form will be faxed or emailed to the sponsor's designee (see the Serious Adverse Event Reporting details on page 2 of this protocol).

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Women of Childbearing Potential Definition

A female is considered a WOCBP unless she is either:

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

10.4.2. 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:

The following Clinical Trials Facilitation and Coordination Group[28] acceptable methods are permitted for efgartigimod studies:

- Progestogen-only oral hormonal contraception in which inhibition of ovulation is not the primary mode of action
- 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

Participants will be tested for SARS-CoV-2 if they are symptomatic or if applicable law requires testing; if applicable, a negative polymerase chain reaction test (central or local laboratory) is required within 72 hours before enrollment regardless of a participant's vaccination status.

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 for use 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.

Additional testing for COVID-19 beyond what is listed in the SoAs (Section 1.3) is not required during the study unless required by local authorities. However, it is recommended that participants who develop COVID-19 symptoms while receiving IMP be tested, with results reported for the study.

Critical Parameters to Be Collected During the Study

All assessments will be performed as indicated in the SoAs (Section 1.3). If assessments cannot be performed due to the COVID-19 pandemic, the following information must be collected from the first visit through end of study: all AE and concomitant medication reporting, IMP administration, questionnaires, and protocol-required laboratory assessments.

10.6. Appendix 6: Home Study Visits

A home nurse can travel to the participant's home to conduct visits or meet the participant at 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.

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