TITLE PAGE

Protocol Title:	An Open-label Extension Study of ARGX-113-2009 to Evaluate the Long-term Safety, Tolerability, and Efficacy of Efgartigimod PH20 SC in Adult Participants With Bullous Pemphigoid
Protocol Number:	ARGX-113-2010
Version Number:	4.0 (Amendment 3)
Compound:	Efgartigimod (ARGX-113)
Study Phase:	3
Acronym:	BALLAD+
Sponsor Name:	argenx BV
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Regulatory Agency Identifier Number(s):	EudraCT: 2021-003063-10
Approval Date:	02 May 2024

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SIGNATURE OF THE SPONSOR

Protocol Title: An Open-label Extension Study of ARGX-113-2009 to Evaluate the Long-term Safety, Tolerability, and Efficacy of Efgartigimod PH20 SC in Adult Participants With Bullous Pemphigoid

Protocol Number: ARGX-113-2010

Sponsor Signatory:

See appended signature page

[redacted], MD, PhD **Chief Medical Officer**	**Date**

SIGNATURE OF THE INVESTIGATOR

Investigator's Acknowledgment

I have read the protocol for study ARGX-113-2010.

Title: An Open-label Extension Study of ARGX-113-2009 to Evaluate the Long-term Safety, Tolerability, and Efficacy of Efgartigimod PH20 SC in Adult Participants With Bullous Pemphigoid

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 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 any 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 3 v4.0	02 May 2024
Amendment 2 v3.0	26 Apr 2024
Amendment 1 v2.0	02 Jun 2023
Original v1.0	07 Oct 2022

Amendment 3 (02 May 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 primary rationale for amendment 2 (v3.0, 26 Apr 2024) was to make changes to the principles for treatment with efgartigimod for subcutaneous (SC) administration coformulated with rHuPH20 (efgartigimod PH20 SC) and concomitant therapies. All participants who initiate or continue efgartigimod PH20 SC will now receive it for the duration of the treatment period. Efgartigimod PH20 SC may be initiated without concurrent oral corticosteroids, and the requirement to stop efgartigimod PH20 SC when participants are in complete remission or partial remission while off concurrent bullous pemphigoid (BP) therapy for ≥8 weeks was removed. Those changes are implemented to gain better insight into the safety and efficacy of efgartigimod PH20 SC in adult participants with BP.

The reason for amendment 3 (v4.0) is to correct an error in the schedule of activities (Table 2). The administration of efgartigimod PH20 SC no longer stops when participants are in complete remission or partial remission while off concurrent BP therapy for ≥8 weeks.

The major changes from the protocol v2.0 to protocol v3.0 and v3.0 to v4.0 are summarized in the following table. Added text is indicated with bold font and deleted text by strikethrough font. Minor editorial changes are not summarized in the table. Refer to the List of Abbreviations and Definitions of Terms for any undefined abbreviations or terms.

Section	Change in study conduct or planned analysis	Brief rationale
Version 4.0		
1.3. Schedule of Activities	The following change was made in the "Efgartigimod PH20 SC administration" row of Table 2: Once weekly ~~until CR/PR off concurrent BP therapy ≥8 weeks~~	To align with updated design

Section	Change in study conduct or planned analysis	Brief rationale
Version 3.0		
6.3 Assignment to Study Intervention Other sections impacted are Definition of Terms 1.1 Synopsis 1.2. Schema 1.3. Schedule of Activities 4. Study Design	The study design was modified as follows: The requirement to stop efgartigimod PH20 SC when participants are in CR or PR while off concurrent BP therapy for ≥8 weeks was removed. Guidance was added for initiating efgartigimod PH20 SC without concurrent OCS and tapering or discontinuing rescue therapy started in ARGX-113-2009. IMP will be permanently discontinued if the investigator considers it not to be in the participant's best interest to taper or discontinue rescue therapy, or initiate efgartigimod PH20 SC.	To gain better insight into the safety and efficacy of efgartigimod PH20 SC without concurrent OCS or other BP therapy, and allow evaluation of whether maintenance therapy with efgartigimod PH20 SC can prevent relapse
3. Objectives, Endpoints, and Estimands Other sections impacted are 1.1 Synopsis	The following footnote was added to the endpoints "Proportion of participants achieving CR while off both OCS and efgartigimod PH20 SC for ≥8 weeks" and "Proportion of participants achieving CR or PR while off both OCS and efgartigimod PH20 SC for ≥8 weeks": **The endpoint applies only to participants who have stopped receiving efgartigimod PH20 SC before protocol amendment 2 is effective.**	To align with updated design
6.1. Investigational Medicinal Product Administered	The following changes were made in the "intervention description" and "dosage level(s)" rows of Table 5: ~~At the start of a treatment course: 0.2 to 0.5 mg/kg/day~~ ~~Thereafter:~~ **Initiated and** adjusted according to clinical judgment	Concurrent OCS therapy is no longer required to be started at the same time as efgartigimod PH20 SC initiation

Section	Change in study conduct or planned analysis	Brief rationale
	~~At the start of a treatment course: 0.2 to 0.5 mg/kg/day~~ ~~Thereafter:~~ adjusted according to clinical judgment	
6.9. Prior and Concomitant Therapy	The following medications or treatments are not permitted ~~during the period when the participant is receiving IMP~~ **as of when the ICF has been signed through the completion of the EoTP visit or EDV, as applicable**: – Any systemic treatment for BP (eg, IV or intramuscular corticosteroids, **systemic immunosuppressants**) except ~~for:~~ OCS ~~– Concurrent BP therapy started in ARGX-113-2009: Participants who received rescue therapy in ARGX-113-2009 can maintain, taper, or discontinue this treatment according to the clinical judgment of the investigator (refer to Section 6.3)~~	Rescue therapy started in ARGX-113-2009 should now be tapered or discontinued
6.9.1. Oral Prednisone Tapering and Escalation	~~• At enrollment in ARGX-113-2010, participants will continue OCS following the tapering course used in ARGX-113-2009, if applicable.~~ • **Participants who were receiving concurrent OCS in ARGX-113-2009 will continue their OCS tapering course, as outlined in this section.** ~~• New treatment courses with oral prednisone may be started at a dose of 0.2 to 0.5 mg/kg/day per the investigator's discretion. If CDA is not achieved at a dose of ≤0.5 mg/kg/day, it is~~	To rely more on the investigator's clinical judgment for decisions on tapering or increasing OCS dosage

Section	Change in study conduct or planned analysis	Brief rationale
	~~recommended to increase to 0.5 mg/kg/day.~~ • **New treatment courses with oral prednisone may be initiated if there is a lack of clinical improvement in the participant's BP disease status and additional BP therapy is required. The starting dose of oral prednisone should be the lowest advisable dose and must not exceed 0.5 mg/kg/day. The choice of the starting dose within the specified range is at the investigator's discretion.** • Escalated doses of oral prednisone may be considered if the participant does not achieve CDA within 1 to 3 weeks of prednisone at or below 0.5 mg/kg/day. Participants who do not achieve CDA despite receiving efgartigimod PH20 SC with escalated dosages of OCS (0.75 mg/kg/day or higher) will be considered treatment failures (refer to the Definitions of Terms for a full description) **and IMP will be permanently discontinued**. • When CDA is achieved, the oral prednisone dose regimen is adjusted ~~as follows~~ **based on the investigator's clinical judgment. Recommendations for tapering are as follows**: – After CDA has been sustained for ≥2 weeks, the tapering schedule begins	

Section	Change in study conduct or planned analysis	Brief rationale
	with the next lower oral prednisone dosage, as listed in Table 6. ~~Each new dosage must be maintained for at least 2 weeks provided that no new lesions (transient or nontransient) appear. Duration of tapering steps from escalated doses (>0.5 mg/kg/day) may be shortened based on clinical judgment~~ **Each new dosage will be maintained for 2 weeks or less, based on clinical judgment**. ~~– Further tapering below the level of minimal OCS therapy can be performed in steps of 2.5 mg/day until the participant is off oral prednisone therapy (Table 7). Each new dosage step must be maintained for at least 2 weeks, provided that no new lesions (transient or nontransient) appear.~~ ~~– If a participant has new lesions but the investigator determines that it is not a relapse, prednisone tapering will be delayed. Under these circumstances, tapering can resume when no new lesions have appeared for at least 1 week (Table 7).~~ ~~• If a participant relapses:~~ ~~– The oral prednisone dosage is increased based on the clinical judgment of the investigator, with the recommendation to return to the dose administered 2 tapering steps before the relapse. Tapering from this increased dose can start after CDA has been sustained for at least 2 weeks on this increased dose.~~	

Section	Change in study conduct or planned analysis	Brief rationale
	– ~~If CDA is not achieved on an increased dose, it is recommended to return to an oral prednisone dose of 0.5 mg/kg/day.~~ • **The OCS dosage may be adjusted according to the investigator's clinical judgment if disease activity occurs during the OCS tapering.**	
6.9.2. Rescue Therapy Tapering and Discontinuation	A new section was added to specify how rescue therapy started in ARGX-113-2009 should be tapered or discontinued.	To align with updated design
7.1.1. Permanent Discontinuation	• **Investigator considers tapering or discontinuing rescue therapy started in ARGX-113-2009 not to be in the participant's best interest.**	To align with updated design
1.3. Schedule of Activities (SoA) 2.3. Benefit/Risk Assessment	~~The participant must be monitored for safety for at least 30 minutes after efgartigimod PH20 SC administration when treatment is administered on-site.~~ ~~Monitor participants during administration and for at least 30 minutes thereafter for clinical signs and symptoms of infusion/injection-related reactions when treatment is administered on-site.~~ **Participants for whom efgartigimod PH20 SC is administered at the site will be monitored for infusion/injection-related reactions.** **Participants and/or their caregivers who receive training on self-administration will be educated on symptoms of infusion/injection-related reactions.**	To align with the current efgartigimod IB

Section	Change in study conduct or planned analysis	Brief rationale
6.2. Preparation, Handling, Storage, and Accountability	**In exceptional cases, IMP, other BP therapies, and ancillaries may be shipped to participants by courier.**	To reduce the travel burden on participants
7.2. Participant Discontinuation/Withdrawal From 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 consent was withdrawn.~~ ~~The samples collected from participants who have withdrawn from the study will still be used for the study results but not for future research.~~ **If the participant withdraws consent to participate in the study, the sponsor can retain and continue to use any data collected before consent was withdrawn. Future research on samples collected from participants who withdraw consent to participate in the study will not be affected unless the participant also withdraws the consent for future research.**	To clarify the guidance on sample use for future research
8.3.5. Pregnancy Testing	• **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 to12 months after the baby's birth.**	To align with the current argenx policy
8.6. Pharmacodynamics 8.9. Immunogenicity Assessments	**(preferably** within 2 hours before IMP administration)	To offer flexibility for the collection of predose blood samples

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

List of Abbreviations

Abbreviation	Expansion
21 CFR	Title 21 of the Code of Federal Regulations
ABQoL	Autoimmune Bullous Disease Quality of Life
ADA	antidrug antibody(ies)
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
AIBD	autoimmune blistering disease
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	bullous pemphigoid
BPDAI	Bullous Pemphigoid Disease Area Index
CDA	control of disease activity
C-GTI	Composite Glucocorticoid Toxicity Index
CR	complete remission
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trials Facilitation and Coordination Group
DLQI	Dermatology Life Quality Index
eCRF	electronic case report form
EDV	early discontinuation visit
efgartigimod PH20 SC	efgartigimod for SC administration coformulated with rHuPH20
EoTP	end-of-treatment period
FcRn	neonatal crystallizable fragment receptor
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
gMG	generalized myasthenia gravis
GTI	Glucocorticoid Toxicity Index
GTI-AIS	GTI Aggregate Improvement Score
GTI-CWS	GTI Cumulative Worsening Score
GTI-SL	GTI Specific List
HGRAC	Human Genetic Resources Administration of China

Abbreviation	Expansion
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
IGA-BP	Investigator Global Assessment of Bullous Pemphigoid
IgG	immunoglobulin γ
IMP	investigational medicinal product
ITP	immune thrombocytopenia
IV	intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NRS	numerical rating scale
OCS	oral corticosteroids
OLE	open-label extension
PD	pharmacodynamic(s)
PR	partial remission
PRO	participant-reported outcome
PT	Preferred Term
QoL	quality of life
QTL	quality tolerance limit
rHuPH20	recombinant human hyaluronidase PH20
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SoA	schedule of activities
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
TCS	topical corticosteroids
ULN	upper limit of normal
WOCBP	women of childbearing potential

Definitions of Terms

- Efgartigimod PH20 SC — Efgartigimod for SC administration coformulated with rHuPH20
- Concurrent BP therapy — Therapy administered in this study for the treatment of BP other than efgartigimod PH20 SC. This may include:
  - Rescue therapy administered in ARGX-113-2009
  - OCS
  - TCS
- Stop of efgartigimod PH20 SC — Occurs when the participant stops receiving efgartigimod PH20 SC after achieving CR or PR off concurrent BP therapy for ≥8 weeks.
  Only applicable before protocol amendment 2 was effective.
- Discontinuation of efgartigimod PH20 SC — Occurs when the participant stops receiving efgartigimod PH20 SC before the end of the study for reasons other than achieving CR or PR off concurrent BP therapy for ≥8 weeks (refer to Section 7.1)

The following definitions are based on consensus definitions (Murrell et al, 2012[1]) and will be applied in ARGX-113-2010:

- Control of disease activity (CDA) — The point at which new lesions cease to form and established lesions begin to heal, and pruritic symptoms start to abate
- Treatment failure — The absence of CDA despite receiving efgartigimod PH20 SC with escalated dosages of prednisone (or equivalent OCS)
  Escalated dosages of OCS are defined as prednisone (or equivalent OCS) 0.5 mg/kg/day for 1 to 3 weeks, followed by 0.75 mg/kg/day for ≤3 weeks, and 0.75 or 1.0 mg/kg/day for a final optional week.
- Transient lesions — New lesions that heal within 1 week or pruritus lasting <1 week
- Nontransient lesions — New lesions that do not heal within 1 week or pruritus continuing >1 week
- Minimal OCS therapy — An oral prednisone (or equivalent OCS) dosage of ≤0.10 mg/kg/day
  Note: For the purpose of this protocol, "oral prednisone" refers to doses/dosages of prednisone or an alternative, equivalent OCS (eg, prednisolone).
- Complete remission (CR) — The absence of new lesions, complete healing of existing lesions, and absence of pruritus (except postinflammatory changes, including hypo/hyper pigmentation or skin damage)
- Partial remission (PR) — The presence of only new transient lesions

- Sustained remission

  For participants ongoing in the study when protocol amendment 2 is effective:

  Healing of lesions with no nontransient lesions (ie, BPDAI activity score of 0) and absence of pruritus while the participant has been off both concurrent BP therapy and off efgartigimod PH20 SC for ≥8 weeks
  New lesions that heal within 1 week or pruritus lasting <1 week and clearing without treatment will not be considered to change the condition of sustained remission.

  For participants rolling over after protocol amendment 2 is effective:

  Healing of lesions with no nontransient lesions (ie, BPDAI activity score of 0) and absence of pruritus while the participant has been off concurrent BP therapy for ≥8 weeks.
  New lesions that heal within 1 week or pruritus lasting <1 week and clearing without treatment will not be considered to change the condition of sustained remission.

- Relapse

  Appearance of 3 or more new lesions/month (blisters, eczematous lesions, or urticarial plaques) or at least 1 large (>10 cm diameter) eczematous lesion or urticarial plaque that does not heal within 1 week, or extension of established lesions or daily pruritus in a participant who has achieved CDA.

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: An Open-label Extension Study of ARGX-113-2009 to Evaluate the Long-term Safety, Tolerability, and Efficacy of Efgartigimod PH20 SC in Adult Participants With Bullous Pemphigoid

Rationale: This OLE study will assess whether long-term administration of efgartigimod PH20 SC is safe and effective in adults with BP who participated in ARGX-113-2009 (a phase 2/3 study of efgartigimod PH20 SC in adult participants with BP).

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
To assess the long-term safety and tolerability of treatment with efgartigimod PH20 SC in participants with BP	• Incidence and severity of treatment-emergent AEs, SAEs, and AESIs • Rate of treatment discontinuation because of safety concerns
Secondary	
To assess the long-term efficacy and durability of response with efgartigimod PH20 SC treatment in participants with BP	• Proportions of participants achieving[a]: – CR while off OCS for ≥8 weeks – CR or PR while off OCS for ≥8 weeks – CR while on minimal OCS therapy for ≥8 weeks. (Minimal OCS therapy is defined as ≤0.10 mg/kg/day of prednisone [or an equivalent dose of another OCS]) – CR while off both OCS and efgartigimod PH20 SC for ≥8 weeks[b] – CR or PR while off both OCS and efgartigimod PH20 SC for ≥8 weeks[b] • Duration of sustained remission • Proportion of participants who relapse • Time to relapse • Incidence and severity of relapse • BPDAI activity scores, IGA-BP scores, and itch NRS over time • Rate of treatment failure

[a] These endpoint criteria can only be met when participants are off rescue therapy.

[b] The endpoint applies only to participants who have stopped receiving efgartigimod PH20 SC before protocol amendment 2 is effective.

No estimands have been defined for this OLE study.

Overall Design: This is a phase 3, prospective, global, multicenter, OLE study to investigate the long-term safety, tolerability, efficacy, QoL, PD, and immunogenicity of efgartigimod PH20 SC in adult participants with BP who have completed ARGX-113-2009. The study will be conducted globally, at the same sites as ARGX-113-2009.

In ARGX-113-2009, participants received efgartigimod PH20 SC or placebo with concurrent OCS, or rescue therapy (without efgartigimod PH20 SC or placebo). When rolling over to ARGX-113-2010, participants will either initiate or continue efgartigimod PH20 SC treatment, while maintaining the blinded treatment allocation of ARGX-113-2009 (refer to Section 6.4).

Before protocol amendment 2, participants had to stop receiving efgartigimod PH20 SC upon achieving CR or PR while off concurrent BP therapy for ≥8 weeks. After protocol amendment 2, participants who stopped efgartigimod PH20 SC will reinitiate treatment at the investigator's discretion. If they relapse, reinitiation of efgartigimod PH20 SC treatment is mandatory. All other participants (ongoing and newly enrolled) will continue to receive efgartigimod PH20 SC until the end of the treatment period. Concurrent BP therapies, including rescue therapies started during ARGX-113-2009, will be tapered or discontinued. IMP will be permanently discontinued if the investigator considers it not to be in the participant's best interest to taper or discontinue rescue therapy or initiate efgartigimod PH20 SC.

Brief Summary: The purpose of this study is to evaluate the safety of efgartigimod PH20 SC over a longer period of time in adult participants with moderate-to-severe BP. The study will also evaluate the efficacy of efgartigimod PH20 SC.

Health Measurement/Outcome: The primary outcome measure is the long-term safety and tolerability of open-label efgartigimod PH20 SC for approximately 1 year after completing ARGX-113-2009.

Investigational Medicinal Product and Investigational Medicinal Product Formulation: Efgartigimod PH20 SC [redacted]

Condition/Disease: Bullous pemphigoid

Study Duration: Approximately 56 weeks

Treatment Duration: Up to 48 weeks

Visit Frequency: Participants will visit the site at weeks 0 (baseline), 1, 2, 4, and 8. After that, participants will visit every 4 weeks. Participants not receiving efgartigimod PH20 SC will visit every 8 weeks. A treatment-free period of 8 weeks follows the EoTP visit at week 48, with visits at EoTP + 4 weeks (if receiving efgartigimod PH20 SC) and EoTP + 8 weeks.

Number of Participants: All participants who complete the EoTP visit (week 36) in ARGX-113-2009 and meet the eligibility criteria can roll over to this study. All participants rolling over agree to participate in the clinical study by completing the informed consent process.

Study Arms and Duration: This is a single-arm study comprising a 48-week treatment period and a follow-up period of 8 weeks.

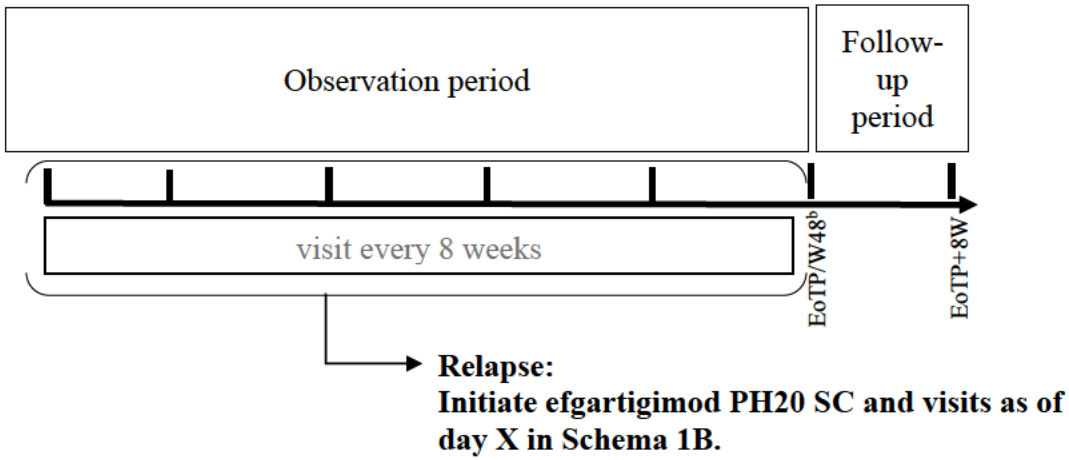
Data Monitoring/Other Committee: No

Ethical Considerations: The potential risks associated with efgartigimod PH20 SC are justified by the anticipated benefits that may be afforded to participants with BP in this study.

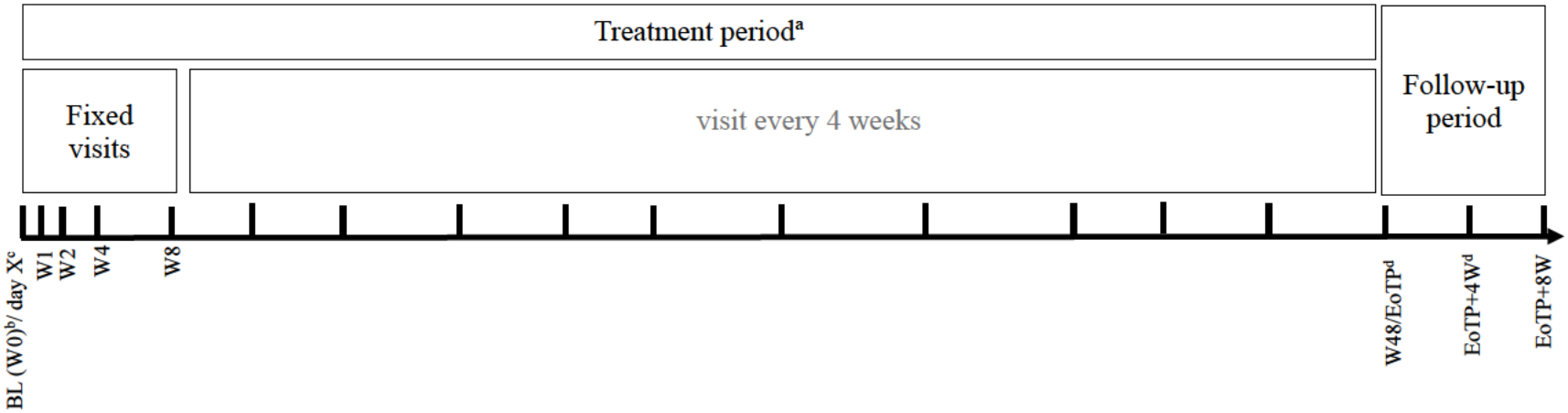
1.2. Schema

Figure 1: ARGX-113-2010 Study Overview

A. Participants not receiving efgartigimod PH20 SC



B. Participants who roll over or initiate efgartigimod PH20 SC after protocol amendment 2 is effective



BL=baseline; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; EoTP=end-of-treatment period; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous; W=week

[a] Efgartigimod PH20 SC [redacted] on days 1 and 8 and weekly maintenance doses of 1000 mg will be administered. Refer to Section 6.3 for more information.

[b] The BL (week 0) visit will occur on the same day as the EoTP visit (week 36) of ARGX-113-2009.

[c] Day X is defined as the day efgartigimod PH20 SC (refer to footnote a) is initiated and applies only to participants not receiving efgartigimod PH20 SC when protocol amendment 2 is effective.

[d] The EoTP visit will take place 48 weeks after baseline for all participants.

1.3. Schedule of Activities

Table 1: Schedule of Activities for Participants Who Have Not Received Efgartigimod PH20 SC Since Baseline and Rolled Over Before Protocol Amendment 2 Is Effective

Study period		Observation period								Follow-up period	Other visits		
Study week(s)	Baseline/ rollover (W0)[a,b]	W2	W4	W8	W16	W24	W32	W40	EoTP/W48	EoTP + 8 weeks	EDV[c]	UNS[d]	Applicable protocol section(s)
Visit window		±2 d	±2 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±3 d			
Eligibility (baseline only)													
Informed consent	X												Section 10.1.3
Eligibility check	X												Section 5.1 Section 5.2
Safety													
Physical examination (complete)	X								X		X		Section 8.3.1
Physical examination (brief)			X	X						X			Section 8.3.1
Weight	X					X			X		X	X	Section 8.3.1
Vital sign measurements	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.3.1
ECG	X					X							Section 8.3.3
Urine pregnancy test[e]	X		X	X	Every 4 weeks				X		X		Section 8.3.5
Urinalysis	X	X	X	X		X		X	X	X	X	X	Table 7
Clinical chemistry and hematology	X	X	X	X	X	X	X	X	X	X	X	X	Table 7
GTI assessments (GTI-AIS, GTI-CWS, GTI-SL)	X					X			X		X		Section 8.3.6

Study period		**Observation period**								**Follow-up period**	**Other visits**		
Study week(s)	**Baseline/ rollover (W0)[a,b]**	**W2**	**W4**	**W8**	**W16**	**W24**	**W32**	**W40**	**EoTP/W48**	**EoTP + 8 weeks**	**EDV[c]**	**UNS[d]**	**Applicable protocol section(s)**
Visit window		**±2 d**	**±2 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±3 d**			
Concomitant therapies/procedures	Continuous monitoring												Section 6.9
AE monitoring	Continuous monitoring												Section 8.4
Efficacy/disease monitoring													
Disease assessment[b]	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.1.1
IGA-BP	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.1.2
BPDAI	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.1.3
Itch NRS	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.1.4
Blood sample collection													
Immunogenicity	X		X	X	X	X	X	X	X	X	X	X	Section 8.9
PD (anti-BP180, anti-BP230[redacted])	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.6
PK	X												NA
Substudy: vaccination antibody titers (serum)	Relative to the time of vaccination in ARGX-113-2009												Section 8.3.4.1
Substudy: vaccination antibody titers (PBMCs)	Relative to the time of vaccination in ARGX-113-2009												Section 8.3.4.1
Other													
Monitoring of concurrent BP therapy (Definitions of Terms)	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.9 Section 8.2.1.1

Study period	Baseline/ rollover (W0)[a,b]	Observation period								Follow-up period	Other visits		Applicable protocol section(s)
Study week(s)		W2	W4	W8	W16	W24	W32	W40	EoTP/W48	EoTP + 8 weeks	EDV[c]	UNS[d]	
Visit window		±2 d	±2 d	±7 d	±7 d	±7 d	±7 d	±7 d	±7 d	±3 d			
QoL questionnaires (EQ-5D-5L, DLQI, ABQoL)	X					X			X		X		Section 8.2.2

ABQoL=Autoimmune Bullous Disease Quality of Life; AE=adverse event; BP=bullous pemphigoid; BPDAI=Bullous Pemphigoid Disease Area Index; CDA=control of disease activity; DLQI=Dermatology Life Quality Index; ECG=electrocardiogram; eCRF=electronic case report form; EDV=early discontinuation visit; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; EoTP=end-of-treatment period (visit); GTI=Glucocorticoid Toxicity Index; GTI-AIS=GTI Aggregate Improvement Score; GTI-CWS=GTI Cumulative Worsening Score; GTI-SL=GTI Specific List; IGA-BP=Investigator Global Assessment of Bullous Pemphigoid; [redacted] IMP=investigational medicinal product; NA=not applicable; NRS=numerical rating scale; PBMC=peripheral blood mononuclear cell; PD=pharmacodynamics; PK=pharmacokinetics; QoL=quality of life; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous; SoA=schedule of activities; UNS=unscheduled visit; W=week

Note: Assessments indicated in gray font will only be recorded on the ARGX-113-2009 eCRF and not on the ARGX-113-2010 eCRF.

[a] Participants for whom IMP was temporarily interrupted at the time of the EoTP in ARGX-113-2009 must follow the SoA in Table 1 until the investigator has determined that it is safe for the participant to receive treatment. If the participant requires treatment with efgartigimod PH20 SC, they must follow the SoA in Table 2 as of day X (refer to Section 5.5).

[b] Participants who have not received efgartigimod PH 20 SC since baseline must follow the SoA in Table 1 until the investigator decides that efgartigimod PH20 SC should be initiated. If relapse occurs during the study, efgartigimod PH20 SC must be initiated. Participants who initiate efgartigimod PH20 SC must follow the SoA in Table 2 as of day X (refer to Section 6.3 for more details).

[c] When a participant is withdrawn from the study (for any reason listed in Section 7.2), study sites should make every effort to schedule the EDV within 7 days after the last contact with the participant and a safety follow-up visit 8 weeks after the previous contact.

[d] A UNS may be performed if the participant has (or suspects they have) new BP lesions or other issues requiring site staff intervention, such as notable weight change. At these visits, the investigator will determine whether efgartigimod PH20 SC therapy must be started/resumed and will decide which assessments to conduct based on the purpose of the UNS. If relapse occurs, IGA-BP, BPDAI, and itch NRS assessments must be performed.

[e] The urine pregnancy test is only applicable to WOCBP.

Table 2: Schedule of Activities for Participants Who Roll Over or Initiate Efgartigimod PH20 SC After Protocol Amendment 2 Is Effective, and Participants Who Stopped Receiving Efgartigimod PH20 SC After Roll Over but Before Protocol Amendment 2 Is Effective

Study period	**Baseline/ rollover (W0)[a]**	**Day X[b]**	**Treatment period**					**Observation period[c]**		**Follow-up period**		**Other visits**		**Applicable protocol section(s)**
Study week(s)			**W1**	**W2**	**W4**	**W8**	**Every 4 W until EFG stop**	**Every 8 W after EFG stop**	**W48/ EoTP**	**F1[d]**	**F2**	**EDV[e]**	**UNS[f]**	
Visit timing (relative to day X, where applicable)		**X**	**+1 W**	**+2 W**	**+4 W**	**+8 W**	**+ Every 4 W**	**+ Every 8 W**	**W48**	**EoTP +4 W**	**EoTP +8 W**			
Visit windows			**±2 d**	**±2 d**	**±2 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±3 d**	**±3 d**			
Eligibility (baseline only)														
Informed consent	X													Section 10.1.3
Eligibility check	X													Section 5.1 Section 5.2
Safety														
Physical examination (complete)	X	X[g]							X			X		Section 8.3.1
Physical examination (brief)						X	Every 16 weeks	Every 16 weeks [h,i]		X	X		X	Section 8.3.1
Weight[j]	X	X[j]		X[j]	X[j]	X	X[j]	X	X			X	X	Section 8.3.1
Vital sign measurements	X	X		X	X	X	X	X	X	X	X	X	X	Section 8.3.1
ECG	X						Week 24	Week 24[i]	X			X		Section 8.3.3
Urine pregnancy test[k]	X	X			X	X	X	Every 4 weeks[h]	X	X	X	X		Section 8.3.5

Study period	**Baseline/ rollover (W0)[a]**	**Day X[b]**	**Treatment period**					**Observation period[c]**		**Follow-up period**		**Other visits**		**Applicable protocol section(s)**
Study week(s)			**W1**	**W2**	**W4**	**W8**	**Every 4 W until EFG stop**	**Every 8 W after EFG stop**	**W48/ EoTP**	**F1[d]**	**F2**	**EDV[e]**	**UNS[f]**	
Visit timing (relative to day X, where applicable)		**X**	**+1 W**	**+2 W**	**+4 W**	**+8 W**	**+ Every 4 W**	**+ Every 8 W**	**W48**	**EoTP +4 W**	**EoTP +8 W**			
Visit windows			**±2 d**	**±2 d**	**±2 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±3 d**	**±3 d**			
Urinalysis	X	X		X	X	X	X	X	X	X	X	X	X	Table 7
Clinical chemistry and hematology	X	X		X	X	X	X	X	X	X	X	X	X	Table 7
GTI assessments (GTI-AIS, GTI-CWS, GTI-SL)	X					X	Every 16 weeks	Every 16 weeks [h,i]	X			X		Section 8.3.6
Concomitant therapies/procedures	Continuous monitoring													Section 6.9
AE monitoring	Continuous monitoring													Section 8.4
Substudy (selected sites): photography of BP lesions	(X)													NA
Efficacy/disease monitoring														
Disease assessment	X	X		X	X	X	X	X	X	X	X	X	X	Section 8.2.1.1
IGA-BP	X	X		X	X	X	X	X	X	X	X	X	X	Section 8.2.1.2
BPDAI	X	X		X	X	X	X	X	X	X	X	X	X	Section 8.2.1.3
Itch NRS	X	X		X	X	X	X	X	X	X	X	X	X	Section 8.2.1.4
Blood sample collection														

Study period	**Baseline/ rollover (W0)[a]**	**Day X[b]**	**Treatment period**					**Observation period[c]**		**Follow-up period**		**Other visits**		**Applicable protocol section(s)**
Study week(s)			**W1**	**W2**	**W4**	**W8**	**Every 4 W until EFG stop**	**Every 8 W after EFG stop**	**W48/ EoTP**	**F1[d]**	**F2**	**EDV[e]**	**UNS[f]**	
Visit timing (relative to day X, where applicable)		**X**	**+1 W**	**+2 W**	**+4 W**	**+8 W**	**+ Every 4 W**	**+ Every 8 W**	**W48**	**EoTP +4 W**	**EoTP +8 W**			
Visit windows			**±2 d**	**±2 d**	**±2 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±3 d**	**±3 d**			
Immunogenicity	X	X			X	X	Every 8 weeks	X	X	X	X	X	X	Section 8.9
PD (anti-BP180, anti-BP230[redacted])	X	X		X	X	X	X	X	X	X	X	X	X	Section 8.6
PK	X													NA
Substudy: vaccination antibody titers (serum)	Relative to the time of vaccination in ARGX-113-2009													Section 8.3.4
Substudy: vaccination antibody titers (PBMCs)	Relative to the time of vaccination in ARGX-113-2009													Section 8.3.4
Other														
Efgartigimod PH20 SC administration[l]	Once weekly								X if applicable					Section 6.3
Efgartigimod PH20 SC (self-)administration refresher training[m]	At least once during the study													Section 6.5

Study period	**Baseline/ rollover (W0)[a]**	**Day X[b]**	**Treatment period**					**Observation period[c]**		**Follow-up period**		**Other visits**		**Applicable protocol section(s)**
Study week(s)			**W1**	**W2**	**W4**	**W8**	**Every 4 W until EFG stop**	**Every 8 W after EFG stop**	**W48/ EoTP**	**F1[d]**	**F2**	**EDV[e]**	**UNS[f]**	
Visit timing (relative to day X, where applicable)		**X**	**+1 W**	**+2 W**	**+4 W**	**+8 W**	**+ Every 4 W**	**+ Every 8 W**	**W48**	**EoTP +4 W**	**EoTP +8 W**			
Visit windows			**±2 d**	**±2 d**	**±2 d**	**±7 d**	**±7 d**	**±7 d**	**±7 d**	**±3 d**	**±3 d**			
Monitoring of concurrent BP therapy (Definitions of Terms)	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.9 Section 8.2.1.1
QoL questionnaires (EQ-5D-5L, DLQI, ABQoL)	X					X	Every 16 weeks	Every 16 weeks [h,i]	X			X		Section 8.2.2

ABQoL=Autoimmune Bullous Disease Quality of Life questionnaire; AE=adverse event; BP=bullous pemphigoid; BPDAI=Bullous Pemphigoid Disease Area Index; CR=complete remission; DLQI=Dermatology Life Quality Index; ECG=electrocardiogram; eCRF=electronic case report form; EDV=early discontinuation visit; EFG=efgartigimod PH20 SC; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; EoTP=end-of-treatment period (visit); F1/F2=follow-up visits 1 and 2; GTI=Glucocorticoid Toxicity Index; GTI-AIS=GTI Aggregate Improvement Score; GTI-CWS=GTI Cumulative Worsening Score; GTI-SL=GTI Specific List; IGA-BP=Investigator Global Assessment of Bullous Pemphigoid; [redacted] NA=not applicable; NRS=numerical rating scale; OCS=oral corticosteroids; PBMC=peripheral blood mononuclear cell; PD=pharmacodynamics; PK=pharmacokinetics; PR=partial remission; QoL=quality of life; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous; SoA=schedule of activities; UNS=unscheduled visit; W=week

Note: Assessments indicated in gray font will only be recorded on the ARGX-113-2009 eCRF and not on the ARGX-113-2010 eCRF.

[a] The baseline visit will occur on the same day as the EoTP visit of ARGX-113-2009. All baseline assessments will be performed before administration of efgartigimod PH20 SC. Assessments do not need to be repeated if performed as part of the ARGX-113-2009 EoTP visit.

[b] Day X applies when efgartigimod PH20 SC is initiated (refer to Section 6.3). Efgartigimod PH20 SC treatment will be started on day X, which can be the same day as the day the relapse is confirmed. Subsequent visits will be relative to day X, except for the EoTP visit that will take place 48 weeks after baseline for all participants.

[c] Participants who stopped receiving efgartigimod PH20 SC after rollover but before protocol amendment 2 is effective will enter the observation period with visits every 8 weeks. Efgartigimod PH20 SC will be initiated at the investigator's discretion or if relapse occurs during the study. Participants who initiate efgartigimod PH20 SC must follow the SoA in Table 2 as of day X (refer to Section 6.3 for more details).

[d] Visit F1 (EoTP + 4 weeks) is only applicable for participants receiving efgartigimod PH20 SC at week 48.

[e] When a participant permanently discontinues IMP and/or is withdrawn from the study during the treatment period, study sites should attempt to perform the EDV within 7 days after the participant's final IMP administration and safety follow-up visits 4 and 8 weeks after the participant's final IMP administration. If a participant is withdrawn from the study during the observation period, refer to the SoA in Table 1.

[f] A UNS may be performed if the participant has (or suspects they have) new BP lesions or other issues requiring site staff intervention, such as notable weight change. At these visits, the investigator will determine whether efgartigimod PH20 SC therapy must be started/resumed and will decide which assessments to conduct based on the purpose of the UNS. If relapse occurs, IGA-BP, BPDAI, and itch NRS assessments must be performed.

[g] A brief physical examination should be performed instead of a complete examination if the participant had a complete physical examination ≤4 weeks before day X.

[h] Brief physical examinations, GTI, and QoL will be assessed every 16 weeks relative to the last performed assessment. WOCBP will have urine pregnancy tests every 4 weeks relative to the last performed assessment.

[i] If the time point of the assessment does not coincide with a planned on-site visit, the assessment should be performed at the next on-site visit.

[j] Weight must be measured only if the participant is being administered OCS.

[k] The urine pregnancy test is only applicable for WOCBP. The pregnancy test at the F2 visit is only applicable for participants on efgartigimod PH20 SC at EoTP/EDV.

[l] Efgartigimod PH20 SC will be administered once weekly [redacted] (on days 1 and 8 of treatment) and weekly maintenance doses of 1000 mg will be used. Refer to Section 6.3 for more information and to Section 6.5 for information about (self-)administration. Week 48 is the last time point that participants may receive doses of efgartigimod PH20 SC.

[m] Participants and/or their caregivers will be invited to receive at least 1 refresher training course for efgartigimod PH20 SC (self-)administration. Training may continue or be repeated until the participant (or caregiver) is considered capable of performing the (self-)administration.

2. INTRODUCTION

ARGX-113-2010 intends to demonstrate that efgartigimod PH20 SC is a safe and effective long-term treatment for BP, providing symptom control and eventually remission, while also reducing the cumulative exposure to OCS. Additionally, the study will evaluate if long-term treatment with efgartigimod PH20 SC can prevent relapse.

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 has been approved by the US Food and Drug Administration for use in adult patients with acetylcholine receptor antibody-seropositive gMG, and is also being clinically developed in other autoimmune diseases mediated by pathogenic IgG autoantibodies.

Efgartigimod may be a viable treatment option for individuals with BP, an autoimmune disease mediated by IgG autoantibodies, because it has been shown to reduce IgG levels, including IgG autoantibodies.

2.2. Background

BP is a subepidermal AIBD that predominantly affects older adults. It is a chronic disease that significantly affects morbidity and QoL; additionally, the disease can worsen spontaneously, even when the patient is treated with the current standard of care. The pathogenesis of BP is driven by IgG and IgE autoantibodies against the hemidesmosomal proteins BP180 and BP230, acting as key antigens for pathogenic autoantibodies. These pathogenic autoantibodies are understood to result in direct interference of autoantigen adherence, activation of complement, recruitment of inflammatory cells (eg, eosinophils), and release of proteolytic enzymes, causing skin blistering and pruritus. IgG autoantibodies against BP180 and BP230 have been demonstrated to induce BP-like symptoms in animal models, and disease activity is associated with serum levels of anti-BP180 autoantibodies.[2,3]

At this time, no results from registrational clinical studies with therapies specifically developed for the treatment of patients with BP are available. The current standard of care for BP is treatment with TCS or OCS, either of which can be combined with conventional immunosuppressant therapy. Unfortunately, corticosteroid therapy in patients with BP typically causes comorbidities, which can be severe and even life-threatening, especially in older adults. As a result, patients with BP have a higher mortality rate than their peers, even when their disease is being treated. Alternative therapies targeting IgG (eg, IV administration of immunoglobulin, plasma exchange, or protein A immunoadsorption) or biologics (eg, rituximab, omalizumab) have shown potential in small numbers of patients with BP. However, the efficacy and safety of these treatments have not been assessed in registrational studies.[4,5,6]

In summary, there is currently an unmet medical need for new BP treatments that provide rapid CDA and remission, minimize or prevent relapse, and reduce the burdens placed on patients caused by cumulative corticosteroid exposure. This OLE study aims to evaluate the safety, tolerability, long-term efficacy, immunogenicity, PRO measures, and PD of efgartigimod PH20 SC in adult participants with BP, who completed the antecedent study ARGX-113-2009.

A detailed description of the chemistry, pharmacology, efficacy, and safety of efgartigimod PH20 SC is provided in the current IB.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of efgartigimod PH20 SC is provided in the current IB.

2.3.1. Risk Assessment

Overall, available data confirm that efgartigimod—both as an IV formulation and as efgartigimod PH20 SC—has been well tolerated across studies in different indications and has an acceptable safety profile.

Table 3 lists the potential risks that may be encountered in the study and the associated strategies to mitigate these risks.

Table 3: Potential Risks and Mitigation Strategies

Potential clinically significant risk	Summary of data/rationale for risk	Mitigation strategy
Serious infection	Efgartigimod reduces IgG levels, potentially hindering immune response and increasing the risk for infection.	Exclude participants with clinically significant active infection not sufficiently resolved in the investigator's opinion (Section 5.2). Infections are considered AESIs (Section 8.4.6). Monitor for infections and temporarily interrupt IMP dosing as specified in Section 7.1. Recommendations for measures before and during the study are provided in Section 8.3.7.
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. Overall, the frequency of infusion/injection-related reactions in the studies was low. Pretreatment to prevent an infusion/injection-related reaction is not required.	Participants for whom efgartigimod PH20 SC is administered at the site will be monitored for infusion/injection-related reactions. Participants and/or their caregivers who receive training on self-administration will be educated on symptoms of infusion/injection-related reactions. Infusion/injection-related reactions are considered AEs of clinical interest (Section 8.4.7).

Potential clinically significant risk	Summary of data/rationale for risk	Mitigation strategy
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. Localized injection site reactions have been observed in studies with efgartigimod and PH20 and administered SC	Continuously monitor participants for injection site reactions when treatment is administered on-site. Injection site reactions are considered AEs of clinical interest (Section 8.4.7).
Potential complications from exposure to OCS	OCS are considered a first-line therapy for patients with moderate-to-severe BP; however, these drugs cause various adverse side effects. Therefore, a therapeutic goal in the treatment of patients with BP is a reduction in OCS exposure.	Rapidly taper OCS doses based on the clinical status of the participant (Section 6.3). Continuously monitor safety, including glucocorticoid-mediated toxicity, throughout the study (Section 8.3.6). Provide prophylactic and supportive care to diminish the expected side effects of OCS (ie, antiosteoporotic treatments, calcium supplements and vitamin D) are allowed in the study.
Older adult population	Patients with BP are typically older adults who can have comorbidities that result in a general poorer condition compared to the general population.	The investigator will assess if it is appropriate for the participant to be included in the study (Section 5.2, criterion 1).

AE=adverse event; AESI=adverse event of special interest; BP=bullous pemphigoid; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IgG=immunoglobulin gamma; OCS=oral corticosteroid; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous

2.3.2. Benefit Assessment

Efgartigimod—either as an IV formulation or as efgartigimod PH20 SC—has been investigated in nonclinical studies, phase 1 clinical pharmacology studies in healthy participants, and phase 2-3 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 reduced 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 a phase 2 study in primary ITP (ARGX-113-1603), in which pathogenic autoantibodies underlie the disease pathology (refer to the current efgartigimod IB). The available clinical data support the clinical benefit of

efgartigimod for reducing pathogenic IgG autoantibodies in participants with autoimmune diseases mediated by IgG autoantibodies, such as BP, which may result in clinical or even sustained remission.

In this study, efgartigimod PH20 SC can be administered alone or in combination with OCS. When efgartigimod PH20 SC is administered in combination with OCS, rapid OCS tapering based on the participant's clinical status will reduce the risks associated with those medications, especially high doses of OCS administered in the older adult study population, which is especially prone to comorbidities.

2.3.3. Overall Benefit-Risk Conclusion

The favorable balance between the risks and anticipated efficacy/benefits supports the administration of efgartigimod PH20 SC to participants with BP in ARGX-113-2010.

More detailed information about the known and expected benefits and risks of efgartigimod, both as an IV formulation and as efgartigimod PH20 SC, and reasonably expected AEs is provided in the current IB.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 4: Study ARGX-113-2010 Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the long-term safety and tolerability of treatment with efgartigimod PH20 SC in participants with BP	• Incidence and severity of treatment-emergent AEs, SAEs, and AESIs • Rate of treatment discontinuation because of safety concerns
Secondary	
To assess the long-term efficacy and durability of response with efgartigimod PH20 SC treatment in participants with BP	• Proportions of participants achieving[a]: – CR while off OCS for ≥8 weeks – CR or PR while off OCS for ≥8 weeks – CR while on minimal OCS therapy for ≥8 weeks. (Minimal OCS therapy is defined as ≤0.10 mg/kg/day of prednisone [or an equivalent dose of another OCS]) – CR while off both OCS and efgartigimod PH20 SC for ≥8 weeks[b] – CR or PR while off both OCS and efgartigimod PH20 SC for ≥8 weeks[b] • Duration of sustained remission • Proportion of participants who relapse • Time to relapse • Incidence and severity of relapse • BPDAI activity scores, IGA-BP scores, and itch NRS over time • Rate of treatment failure
Additional secondary	
To evaluate the impact of efgartigimod PH20 SC treatment in reducing long-term glucocorticoid-associated toxicity in participants with BP	GTI-related scores, including the GTI-AIS, GTI-CWS, and GTI-SL over time
To evaluate the impact of efgartigimod PH20 SC treatment on QoL in participants with BP	EQ-5D-5L, DLQI, and ABQoL scores over time
To evaluate the PD and immunogenicity of efgartigimod PH20 SC in participants with BP	• Percent change from baseline over time for anti-BP180 and anti-BP230 antibody levels • Incidence and prevalence of ADA against efgartigimod (serum levels)

Objectives	Endpoints
Exploratory	
[redacted]	[redacted]

[a] These endpoint criteria can only be met when participants are off rescue therapy.
[b] The endpoint applies only to participants who have stopped receiving efgartigimod PH20 SC before protocol amendment 2 is effective.

No estimands have been defined for this OLE study.

4. STUDY DESIGN

4.1. Overall Design

This is a phase 3, open-label, prospective, global, multicenter, OLE study.

The total study duration is approximately 56 weeks comprising a treatment period of up to 48 weeks and a follow-up of approximately 8 weeks.

The study population is adult patients with BP who have completed ARGX-113-2009.

At rollover, all participants will receive efgartigimod PH20 SC after this amendment is effective. The treatment allocation of ARGX-113-2009 will remain blinded (refer to Section 6.4).

Participants who received placebo in ARGX-113-2009 and participants who have reinitiated efgartigimod PH20 SC treatment will receive [redacted] of efgartigimod PH20 SC [redacted] (on days 1 and 8) followed by once-weekly maintenance doses of efgartigimod PH20 SC1000 mg.

Participants who received efgartigimod PH20 SC in ARGX-113-2009 will continue to receive once-weekly efgartigimod PH20 SC 1000 mg maintenance doses.

In the previous protocol version (v2.0), participants had to stop receiving efgartigimod PH20 SC after achieving CR or PR while off concurrent BP therapy for ≥8 weeks. For these participants, reinitiation of efgartigimod PH20 SC treatment will be at the investigator's discretion unless the participant relapses. Participants who relapse will initiate efgartigimod PH20 SC treatment (more details are provided in Section 6.3).

Participants will visit the site at weeks 0 (baseline), 1, 2, 4, and 8. Thereafter, participants will attend site visits every 4 weeks. Participants not receiving efgartigimod PH20 SC will attend site visits every 8 weeks.

The OLE study will remain open in all countries for a maximum of 2 years after completion of ARGX-113-2009.

4.2. Scientific Rationale for Study Design

This is an open-label study to evaluate the long-term safety, tolerability, efficacy, QoL, PD, and immunogenicity of efgartigimod PH20 SC in adult participants with BP who have completed ARGX-113-2009, and to evaluate whether participants can achieve sustained remission after stopping efgartigimod PH20 SC treatment.

This study provides the option to all eligible participants to continue (ARGX-113-2009 efgartigimod PH20 SC arm) or initiate (ARGX-113-2009 placebo arm) efgartigimod PH20 SC.

Participants who discontinued IMP (efgartigimod PH20 SC or placebo) and required rescue therapy in ARGX-113-2009 are eligible for this study. They will initiate efgartigimod PH20 SC, and rescue therapy will be tapered or discontinued (refer to Section 6.9.2). IMP will be permanently discontinued if the investigator considers it not to be in the participant's best interest to taper or discontinue rescue therapy or initiate efgartigimod PH20 SC.

Measures are in place to ensure the blinded allocation (efgartigimod PH20 SC or placebo) from ARGX-113-2009 is maintained (Section 6.3 and Section 6.4).

The primary outcome measure is the ongoing safety and tolerability of open-label efgartigimod PH20 SC for approximately 1 year (long-term) after completing ARGX-113-2009. The endpoints aim to demonstrate that efgartigimod PH20 SC is a safe long-term treatment option for BP. The safety and tolerability endpoints for this study are considered to be standard for any clinical study evaluating the safety of an IMP.

Secondary endpoints aim to demonstrate that efgartigimod PH20 SC treatment can provide symptom control and eventually remission for patients with BP, while also reducing the cumulative exposure to OCS. These endpoints are in line with the efficacy endpoints in ARGX-113-2009 and are selected based on the disease terminology described by Murrell et al (2012).[1]

4.3. Justification for Dose

In ARGX-113-2010, efgartigimod will be administered as SC injections because they are easier to administer than IV infusions and offer convenience for participants with BP, their caregivers, and health care providers. Additionally, the coformulation of efgartigimod with rHuPH20 permits SC dosing of higher volumes than typical SC injections with limited skin swelling or pain.

The dosing regimens in ARGX-113-2010 follow the same principles as in ARGX-113-2009. In ARGX-113-2009, participants in the efgartigimod PH20 SC arm received [redacted] of [redacted] (on days 1 and 8 of treatment) followed by maintenance doses of 1000 mg. The regimen aimed to achieve a nearly maximal reduction in total IgG serum levels at the start of the treatment followed by a convenient maintenance dose equivalent to a weekly dose of efgartigimod IV 10 mg/kg which has proven efficacy in the treatment of other autoimmune diseases (gMG and ITP). For more information, refer to the current efgartigimod IB.

Treatment allocation in ARGX-113-2009 will remain blinded in ARGX-113-2010 until the database lock of ARGX-113-2009 (refer to Section 6.4).

Efgartigimod PH20 SC can be provided in combination with tapering courses of concurrent BP therapy (Definitions of Terms) to reduce the risks associated with those medications, especially high doses of OCS, in the older adult participant study population who are especially prone to comorbidities.

4.4. End-of-the-Study Definition

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

A participant is considered to have completed the study if the follow-up visit at EoTP + 8 weeks 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 can be included in the study only if all of the following criteria apply:

1. Has completed the week 36 visit of ARGX-113-2009
2. Is capable of providing signed informed consent, as described in Section 10.1.3, and complying with protocol requirements
3. Agrees to use contraceptive measures consistent with local regulations and the following:
   a. Male participants (contraceptive measures provided in Section 10.4.2.2)
   b. WOCBP (defined in Section 10.4.1) must have a negative urine pregnancy test at baseline before receiving IMP. (Section 10.4.2.1)

5.2. Exclusion Criteria

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

1. Clinically significant disease, recent major surgery (within 3 months of baseline), or intention to have surgery during the study; or any other medical condition that, in the investigator's opinion, would confound the results of the study or put the participant at undue risk
2. Known hypersensitivity to IMP or 1 of its excipients
3. Permanently discontinued IMP in ARGX-113-2009 due to an AE considered related to IMP and for whom the benefit/risk balance is not considered positive

5.3. Lifestyle Considerations

Participants will not be required to restrict or limit any of their normal lifestyle activities (eg, food and drink consumption; caffeine, tobacco, or alcohol consumption; exercise or physical activity) during this study.

5.4. Screen Failures

Not applicable.

5.5. Criteria for Temporarily Delaying Enrollment/IMP Administration

If IMP was temporarily interrupted at the time of the week 36/EoTP visit in ARGX-113-2009 (because of any reason as described in the ARGX-113-2009 protocol), participants can roll over to ARGX-113-2010 and have to follow the SoA per Table 1 until the investigator has determined that it is safe for the participant to receive treatment. If the participant requires treatment with efgartigimod PH20 SC, they must follow SoA per Table 2 as of day X.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

All IMP is manufactured according to Good Manufacturing Practice regulations.

6.1. Investigational Medicinal Product Administered

In addition to the IMP, OCS will be provided by the sponsor as outlined in Table 5. TCS and rescue treatment will not be provided by the sponsor.

Table 5: Study Intervention(s) Administered

Intervention label	Efgartigimod PH20 SC	Placebo PH20 SC	Oral OCS (prednisone or equivalent)
Intervention name	Efgartigimod for SC administration coformulated with rHuPH20	Vehicle + rHuPH20	Prednisone or equivalent tablets for oral administration
Intervention description	[redacted] SC doses administered [redacted] on days 1 and 8 of the treatment Maintenance doses of 1000 mg SC administered once weekly Refer to Section 6.3	SC dose administered at [redacted] as the efgartigimod SC dose on days 1 and 8 (if applicable) Refer to Section 6.3	Initiated and adjusted according to the investigator's clinical judgment Refer to Section 6.3
Type	Biologic	Placebo	NIMP/AxMP, concurrent therapy
Dose formulation	Solution for SC injection	Solution for SC injection	Prednisone (or equivalent) tablets for oral administration
Unit dose strength(s)	Efgartigimod 180 mg/mL rHuPH20 2000 U/mL	rHuPH20 2000 U/mL	Prednisone 2.5 mg, 5 mg, 10 mg, and/or 20 mg (or equivalent)
Dosage level(s)	Refer to Section 6.3	Refer to Section 6.3	Adjusted according to the investigator's clinical judgment
Route of administration	SC injection	SC injection	Oral administration
Use	Experimental	Placebo	Concurrent therapy
IMP and NIMP/AxMP	IMP	IMP	NIMP/AxMP

Intervention label	Efgartigimod PH20 SC	Placebo PH20 SC	Oral OCS (prednisone or equivalent)
Sourcing	Centrally by the sponsor	Centrally by the sponsor	Provided by the sponsor to the site Local sourcing is permitted only if no doses are available at the site and only after consultation with the sponsor (or designee)
Packaging and labeling	IMP will be provided in glass vials. Each vial will be labeled per country requirements.	IMP will be provided in glass vials. Each vial will be labeled per country requirements.	NIMP/AxMP will be provided as 1 of the following: In the commercial package and labeled as required per country requirements, or As a magistral preparation upon prescription by the investigator, or In the commercial package sourced locally
Former name	ARGX-113	Not applicable	Not applicable

AxMP=auxiliary medicinal product; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IMP=investigational medicinal product; NIMP=noninvestigational medicinal product; OCS=oral corticosteroids; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous

6.2. Preparation, Handling, Storage, and Accountability

- The IMP will be supplied to the investigational site by the sponsor's designated IMP supply vendor.
- The pharmacy manual provides detailed instructions on the preparation, handling, storage, accountability, and disposition of unused IMP.
- The investigator or designee is responsible for the correct and safe storage of 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.
- Only participants enrolled in the study are permitted to receive IMP, and only authorized site staff or designee are allowed to supply IMP.

- IMP must be stored in secondary packaging, refrigerated (2 °C to 8 °C) and protected from direct sunlight. Do not shake IMP or expose it to freezing temperatures.
- In exceptional cases, IMP, other BP therapies, and ancillaries may be shipped to participants by courier.

6.3. Assignment to Study Intervention

The following general principles apply to all participants. These principles apply to the specific situations described in Section 6.3.1 and Section 6.3.2 unless mentioned otherwise.

- Efgartigimod PH20 SC can be initiated until week 45 to ensure a minimum of 4 weeks of treatment.
- Efgartigimod PH20 SC should be initiated without concurrent OCS if the participant's BP disease status permits it, according to the investigator's clinical judgment.
- Localized lesions should be treated with TCS before concurrent OCS treatment is considered, if possible.
- If there is no improvement in the participant's BP disease status and additional BP therapy is required while receiving efgartigimod PH20 SC, concurrent OCS treatment may be initiated according to the investigator's clinical judgment. Recommendations for OCS therapy initiation and tapering are provided in Section 6.9.1.
- As described in Section 6.9.2, rescue therapy will be tapered or discontinued in participants who received it in ARGX-113-2009. IMP will be permanently discontinued if the investigator considers it not to be in the participant's best interest to taper or discontinue rescue therapy.

6.3.1. Participants Who Roll Over After Protocol Amendment 2 Is Effective

Situation 1: At roll over to this study

These participants will receive efgartigimod PH20 SC while maintaining the ARGX-113-2009 blinded treatment allocation of IMP (refer to Section 6.4).

- Participants in the placebo arm in ARGX-113-2009 will receive [redacted] of efgartigimod PH20 SC 1000 mg ([redacted] efgartigimod PH20 SC [redacted] on days 1 and 8, followed by once-weekly injections of efgartigimod PH20 SC 1000 mg.
- Participants in the efgartigimod PH20 SC arm in ARGX-113-2009 will receive [redacted] followed by once-weekly injections of efgartigimod PH20 SC 1000 mg.

Situation 2: During this study's treatment period

Participants will continue receiving efgartigimod PH20 SC and may receive TCS or concurrent OCS according to the investigator's clinical judgment (refer to Section 6.9.1).

6.3.2. Participants Who Are Ongoing in This Study When Protocol Amendment 2 Is Effective

Situation 3: Participants not receiving efgartigimod PH20 SC when protocol amendment 2 is effective

3A: Participants who are not receiving any BP therapy (ie, these participants achieved CR or PR while off concurrent BP therapy for ≥8 weeks before protocol amendment 2 was effective)

- Once protocol amendment 2 is effective, efgartigimod PH20 SC may be initiated at the investigator's discretion. If the participant relapses and requires additional BP therapy, efgartigimod PH20 SC must be initiated ([redacted] on days 1 and 8 followed by once-weekly injections of efgartigimod PH20 SC 1000 mg).

3B: Participants who are being treated with rescue therapy that started in ARGX-113-2009

- Rescue therapy will be tapered or discontinued (refer to Section 6.9.2) and efgartigimod PH20 SC will be initiated ([redacted] on days 1 and 8 followed by once-weekly injections of efgartigimod PH20 SC 1000 mg).

Situation 4: Participants who are receiving efgartigimod PH20 SC when protocol amendment 2 is effective

4A: Participants who are receiving efgartigimod PH20 SC with or without concurrent OCS

- These participants will continue receiving efgartigimod PH20 SC and will continue their OCS tapering course.

4B: Participants who are receiving efgartigimod PH20 SC and who are receiving rescue therapy that started in ARGX-113-2009

- Rescue therapy will be tapered or discontinued (refer to Section 6.9.2) and efgartigimod PH20 SC treatment will be maintained.

6.4. Blinding

ARGX-113-2010 is open-label. The blinded allocation to efgartigimod PH20 SC or placebo from ARGX-113-2009 will be maintained until the database lock of ARGX-113-2009. Therefore, at rollover, participants receiving [redacted] on days 1 and 8 (Section 6.3) will receive [redacted] This will be handled via interactive response technology.

The blinding of IgG and immunogenicity data for ARGX-113-2010 will also be maintained until the database lock of ARGX-113-2009.

BP autoantibody data and albumin and total protein data collected from baseline through week 4 will remain blinded.

6.5. Study Compliance

IMP must be administered at the site for a minimum of 3 consecutive visits before (self-)administration of IMP by the participant or caregiver is allowed at home. Participants or

caregivers must also have completed (self-)administration training at the site during ARGX-113-2009 and be considered capable by the site of performing the (self-)administration.

At mandatory on-site visits, participants will receive IMP under medical supervision at the site. The date and time of each dose administered will be recorded in the source documents.

Participant compliance with IMP administration at home will be assessed by direct questioning during the on-site visit and documented in the source documents and relevant forms. Deviation(s) from the prescribed dosage regimen will be recorded.

6.6. Dose Modification

Dose modifications are not permitted.

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

At the end of the study, argenx cannot guarantee continued access for participants but will comply with all local laws and regulations.

6.8. Treatment of Overdose

Any variation of >10% of the intended weekly dose of efgartigimod PH20 SC will be considered an overdose.

The sponsor does not recommend specific treatment for an overdose.

If an overdose occurs, the investigator/treating physician 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, the quantity of the excess dose, and the overdose duration to the sponsor.

6.9. Prior and Concomitant Therapy

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 baseline or 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)
- Brand name (for vaccines only)

The following medications or treatments are not permitted as of when the ICF has been signed through the completion of the EoTP visit or EDV, as applicable:

- SC immunoglobulin

- IV immunoglobulin unless initiated as rescue therapy in ARGX-113-2009 (refer to Section 6.9.2)
- Plasma exchange
- Immunoadsorption
- Monoclonal antibodies:
  - Rituximab
  - Other anti-CD20 biologics
  - Other monoclonal antibodies
- Sulfasalazine
- Any systemic treatment for BP (eg, IV or intramuscular corticosteroids, systemic immunosuppressants) except OCS
- Complementary therapies, including traditional Chinese medicines, herbs, or procedures (eg, acupuncture) that may interfere with the study's efficacy assessments and/or potentially risk the safety of the participant
- Live or live-attenuated vaccines
- Any other systemic biologic agent or experimental/study IMP

6.9.1. Oral Prednisone Tapering and Escalation

Participants may receive concurrent therapy with OCS, ie, prednisone or an alternative OCS. If on OCS, the dosage will be adjusted according to each participant's BP disease status throughout the study. The goal is to taper systemic corticosteroid exposure rapidly.

Note: For the following list, "oral prednisone" refers to prednisone or an alternative OCS of equivalent dose strength.

- Participants who were receiving concurrent OCS in ARGX-113-2009 will continue their OCS tapering course, as outlined in this section.
- New treatment courses with oral prednisone may be initiated if there is a lack of clinical improvement in the participant's BP disease status and additional BP therapy is required. The starting dose of oral prednisone should be the lowest advisable dose and must not exceed 0.5 mg/kg/day. The choice of the starting dose within the specified range is at the investigator's discretion.
- Escalated doses of oral prednisone may be considered if the participant does not achieve CDA within 1 to 3 weeks of prednisone at or below 0.5 mg/kg/day. Participants who do not achieve CDA despite receiving efgartigimod PH20 SC with escalated dosages of OCS (0.75 mg/kg/day or higher) will be considered treatment failures (refer to the Definitions of Terms for a full description) and IMP will be permanently discontinued.
- When CDA is achieved, the oral prednisone dose regimen is adjusted based on the investigator's clinical judgment. Recommendations for tapering are as follows:

  - After CDA has been sustained for ≥2 weeks, the tapering schedule begins with the next lower oral prednisone dosage, as listed in Table 6. Each new dosage will be maintained for 2 weeks or less, based on the investigator's clinical judgment.

    Note: For participants with body weights <45 kg and ≥110 kg, the investigator should propose an OCS dose per the recommended doses in Table 6 and inform the medical monitor to ensure consistency in the study.

- The OCS dosage may be adjusted according to the investigator's clinical judgment if disease activity occurs during the OCS tapering.

Refer to Table 9 for concurrent oral methylprednisolone equivalent doses.

Notes:

- Prophylactic and supportive care to diminish the expected side effects of OCS (ie, antiosteoporotic treatments, calcium supplements and vitamin D) are allowed in the study.

Table 6: Concurrent Oral Prednisone Equivalent Doses (in mg) Based on Participant Body Weight

Oral prednisone dose level	Body weight category[a] (kg)													
	<45	≥45 to <50	≥50 to <55	≥55 to <60	≥60 to <65	≥65 to <70	≥70 to <75	≥75 to <80	≥80 to <85	≥85 to <90	≥90 to <95	≥95 to <100	≥100 to <105	≥105 to <110	≥110
	Minimum recommended daily OCS dose	Daily OCS dose[b]													Maximum recommended daily OCS dose
mg/kg/day		mg/day													
1.0	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110
0.75	30	30	35	40	45	45	50	55	60	60	65	70	75	75	80
0.50	20	22.5	25	25	30	30	35	35	40	40	45	45	50	50	60
0.30	12.5	12.5	15	15	17.5	17.5	20	22.5	22.5	25	25	25	30	30	40
0.20	7.5	7.5	10	10	10	12.5	12.5	15	15	15	17.5	17.5	20	20	25
0.15	5	5	7.5	7.5	7.5	7.5	10	10	10	12.5	12.5	12.5	15	15	17.5
Minimal OCS therapy: ≤0.10	2.5	2.5	5	5	5	5	5	7.5	7.5	7.5	7.5	7.5	10	10	12.5
mg/day		mg/day													
7.5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	7.5	7.5	7.5
5.0	NA	NA	NA	NA	NA	NA	NA	5	5	5	5	5	5	5	5
2.5	NA	NA	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Off OCS therapy: 0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

NA=not applicable; OCS=oral corticosteroids (oral prednisone or equivalent)
Note: Each new dosage will be maintained for 2 weeks or less, based on the investigator's clinical judgment.
[a] Body weight should be rounded to the nearest whole number.
[b] The investigator should not deviate from the concurrent oral prednisone dose levels specified in the table, except if the participant's safety could be compromised.

6.9.2. Rescue Therapy Tapering and Discontinuation

Once protocol amendment 2 is effective, newly enrolled and ongoing participants who receive rescue therapy started in ARGX-113-2009 will initiate or continue efgartigimod PH20 SC and rescue therapy will be tapered or discontinued. IMP will be permanently discontinued if the investigator considers it not to be in the participant's best interest to taper or discontinue rescue therapy or initiate efgartigimod PH20 SC (refer to Section 7.1.1).

Guidelines for rescue therapy types are as follows:

- Whole body TCS application should be stopped immediately.
- OCS used as rescue therapy should be tapered according to the instructions in Section 6.9.1.
- Immunosuppressants should be stopped immediately.
- Tetracyclines should be stopped immediately.
- IVIg should be stopped immediately and a 2-week washout period must be implemented before initiating efgartigimod PH20 SC.

7. IMP DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

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

7.1. IMP Discontinuation

7.1.1. Permanent Discontinuation

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

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

Unless consent from the study has been withdrawn, the participant will attend an EDV and safety follow-up visits on-site, as specified in the SoA (Section 1.3). Study sites should perform the EDV within 7 days after the participant's final IMP administration and safety follow-up visits 4 and 8 weeks after the participant's final IMP administration.

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

- Participant becomes pregnant or intends to become pregnant (refer to Section 8.3.5).
- Investigator decides that discontinuing IMP is in the participant's best interest (the sponsor will be informed).
- Participant develops an SAE or AE that contraindicates further administration of IMP in the investigator's opinion.
- Treatment failure (Definitions of Terms).
- Investigator decides to not initiate efgartigimod PH20 SC treatment at rollover or after relapse.
- Investigator considers tapering or discontinuing rescue therapy started in ARGX-113-2009 not to be in the participant's best interest.
- Any of the liver chemistry criteria resulting in temporary IMP discontinuation outlined in Section 7.1.2 is met, and the event is considered by the investigator to be related to IMP.
- Participant develops any of the following, based on the sponsor's determination of relatedness:
  - Any treatment-emergent AE of NCI CTCAE grade 4 considered related to IMP
  - Any treatment-emergent SAE of grade 3 considered related to IMP
  - Any infections of grade 3 or any serious infection considered related to IMP
- Participant develops any malignancy, either new or recurrent, other than basal cell carcinoma of the skin, regardless of relatedness to IMP.

7.1.2. Temporary Discontinuation

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

Reasons for temporary discontinuation may include any of the following:

- Any SAE considered related to IMP by the sponsor
- Clinically significant active infection considered related to IMP by the sponsor
- Any of the following liver chemistry laboratory results:
  - ALT or AST values >8 × ULN
  - ALT or AST values >5 × ULN sustained for more than 2 weeks
  - ALT or AST values >3 × ULN plus total bilirubin >2 × ULN
  - ALT or AST values >3 × ULN plus international normalized ratio >1.5
  - ALT or AST values >3 × ULN with the appearance of any of the following signs and symptoms of liver toxicity:
    - Fatigue
    - Nausea
    - Vomiting
    - Pain or tenderness in the upper-right quadrant of the abdomen
    - Fever
    - Rash
    - Eosinophilia (eosinophil count >5 × 10^8/L)

  Note: Participants with any of these events will have the laboratory tests repeated within 48 hours. These participants will also be evaluated to determine whether the cause of the liver enzyme elevation is a disease/condition other than toxicity related to study intervention (eg, viral hepatitis, preexisting or acute liver disease, or toxicity related to concomitant medications other than study intervention). If the event is considered by the investigator to be related to the IMP, treatment will be permanently discontinued (Section 7.1.1).

7.2. Participant Discontinuation/Withdrawal From the Study

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

The primary reason for permanent study withdrawal will be recorded.

If possible, an EDV and safety follow-up visit(s) should be conducted when the participant is withdrawn from the study. Study sites should make every effort to schedule the EDV and safety follow-up visit(s) as follows:

- Participants on efgartigimod PH20 SC treatment should attend the EDV 7 days after the participant's final IMP administration; the safety follow-up visits should occur 4 and 8 weeks after the participant's final IMP administration.
- Participants in the observation period should attend the EDV within 7 days after the last contact with the site and a safety follow-up visit 8 weeks after the previous contact.

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

- Participant withdrawal of consent
- Sponsor request
- Investigator request due to noncompliance with study protocol procedures

If the participant withdraws consent to participate in the study, the sponsor can retain and continue to use any data collected before consent was withdrawn. Future research on samples collected from participants who withdraw consent to participate in the study will not be affected unless the participant also withdraws the consent for future research.

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 SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is required for study conduct.
- Visits that must be attended at the site are baseline; weeks 1, 2, 4 and 8; and thereafter every 4 weeks while on efgartigimod PH20 SC treatment or every 8 weeks while off efgartigimod PH20 SC treatment (observation period), week 48 (EoTP), EoTP + 4 weeks for participants on efgartigimod PH20 SC treatment at week 48, and EoTP + 8 weeks for all participants.
- Weekly efgartigimod PH20 SC injections that are scheduled between mandatory on-site visits may be administered by a home nurse (either a nurse from the study site or a nurse from a commercial nursing vendor who is delegated by the investigator), the participant, or a caregiver (Section 6.5).
- Operational considerations related to the COVID-19 pandemic are provided in Section 10.5.

8.1. Administrative and General/Baseline Procedures

The baseline visit will occur on the same day as the EoTP visit of ARGX-113-2009. All baseline assessments will be performed before administration of efgartigimod PH20 SC. Assessments do not need to be repeated if they are performed as part of ARGX-113-2009.

8.1.1. Use and Storage of Biological Samples

After the protocol-defined laboratory analyses have been completed, any samples remaining 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. These samples may be used for future additional medical, academic, or scientific research to address any scientific questions related to efgartigimod, FcRn biology, or BP, unless prohibited by local regulations or the participant.

In addition, blood samples may be used to validate methods to measure efgartigimod, antibodies, and biomarkers. Participants must consent to having their samples used in this manner before such measurements are performed.

8.2. Efficacy Assessments

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

Investigators are trained in completing efficacy assessments. Instructions on completing PRO questionnaires are provided in the applicable study manuals.

8.2.1. Efficacy Measures

8.2.1.1. Assessment of BP Disease Status and OCS Dose Monitoring

The BP disease status will be assessed by the investigator at on-site visits according to the definitions/criteria presented in the Definitions of Terms. During these visits, the investigator will examine the participant for new lesions (transient or nontransient), record the daily concurrent BP therapy (if applicable) administered to the participant since the last visit, including the dose, adjust the daily OCS dose (taper, stop, reinitiate, or increase; if applicable) based on the participant's BP disease status, and record treatment failure.

8.2.1.2. Investigator Global Assessment of Bullous Pemphigoid

BP disease activity and severity will be assessed by the investigator using the IGA-BP, an assessment tool that was developed in 2021 by medical experts in the field of AIBDs. It is currently being used (along with the BPDAI) in other BP clinical studies. The IGA-BP categorizes the severity of BP on a numerical scale of 0 (clear) to 4 (severe).

8.2.1.3. Bullous Pemphigoid Disease Area Index

BP disease activity will be assessed by the investigator using the BPDAI.[3] The BPDAI is an internationally validated tool to objectively measure disease activity. The BPDAI differentiates scores for skin (erosions/blisters and urticaria/erythema) and mucous membrane activity in several anatomical locations. In addition, separate scores for damage (eg, pigmentation) are recorded to account for healing lesions.[1,3]

8.2.1.4. Itch Numerical Rating Scale

Participants will indicate pruritic symptoms of BP on the 11-point itch NRS (0 [no itch], 10 [worst itch imaginable]). An average and the worst score for itch suffered within the past 24 hours will be recorded.[7,8]

8.2.2. Quality of Life Assessments

Time points for all PRO assessments are provided in the SoA (Section 1.3). If the time point of the assessment does not coincide with a planned on-site visit, the assessment should be performed at the next on-site visit. Subsequent PRO assessments should then be calculated based on that last PRO assessment.

8.2.2.1. EQ-5D-5L

The EQ-5D-5L is a standardized measure of health status developed by the EuroQol Group to provide a simple, generic measure of health for clinical and economic appraisal.

The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems.

8.2.2.2. Dermatology Life Quality Index

The DLQI consists of 10 questions concerning the participant's perception of the impact of skin diseases on different aspects of their health-related QoL the previous week. The impact of each aspect on the QoL assessment is scored qualitatively, ranging from "not at all" to "very much."[9]

8.2.2.3. Autoimmune Bullous Disease Quality of Life Index

The ABQoL was developed and validated for determining the impact of AIBDs and their therapies on the daily lives of patients. The series of 17 questions concerns the participant's perceptions of how AIBD affects their daily lives, and includes comfort, hygiene, eating/drinking, appearance, social interactions, sexual activity, and employment.[10]

8.3. Safety Assessments

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

8.3.1. Vital Signs

- Body 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.

8.3.2. 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.

8.3.3. Electrocardiograms

ECGs will be performed according to instructions provided by a centralized ECG reading facility. At a minimum, interval data (PR, QT, QTcF, and QRS intervals); ventricular rate; and overall interpretation will be recorded for each ECG.

At all planned on-site visits per the SoA in Section 1.3, new clinically significant abnormal or worsened preexisting ECG abnormalities will be reported as AEs.

8.3.4. Protocol-Required Laboratory Tests

- Blood and urine samples will be analyzed at a central laboratory for serum chemistry and hematology, coagulation, urinalysis, serology (eg, viral marker testing), and specialty laboratory parameters (eg, PD, immunogenicity, vaccination substudy). In China, laboratory parameters will be analyzed using central and/or local laboratory facilities.

- Refer to Appendix 2 (Table 7) for the list of protocol-required laboratory tests to be performed and the SoA (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 considered by the investigator to be more severe than expected for the participant's condition.

8.3.4.1. Substudy—Vaccination Response

The vaccination substudy from ARGX-113-2009 will continue in this OLE study in participants who provided additional consent for collecting blood samples postvaccination and for whom this substudy has not been completed yet. Postvaccination samples may be collected for additional/optional/future vaccination research at the visits identified in the SoA (Section 1.3). Such research may include, but is not limited to, the following:

- Humoral (serum) responses to vaccinations received in ARGX-113-2009
- Cellular (peripheral blood mononuclear cells) responses to vaccinations received in ARGX-113-2009

Data obtained from this substudy will not be included in the clinical database; the results may be described in a separate report.

8.3.5. Pregnancy Testing

- WOCBP will be tested for pregnancy. Urine tests for pregnancy will occur at the time points specified in the SoA (Section 1.3).
- Home testing kits will be provided to the participants for urine pregnancy tests scheduled between mandatory on-site visits.
- Pregnancy testing in WOCBP will be conducted at the end of relevant systemic exposure, as specified in the SoA (Section 1.3).
- Additional pregnancy testing may be performed, as necessary by the investigator or as 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 to12 months after the baby's birth.

8.3.6. Glucocorticoid Toxicity Index

The GTI v2.0 is a complementary scoring system to the overall report of AEs that are considered related to glucocorticoids by investigators during interventional studies. It also enables the

monitoring of the long-term tolerability of glucocorticoids during their prolonged use during clinical practice.[11]

The GTI should be assessed per the SoA in Section 1.3. If the time point of the assessment does not coincide with a planned on-site visit, the assessment should be performed at the next on-site visit. Subsequent GTI assessments should then be calculated based on that last GTI assessment.

The GTI v2.0 consists of the following 2 instruments:

- The C-GTI serves as a primary instrument intended to capture toxicities that are likely related to glucocorticoid exposure. The C-GTI has 9 functional domains: body mass index, glucose control, blood pressure, lipid metabolism, bone mineral density, muscle strength, skin toxicity, neuropsychiatric effects, and infection. Each domain includes several weighted items that correspond to varying degrees of glucocorticoid toxicity.

  Note: The bone mineral density domain will not be used in this study. It is typically excluded from studies <1 year in duration, because bone densitometry is not sufficiently reliable in measuring changes over shorter durations.[11]

  Two analytical scores are generated from the weighted C-GTI items: the GTI-CWS and the GTI-AIS. The GTI-CWS is designed to assess cumulative glucocorticoid toxicity, and the GTI-AIS can be used to assess whether a new therapy is effective in reducing glucocorticoid toxicity over time. Together, the GTI-CWS and GTI-AIS provide complementary information about the ability of an investigational agent to reduce overall glucocorticoid toxicity.
- The GTI-SL captures well-known glucocorticoid-related side effects. This nonweighted instrument provides additional information for the domains most affected by glucocorticoid use during the participant's treatment. It comprises 11 domains (9 of which are shared with the C-GTI) and 23 items.

  Note: For the reason mentioned previously, the GTI-SL item covering bone mineral density decrease (part of the bone health domain) will not be used in this study.

8.3.7. Infections and Vaccinations

Patients with BP are susceptible to developing opportunistic infections. Concomitant and historical treatments by immunosuppressive or immunomodulatory therapies are comorbidity factors able to trigger or aggravate these infections.

The following measures are recommended during the study:

- Initiate or renew administration of non-live, inactivated, polysaccharide, or recombinant vaccines (eg, tetanus, hepatitis A, hepatitis B, shingles).
- Vaccinate participants who are especially prone to or have a history of respiratory infections against *Pneumococcus* or *Streptococcus pneumoniae*.
- Vaccinate participants with seasonal vaccines (eg, influenza virus), especially those entering the study in the winter months.
- Screen for possible infections (eg, respiratory, skin, mouth, eyes, nose and throat, genitals) and, if appropriate, initiate antibiotic treatment.

- Provide participants suffering from recurrent episodes of herpes simplex or herpes zoster with antiviral treatment throughout the treatment period of the study.

Any inactivated, subunit, polysaccharide, or conjugate vaccine will be allowed at the investigator's discretion and if it is administered at least 48 hours predose or 48 hours postdose of efgartigimod PH20 SC.

Any other preventive measure that may be considered for the safety of the participants can also be discussed on a case-by-case basis with the sponsor's medical monitor and designee before the participant enters the study.

Any vaccination received during the study should be recorded on the eCRF with the brand name of the vaccine and the date of vaccine administration.

8.3.8. Suicidal Ideation and Behavior Monitoring

Not applicable.

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

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

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

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

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

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

All AEs will be collected from the signing of the ICF until the EoTP + 8 weeks visit, as specified in the SoA (Section 1.3).

All SAEs and AESIs will be recorded and reported to the sponsor or designee immediately, and under no circumstance will this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including death, at any time after a participant has been discharged from the study, and they consider the event to be reasonably related to IMP or study participation, the investigator must promptly notify the sponsor.

8.4.2. Method of Detecting AEs and SAEs

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

8.4.3. Follow-up of AEs and SAEs

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

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of 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, 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 of a participant, 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 event of scientific and medical concern specific to the sponsor's product or program. An AESI can be serious or nonserious, related or not related to the IMP or study procedures. These events will be reported according to the same time frame 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 in the MedDRA SOC *Infections and infestations* are considered AESIs in this study. These events will be reported according to the time frame 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.

Refer to the current IB for more information on infusion/injection-related reactions.

8.4.7.2. Injection Site Reactions

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

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

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

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

8.5. Pharmacokinetics

Pharmacokinetics are not evaluated in this study.

8.6. Pharmacodynamics

Baseline and postbaseline PD blood samples will be collected predose on IMP administration visits (preferably within 2 hours before IMP administration) as described in the SoA (Section 1.3).

Anti-BP180 antibodies, anti-BP230 antibodies, [redacted] will be determined using validated assays.

PD blood samples may be used for methodology validation and/or for future research purposes (Section 8.1.1). Such use of these samples is only permitted after obtaining consent from the participant.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Blood samples will be collected at the time points indicated in the SoA (Section 1.3), predose on IMP administration visits (preferably within 2 hours before IMP administration), to evaluate serum levels of ADA against efgartigimod and plasma levels of antibodies against rHuPH20. Samples to determine plasma levels of antibodies against rHuPH20 will be collected and stored and will be analyzed in case of safety concerns.

Samples will be analyzed by the designated laboratory in a tiered approach using validated immunogenicity assays.[12] 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, and a neutralizing antibody assay will be performed to assess the antibodies for neutralizing activity (tier 3).

Immunogenicity blood samples may be used for methodology validation and/or for future research purposes (Section 8.1.1). Such use of these samples is only permitted after obtaining consent from the participant.

8.10. Health Economics and Medical Resource Utilization

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

9. STATISTICAL CONSIDERATIONS

The SAP will be finalized before database lock and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.1. Statistical Hypotheses

No formal hypothesis testing will be conducted in this open-label study.

9.2. Analysis Sets

The following analysis sets are defined:

Analysis set	Description
Rollover set	All participants who rolled over from ARGX-113-2009
Safety set	All participants exposed to IMP
Per protocol set	No per protocol set is defined. *Note: Important protocol deviations will be summarized in a table and presented in a listing.*

Additional analysis sets and/or populations may be further defined in the SAP.

9.3. Statistical Analyses

9.3.1. General Considerations

- Descriptive statistical methods will be used to analyze all primary and secondary endpoints. For continuous variables, summaries will include the number of observations (n), mean, SE, 95% CI, median, minimum, and maximum. For categorical variables, summaries will include the number of participants, frequencies, and percentages. No inferential analyses are foreseen.
- AEs will be classified using the latest version of the MedDRA classification system.
- AEs, AESIs, and SAEs will be listed corresponding to MedDRA SOC and PT.
- All AEs will be summarized by relatedness to efgartigimod PH20 SC.
- Any AEs leading to death or discontinuation of efgartigimod PH20 SC will be summarized.
- Multiple occurrences of a single PT in a participant will be counted only once at the maximum severity/grade.
- Laboratory parameters, physical examinations, vital sign measurements, PD, and immunogenicity results will be analyzed descriptively.

The baseline value for ARGX-113-2010 will be the value at the EoTP visit of ARGX-113-2009. All study visits will be recalculated based on actual dates and will be referred to as “analysis

visits" that will be used in the statistical analyses. The rules for calculating the analysis visits and the rules for imputing partial dates or missing dates will be provided in the SAP.

Analyses will not only refer to the baseline of ARGX-113-2010; the baseline value of ARGX-113-2009 may be used for specific analysis as will be outlined in the SAP for this OLE study.

9.4. Interim Analysis

Administrative interim analyses may be performed in support of potential regulatory authority interactions and will be described in detail in the SAP.

9.5. Sample Size Determination

The maximum number of participants in this study is the number of participants who complete the week 36/EoTP visit in ARGX-113-2009 and meet the eligibility criteria to roll over to this 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 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 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 study conduct at the site and adhering to requirements of 21 CFR, ICH guidelines, the IRB/IEC, local laws and regulations for clinical studies, and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient and 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 study completion.

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, and 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 ICF.
- Potential participants must be informed that their participation is voluntary. An ICF must be signed that meets the requirements of the IRB/IEC or study center, ICH guidelines, local laws and 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 affect participant participation.
- A copy of the ICF(s) must be provided to the participant.

10.1.4. Recruitment Strategy

Not applicable as participants will roll over from ARGX-113-2009.

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 ICF.
- The contract between sponsor and study sites specifies responsibilities of the parties related to 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 clinical study results 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 via paper SAE forms. The investigator is responsible for verifying that data entries are complete, accurate, and verifiable by electronically signing the eCRF.
- Guidance on completing eCRFs is provided on the eCRF completion document.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and direct access to the site and study documentation, including source data documents.
- Study processes, study sites (including but not limited to site visits, central laboratories, vendors), the study database, and study documentation are 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 study completion.
- QTLs will be predefined in the QTL Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Records and documents, including signed ICFs, on the conduct of this study must be retained by the investigator for at least 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 approval.
- Monitoring details describing strategy and activities are outlined in a monitoring plan.
  - Study monitors will perform ongoing source data verification to confirm that data entered on the eCRF by authorized site staff 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 of the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered on the eCRF that are transcribed from source documents must be consistent with the source documents or else the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The 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 on the eCRF.
- The sponsor or designee will perform monitoring to confirm that data entered on the eCRF by authorized site staff 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-113-2009 and rolls over to ARGX-113-2010.

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

- For study termination:
  - Discontinuation of further compound development
- For site termination:
  - Failure of the investigator to comply with the protocol, requirements of the IRB/IEC or local health authorities, 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 enrolled earlier than expected

If the study is prematurely terminated or suspended, the sponsor will 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 so, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and 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 7 will be performed as described in the laboratory manual.
- Protocol-specific requirements for the inclusion and exclusion of participants are detailed in Section 5.1 and Section 5.2, respectively.
- Additional tests 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 7: Protocol-Required Laboratory Tests

Laboratory test	Parameters		
Hematology	RBC count platelet count hemoglobin hematocrit	RBC indices: MCV MCH	WBC count with differential: neutrophils lymphocytes monocytes basophils eosinophils
Serum chemistry	ALT AST ALP albumin[a] bilirubin (total and direct) BUN sodium	calcium creatinine CRP GGT glucose HbA1c potassium	total protein[a] Lipid panel: total cholesterol HDL LDL (measured, not calculated) triglycerides
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, defined in Section 10.4.1)		
Specialty laboratory tests	INR		
Unscheduled SARS-CoV-2 testing	It is recommended that participants who develop COVID-19 symptoms be tested (Section 10.5)		
Pharmacodynamic markers	Anti-BP180 antibodies, anti-BP230 antibodies, [redacted]		
Immunogenicity	• Serum levels of ADA against efgartigimod • Plasma levels of antibodies against rHuPH20 to be tested in case of safety concerns		

ADA=antidrug antibodies; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ALP=alkaline phosphatase; BUN=blood urea nitrogen; CRP=C-reactive protein; GGT=gamma-glutamyl transferase; HbA1c=glycosylated hemoglobin; HDL=high-density lipoprotein; [redacted] INR=international normalized ratio; LDL=low-density lipoprotein; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; rHuPH20=recombinant human hyaluronidase PH20; WBC=white blood cell; WOCBP=women of childbearing potential

[a] Albumin and total protein collected from baseline through week 4 will not be reported to the site. A system will be implemented that will alert the investigator of out-of-range values, to allow for appropriate safety follow-up.

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 preexisting 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 considered 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 preexisting 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 preexisting condition that did not worsen from screening in ARGX-113-2009 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 1 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 definitions (current version).

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 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 have 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 1 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 electronic data capture system.
- The paper SAE report form will be faxed or emailed to the sponsor's designee (refer to 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: 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: Documented permanent sterilization procedure (eg, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy)

10.4.2. Contraception Guidance

10.4.2.1. Female Contraception for WOCBP

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

The following CTFG[13] methods are permitted for efgartigimod:

- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide
- Combined (estrogen-containing and progestogen-containing) hormonal contraception associated with ovulation inhibition:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Progesterone-only hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence

10.4.2.2. Male Contraception

No male contraception is required.

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

During the study, the sites will implement all recommendations issued by the local government regarding 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.

Testing for COVID-19 is not required during the study unless required by local authorities. However, it is recommended that participants who develop COVID-19 symptoms 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 SoA (Section 1.3), if possible. If assessments cannot be performed because of the COVID-19 pandemic, the following information must be collected from the first visit through the end of the study:

- All AE and concomitant medication reporting
- Injection-related reactions
- IMP administration
- Protocol-required laboratory assessments

Study visits, other than the baseline visit, designated as mandatory on-site visits (Section 1.3) may be performed at the participant's home (or an alternative convenient location). Such home visits will include sample collections as described in Table 8. In the exceptional case that a home nurse cannot be identified or cannot travel to the participant's home, vital sign measurements and blood and urine collection will not be performed. IMP may be administered through self-administration or caregiver administration, provided that the participant or caregiver has completed the training and has been considered competent.

Table 8: Scheme for Study Visits Performed at Home During COVID-19 Pandemic

Critical assessment	Performed by	Method of assessment
Updates/addenda to original informed consent (other than those conducted at baseline)	Investigator	Audio or video interview
Disease assessment (CDA, PR, CR, relapse, treatment failure)	Investigator	Audio or video interview
AEs	Investigator	Audio or video interview
Injection-related reactions	Investigator	Audio or video interview
Concomitant medications	Investigator	Audio or video interview
Concurrent BP adjustment evaluation	Investigator	Audio or video interview
Vital sign measurements	Home nurse[a]	In person at participant's home[b]

Critical assessment	Performed by	Method of assessment
Blood collection (for safety assessments only)	Home nurse[a]	In person at participant's home[b]
Urine collection (for safety assessments only)	Home nurse[a]	In person at participant's home[b]
IMP administration	Home nurse[a] or self-administered	In person at participant's home[b]

AE=adverse event; BP=bullous pemphigoid; CDA=control of disease activity; CR=complete remission; IMP=investigational medicinal product; PR=partial remission

[a] Either a nurse from the study site or a nurse from a commercial nursing vendor who is delegated by the investigator.

[b] Study visit may also be performed at an alternative convenient location.

10.6. Appendix 6: Protocol Amendment History

Amendment 1 (02 Jun 2023)

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 primary rationale for this amendment is to incorporate health authority feedback.

In addition, potential risks and mitigation strategies for efgartigimod administration and contraception requirements for men were updated to align with the safety information in the current efgartigimod IB.

If appropriate, protocol text has been aligned with the most recent protocol version (amendment 2 [v3.0], 27 Mar 2023) of the antecedent study ARGX-113-2009.

The major changes from the original protocol v1.0 to protocol v2.0 are summarized in the following table. Minor editorial changes are not summarized in the table. Refer to the List of Abbreviations and Definitions of Terms for any undefined abbreviations or terms.

Section	Description of change	Brief rationale
5.2. Exclusion Criteria	Added exclusion criterion 3.	Health authority requested update to exclude participants who permanently discontinued IMP (efgartigimod PH20 SC or placebo) in ARGX-113-2009 because of an AE considered related to IMP and for whom the benefit/risk balance is not considered positive.
1.1. Synopsis	The description of number of participants was revised per new exclusion criterion 3.	
1.3. Schedule of Activities (SoA), Table 1 and Table 2	Brief physical examinations are now included at the week 4 and week 8 visits during the observation period for participants who do not require treatment with efgartigimod PH20 SC at rollover (Table 1). When participants start or continue efgartigimod SC treatment, brief physical examinations now occur at the week 8 visit (relative to day X) and every 16 weeks thereafter.	Health authority requested update to increase the frequency of physical examinations.

Section	Description of change	Brief rationale
	Tables 1 and 2 were updated accordingly, and footnotes h and i were added in Table 2. These footnotes are also applicable to GTI assessments and QoL questionnaires, and footnote h to urine pregnancy tests.	
8.3.3. Electrocardiograms 1.3. Schedule of Activities (SoA), Table 1 and Table 2	ECG assessments are now included at the week 24 visit regardless of treatment (Table 1 and Table 2) and at the week 48 visit when participants are on efgartigimod PH20 SC treatment or at the EDV, if applicable (Table 2). Tables 1 and 2 were updated accordingly, and footnote i was added in Table 2 at the week 24 visit during the observation period.	Health authority requested update to allow for routine cardiac safety monitoring.
4.2. Scientific Rationale for Study Design	Clarification that participants who discontinued IMP (efgartigimod PH20 SC or placebo) and required rescue therapy in ARGX-113-2009 can be eligible for this study.	Provide clarification in response to a health authority request for information.
1.1. Synopsis 3. Objectives, Endpoints, and Estimands, Table 4: Study ARGX-113-2010 Objectives and Endpoints	A footnote was added to secondary efficacy endpoints containing “while off OCS,” “while on minimal OCS therapy,” and “while off both OCS and efgartigimod PH20 SC” to clarify that those endpoint criteria can only be met when participants are off rescue therapy.	
6.3. Assignment to Study Intervention Table 6: Study Intervention Summary Table 6.9. Prior and Concomitant therapy	Status C2a (for participants who received rescue therapy in ARGX-113-2009 and have not achieved CR or PR) was revised to allow the investigator to maintain, taper, or discontinue the participant’s rescue therapy (all or partly) while the participant requires treatment with efgartigimod, accounting for the type of rescue therapy received and the participant’s best interest.	Health authority requested update to increase the investigator’s flexibility regarding the potential combination of rescue therapy and efgartigimod PH20 SC.

Section	Description of change	Brief rationale
6.3. Assignment to Study Intervention Table 6: Study Intervention Summary Table	Participants who received OCS, TCS, conventional immunosuppressants, tetracyclines with or without nicotinamide, and/or dapsone as rescue therapy in ARGX-113-2009 and have not achieved CR or PR may combine it with efgartigimod PH20 SC. Participants who received IV immunoglobulin may only start efgartigimod PH20 SC treatment 4 weeks after the start of their last IV immunoglobulin cycle.	IV immunoglobulin was added as a nonimmunosuppressive rescue therapy in ARGX-113-2009 for participants who permanently discontinued IMP.
6.3. Assignment to Study Intervention Table 6: Study Intervention Summary Table 1.3. Schedule of Activities (SoA), Table 2	Statuses E and F2 were updated to clarify that participants will be monitored for safety for 8 weeks after the participant's final IMP administration.	Health authority requested update to monitor participant safety after efgartigimod PH20 SC discontinuation.
2.3.1. Risk Assessment, Table 3: Potential Risks and Mitigation Strategies, Infusion/injection-related reactions	The frequency of infusion/injection-related reactions in the studies was added in Table 3.	Alignment with the current efgartigimod IB.
2.3.1. Risk Assessment, Table 3: Potential Risks and Mitigation Strategies, Injection-site reactions	Injection-site reactions were added in Table 3 as a potential clinically significant risk that could be encountered and requires attention or special monitoring.	Injection-site reactions are now defined as adverse events of clinical interest and will be monitored as such.
2.3.1. Risk Assessment, Table 3: Potential Risks and Mitigation Strategies, Potential complications from exposure to OCS	"Increase OCS doses" was deleted in Table 3 as a mitigation strategy.	Increasing OCS doses is not a mitigation strategy for potential complications from exposure to OCS.

Section	Description of change	Brief rationale
7.1.1. Permanent Discontinuation 1.3. Schedule of Activities (SoA), Table 2	The criteria requiring permanent IMP discontinuation were updated. Revision so that participants permanently discontinuing IMP attend an EDV and 2 safety follow-up visits over a period of 8 weeks after the participant's final IMP administration. EDV column and associated footnote e were added in Table 2.	Health authority requested update to monitor participant safety after efgartigimod PH20 SC discontinuation.
7.2. Participant Discontinuation/Withdrawal From the Study 1.3. Schedule of Activities (SoA), Table 1 and Table 2	The criteria requiring withdrawal from the study were updated. Clarification that, if possible, an EDV and safety follow-up visit(s) should be conducted when the participant is withdrawn from the study. EDV column and associated footnote c were added in Table 1.	Provide more information and specific instructions to the investigator and site staff about study withdrawal.
9.5. Sample Size Determination	Clarification that sample size determination is part of the antecedent study ARGX-113-2009.	Ethics Committee requested update since the statement "not applicable" for the number of cases was unacceptable.
10.4.2.2. Male Contraception	Male contraception is no longer required in efgartigimod clinical studies.	Nonclinical reproductive toxicology studies with efgartigimod indicated no influence on male or female reproductive potential or embryo-fetal development.
6.9.1. Oral Prednisone Tapering and Escalation Table 7: Concurrent Oral Prednisone Equivalent Doses (in	Table 7 was revised to include minimum and maximum recommended doses for participants with body weights <45 kg and ≥110 kg, respectively. Clarification that for these participants the investigator should propose an OCS dose per Table 7 and inform the medical	Provide additional, specific guidance for the investigator and site staff.

Section	Description of change	Brief rationale
mg) Based on Participant Body Weight	monitor to ensure consistency in the study.	
10.7. Appendix 7: Country-specific Requirements 10.7.1. China	A table with recommendations on the concurrent oral methylprednisolone dosing regimen was added.	Methylprednisolone rather than prednisone is prescribed in China.
8.3.4.1. Substudy—Vaccination Response 1.3. Schedule of Activities (SoA), Table 1 and Table 2	Clarification that postvaccination blood sampling, as part of the vaccination substudy from ARGX-113-2009, can continue in this OLE study to assess humoral or cellular responses to vaccinations received in ARGX-113-2009. Removed Table 1 original footnote e and Table 2 original footnote h.	Provide explicit guidance for site staff.
8.2.1.1. Assessment of BP Disease Status and OCS Dose Monitoring	Added an instruction for the investigator to examine the participant for new lesions as this is part of the BP disease assessment.	Ensure lesions assessment is performed.
6.3. Assignment to Study Intervention	Correction that a new treatment course of efgartigimod PH20 SC may be initiated in eligible participants until week 45 instead of week 44.	Efgartigimod PH20 SC can be administered up to the week 48 visit to ensure a minimum of 4 weeks of treatment.
6.3. Assignment to Study Intervention Table 6: Study Intervention Summary Table	Clarification that TCS may be used to treat localized lesions rather than transient lesions at the investigator's discretion.	Provide specific guidance for the investigator and site staff.
1.3. Schedule of Activities (SoA), Table 1 and Table 2	Table 1 footnote d (previously c) and Table 2 footnote f (previously e) were revised to explain in which situations a UNS is performed (including a notable weight change) and that the investigator decides which assessments to conduct based on the purpose of the UNS.	Provide additional, specific information for the investigator and site staff.
1.3. Schedule of Activities (SoA), Table 2 8.3.1. Physical Examinations	Table 2 footnote g has been added to clarify when to perform a brief physical examination instead of a complete physical examination. This instruction	Facilitate protocol compliance by the

Section	Description of change	Brief rationale
	was removed from the body protocol text.	investigator and site staff
4.1. Overall Design	Text was added to specify that this study will remain open for a maximum of 2 years after completion of ARGX-113-2009.	Compliance with argenx continued access policy.
6.7. Continued Access to IMP After the End of the Study	The following text has been removed: "argenx will comply with all local laws and regulations to ensure participants have access to care that has been medically identified as essential" because argenx cannot guarantee continued access for IMP at the end of the study.	
6.9. Prior and Concomitant Therapy	Added that the brand name of vaccines received at baseline or during the study should be recorded.	Missing information from the original protocol version.
	The following text has been added to the list of medications prohibited when the participant receives efgartigimod PH20 SC: "any other biologic agent or experimental/study IMP."	Ensure individuals participating in another interventional research study are excluded from this study.
8.3.2. Vital Signs	Removed the requirement that participants must be seated while blood pressure and pulse rate are assessed.	The participant's position during measurement of blood pressure and pulse rate is not relevant in this study.
Definitions of Terms	Definition of concurrent BP therapy was updated: • "TCS" was added • "and continued after rollover to ARGX-113-2010" was removed because IV immunoglobulin can be part of the rescue therapy used in ARGX-113-2009.	Alignment with the revised definitions and updates to allowed rescue therapy in ARGX-113-2009 protocol amendment 2 (v3.0).

Section	Description of change	Brief rationale
	The definition of CR was revised to: "The absence of new lesions, complete healing of existing lesions, and absence of pruritus (except postinflammatory, including hypo/hyperpigmentation or skin damage)"	
	The definition of relapse was aligned with consensus terminology.	
10.1.1. Regulatory and Ethical Considerations	The section was completed with regulatory or ethical considerations for study conduct.	Deletion error from the original protocol version.
10.1.3. Informed Consent Process	The following statement was removed: "Participants who are rescreened are required to sign a new ICF (Section 5.4)."	(Re)screening does not apply for this OLE study.
2.2. Background 2.3. Benefit/Risk Assessment	Reference to the rHuPH20 IB was removed.	The rHuPH20 IB is no longer part of the submission in countries where rHuPH20 is considered an excipient and not IMP.
6.4. Blinding	[redacted] are administered on days 1 and 8 and not at baseline as was described in the original protocol.	Correction.

10.7. Appendix 7: Country-specific Requirements

The following lists modifications to the protocol's existing text that are required for specific countries. Cross-references to applicable sections of the protocol are included with each item.

10.7.1. China

PD and immunogenicity blood samples that are collected from participants in China may be used to develop and validate methods to support the efgartigimod development program. Such use of these samples is only permitted after obtaining approval from the HGRAC, and the methods in which they are used must comply with local regulations. Additionally, the conditions in which these samples are stored and ultimately destroyed must comply with HGRAC requirements and other relevant regulations (Section 8.6 and Section 8.9).

In China, oral methylprednisolone will be provided instead of oral prednisone (Section 6.9.1). Refer to Table 9 for the concurrent oral methylprednisolone dose regimen.

Table 9: Concurrent Oral Methylprednisolone Equivalent Doses (in mg) Based on Participant Body Weight

Oral prednisone dose level	Body weight category[a] (kg)													
	<45 kg	≥45 to <50	≥50 to <55	≥55 to <60	≥60 to <65	≥65 to <70	≥70 to <75	≥75 to <80	≥80 to <85	≥85 to <90	≥90 to <95	≥95 to <100	≥100 to <105	≥105 to <110	≥110
	Minimum recommended daily methylprednisolone dose	Daily methylprednisolone dose[b]													Maximum recommended daily methylprednisolone dose
mg/kg/day	mg/day														
1.0	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88
0.75	24	24	28	32	36	36	40	44	48	48	52	56	60	60	64
0.50	16	18	20	20	24	24	28	28	32	32	36	36	40	40	48
0.30	10	10	12	12	14	14	16	18	18	20	20	20	24	24	32
0.20	6	6	8	8	8	10	10	12	12	12	14	14	16	16	20
0.15	4	4	6	6	6	6	8	8	8	10	10	10	12	12	14
Minimal OCS therapy: ≤0.10	2	2	4	4	4	4	4	6	6	6	6	6	8	8	10
mg/day	mg/day														
7.5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	6	6	6
5.0	NA	NA	NA	NA	NA	NA	NA	4	4	4	4	4	4	4	4
2.5	NA	NA	2	2	2	2	2	2	2	2	2	2	2	2	2
Off OCS therapy: 0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

NA=not applicable; OCS=oral corticosteroids (oral methylprednisolone)
Notes: Each new dosage will be maintained for 2 weeks or less, based on the investigator's clinical judgment.
[a] Body weight should be rounded to the nearest whole number.

[b] The investigator should not deviate from the concurrent oral methylprednisolone dose levels specified in the table, except if the participant's safety could be compromised.

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