Clinical Study Protocol

Protocol Title:	A Phase 2/3, Randomized, Double-Blinded, Placebo-Controlled, Parallel-Group Study to Investigate the Efficacy and Safety of Efgartigimod PH20 SC in Adult Participants With Bullous Pemphigoid
Protocol Number:	ARGX-113-2009
Version Number:	4.0 (Amendment 3)
Compound:	Efgartigimod (ARGX-113)
Brief Title:	A phase 2/3 study of efgartigimod PH20 SC in adult participants with bullous pemphigoid
Study Phase:	2/3
Acronym:	BALLAD
Sponsor Name:	argenx BV
Legal Registered Address:	Industriepark Zwijnaarde 7 9052 Zwijnaarde (Ghent) Belgium Phone: +32 9 310 34 00 Fax: +32 9 310 34 99
Regulatory Agency Identifier Number(s):	IND: [redacted] EU CT: 2023-508645-40
Approval Date:	27 Feb 2024

Sponsor's Medical Contact:	[redacted], MD, PhD Senior Medical Director, Clinical Development argenx BV Industriepark Zwijnaarde 7 9052 Zwijnaarde (Ghent) Belgium Office Phone: [redacted] Email: [redacted]
Contract Research Organization: (Globally except for China)	Pharmaceutical Product Development (PPD) Global Ltd Granta Park, Great Abington Cambridge, CB21 6GQ, United Kingdom Phone: +44 1223 374100
Sponsor's Designee (China only):	Zai Lab (Shanghai) 4/F, No. 1 South Tower 4560 Jinke Rd. Pilot Free Trade Zone (Shanghai) P.R. China
24-Hour Urgent Medical Helpline:	Europe/Asia-Pacific: +44 1223 374240 North America: +1 800 201 8725
Serious Adverse Event Reporting:	Email: safety@argenx.com Fax: +1 833 874 7325

SIGNATURE OF THE SPONSOR

Protocol Title:	A Phase 2/3, Randomized, Double-Blinded, Placebo-Controlled, Parallel-Group Study to Investigate the Efficacy and Safety of Efgartigimod PH20 SC in Adult Participants With Bullous Pemphigoid
Protocol Number:	ARGX-113-2009
Acronym:	BALLAD
Sponsor Signatory:	

See appended signature page

[redacted], MD, PhD
Chief Medical Officer

Date

SIGNATURE OF THE INVESTIGATOR

Investigator's Acknowledgment

I have read this protocol for study ARGX-113-2009.

Title: A Phase 2/3, Randomized, Double-Blinded, Placebo-Controlled, Parallel-Group Study to Investigate the Efficacy and Safety 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 should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a participant to obtain their consent to participate.

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

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

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

Investigator Name, Institution, and Address: _____

(please hand print or type) _____

_____

_____

Signature: _____

Date: _____

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Global protocol document history	Date
Amendment 3 v4.0	27 Feb 2024
Amendment 2 v3.0	27 Mar 2023
Amendment 1 v2.0	10 May 2022
Original v1.0	10 Dec 2021

Amendment 3 (27 Feb 2024)

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

Overall Rationale for This Amendment

The primary rationale for this amendment is to comply with Clinical Trial Regulations.

The major changes from protocol version 3.0 to protocol version 4.0 are summarized in the following table. Minor editorial changes, including the correction of typographical errors and formatting inconsistencies, are not summarized. Refer to the Abbreviations and Definitions for any undefined terms or abbreviations.

Section	Change in study operation or planned analysis	Brief rationale
1.1. Synopsis	Synopsis has been shortened and restructured.	To comply with Clinical Trial Regulations
2.3.2. Benefit Assessment	Anticipated benefit based on results from the pemphigus phase 2 study (ARGX-113-1701) was removed.	To reflect the results of the pemphigus phase 3 study (ARGX-113-1904), which did not meet its primary and secondary efficacy endpoints
9.3.3.5. Other Analyses	Pooled analyses of parts A and B were added.	To explore the effect of efgartigimod across parts A and B
7.2. Participant Discontinuation/Withdrawal From the Study	Revised text (deleted text is shown in strikethrough font; new text is shown in bold font): ~~If the participant also withdraws consent to disclose future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.~~ ~~The samples from participants withdrawing from the study that have already been collected (but may not have been analyzed) before withdrawal will still be used for the study 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 guidance on future sample use

Section	Change in study operation or planned analysis	Brief rationale
5.2. Exclusion Criteria 2.3.1., Table 2: Potential Risks and Mitigation Strategies for ARGX-113-2009 8.3.7. Infections and Vaccinations 8.4.7.1. Risk Mitigation for COVID-19 and Other Significant Infections	Exclusion criterion "5B. Active, chronic, or latent infection at screening" has been revised and renumbered to "5C. Clinically significant active infection that is not sufficiently resolved before baseline in the investigator's opinion."	To align with the current efgartigimod IB
1.3. Schedule of Activities (SoA) 2.3. Benefit/Risk Assessment 6.4. Study Compliance	Participants no longer need to be monitored for at least 30 minutes after IMP administration.	
8.3.8. Pregnancy Testing	Participants or their partners who become pregnant during the study will be asked to consent to be followed for up to 12 months after the baby's birth.	To ensure follow-up on the baby's health
1.3. Schedule of Activities (SoA)	The SoA was simplified: • Cross-references to applicable protocol sections were listed in a new column • Information on treatment period, mandatory visits, and other weekly visits included in footnote b was split into 3 footnotes • Nonessential footnotes were removed.	To ensure protocol compliance
6.3. Measures to Minimize Bias: Randomization and Blinding	Correction was implemented: The site enrolls the participants and assigns them a unique participant ID at the first screening visit, and not upon signing informed consent.	
8.1.5. Unscheduled Visits 1.3. Schedule of Activities (SoA) – footnote h	Clarification was added that in case of relapse, IGA-BP, BPDAI, and	

Section	Change in study operation or planned analysis	Brief rationale
	Itch NRS assessments must be performed.	
6.8.1.3. Oral Prednisone Dose Adjustment Regimen (Based on BP Disease Assessment)	Clarification was added that OCS tapering will be delayed if a participant has new lesions after the start of OCS tapering.	
8.5. Pharmacokinetics	Clarification was added that blood samples for PK analysis can be collected at any time if no IMP is administered.	

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS AND DEFINITIONS

Abbreviation/Term	Expansion/Definition
ABQoL	Autoimmune Bullous Disease Quality of Life questionnaire
ADA	antidrug antibody(ies)
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
AIBD	autoimmune blistering disease
AIS	Aggregate Improvement Score (calculated from the C-GTI)
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BL	baseline
BMI	body mass index
BP	bullous pemphigoid
BPDAI	Bullous Pemphigoid Disease Area Index
Caregiver	A person of legal age from the participant's social network (eg, family, relatives, friends), chosen by the participant. Once they receive the necessary training and are found competent by the authorized site staff to perform IMP administration, the caregiver can administer SC injections to the participant.
CDA	control of disease activity
CFR	Code of Federal Regulations
C-GTI	Composite Glucocorticoid Toxicity Index
CIDP	chronic inflammatory demyelinating polyneuropathy
CIOMS	Council for International Organizations of Medical Sciences
CLEIA	chemiluminescence enzyme immunoassay
CMH	Cochran-Mantel-Haenszel (test)
CONSORT	Consolidated Standards of Reporting Trials
CR	complete remission
CSR	clinical study report
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CWS	cumulative worsening score (calculated from the C-GTI)
DC	disease control
DIF	direct immunofluorescence

Abbreviation/Term	Expansion/Definition
DLQI	Dermatology Life Quality Index
DRI	dietary reference intake
DSMB	data and safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
efgartigimod PH20 SC	efgartigimod for SC administration coformulated with rHuPH20
ELISA	enzyme-linked immunosorbent assay
EoTP	end of treatment period
ESD	early study discontinuation
ETD	early treatment discontinuation
FcRn	neonatal crystallizable fragment receptor
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
gMG	generalized myasthenia gravis
GMP	Good Manufacturing Practice
GTI	Glucocorticoid Toxicity Index
GTI-SL	Glucocorticoid Toxicity Index Specific List
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDL	high-density lipoprotein
HGRAC	Human Genetic Resources Administration of China
HR	heart rate
IB	Investigator's Brochure
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	Independent Ethics Committee
Ig	immunoglobulin
IGA-BP	Investigator Global Assessment of Bullous Pemphigoid
IgE	immunoglobulin ε
IgG	immunoglobulin γ

Abbreviation/Term	Expansion/Definition
IGRA	interferon gamma release assay
IIF	indirect immunofluorescence
IM	intramuscular
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
Itch NRS	Itch Numerical Rating Scale
ITP	immune thrombocytopenia
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous(ly)
IVIg	intravenous administration of immunoglobulin
LDL	low-density lipoprotein
LRV	lower reference value
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NAb	neutralizing antibody
NCI	National Cancer Institute
NCOD	normalized cumulative oral corticosteroid dose
OCS	oral corticosteroid(s)
OLE	open-label extension (study)
PBMC	peripheral blood mononuclear cell
placebo	placebo for SC administration coformulated with rHuPH20 (dosing formulation)
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PPE	personal protection equipment
PR	partial remission
PRO	patient-reported outcome (assessment)
PT	Preferred Term
QoL	quality of life
QTcF	Fridericia-corrected QT (interval)

Abbreviation/Term	Expansion/Definition
RBC	red blood cell
RDA	recommended daily allowance
rHuPH20	recombinant human hyaluronidase PH20
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SCR	screening
SE	standard error
SoA	schedule of activities
SOC	System Organ Class
SOP	standard operating procedure
TB	tuberculosis
TCS	topical corticosteroid(s)
TEAE	treatment-emergent adverse event
TNM	tumor-node metastasis
TP	treatment period
TV	target value
ULN	upper limit of normal
UNS	unscheduled
WBC	white blood cell
WHO	World Health Organization
WHODD	World Health Organization drug dictionary
WOCBP	women of childbearing potential

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 2/3, Randomized, Double-Blinded, Placebo-Controlled, Parallel-Group Study to Investigate the Efficacy and Safety of Efgartigimod PH20 SC in Adult Participants With Bullous Pemphigoid

Brief Title: A phase 2/3 study of efgartigimod PH20 SC in adults with bullous pemphigoid

Rationale:

Bullous pemphigoid (BP) is a chronic autoimmune blistering disease that predominantly affects older adults and is caused by immunoglobulin γ and ε (IgG and IgE, respectively) autoantibody activity against BP180 and BP230 (hemidesmosomal proteins of the dermal-epidermal junction). This autoantibody activity triggers a variety of immune responses in the skin that lead to blistering and pruritus.

Efgartigimod is a neonatal crystallizable fragment receptor (FcRn) antagonist that blocks FcRn-mediated recycling of IgG, thereby reducing total IgG serum levels, including IgG autoantibodies. Thus, efgartigimod provides a rational approach for treating autoimmune diseases mediated by IgG autoantibodies, such as BP.

Objectives, Endpoints, and Estimands:

Primary Objective (Parts A and B)
To evaluate the efficacy of efgartigimod for subcutaneous (SC) administration coformulated with recombinant human hyaluronidase PH20 (efgartigimod PH20 SC) on achieving sustained remission in the treatment of participants with BP
Primary Endpoint (Parts A and B)
Proportion of participants who are in complete remission (CR) while receiving efgartigimod PH20 SC or placebo and have been off oral corticosteroid (OCS) therapy for ≥8 weeks at week 36
Key Secondary Endpoints – Subject to Alpha Control (Part B Only)
1. Cumulative dose of OCS from baseline to week 36 2. Proportion of participants who achieve an Investigator Global Assessment of Bullous Pemphigoid (IGA-BP) score of 0 while receiving efgartigimod PH20 SC or placebo and have been off OCS therapy for ≥8 weeks at week 36 3. Proportion of participants who achieve control of disease activity (CDA) while receiving efgartigimod PH20 SC or placebo and remain free of relapse through week 36 4. Proportion of participants who are in CR while receiving efgartigimod PH20 SC or placebo and have been receiving minimal OCS therapy for ≥8 weeks at week 36. (Minimal OCS therapy is defined as ≤0.1 mg/kg/day of prednisone [or an equivalent dose of another OCS].) 5. Changes from baseline in the 24-hour average itch score from the Itch Numerical Rating Scale (NRS)

The estimand framework for analysis of the primary endpoint applies only to part B of this study. The main attributes of the primary estimand will be:

- Population: participants with BP who comply with the inclusion and exclusion criteria
- Variable: proportion of participants who are in CR while receiving efgartigimod PH20 SC or placebo and have been off OCS therapy for ≥8 weeks at week 36 summarized based on the odds ratio
- Main intercurrent events (ICE): intake of intercurrent treatment or IMP discontinuation due to lack of efficacy before week 36 handled with a composite strategy

Overall Design:

In part A (a phase 2 evaluation), adult participants with moderate-to-severe BP will be randomized in a 1:1 ratio to receive double-blinded IMP, either efgartigimod PH20 SC or placebo. Part B (a phase 3 evaluation) is identical to part A in terms of design, with the goal of confirming the results obtained from part A in a separate, larger group of participants with BP. Efgartigimod PH20 SC will be administered at a dose of [redacted] mg (via [redacted] separate 1000 mg injections) on day 1 and day 8. After that, single injections of efgartigimod PH20 SC 1000 mg will be administered once weekly. Placebo will be administered using the same dose regimen. All participants will receive concurrent oral prednisone at a starting dosage of 0.5 mg/kg/day at baseline (or an equivalent dose of another OCS). Each participant's OCS dosage can be adjusted throughout the study according to their BP disease status.

Brief Summary:

The main purpose of this study is to measure the effect of efgartigimod PH20 SC compared with placebo in adults with moderate-to-severe BP. The safety of efgartigimod will also be evaluated.

Number of Participants (Parts A and B):

This study will enroll approximately 40 participants in part A and 120 participants in part B.

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

Study Arms and Duration:

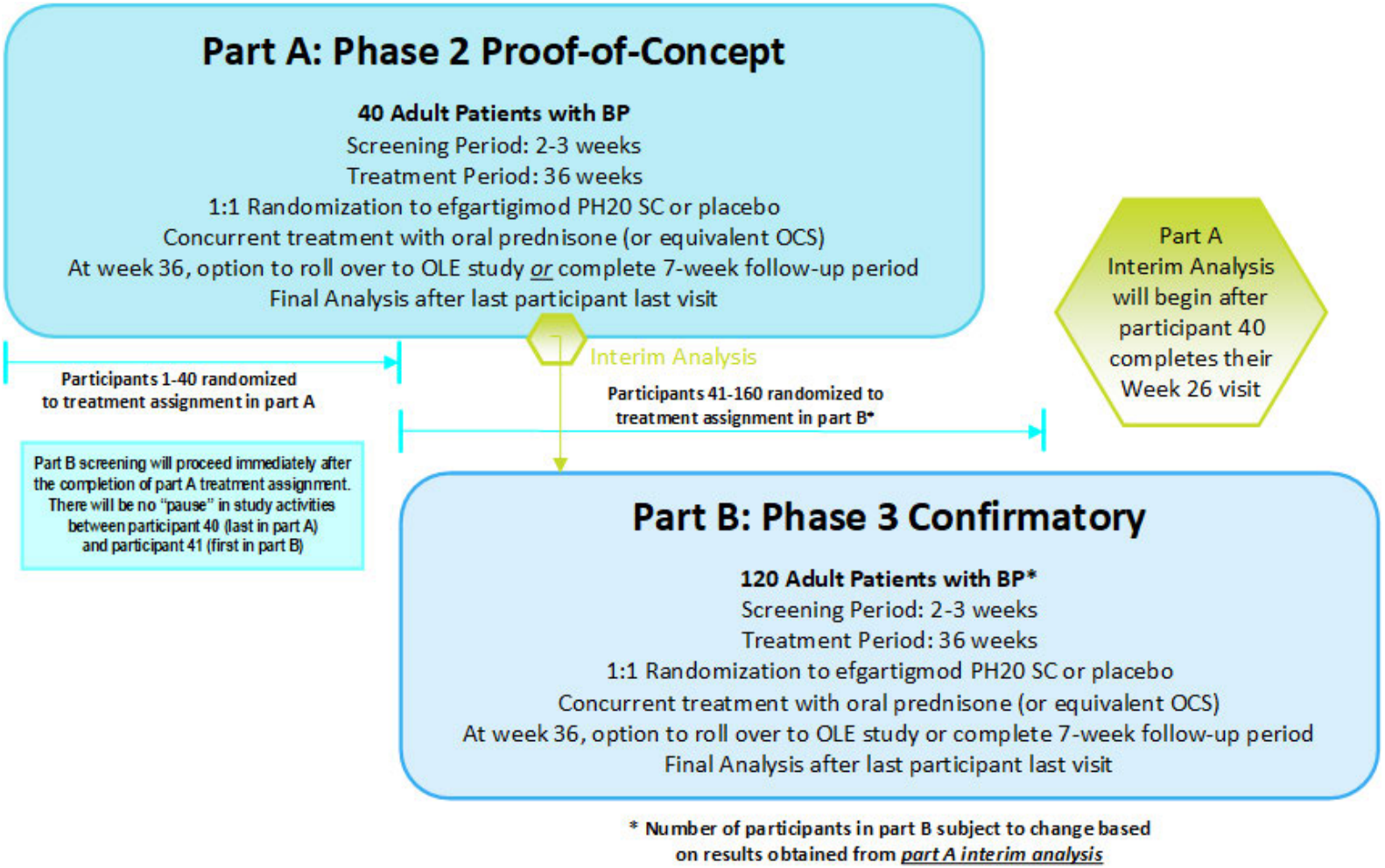
Participants in parts A and B will be randomized in a 1:1 ratio to receive efgartigimod PH20 SC or placebo. The durations of parts A and B are as follows:

- Screening period: 2 to 3 weeks
- Treatment period: 36 weeks
- Treatment-free follow-up period: 7 weeks

Data Monitoring/Other Committee: Yes

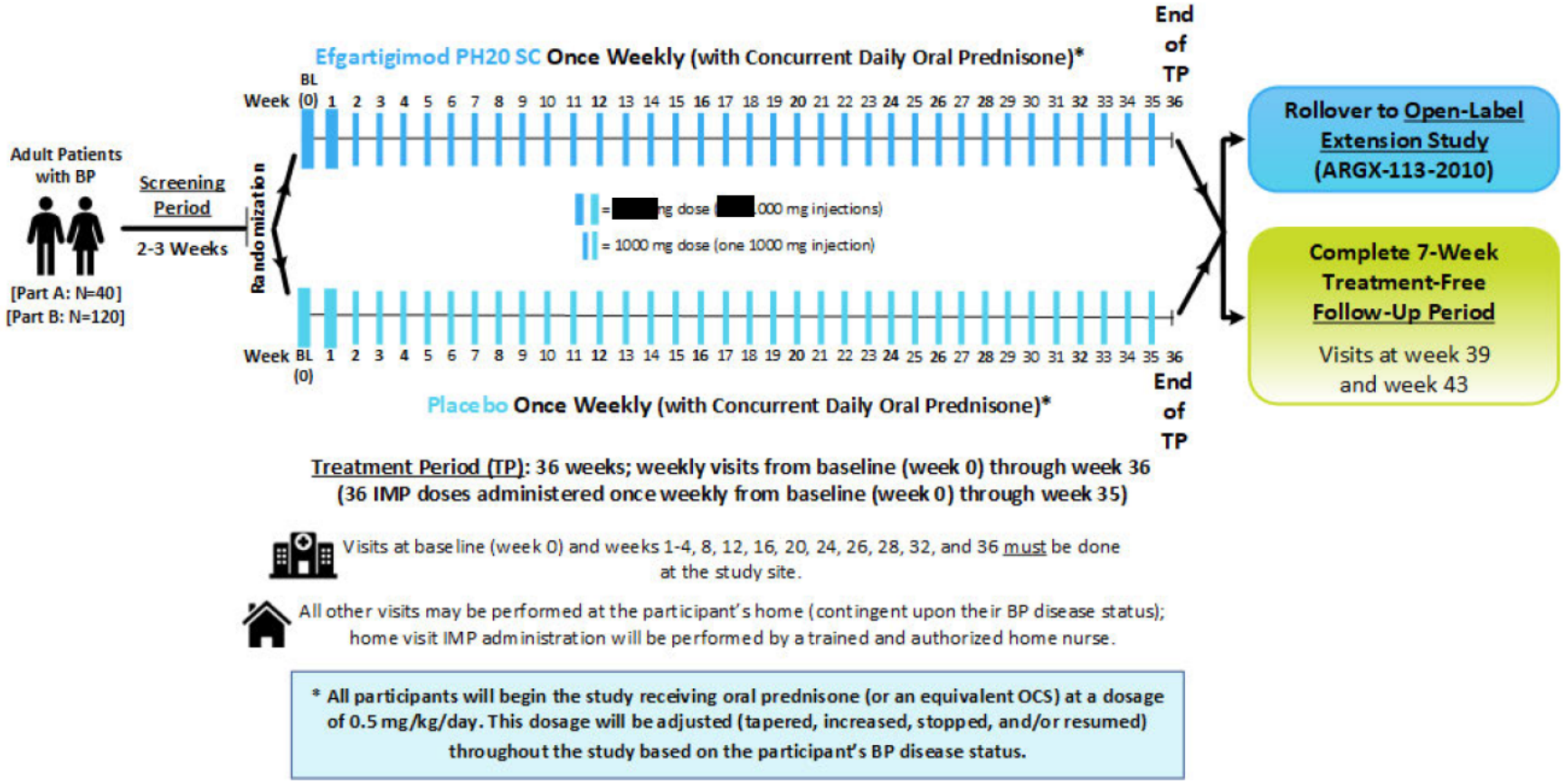
1.2. Schema

Figure 1: Operationally Seamless Design of 2-Part Study



BP=bullous pemphigoid; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; OCS=oral corticosteroids (prednisone or equivalent); OLE=open-label extension study (ARGX-113-2010); placebo=placebo for SC administration coformulated with rHuPH20; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)

Figure 2: Schematic for Both Parts A and B of ARGX-113-2009



BP=bullous pemphigoid; BL=baseline; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IMP=investigational medicinal product (efgartigimod PH20 SC or placebo); N=number of participants in study population; OCS=oral corticosteroids (prednisone or equivalent); placebo=placebo for SC administration coformulated with rHuPH20; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly); TP=treatment period

1.3. Schedule of Activities (SoA)

Table 1 presents the timing of visit activities to be performed throughout the entire study.

Table 1: Schedule of Activities (SoA)

Study period	**Screening period[a]**	**Treatment period[b]**																**Follow-up period[c]**		**Other visits**			**Applicable protocol section**
Visit type	**SCR**	**BL**	**Mandatory on-site visits[d]**													**Other weekly visits[e]**	**EoTP**	**F1**	**F2**	**ETD[f]**	**ESD[g]**	**UNS[h]**	
Visit week		**0**	**1**	**(D10)**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	–	**36**	**39**	**43**	**ETD**	**ESD**		
Visit day	**-14 to -1**	**1**	**8**	**10**	**15**	**22**	**29**	**57**	**85**	**113**	**141**	**169**	**183**	**197**	**225**		**253**						
Visit window (±days)	**+7**	–	**±2**	**±1**	**±2**													**±3**		–			
Informed consent	X																						Section 10.1.3
Inclusion/ exclusion criteria	X	X																					Section 5.1 Section 5.2
Randomization		X																					Section 6.3
Demography	X																						
Medical and surgical history	X																						Section 8.3.5
Histopathology/ DIF[i]	X																						
Karnofsky performance index score	X																						Section 10.5
QoL assessments		X							X				X				X			X	X		Section 8.2.2
Concomitant therapies/ procedures[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(x)	Section 6.8
Height	X																						Section 8.3.2

Study period	**Screening period[a]**	**Treatment period[b]**																**Follow-up period[c]**		**Other visits**			**Applicable protocol section**
Visit type	**SCR**	**BL**	**Mandatory on-site visits[d]**													**Other weekly visits[e]**	**EoTP**	**F1**	**F2**	**ETD[f]**	**ESD[g]**	**UNS[h]**	
Visit week		**0**	**1**	**(D10)**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	–	**36**	**39**	**43**	**ETD**	**ESD**		
Visit day	**-14 to -1**	**1**	**8**	**10**	**15**	**22**	**29**	**57**	**85**	**113**	**141**	**169**	**183**	**197**	**225**		**253**						
Visit window (±days)	+7	–	±2	±1	±2													±3		–			
Weight	X	X	X		X	X	X	X	X	X	X	X	X	X	X	(x)[k]	X	X	X	X	X	(x)	Section 8.3.2
Physical examination and vital signs	X	X	X		X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	(x)	Section 8.3.1 Section 8.3.3
ECG	X												X				X			X	X		Section 8.3.4
Urinalysis	X	X					X	X	X	X	X	X		X	X		X	X	X	X	X	(x)	Section 8.3.6.1
Active viral infection tests	X																						Section 8.3.7
COVID-19 test (performed if required per local regulations)	X																						Section 10.2.1.1
QuantiFERON-TB test	X																						Section 10.2.1.2
Serum pregnancy *or* serum FSH test[l]	X																						Section 8.3.8 Section 10.4.1
Urine pregnancy test for WOCBP (local laboratory)		X					X	X	X	X	X	X		X	X		X	X	X	X	X	(x)	Section 8.3.8
Clinical chemistry and hematology	X	X	X		X		X	X	X	X	X	X	X	X	X		X	X	X	X	X	(x)	Section 8.3.6.1
Pharmacokinetics		X	X	X[m]	X		X	X	X	X	X	X	X	X	X		X	X	X	X	X	(x)	Section 8.5

Study period	**Screening period[a]**	**Treatment period[b]**																**Follow-up period[c]**		**Other visits**			**Applicable protocol section**
Visit type	**SCR**	**BL**	**Mandatory on-site visits[d]**													**Other weekly visits[e]**	**EoTP**	**F1**	**F2**	**ETD[f]**	**ESD[g]**	**UNS[h]**	
Visit week		**0**	**1**	**(D10)**	**2**	**3**	**4**	**8**	**12**	**16**	**20**	**24**	**26**	**28**	**32**	–	**36**	**39**	**43**	**ETD**	**ESD**		
Visit day	**-14 to -1**	**1**	**8**	**10**	**15**	**22**	**29**	**57**	**85**	**113**	**141**	**169**	**183**	**197**	**225**		**253**						
Visit window (±days)	+7	–	±2	±1	±2													±3		–			
Immunogenicity	X	X			X		X	X	X	X	X	X	X	X	X		X	X	X	X	X	(x)	Section 8.9
Pharmacodynamics	X	X	X		X		X	X	X	X	X	X	X	X	X		X	X	X	X	X	(x)	Section 8.6
Substudy (selected sites): historical protective antibody titers (serum)		X					X																Section 8.3.6.2
Substudy (selected sites): vaccination antibody titers (serum)		Before vaccination; first available on-site visits at +4 weeks, +12 weeks, and +24 weeks postvaccination																	(x)		(x)		Section 8.3.6.2
Substudy (selected sites): vaccination cellular responses (PBMCs)		Before vaccination; first available on-site visits at +12 weeks and +24 weeks postvaccination																	(x)		(x)		Section 8.3.6.2
IGA-BP	X	X	X		X	X	X	X	X	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	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	X		X	X	X	X	X	(x)	Section 8.2.1.4
BP disease status		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(x)	Section 8.2.1.1
Concurrent OCS dose monitoring		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(x)	Section 6.8.1.3 Section 8.2.1.1

Study period	Screening period[a]	Treatment period[b]															Follow-up period[c]		Other visits			Applicable protocol section
Visit type	SCR	BL	Mandatory on-site visits[d]													Other weekly visits[e]	EoTP	F1	F2	ETD[f]	ESD[g]	UNS[h]	
Visit week		0	1	(D10)	2	3	4	8	12	16	20	24	26	28	32	–	36	39	43	ETD	ESD		
Visit day	-14 to -1	1	8	10	15	22	29	57	85	113	141	169	183	197	225		253						
Visit window (±days)	+7	–	±2	±1	±2													±3		–			
Investigator telephone calls[n]																X							Section 8.1.4
Substudy (selected sites): photography of BP lesion		The sponsor suggests that photos be taken at BL and when CDA, CR, and relapse occur. Photos may also be taken at intermediate time points per investigator discretion.															The sponsor suggests that photos be taken at BL and when CDA, CR, and relapse occur. Photos may also be taken at intermediate time points per investigator discretion.						Section 8.10
GTI (including C-GTI and GTI-SL)		X							X				X				X			X	X		Section 8.3.9
AEs	Continuous monitoring throughout study																						Section 8.4
IMP administration[o]		X	X		X	X	X	X	X	X	X	X	X	X	X	X							Section 6.1
IMP (self-) administration training					X	X	X	X	X	X	X	X	X	X	X								Section 6.4
Rescue therapy evaluation/ initiation																				X			Section 6.8.3

ABQoL=Autoimmune Bullous Disease Quality of Life questionnaire; AE=adverse event; aPTT=activated partial thromboplastin time; BL=baseline; BP=bullous pemphigoid; BPDAI=Bullous Pemphigoid Disease Area Index; CDA=control of disease activity; C-GTI=Composite Glucocorticoid Toxicity Index; DIF=direct immunofluorescence; DLQI=Dermatology Life Quality Index; ECG=electrocardiogram; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; EoTP=end of treatment period; ESD=early study discontinuation; ETD=early treatment discontinuation; FSH=follicle-stimulating hormone; F1 and F2=follow-up visits 1 and 2; GTI=Glucocorticoid Toxicity Index; GTI-SL=Glucocorticoid Toxicity Index Specific List; HBV=hepatitis B virus; HCV=hepatitis C virus; HR=heart rate; IGA-BP=Investigator Global Assessment of Bullous Pemphigoid; [redacted]

IgG=immunoglobulin γ; IMP=investigational medicinal product (efgartigimod PH20 SC or placebo); INR=international normalized ratio; Itch NRS=Itch Numerical Rating Scale; OCS=oral corticosteroid(s); OLE=open-label extension (study); PBMCs=peripheral blood mononuclear cells; PK=pharmacokinetic; QoL=quality of life; rHuPh20=recombinant human hyaluronidase PH20; SCR=screening; TB=tuberculosis; UNS=unscheduled; WOCBP=women of childbearing potential.
Note: (x)=visit activities that are optional are only required under specific circumstances.

[a] The screening period may be extended by a maximum of 7 days for logistical or administrative reasons (eg, receipt of laboratory results).
[b] The treatment period consists of weekly visits, starting with the BL visit and ending with the EoTP visit.
[c] Follow-up visits are only applicable for participants who choose not to roll over to the OLE study ARGX-113-2010.
[d] Mandatory on-site visits must be performed as indicated. However, the visits at weeks 8 and 16 may also be performed at home, by qualified site staff, for a participant who has achieved CDA. In these cases, collection of the PK, PD, and immunogenicity blood samples and weight measurement are not required.
[e] Weekly visits that are not designated as mandatory on-site visits may be performed at home if the participant has achieved CDA. Home administration of IMP will not be permitted until week 5. During home visits, IMP will be administered by a home nurse. In case of permanent IMP discontinuation, participants will attend mandatory on-site visits only.
[f] The ETD visit must be performed when IMP is discontinued before the EoTP visit; the study site should make every effort to perform this visit within 7 days of the participant's last IMP dose. Participants will remain in the study (provided that they have not withdrawn consent) and will continue to participate in study visits as scheduled, only without IMP administration. Rescue therapy may be initiated at this visit.
[g] The ESD visit must be performed when the participant either withdraws consent or is permanently discontinued from the study. The study site must make every effort to perform this visit within 7 days of the participant's last IMP dose.
[h] An unscheduled visit may be performed if the participant has (or suspects they have) new BP lesions or has other issues requiring site staff intervention, such as notable weight change. The investigator will decide which assessments to conduct based on the purpose of the unscheduled visit. In case of relapse, IGA-BP, BPDAI, and Itch NRS assessments must be performed, and participants should return to weekly on-site visits until CDA is achieved again.
[i] Histopathology/DIF are performed only if positive test results are not available as part of the participant's medical history.
[j] All vaccinations received before the study should be recorded as part of the participant's prior medication history, while all vaccinations received during the study should be recorded as concomitant medications.
[k] Weight may be measured when other weekly visits are performed on-site.
[l] WOCBP must have a negative serum pregnancy test. Postmenopausal female participants must have a serum FSH test to confirm postmenopausal status.
[m] The day 10 PK blood sample will only be collected during part A of the study from at least 28 participants.
[n] For study visits that occur at home (in between mandatory on-site visits), the investigator will call the participant once weekly to assess BP disease status and review/adjust the participant's concurrent prednisone (or equivalent) dosage.
[o] At BL (week 0 [day 1]) and week 1 (day 8), [redacted] mg of IMP (efgartigimod PH20 SC or placebo) will be administered via [redacted] SC injections (Table 6). At weeks 2 through 35, 1000 mg of IMP (efgartigimod PH20 SC or placebo) will be administered via a single SC injection.

2. INTRODUCTION

The proposed study is an operationally seamless 2-part, phase 2/3, prospective, global, multicenter, randomized, double-blinded, placebo-controlled study to investigate the efficacy, safety, tolerability, immunogenicity, participant-reported outcome measures (including those assessing quality of life [QoL]), pharmacokinetics (PK), and pharmacodynamics (PD) of efgartigimod PH20 SC (efgartigimod coformulated with recombinant human PH20 for subcutaneous [SC] injection) in adult participants with moderate-to-severe bullous pemphigoid (BP). This study intends to demonstrate that efgartigimod PH20 SC is an effective and safe treatment for BP, providing participants with control of disease activity (CDA) and eventually remission while reducing their cumulative exposure to oral corticosteroids (OCS).

The study will be conducted in 2 parts:

- Part A is a phase 2 evaluation which intends to provide proof of concept for the therapeutic activity of efgartigimod PH20 SC in participants with BP.
- Part B is a phase 3 evaluation which intends to confirm the results obtained from part A in a separate, larger group of participants with BP.

Parts A and B include different sample sizes, endpoints, and statistical analyses; otherwise, both parts are identical in schedule, structure, assessments, and conduct.

To allow for convenient SC injection of efgartigimod, participants will be administered efgartigimod PH20 SC, a solution of efgartigimod coformulated with recombinant human hyaluronidase PH20 (rHuPH20). rHuPH20 is currently being used in coformulations with approved therapeutic antibodies to facilitate SC injection of volumes >2 mL.

Efgartigimod PH20 SC or placebo will be administered once weekly throughout the 36-week treatment period. All participants will also receive concurrent therapy with OCS: oral prednisone at a starting dosage of 0.5 mg/kg/day (or an alternate OCS of equivalent dose strength) at baseline. The OCS dosage will be adjusted according to each participant's BP disease status throughout the study.

Additional information on efgartigimod is provided in the current IB.

2.1. Study Rationale

BP is a subepidermal autoimmune blistering disease (AIBD) that predominantly affects older adults. It is a chronic disease that significantly impacts 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 directly interfere with 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.[1,2]

At this time, no therapies are specifically licensed for the treatment of patients with BP. The current standard of care for BP is treatment with topical corticosteroids (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 [IVIg], 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.[3,4,5]

Efgartigimod, a neonatal crystallizable fragment receptor (FcRn) antagonist, blocks FcRn-mediated recycling of IgG, effectively reducing IgG levels, including IgG autoantibody levels. The formulation for subcutaneous (SC) administration of efgartigimod PH20 SC (efgartigimod coformulated with recombinant human hyaluronidase PH20 [rHuPH20]) represents a rational and innovative therapeutic approach to autoimmune diseases mediated by IgG autoantibodies, such as BP.

This study will determine whether sustained remission is attainable with efgartigimod PH20 SC treatment (compared with placebo) while minimizing cumulative OCS exposure. efgartigimod PH20 SC will also be evaluated for efficacy, safety, PK/PD, immunogenicity, and impact on the QoL of study participants.

2.2. Background

BP is the most common autoimmune blistering skin disease, with an estimated annual incidence of 2.4 to 23 cases per million individuals. However, among people >80 years of age, the incidence ranges from 190 to 312 cases per million individuals.[6,7] The disease has a poor prognosis, which is directly attributable to the advanced age of the patient population and the comorbidities that can be present in this population. A recent meta-analysis calculated that the relative risk of death among patients with BP during a 1-year period is 2.93 times greater that of the general worldwide population (adjusted for age and sex).[8] Studies examining the all-cause mortality among patients with BP beyond 1 year have reported higher death rates in the first year (20% to 27%) than in subsequent years (9% to 16%). The main causes of death were infections and cardiovascular disorders, which are attributable to both the older age of patients with BP and their use of corticosteroids and/or immunosuppressants.

In BP, the disruption of the dermal-epidermal junction by pathogenic autoantibodies results in large, tense bullae on the skin, progressing to epidermal erosion, crusting, and urticarial plaque formation. Without treatment, BP ultimately progresses to life-threatening complications, including (but not limited to) severe infections, functional impairment of vital organs, and iatrogenic conditions.

Corticosteroids (either topical or oral) are currently the first-line therapy for the treatment of patients with BP. For BP that is either localized or mild/moderate in severity, medical authorities recommend application of high-dose TCS of strong potency (such as clobetasol propionate at doses from 20 to 40 g/day).[9,10] Unfortunately, the use of TCS at such high doses results in a substantial systemic absorption and severe skin atrophy.[11]

For patients who have widespread or moderate-to-severe BP, OCS therapy is the standard of care among most practitioners. Unfortunately, OCS cause significant toxicity in patients with BP, because the cumulative corticosteroid exposure that is typically required to successfully manage the disease is high. Thus, physicians who treat patients with BP must provide the optimal corticosteroid dose to successfully manage the disease, achieve CDA or complete/partial remission (CR/PR), and prevent subsequent relapse, while also mitigating the adverse effects of corticosteroids by minimizing the amount that they prescribe to their patients.

Alternative adjuvant treatments to corticosteroids have been evaluated in patients with severe BP or in those who expressed corticosteroid resistance, including IVIg, plasma exchange, rituximab, and omalizumab. These treatments have either shown inconsistent results, proven to be prohibitively complicated and/or expensive, induced significant side effects in their respective populations of patients with BP, or produced encouraging results only to have significant portions of those who responded to treatment ultimately relapse shortly thereafter.[12,13,14,15,16]

Additionally, dapsone and tetracyclines (with or without nicotinamide) have also been evaluated as treatments for patients with BP who cannot be administered OCS; however, the efficacy of these treatments has been shown to be modest, at best.[17,18]

In summary, there is currently an unmet medical need for new BP treatments that provide rapid CDA and remission, minimize (or even prevent) relapse, and reduce the burdens placed on patients due to cumulative corticosteroid exposure.

2.3. Benefit/Risk Assessment

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

2.3.1. Risk Assessment

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

Table 2: Potential Risks and Mitigation Strategies for ARGX-113-2009

Potential clinically significant risk	Summary of data/ rationale for risk	Mitigation strategy
IMP		
Serious infection	Efgartigimod reduces IgG levels, potentially hindering immune response and increasing the risk for infection.	Exclude participants with clinically significant active infection that is not sufficiently resolved before baseline in the investigator's opinion (Section 5.2). Infections are considered AESIs (Section 8.4.7). Monitor for infections and temporarily interrupt IMP dosing as specified in Section 7.1.
Infusion/injection-related reactions	All therapeutic proteins can elicit immune responses, potentially resulting in hypersensitivity or allergic reactions such as rash, urticaria, angioedema, serum sickness, and anaphylactoid or anaphylactic reactions. Overall, the frequency of infusion/injection-related reactions in the studies was low. Pretreatment to prevent infusion/injection-related reactions is not required.	Participants 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 8.4.8).
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 are frequently observed in studies in which efgartigimod is comixed with PH20 and administered SC.	Continuously monitor participants for injection site reactions. Injection site reactions are considered AEs of clinical interest (Section 8.4.8).

Table 2: Potential Risks and Mitigation Strategies for ARGX-113-2009 (Continued)

Potential clinically significant risk	Summary of data/ rationale for risk	Mitigation strategy
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 6.8.1.3). Continuously monitor safety, including glucocorticoid-mediated toxicity, throughout the study (Section 8.3.9).
Study procedures		
Skin reactions due to blood collection	N/A	Blood sample collection has been minimized for this study.
Participant population		
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.	Participants with a Karnofsky Performance Index score of less than 60% will be excluded (Section 4.2.2 and inclusion criterion 5).

AESI=adverse event of special interest; BP=bullous pemphigoid; DSMB=data and safety monitoring board; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IgG=immunoglobulin γ; IMP=investigational medicinal product (efgartigimod PH20 SC or placebo); N=number of total participants in the study; OCS=oral corticosteroid (oral prednisone or an alternate OCS of equivalent dose strength); rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous

2.3.2. Benefit Assessment

Efgartigimod—both as an IV formulation and as efgartigimod PH20 SC—has been investigated in nonclinical studies, clinical studies of healthy participants, and clinical studies of participants with generalized myasthenia gravis (gMG), primary immune thrombocytopenia (ITP), chronic inflammatory demyelinating polyneuropathy (CIDP), and pemphigus. In clinical studies that included PD and efficacy assessments, efgartigimod effectively reduced IgG antibodies and improved clinical outcomes in participants with gMG, and primary ITP.

Additional safety findings from other clinical studies of efgartigimod are listed below:

- Single-dose administration of efgartigimod SC was safe and well tolerated by healthy participants (ARGX-113-1702).
- Single-dose administration of efgartigimod PH20 SC resulted in no significant safety findings (ARGX 113-1901).
- Efgartigimod PH20 SC administered once weekly for 4 weeks was safe and well tolerated in healthy adult participants (ARGX-113-1907).

Based on the results described above, the sponsor believes that efgartigimod PH20 SC will also be a safe and effective treatment for patients with BP.

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-113-2009.

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

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

3.1. Objectives and Endpoints for Part A of ARGX-113-2009 (Phase 2 Proof-of-Concept Part of Study)

Table 3: Part A Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of efgartigimod PH20 SC on achieving sustained remission in the treatment of participants with BP	• Proportion of participants who are in CR while receiving efgartigimod PH20 SC or placebo and have been off OCS therapy for ≥8 weeks at week 36
Secondary	
• To evaluate the corticosteroid-sparing effects of efgartigimod PH20 SC in participants with BP	• Cumulative dose of OCS from baseline to week 36
• To characterize the overall efficacy of efgartigimod PH20 SC in the treatment of participants with BP	• Proportion of participants who achieve an IGA-BP score of 0 while receiving efgartigimod PH20 SC or placebo and have been off OCS therapy for ≥8 weeks at week 36 • Proportion of participants who achieve an IGA-BP score of 0 or 1 while receiving efgartigimod PH20 SC or placebo and have been off OCS therapy for ≥8 weeks at week 36 • Proportion of participants who achieve an IGA-BP score of 0 or 1 while receiving efgartigimod PH20 SC or placebo at any time through week 36 • Changes from baseline in the BPDAI activity score • Proportion of participants who are in CR while receiving efgartigimod PH20 SC or placebo and have been receiving minimal OCS therapy for ≥8 weeks at week 36. (Minimal OCS therapy is defined as ≤0.1 mg/kg/day of prednisone [or an equivalent dose of another OCS]) • Time to achieve the following: o CDA o CR o CR while on minimal OCS therapy for ≥8 weeks o CR/PR while off OCS therapy for ≥8 weeks o CR while off OCS therapy for ≥8 weeks o Relapse

Table 3: Part A Objectives and Endpoints (Continued)

Objectives	Endpoints
Secondary (continued)	
• To characterize the overall efficacy of efgartigimod PH20 SC in the treatment of participants with BP (*continued*)	• Cumulative OCS dose for the participant at the time points when they exhibit the following: o CDA o CR o CR while on minimal OCS therapy for ≥8 weeks o CR/PR while off OCS therapy for ≥8 weeks o CR while off OCS therapy for ≥8 weeks o Relapse • Proportion of participants who receive rescue therapy before week 36
• To evaluate the efficacy of efgartigimod PH20 SC in preventing relapse of BP	• Proportion of participants who achieve CDA while receiving efgartigimod PH20 SC or placebo and remain free of relapse through week 36
• To evaluate the effect of efgartigimod PH20 SC on pruritus in participants with BP	• Changes from baseline in the 24-hour average itch score from the Itch NRS • Changes from baseline in the 24-hour worst itch score from the Itch NRS
• To assess the safety and tolerability of efgartigimod PH20 SC administered to participants with BP	• Incidence and severity of TEAEs, AESIs, and SAEs • Vital sign measurements, physical examinations, ECGs, and clinical laboratory safety evaluations
• To assess glucocorticoid-associated morbidity and evaluate the impact of efgartigimod PH20 SC in reduction of glucocorticoid toxicity	• The Aggregate Improvement Score (AIS) from the GTI • The Cumulative Worsening Score (CWS) from the GTI • The GTI Specific List (GTI-SL)
• To evaluate the effects of efgartigimod PH20 SC on the QoL of participants with BP	• EQ-5D-5L scores over time • DLQI scores over time • ABQoL scores over time
• To evaluate the pharmacokinetics of efgartigimod PH20 SC in participants with BP	• Efgartigimod serum concentrations
• To evaluate the pharmacodynamics of efgartigimod PH20 SC in participants with BP	• % Change of total IgG serum levels from baseline over time • % Change of anti-BP180 and anti-BP230 antibodies from baseline over time
• To evaluate the immunogenicity of efgartigimod PH20 SC in participants with BP	• Incidence and prevalence of antidrug antibodies (ADA) against efgartigimod (in serum) and antibodies against rHuPH20 (in plasma)

Table 3: Part A Objectives and Endpoints (Continued)

Objectives	Endpoints
Secondary (continued)	
• To evaluate the competency of participants or caregivers to (self-)administer efgartigimod PH20 SC	• Number and percentage of participants (or their caregivers) who complete the (self-)administration training at study sites • Number and percentage of participants (or their caregivers) who are determined by site staff to be sufficiently competent in (self-)administering efgartigimod PH20 SC • Number and percentage of participants (or their caregivers) who successfully (self-)administer efgartigimod PH20 SC under site staff supervision
Exploratory	
• To further explore the pharmacodynamics of efgartigimod PH20 SC in participants with BP	• [redacted]

ABQoL=Autoimmune Bullous Disease Quality of Life questionnaire; AE=adverse event; AESI=adverse event of special interest; BP=bullous pemphigoid; BPDAI=Bullous Pemphigoid Disease Area Index; CDA=control of disease activity; CR=complete remission; DLQI=Dermatology Life Quality Index; ECG=electrocardiogram; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; GTI=Glucocorticoid Toxicity Index; IGA-BP=Investigator Global Assessment of Bullous Pemphigoid; [redacted]; IgG=immunoglobulin γ; IMP=investigational medicinal product (efgartigimod PH20 SC or placebo); NRS=numerical rating scale; OCS=oral corticosteroid (oral prednisone or an alternate corticosteroid of equivalent dose strength); PR=partial remission; QoL=quality of life; rHuPH20=recombinant human hyaluronidase PH20; SAE=serious adverse event; TEAE=treatment-emergent adverse event

3.2. Objectives and Endpoints for Part B of ARGX-113-2009 (Phase 3 Confirmatory Part of Study)

Section 9.3.2 describes the estimand and analytical methodology for the primary endpoint of part B.

Table 4: Part B Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of efgartigimod PH20 SC on achieving sustained remission in the treatment of participants with BP	• Proportion of participants who are in CR while receiving efgartigimod PH20 SC or placebo and have been off OCS therapy for ≥8 weeks at week 36
Key Secondary – Subject to Alpha Control	
1. To evaluate the corticosteroid-sparing effects of efgartigimod PH20 SC in participants with BP	1. Cumulative dose of OCS from baseline to week 36

Table 4: Part B Objectives and Endpoints (Continued)

Objectives	Endpoints
Key Secondary – Subject to Alpha Control (continued)	
2. To characterize the overall efficacy of efgartigimod PH20 SC in the treatment of participants with BP	2. Proportion of participants who achieve an IGA-BP score of 0 while receiving efgartigimod PH20 SC or placebo and have been off OCS therapy for ≥8 weeks at week 36
3. To evaluate the efficacy of efgartigimod PH20 SC in preventing relapse of BP	3. Proportion of participants who achieve control of disease activity (CDA) while receiving efgartigimod PH20 SC or placebo and remain free of relapse through week 36
4. To characterize the efficacy of efgartigimod PH20 SC in the treatment of participants with BP	4. Proportion of participants who are in CR while receiving efgartigimod PH20 SC or placebo and have been receiving minimal OCS therapy for ≥8 weeks at week 36. (Minimal OCS therapy is defined as ≤0.1 mg/kg/day of prednisone [or an equivalent dose of another OCS].)
5. To evaluate the effect of efgartigimod PH20 SC on pruritus in participants with BP	5. Changes from baseline in the 24-hour average itch score from the Itch NRS
Other Secondary	
• To further characterize the overall efficacy of efgartigimod PH20 SC in the treatment of participants with BP	• Proportion of participants who achieve an IGA-BP score of 0 or 1 while receiving efgartigimod PH20 SC or placebo and have been off OCS therapy for ≥8 weeks at week 36 • Proportion of participants who achieve an IGA-BP score of 0 or 1 while receiving efgartigimod PH20 SC or placebo at any time through week 36 • Changes from baseline in the BPDAI activity score • Time to achieve the following: o CDA o CR o CR while on minimal OCS therapy for ≥8 weeks o CR/PR while off OCS therapy for ≥8 weeks o CR while off OCS therapy for ≥8 weeks o Relapse • Cumulative OCS dose for the participant at the time points where they exhibit the following: o CDA o CR o CR while on minimal OCS therapy for ≥8 weeks o CR/PR while off OCS therapy for ≥8 weeks o CR while off OCS therapy for ≥8 weeks o Relapse

Table 4: Part B Objectives and Endpoints (Continued)

Objectives	Endpoints
Other Secondary (continued)	
• To further characterize the overall efficacy of efgartigimod PH20 SC in the treatment of participants with BP (*continued*)	• Changes from baseline in the 24-hour worst itch score from the Itch NRS • Proportion of participants who receive rescue therapy before week 36
• To assess the safety and tolerability of efgartigimod PH20 SC administered to participants with BP	• Incidence and severity of TEAEs, AESIs, and SAEs • Vital sign measurements, physical examinations, ECGs, and clinical laboratory safety evaluations
• To assess glucocorticoid-associated morbidity and evaluate the impact of efgartigimod PH20 SC in reduction of glucocorticoid toxicity	• The Aggregate Improvement Score (AIS) from the GTI • The Cumulative Worsening Score (CWS) from the GTI • The GTI Specific List (GTI-SL)
• To evaluate the effects of efgartigimod PH20 SC on the QoL of participants with BP	• EQ-5D-5L scores over time • DLQI scores over time • ABQoL scores over time
• To evaluate the pharmacokinetics of efgartigimod PH20 SC in participants with BP	• Efgartigimod serum concentrations
• To evaluate the pharmacodynamics of efgartigimod PH20 SC in participants with BP	• % Change of total IgG serum levels from baseline over time • % Change of anti-BP180 and anti-BP230 antibodies from baseline over time
• To evaluate the immunogenicity of efgartigimod PH20 SC in participants with BP	• Incidence and prevalence of antidrug antibodies (ADA) against efgartigimod (in serum) and antibodies produced against rHuPH20 (in plasma)
• To evaluate the competency of participants or caregivers to (self-)administer efgartigimod PH20 SC	• Number and percentage of participants (or their caregivers) who complete the (self-)administration training at study sites • Number and percentage of participants (or their caregivers) who are determined by site staff to be sufficiently competent in (self-)administering efgartigimod PH20 SC • Number and percentage of participants (or their caregivers) who successfully (self-)administer efgartigimod PH20 SC under site staff supervision

Table 4: Part B Objectives and Endpoints (Continued)

Objectives	Endpoints
Exploratory	
• To further explore the pharmacodynamics of efgartigimod PH20 SC in participants with BP	• [redacted]

ABQoL=Autoimmune Disease Quality of Life (questionnaire); AE=adverse event; AESI=adverse event of special interest; BP=bullous pemphigoid; BPDAI=Bullous Pemphigoid Disease Area Index; CDA=control of disease activity; CR=complete remission; DLQI=Dermatology Life Quality Index; ECG=electrocardiogram; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; GTI=Glucocorticoid Toxicity Index; IGA-BP=Investigator Global Assessment of Bullous Pemphigoid; [redacted] IgG=immunoglobulin γ; IMP=investigational medicinal product (efgartigimod PH20 SC or placebo); NRS=numerical rating scale; OCS=oral corticosteroid (oral prednisone or an alternate corticosteroid of equivalent dose strength); PR=partial remission; QoL=quality of life; rHuPH20=recombinant human hyaluronidase PH20; SAE=serious adverse event; TEAE=treatment-emergent adverse event

4. STUDY DESIGN

4.1. Overall Design

This is an operationally seamless 2-part, phase 2/3, prospective, global, multicenter, randomized, double-blinded, placebo-controlled study to investigate the efficacy, safety, tolerability, immunogenicity, participant-reported outcome measures (including QoL assessments), PK, and PD of efgartigimod PH20 SC in adult participants with moderate-to-severe BP.

During both parts of the study, participants will be administered investigational medicinal product (IMP): efgartigimod PH20 SC or placebo) once weekly for 36 weeks. All participants will also receive concurrent therapy with OCS, ie, prednisone at a starting dosage of 0.5 mg/kg/day at baseline, or an alternate OCS at an equivalent dose strength. The OCS dosage will be adjusted according to each participant's BP disease status throughout the study.

4.1.1. Description of Part A and Part B

A 2-part schematic of the overall study design is presented in Section 1.2; brief descriptions of both parts of ARGX-113-2009 are presented below:

Part A is a phase 2, proof-of-concept study in which approximately 40 adult participants with moderate-to-severe BP will be randomized in a 1:1 ratio to receive either efgartigimod PH20 SC or placebo. The main goal of part A is to determine whether efgartigimod PH20 SC is effective in the treatment of participants with BP via assessment of the study's primary endpoint: the proportion of participants who are in CR while receiving efgartigimod PH20 SC or placebo and have been off OCS therapy for ≥8 weeks at week 36. Other part A objectives and endpoints are listed in Table 3.

An interim analysis will be conducted from data obtained from all part A participants through the week 26 visit. The interim analysis will be conducted to assess the primary endpoint, assess several of the study's secondary endpoints, confirm the appropriate sample size for part B of the study, and determine whether the efficacy results observed through week 26 warrant continued study of efgartigimod PH20 SC for the treatment of participants with BP (futility analysis). The part A interim analysis is described in Section 9.4.

The final analysis of part A data will be performed after its last participant completes their last visit (Section 4.4).

Part B is a phase 3 confirmatory study in which approximately 120 adult participants with moderate-to-severe BP will be randomized in a 1:1 ratio to receive either efgartigimod PH20 SC or placebo. The main goal of part B is to confirm the results obtained for the primary endpoint from part A (the proportion of participants who are in CR while receiving efgartigimod PH20 SC or placebo and have been off OCS therapy for ≥8 weeks at week 36), but in a separate, larger group of participants with BP. Other part B objectives and endpoints are listed in Table 4. The proposed order of the key secondary endpoints for part B may be adjusted based on the results obtained from the part A interim analysis (Section 9.1.1).

4.1.2. Conduct of Both Parts A and B

Parts A and B of the study have different sample sizes; otherwise, both parts are identical in schedule, structure, assessments, and conduct. Both parts A and B have screening periods

of up to 2 weeks (extendable to 3 weeks per investigator discretion) followed by treatment periods of 36 weeks, during which participants will receive either efgartigimod PH20 SC or placebo. Finally, all part A and part B participants who complete the end of treatment period (EoTP) visit at week 36 will be offered the option to either enroll in an open-label extension (OLE) study or complete a 7-week treatment-free follow-up period.

To enter the study, participants must have a diagnosis of BP that complies with the international guidelines for the diagnosis of BP.[19,20,21] The diagnosis of BP must be confirmed by all 3 of the following methods before the participant is randomized to a study arm (refer to inclusion criterion 3):

- Clinical signs of BP (presence of bullae), with or without the presence of urticarial, eczematous, or erythematous plaques, and with or without pruritus.
- Histopathological and direct immunofluorescence (DIF) examination of a cutaneous biopsy.
- Serology by indirect immunofluorescence (IIF), chemiluminescence enzyme immunoassay (CLEIA), or ELISA.

In part B, study participants will be stratified by disease history (newly diagnosed or relapsing) and disease severity (moderate BP [an Investigator Global Assessment of Bullous Pemphigoid {IGA-BP} score of 3] or severe BP [an IGA-BP score of 4]). The participants will be randomized in a 1:1 ratio to receive either efgartigimod PH20 SC or placebo as follows:

- Efgartigimod PH20 SC will be administered by SC injection on day 1 and day 8 at a dose of [redacted] mg (administered as [redacted] separate SC injections of 1000 mg each), followed by single weekly SC injections of 1000 mg from week 2 through week 35.
- Placebo (injection vehicle coformulated with 2000 U/mL of rHuPH20) will be administered using the same regimen described above.

All participants will also receive concurrent therapy with OCS, ie, prednisone at a starting dosage of 0.5 mg/kg/day at baseline, or an alternate OCS at an equivalent dose strength. The OCS dosage will be adjusted according to each participant's BP disease status throughout the study. BP disease status terminology definitions are listed in Section 4.1.3 and the oral prednisone dose adjustment procedure is described in Section 6.8.1.3.

Efficacy and QoL measures to be assessed during the study (other than BP disease status assessment) include the following:

- Investigator Global Assessment of Bullous Pemphigoid (IGA-BP)
- Bullous Pemphigoid Disease Area Index (BPDAI)
- Itch Numerical Rating Scale (Itch NRS)
- EuroQol 5-Dimension 5-Level (EQ-5D-5L)
- Dermatology Life Quality Index (DLQI)
- Autoimmune Bullous Disease Quality of Life (ABQoL) questionnaire.

Brief descriptions of these efficacy and QoL measurements are provided in Section 8.2; the time points when they are administered during the study are provided in the SoA (Table 1).

PK measures include the quantification of efgartigimod serum concentrations. PD measures include the quantification of total IgG serum levels, anti-BP180 and anti-BP230 antibodies, and [redacted]. Refer to the SoA (Table 1) for the time points when PK and PD blood samples are collected during the study; each of the study's PK and PD measures is briefly described in Section 8.5 and Section 8.6, respectively.

Immunogenicity measures include the determination of both ADAs against efgartigimod in serum and antibodies against rHuPH20 in plasma. Refer to the SoA (Table 1) for the time points when immunogenicity blood samples are collected during the study; additional information regarding the immunogenicity measures is presented in Section 8.9.

Safety measures for the study include the following:

- Physical examinations
- Height, body weight, and vital signs measurements
- Electrocardiograms (ECGs)
- Recording of medical, surgical, and vaccination histories
- Clinical safety laboratory tests, including clinical chemistry, hematology, coagulation, urinalysis, and virus serology
- Serum and urine pregnancy tests for women of childbearing potential (WOCBP) or a follicle-stimulating hormone (FSH) test to confirm postmenopausal status
- The Glucocorticoid Toxicity Index (GTI), consisting of the Composite Glucocorticoid Toxicity Index (C-GTI) and the Glucocorticoid Toxicity Index Specific List (GTI-SL)
- Recording of adverse events (AEs), serious adverse events (SAEs), and adverse events of special interest (AESIs)

AE, SAE, and AESI reporting are described in detail in Section 8.4; refer to Section 8.3 for brief descriptions of the other safety measures.

In addition, selected study sites will participate in the following substudies:

- Photography substudy: Site staff will take photographs of bullous lesions located at various anatomical regions of participants per the discretion of the investigator. As a guidance, time points of baseline, CDA, CR, and relapse are indicated; however, photographs may also be taken at intermediate time points (Section 8.10).
- Vaccination response substudy: This substudy will investigate the influence of efgartigimod PH20 SC treatment on historical protective antibody titers and humoral and/or cellular responses to vaccines received during the study among participants who provide additional consent to participate in this substudy. (Section 8.3.6.2).

Participants and/or their caregivers (defined in Abbreviations and Definitions) will be invited to receive training for (self-)administration of the IMP. In this study, participants (and/or their

caregivers) will only be permitted to (self-)administer IMP at on-site visits under the supervision of site staff, and only after they have completed training and are determined competent enough to do so by site staff. Successful completion of this training is intended to enable IMP self-administration or caregiver-supported administration at home in the OLE study ARGX-113-2010.

4.1.3. Bullous Pemphigoid Disease Status Terminology to Be Used in the Study

The following terms and definitions will be used in ARGX-113-2009 to conduct the study, monitor BP disease status, and assess the study endpoints aligned with consensus terminology (according to Murrell et al. in 2012[22]):

- 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 after being administered oral prednisone at 0.75 mg/kg/day (or equivalent OCS) for 3 weeks. The investigator has the option to add a fourth week of therapy with oral prednisone 0.75 or 1 mg/kg/day (or equivalent) (based on clinical judgment) before declaring treatment failure.
- Transient lesions – new lesions that heal within 1 week or pruritus lasting less than 1 week.
- Nontransient lesions – new lesions that do not heal within 1 week or pruritus continuing longer than 1 week.
- Minimal OCS therapy – an oral prednisone dosage of ≤0.10 mg/kg/day (or an equivalent dose of another OCS).
- Complete remission (CR) – the absence of new lesions, complete healing of existing lesions, and absence of pruritus (except postinflammatory changes, including hyper/hypopigmentation or skin damage).
- Partial remission (PR) – the presence of only new transient lesions.
- Relapse – appearance of 3 or more new lesions a month (blisters, eczematous lesions, or urticarial plaques) or at least 1 large (>10 cm diameter) eczematous lesion or urticarial plaque that do not heal within 1 week, or extension of established lesions or daily pruritus in a participant who has achieved CDA.

ALSO: For the purposes of this protocol, “oral prednisone” refers to doses/dosages of prednisone ***or*** an alternate, equivalent OCS (eg, prednisolone).

4.2. Scientific Rationale for Study Design

4.2.1. Rationale for Selection of a Phase 2/3 Study

Efgartigimod IV and/or efgartigimod PH20 SC have been investigated in clinical studies of healthy participants and participants with gMG, primary ITP, CIDP, and pemphigus. The clinical pharmacology, efficacy, and safety/tolerability results from these studies are described in Section 5 of the efgartigimod IB.

The results obtained from the phase 2 study of efgartigimod IV in participants with pemphigus (ARGX-113-1701) are of particular importance, because they demonstrated that efgartigimod can be an effective therapy in patients who have an IgG-driven autoimmune disease involving the skin (similar to BP). The results from this phase 2 study, coupled with the body of results obtained from other phase 2 and phase 3 studies of efgartigimod for several other autoimmune diseases, lead the sponsor to believe that it is appropriate to conduct a 2-part, phase 2/3 study to investigate the efficacy, safety, and other effects of efgartigimod PH20 SC in participants with BP.

The sponsor recognizes that efgartigimod PH20 SC has not yet been administered to participants with BP and that the pathophysiology of BP is more complex than that of pemphigus. As a result, ARGX-113-2009 has been designed to ensure the safety of its participants by including guidelines for stopping treatment with efgartigimod PH20 SC and initiating rescue therapy using standard of care for BP. Additionally, the study includes an interim analysis (Section 9.4) that will be performed using week 26 data collected from participants who are enrolled in part A. This analysis is being conducted to assess the study's primary endpoint (Table 3) at week 26, assess selected secondary endpoints (Table 3), determine the appropriate sample size for part B of the study, and determine whether the efficacy results observed through week 26 warrant continued study (futility analysis; Section 9.4).

4.2.2. Rationale for the Selection of the Participant Population

To ensure that the study population aligns with the demographics of the general population of patients with BP (which occurs predominantly in people ≥65 years of age), ARGX-113-2009 study participants will include males and females who have reached the age of consent with no upper age limit.

The sponsor has designed the participant eligibility criteria of ARGX-113-2009 to comply with international guidelines for the diagnosis of BP (criteria listed in Section 4.1),[19,20,21] which will ensure that the study population is representative of the general worldwide population of patients with BP.

Participants will receive either efgartigimod PH20 SC or placebo. All participants will receive concurrent therapy with OCS, ie, prednisone at a starting dosage of 0.5 mg/kg/day at baseline or an alternate OCS at an equivalent dose strength. The OCS dosage will be adjusted according to each participant's BP disease status throughout the study (disease status terminology is provided in Section 4.1.3).

ARGX-113-2009 will enroll participants with moderate-to-severe BP. This subgroup of patients was selected because it represents those patients in the general population who have the greatest medical need for new BP treatment modalities that can reduce their cumulative OCS exposure.[19,23,24]

The IGA-BP will be used to assess the severity of BP for each participant. It is a new assessment tool that was developed in 2021 by AIBD experts and is currently being used (along with the BPDAI) in other clinical studies of BP. The IGA-BP categorizes the severity of BP on a numerical scale of 0 to 4, with a score of 0 representing no overt signs of BP and a score of 4 representing severe BP. Given that this study is designed to investigate the effects

of efgartigimod PH20 SC on participants with moderate-to-severe BP, ARGX-113-2009 will enroll participants whose IGA-BP score is 3 or 4.

Patients with BP can have comorbidities that may limit day-to-day functioning. Moreover, ARGX-113-2009 will not have an upper age limit for participation; therefore, the sponsor anticipates the study to include a large number of older adult participants with BP. Also, the sponsor wants to ensure that study participants will be able to adequately complete patient-reported outcome (PRO) assessments without placing any undue burden on them. Therefore, ARGX-113-2009 participants will be required to have a Karnofsky Performance Index (Section 10.5) score of ≥60%.

Atypical types of BP and AIBDs other than BP may have pathogeneses and disease courses that differ from those of typical BP. Therefore, participants with other AIBDs or atypical forms of BP (listed in exclusion criterion 1) will be excluded from participating in the study.

Participants with BP who have been treated with any systemic therapies for the disease other than corticosteroids (listed in exclusion criterion 3B) but still wish to participate in the study will be required to complete a wash-out period before they can begin study participation (Section 5.5). The durations of these required wash-out periods (described in Section 5.5) were selected based on the known PK properties of each of these therapies. [Note: prior therapy with conventional immunosuppressants (eg, azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil) or with dapsone require no wash-out period; however, these therapies must be discontinued before baseline.]

4.2.3. Rationale for the Selection of the Oral Corticosteroid Dosing Regimen

The oral prednisone starting dosage of 0.5 mg/kg/day (or equivalent OCS) and the subsequent dosage modification regimen (described in Section 6.8.1.3) are based on recommendations from European and Japanese guidelines[25,26] Oral prednisone doses will be adjusted throughout the study for each participant based on their current BP disease activity to maintain CDA and to avoid relapse (Section 6.8.1.3).

4.2.4. Rationale for the Selection of Study Endpoints

4.2.4.1. Primary Endpoint

The primary endpoint was selected based on the BP disease status terminology described by Murrell et al. in 2012,[22] in which the term CR off therapy is defined as “the absence of new or established lesions or pruritus while the patient is off all therapy for at least 2 months.” Achieving a complete and stable absence of BP symptoms represents a clinically meaningful outcome and is expected to result in a significant improvement in patient quality of life.

Other than IMP, the only concurrent BP therapy permitted in ARGX-113-2009 is OCS; therefore, within the parameters of this study, “off OCS therapy” is considered equivalent to the AIBD expert definition of “off therapy.”[22]

In ARGX-113-2009, tapering of concurrent OCS therapy will be performed in a manner consistent with treatment guidelines,[24,25,26] while once-weekly dosing of IMP will be continued until the end of the 36-week treatment period. Tapering, and ultimately eliminating, concurrent OCS therapy reduces the risks of developing comorbidities associated with steroid therapy.

Avoiding such risks is particularly important for older adults (like those with BP), who historically develop serious comorbidities like osteoporosis, diabetes, and glaucoma following prolonged exposure to high doses of OCS.[27,28,29]

ARGX-113-2009 will assess whether participants have remained in CR while receiving efgartigimod PH20 SC or placebo and after having been off OCS for at least 8 weeks at the end of the 36-week treatment period. Achieving a sustained response to treatment is of particular importance to patients with BP, as the available evidence shows that many patients who achieve CR subsequently relapse within months.[30,31]

The selection of a 36-week treatment period is based on international guidelines for the treatment of BP, which recommend that systemic steroid doses should be tapered gradually so that minimal OCS therapy is achieved within 4 to 6 months after beginning treatment, and that OCS therapy may be subsequently stopped after the patient has sustained CR for 3 to 6 months. Therefore, a 36-week treatment period (approximately 9 months) is considered an appropriate duration to allow participants to achieve CR and stop concurrent OCS therapy.[24]

4.2.4.2. Secondary Efficacy Endpoints

4.2.4.2.1. Key Secondary Endpoints (Part B Only)

Rationales for the selection of the key secondary efficacy endpoints for part B are summarized below. [**Note**: "Key" secondary endpoints are subject to hierarchical testing and alpha-control during part B only. During part A of the study, they will be assessed as standard secondary efficacy endpoints (without hierarchical testing/alpha-control).]

1. Cumulative dose of OCS from baseline to week 36: Currently, the standard of care for moderate-to-severe BP is OCS. Unfortunately, exposure to high doses of OCS results in an increased risk of developing serious comorbidities, especially in older adults. As a result, a goal in BP treatment is to reduce the patient's cumulative exposure to OCS. Therefore, this endpoint was selected to ascertain whether participants who are administered efgartigimod PH20 SC have lower cumulative OCS exposure values than participants who are administered placebo.
2. Proportion of participants who achieve an IGA-BP score of 0 while receiving efgartigimod PH20 SC or placebo and have been off OCS therapy for ≥8 weeks at week 36: This endpoint was selected because an IGA-BP score of 0 (defined in Section 4.2.2 and Section 10.6) represents a complete absence of BP skin lesions. As described in Section 4.2.4.1, the ability to remain free of clinical disease activity while limiting one's cumulative exposure to OCS for prolonged periods is particularly important for older adults with BP, who are more susceptible to serious comorbidities due to prolonged OCS exposure.[27,28,29]
3. Proportion of participants who achieve CDA while receiving efgartigimod PH20 SC or placebo and remain free of relapse through week 36: This endpoint was selected because it is important to ascertain whether treatment with efgartigimod PH20 SC provides participants with BP prolonged and sustained relief from BP symptoms, and whether efgartigimod PH20 SC effectively prevents relapse.

4. Proportion of participants who are in CR while receiving efgartigimod PH20 SC or placebo and have been receiving minimal OCS therapy for ≥8 weeks at week 36: This endpoint was selected for the same reasons as those described for key secondary endpoint 3.
5. Changes from baseline in the 24-hour average itch score from the Itch NRS: As noted in Section 2.1, pruritus is among the signs/symptoms of BP; moreover, the itching that is associated with BP can be debilitating. This endpoint will determine if treatment with efgartigimod PH20 SC provides relief from pruritus, which is considered a clinically meaningful disease improvement.

4.2.4.2.2. Additional (or Other) Secondary Efficacy Endpoints (Parts A and B)

The additional secondary efficacy endpoints of this study (listed in Table 3 and Table 4) were selected to further characterize the efficacy of efgartigimod PH20 SC in participants with BP.

4.2.4.3. Safety Endpoints

The safety, tolerability, and health impact endpoints selected for this study are those considered to be standard for any clinical study evaluating the safety of an IMP.

4.2.4.4. Pharmacokinetics, Pharmacodynamics, and Immunogenicity Endpoints

The PK, PD, and immunogenicity endpoints selected for this study are those considered to be standard for any clinical study evaluating the manner in which an immunological IMP is processed by the body and how it targets the immune system.

4.2.5. Rationale for the Selection of Study Assessments

The BP disease assessment terminology and definitions applied in this study were adapted from those established by Murrell et al. in 2012.[22] These terms and definitions are internationally accepted by AIBD medical experts and clinicians who treat patients with BP.

Disease severity and symptoms will be monitored throughout the study using the IGA-BP scale, the BPDAI, and the Itch NRS. The IGA-BP was developed in 2021 by medical experts in the field of AIBDs, and it is currently being used (along with the BPDAI) in other clinical studies of therapies for BP. The IGA-BP scale has specific guidance on equating the extent of skin lesions to disease severity (Section 10.6), while the BPDAI score also considers the presence of mucosal lesions (Section 10.7).[2] Pruritic symptoms will be measured using the Itch NRS (Section 10.8).[32,33,34]

The BPDAI[2] and the Itch NRS[32,33,34] are validated and internationally accepted measures of BP disease severity and pruritus intensity, respectively.

The EQ-5D-5L,[35] DLQI,[36] and ABQoL[37] are validated and internationally accepted measures of patient QoL.

4.3. Justification for Selection of the Treatment Regimen and Dose

In ARGX-113-2009, study participants will either receive efgartigimod PH20 SC or placebo. At the time of this protocol's initial approval, efgartigimod PH20 SC had been safely administered to healthy participants and participants with gMG, primary ITP, CIDP, and pemphigus.

The SC route of administration offers convenience for participants with BP, their caregivers, and health care providers, because SC injections are easier to administer than IV injections. Additionally, the coformulation of efgartigimod with rHuPH20 permits SC dosing of higher volumes than typical SC injections, because rHuPH20 reduces resistance to fluid flow and increases dispersion and absorption of injected medicines and fluids, which allows for a larger volume to be injected with limited skin swelling or pain.

In BP, patients typically achieve CDA, PR, or CR only after receiving treatment for several weeks; sometimes even months of treatment are required before CR or PR is achieved. Moreover, patients with BP tend to relapse within a few months after achieving remission.[30,31] Therefore, studies of BP must be of sufficient duration to assess the durability of efficacy of the IMP and the sustainability of remission while the patient is off OCS therapy. It is for these reasons that the sponsor has selected a 36-week treatment period for ARGX-113-2009.

Initially, the clinical development of efgartigimod was based on IV dosing. Results from phase 1 studies in healthy participants, phase 2/3 studies in participants with gMG, a phase 2 study in participants with ITP, and PK/PD modeling analysis showed that efgartigimod IV 10 mg/kg administered once weekly achieved nearly maximal reduction in serum IgG levels. Studies of participants with gMG and ITP also showed that efgartigimod IV 10 mg/kg administered once weekly resulted in clinical efficacy coupled with reductions in serum pathogenic autoantibody levels while maintaining a favorable safety/tolerability profile.

In ARGX-113-2009, participants will be administered efgartigimod PH20 SC as a fixed dose (rather than a dose that is adjusted weekly based on body mass), because this is more convenient for both the study participants and site staff. Results from a PK/PD modeling analysis indicated that efgartigimod PH20 SC 1000 mg administered once weekly would result in reductions in total IgG serum levels equivalent to a weekly dose of efgartigimod IV 10 mg/kg. Results from a phase 1 study comparing the PK and PD properties of IV and SC administration of efgartigimod in healthy participants (ARGX-113-1907) confirmed that 4 once-weekly injections of efgartigimod PH20 SC 1000 mg were noninferior to 4 once-weekly infusions of efgartigimod IV 10 mg/kg in reducing total IgG serum levels. Therefore, the sponsor has selected efgartigimod PH20 SC 1000 mg administered once weekly as the maintenance dose for ARGX-113-2009.

Still, given that IgG autoimmune activity is considered to cause the pathophysiology of BP, any therapy that targets this activity should be designed so that maximum reduction of total IgG serum levels occurs as rapidly as possible. Therefore, ARGX-113-2009 participants who are assigned to the efgartigimod PH20 SC arm will receive a dose of [redacted] mg at baseline (week 0) and week 1. Initiation of treatment with 2 once-weekly doses of efgartigimod PH20 SC [redacted] mg is predicted to achieve a nearly maximal reduction in total IgG serum levels within 2 weeks that is similar to that for once-weekly injections of efgartigimod PH20 SC 1000 mg at steady state.

4.4. End of Study Definition

The end-of-study definitions for ARGX-113-2009 are listed below:

- The end of part A of the study is defined as the date of the last visit of its last participant.
- The end of part B of the study is defined as the date of the last visit of its last participant.
- The end of the study is defined as the date of the last visit of the last participant in part B of the study. Alternatively, it is defined as the date of the last participant visit following the sponsor's decision to terminate the study for any reason.

A participant is considered to have completed the study under either of the following scenarios:

- The participant completes the EoTP visit at week 36 and chooses to immediately enroll in the OLE study ARGX-113-2010. The moment that a participant decides to roll over to the OLE study, they are considered to have completed ARGX-113-2009.
- The participant chooses not to enroll in the OLE study after completing the EoTP visit at week 36 and instead completes the 7-week treatment-free follow-up period (through week 43).

5. STUDY POPULATION

Prospective approvals of protocol deviations to recruitment and 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. The participant is willing and able to do the following:
   a. understand the requirements of the study
   b. provide written informed consent (including consent for the use and disclosure of research-related health information)
   c. comply with the study protocol procedures (including required study visits).

2B. The participant is male or female and has reached the local legal age of consent at the time of signing the informed consent form (ICF).

3. The participants have clinical signs of BP (ie, presence of bullae), with or without the presence of urticarial/eczematous/erythematous plaques or pruritus at the screening and baseline visits. The diagnosis of BP must be confirmed by positive histopathology and DIF before randomization to treatment assignment, and by positive serology (by IIF, CLEIA, or ELISA, according to local practice) at screening (Section 8.1.2).

4. The participant has an IGA-BP score of 3 or 4 at screening and baseline.

5. The participant has a Karnofsky performance status of at least 60% at screening.

6B. The participant 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 serum pregnancy test at screening and a negative urine pregnancy test at baseline before receiving IMP. (Section 10.4.2.1)

5.2. Exclusion Criteria

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

1. Other forms of pemphigoid (including but not limited to pemphigoid gestationis, drug-induced BP that resolves after culprit-drug withdrawal, anti-p200 pemphigoid, mucous membrane pemphigoid, and cicatricial pemphigoid), or other AIBDs (including but not limited to epidermolysis bullosa acquisita, pemphigus vulgaris, and exfoliative erythroderma)

2. Received unstable dose of treatments known to cause or exacerbate BP (eg, angiotensin converting enzyme inhibitors, penicillamine, furosemide, phenacetin, dipeptidyl peptidase 4 inhibitor) for at least 4 weeks prior the baseline visit

3B. Use of BP treatments other than OCS, such as TCS, conventional immunosuppressants (eg, azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil), or dapsone, including the following:

a. sulfasalazine, IVIg, subcutaneous administration of immunoglobulin (SCIg), immunoadsorption or plasma exchange within 8 weeks of the baseline visit
b. tetracyclines with or without nicotinamide at doses higher than the recommended daily allowance (RDA)/dietary reference intake (DRI) within 2 weeks of the baseline visit
c. any monoclonal antibody (including rituximab or another anti-CD20 biologic) within 6 months of the baseline visit
d. complementary therapies—such as traditional Chinese medicines, herbs, or procedures (eg, acupuncture)—within 4 weeks (or 5 half-lives) of the baseline visit, if the investigator determines that such therapies may interfere with the study's efficacy assessments and/or potentially risk the safety of the participant

4. Known contraindication to OCS therapy

5C. Clinically significant active infection that is not sufficiently resolved before baseline in the investigator's opinion

6A. Positive COVID-19 test result at screening (testing performed if required per local regulations)

7A. Any other known autoimmune disease or any medical condition that, in the opinion of the investigator, would interfere with an accurate assessment of clinical symptoms of BP, prevent participants from complying with protocol requirements, or put the participant at undue risk

8. History of malignancy unless deemed cured by adequate treatment with no evidence of recurrence for ≥3 years before the first administration of the IMP. Participants with the following cancers can be included at any time, provided they are adequately treated before their participation in the study:

   a. Basal cell or squamous cell skin cancer
   b. Carcinoma in situ of the cervix
   c. Carcinoma in situ of the breast
   d. Incidental histological finding of prostate cancer (tumor-node metastasis [TNM] stage T1a or T1b)

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

10. Use of an investigational product within 3 months or 5 half-lives (whichever is longer) before the first dose of IMP

11. Previously participated in a clinical study with efgartigimod

12. Known hypersensitivity to any of the components of the administered treatments

13A. Positive serum test at screening for an active infection with any of the following conditions:

   a. HBV that is indicative of an acute or chronic infection, unless associated with a negative hBsAg or negative HBV DNA test[38]
   b. HCV based on HCV antibody assay unless a negative RNA test is available

c. HIV based on test results that are associated with an AIDS-defining condition or a CD4 count <200 cells/mm^3
d. HIV based on test results of a CD4 count ≥200 cells/mm^3 not adequately treated with antiviral therapy

14A. Total IgG serum levels <4 g/L at screening.

15A. Current or history (ie, within 12 months of screening) of alcohol, drug, or medication abuse as assessed by the investigator

16A. Pregnant or lactating females and those who intend to become pregnant during the study

17. Live or live-attenuated vaccine received <4 weeks before baseline visit

18. Current participation in another interventional clinical study

19. Severe renal impairment (creatine clearance <30 mL/min/1.73 m^2) at screening

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

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

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

5.5. Criteria for Temporarily Delaying Study Participation

As described in exclusion criterion 3B, participants with BP who have been treated with any of the following will be excluded from study participation:

- Sulfasalazine, IVIg, SCIg, immunoadsorption, or plasma exchange within 8 weeks of the baseline visit
- Tetracyclines (with nicotinamide [at doses higher than the RDA/DRI] or without nicotinamide) within 2 weeks of the baseline visit

- Any monoclonal antibody (including rituximab or another anti-CD20 biologic) within 6 months of the baseline visit

However, any potential ARGX-113-2009 candidate who has been treated with any of the above-noted therapies and still wishes to participate in the study must complete a wash-out period before they can be randomized to IMP. The duration of the required wash-out period must match the duration identified above for each class of medication. Note: therapy with TCS and/or conventional immunosuppressants (eg, azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil) or with dapsone requires no wash-out period; however, these therapies must be discontinued before baseline.

6. IMP(S) AND CONCOMITANT THERAPY

All IMP is manufactured according to Good Manufacturing Practice regulations.

6.1. IMP(s) Administered

A list of IMPs and noninvestigational medicinal products is presented in Table 5, while the characteristics of the 2 treatment arms of ARGX-113-2009 are described in Table 6. Fixed doses of efgartigimod PH20 SC or placebo will be administered at body sites spared of any cutaneous BP lesions, with the abdominal area being the preferred site. Optional sites (such as thighs and arms) may be used. Placebo will contain the same excipients as efgartigimod PH20 SC but without the active ingredient efgartigimod. Masked vials and masked syringes will be provided to preserve the study blind (Section 6.2.1 and Section 6.3).

Refer to the pharmacy manual and preparation guide for further details.

Table 5: IMP(s) Administered

IMP label	Efgartigimod PH20 SC	Placebo	Oral prednisone[a]
IMP and non-IMP name	Efgartigimod for SC administration coformulated with rHuPH20	Placebo	Prednisone for oral administration
IMP description	Solution for SC injection to be administered at a fixed efgartigimod dose of 1000 mg per injection	Vehicle + 2000 U/mL rHuPH20 for SC injection	Prednisone (or equivalent) tablets for oral administration
Type	Biologic	Other: placebo	Non-IMP
Dose formulation	Injection	Injection	Tablet
Unit dose strength(s)	Efgartigimod 180 mg/mL + 2000 U/mL rHuPH20	Placebo + 2000 U/mL rHuPH20	Prednisone (or equivalent) 2.5 mg, 5 mg, 10 mg, 20 mg
Dosage level(s)	[redacted] × 1000 mg SC doses administered at separate sites (ie, [redacted] mg in total) on day 1 and day 8; single 1000 mg SC doses administered weekly from week 2 through week 35	[redacted] SC doses administered at separate sites on day 1 and day 8; single SC doses administered weekly from week 2 through week 35	Refer to Section 6.8.1.3 for oral prednisone dosage taper/increase schedule
Route of administration	Abdominal SC injection(s); preferred site[b]	Abdominal SC injection(s); preferred site[b]	Oral administration

Table 5: IMP(s) Administered (Continued)

Intervention	Efgartigimod PH20 SC	Placebo	Oral prednisone[a]
Use	Investigational drug	Placebo control for investigational drug	Non-IMP; concurrent therapy
IMP and non-IMP	IMP	IMP	Non-IMP
Sourcing	Provided by the sponsor to the study site	Provided by the sponsor to the study site	Provided by the sponsor to the study 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	Provided in glass vials. Each glass vial will be labeled as required per country requirement	Provided in glass vials. Each glass vial will be labeled as required per country requirement	Non-IMP will be provided as 1 of the following: • In the commercial package and labeled as required per country requirements • As a magistral preparation upon prescription by the investigator • In the commercial package sourced locally

BP=bullous pemphigoid; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IMP=investigational medicinal product; OCS=oral corticosteroid (prednisone or equivalent); placebo=placebo for SC administration coformulated with rHuPH20; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)

[a] Refers to oral prednisone or an equivalent OCS.

[b] IMP will be administered on body sites spared of any cutaneous BP lesions; the abdomen is the preferred site. Optional sites (such as thighs or arms) may be chosen.

Table 6: Study Arm(s)

Arm Title	Efgartigimod PH20 SC	Placebo
Arm Type	Experimental	Placebo
Arm Description	Participants will receive efgartigimod PH20 SC [redacted] mg (via [redacted] separate 1000 mg SC injections) on day 1 and day 8 Beginning at week 2, participants will receive efgartigimod PH20 SC 1000 mg (via single SC injection) once weekly through week 35. Participants will be administered concurrent OCS (oral prednisone) at 0.5 mg/kg/day, or equivalent OCS) beginning at baseline (week 0); this dosage will be adjusted throughout the study based on the participant's current BP disease status.	Participants will receive placebo (via [redacted] separate SC injections) on day 1 and day 8 Beginning at week 2, participants will receive placebo (via single SC injection) once weekly through week 35. Participants will be administered concurrent OCS (oral prednisone) at 0.5 mg/kg/day (or equivalent OCS) beginning at baseline (week 0); this dosage will be adjusted throughout the study based on the participant's current BP disease status.
Associated Labels	Efgartigimod PH20 SC OCS	Placebo OCS

BP=bullous pemphigoid; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; IMP=investigational medicinal product; OCS=oral corticosteroid (prednisone or equivalent); placebo=placebo for SC administration coformulated with rHuPH20; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)

6.2. Preparation, Handling, Storage, and Accountability

Details about the use of concurrent oral prednisone (or equivalent OCS) are described in Section 6.8.1.

6.2.1. Preparation

Efgartigimod PH20 SC will be provided as a sterile, clear to opalescent, colorless to yellowish solution for SC injection in masked glass vials.

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

Trained and authorized study staff will use an amber colored syringe for preparation and administration of IMP; refer to Section 6.3 for details.

The IMP will be manufactured in accordance with Good Manufacturing Practice (GMP) regulations.

Detailed instructions for IMP management at the study site are included in the pharmacy manual. Instructions on the preparation and administration of IMP (including the volume of IMP to be administered) will be included in the on-site guide and the home administration guide.

6.2.2. Handling

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

Participants who will be administered IMP during home visits (Table 1) will be given IMP to take home with them at their preceding on-site visit. Participants will be responsible for the correct handling of IMP and will return any used and unused portion back to the study site at their next on-site visit. In the event that COVID-19 pandemic travel/lockdown restrictions are in effect or on-site visits pose a potential risk to participants or site staff, IMP will be shipped to participants per courier.

Only ARGX-113-2009 participants may receive IMP. Participants and/or their caregivers will be invited to receive training for (self-)administration of the IMP. In this study, participants (and/or their caregivers) will only be permitted to (self-)administer IMP at on-site visits under the supervision of site staff, and only after they have completed training and are determined competent enough to do so by site staff. During home visits, IMP may only be administered by a trained and authorized home nurse.

6.2.3. Storage

Both efgartigimod PH20 SC and placebo will be supplied to the pharmacy or dedicated site location at the study site by and under the responsibility of the sponsor's designated IMP supply vendor. For each IMP batch at the site, the investigator will receive the certificate of analysis, certificate of conformity, and European Union qualified person release documents.

All IMP must be stored in a secure, environmentally controlled, and monitored (via manual or automated system) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. Detailed instructions are included in the pharmacy manual.

The IMP must be stored refrigerated (2°C to 8°C [36°F to 46°F]) in its secondary packaging, should not be exposed to freezing temperatures, should not be shaken, and should be protected from direct sunlight during storage at the investigative site.

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

For home administration, the participant is responsible for the correct storage of IMP.

Detailed instructions on accountability for the IMP will be included in the pharmacy manual.

6.2.4. Accountability

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

All used and unused IMP should be returned to the investigator at each dispensing visit. Additional guidance and information for the final disposition of used and unused IMP are provided in the pharmacy manual.

6.2.5. Packaging and Labeling

Packaging and labeling information is presented in Table 5. Additional information is included in the pharmacy manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

The site will enroll the participant and a unique participant ID will be automatically allocated through interactive response technology (IRT) at the first screening visit.

The results of all screening procedures have to be available before baseline (week 0) to determine the eligibility for entering the study. Randomization should be performed as soon as the participants meet the appropriate criteria to begin treatment.

Upon confirmation of eligibility at baseline (week 0), the participant will be randomized through IRT. Participants will be randomized in a 1:1 ratio to receive efgartigimod PH20 SC or placebo.

At randomization, part B participants will be stratified by region (China, Japan, rest of the world). Participants who comprise the “rest of the world” stratum will be further stratified by disease history (newly diagnosed or relapsing) and disease severity (severe [IGA-BP score of 4] or moderate [IGA-BP score of 3]).

Because this is a randomized, double-blinded study, access to the IMP treatment assigned will be limited. No study team members from the investigating staff, sponsor staff who are directly involved in study management, or sponsor designees (except for staff at specialized laboratories who are responsible for PK, PD, and ADA analysis) will have access to the information related to IMP treatment assigned until after database lock.

Efgartigimod PH20 SC is a colorless to yellowish solution, while placebo is a colorless solution. To ensure that participants and site staff remain blinded to IMP, both efgartigimod PH20 SC and placebo will be provided in masked glass vials; additionally, amber-colored syringes will be used for the preparation and administration of IMP (Section 6.2.1).

An independent unblinded data and safety monitoring board (DSMB), including an independent statistician, will review all unblinded safety data as specified in Section 10.1.5.

6.3.1. Emergency Unblinding

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

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

If the blind is broken by the investigator, then it may be broken only for the participant concerned, and the IMP treatment assignment should not be revealed to the study team members from the sponsor, nor from the sponsor's designee, pharmacy staff, or other site staff. Once unblinded, IMP will be permanently discontinued (Section 7.1.1).

6.4. Study Compliance

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 site visit and documented in the source documents and relevant forms. Deviation(s) from the prescribed dosage regimen will be recorded.

For each injection, the start and end times (hour and minute) and details of any interruptions or premature discontinuation of each injection will be recorded on the eCRF. The start time will be when the syringe plunger begins to be pressed; the end time will be when the administration of the total volume of IMP is finished. [Note: For the baseline (week 0) and week 1 IMP injections, site staff must record the start and end times (and the details of any interruptions or premature discontinuation of injections) for each of the [redacted] injections of IMP administered to participants on those days.]

The sponsor's designee will review the pharmacy records at each investigative site, including the IMP accountability and dispensing records. The sponsor's designee will compare the dispensing record and vials with the individual participant's identifiers, kit number, and visit schedule to confirm that the participant received the correct treatment and dose, and that the dosing schedule is correct.

Errors that are identified will be discussed with site staff to ensure they are not repeated. The sponsor designee's report will include details of any missed doses, errors in dose, treatment or scheduling errors, and the associated explanations. The sponsor will determine whether these dosing errors will be reported as protocol deviations in the clinical database. All supplies and pharmacy documentation must be made available throughout the study for the sponsor designee to review.

The investigator should promote treatment compliance by stating that compliance is necessary for the participant's safety and the validity of the study. The prescribed dose, timing, and mode of administration cannot be changed. Any deviations from the intended regimen must be recorded on the eCRF.

Training for (self-) administration of IMP

Participants and/or their caregivers will be invited to receive training for (self-)administration of the IMP. In this study, participants (and/or their caregivers) will only be permitted to (self-)administer IMP at on-site visits under the supervision of site staff, and only after they have completed training and are determined competent enough to do so by site staff. The IMP doses at

baseline (week 0) and week 1 must be administered by the investigator or designee under medical supervision. Starting at week 2, participants or caregivers can choose to be trained in IMP (self-)administration. Note that successful completion of this training is intended to enable self-administration or caregiver-supported administration at home in the OLE study ARGX-113-2010.

6.4.1. Handling Missed Doses of the IMP

All efforts will be made to ensure that the participant receives all administrations of IMP on the days scheduled (within the allowed visit windows).

Incidents of missed IMP doses will be recorded on the eCRF, along with the reason(s) why the dose was missed. These reasons will be assessed by the investigator, site staff, and sponsor, who will agree upon and implement an appropriate set of actions to minimize the possibility of subsequent missed IMP doses.

Participants who meet either of the following conditions will be excluded from the per-protocol analysis set:

- Participants who miss a cumulative total of >50% of their scheduled doses of IMP
- Participants who miss 3 or more consecutive scheduled doses of IMP

6.4.2. Protocol Deviations

The investigator should not implement any deviation from or changes to the approved protocol. Additionally, the investigator should not implement any deviation from or changes to the approved protocol before such deviations/changes are reviewed and approved by the Institutional Review Board/Independent Ethics Committee (IRB/IEC) and regulatory authority per local regulation. Exceptions will be permitted in cases of immediate hazard to study participants or when the change involves only logistical or administrative aspects of the study (eg, changes in contact information). The investigator (or designee) should document and explain any deviation from the approved protocol.

6.5. Dose Modification

Dose modifications are not permitted.

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

Participants who reach the EoTP visit (week 36) may be offered the option to roll over into a long-term, OLE study (ARGX-113-2010).

Participants will not be eligible to roll over into the OLE study if they discontinue from study ARGX-113-2009 (eg, withdrawal of consent). Participants who are eligible but choose not to roll over into the OLE study ARGX-113-2010 will complete a 7-week treatment-free follow-up period.

If a participant permanently withdraws from the study or is permanently withdrawn from the study by the investigator (Section 7.2), standard-of-care BP treatment may be administered by the participant's primary care physician.

6.7. Treatment of Overdose

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

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

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether IMP should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities.
- Document the quantity of the excess dose and the duration of the overdose on the eCRF.

6.8. Concomitant Therapy

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

- Reason for use
- Dates of administration, including start and end dates
- Dosage information including dose and frequency
- Brand name (for vaccines only)

All available vaccination history should be recorded as part of the participant's prior medication for vaccinations received in the past, or as concomitant medication for vaccinations received during the study, as described in the SoA (Table 1). Any vaccination information that the participant, or their caregiver can remember should be recorded on the eCRF (with the brand name of the vaccine and date of vaccination, if possible).

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.8.1. Concurrent Bullous Pemphigoid Therapy – Oral Prednisone

All participants, regardless of study IMP assignment, will also receive concurrent therapy with OCS, ie, prednisone at a starting dosage of 0.5 mg/kg/day at baseline (week 0), or an alternate OCS at an equivalent dose strength. The OCS dosage will be adjusted according to each participant's BP disease status throughout the study, with the goal of rapidly tapering systemic corticosteroid exposure and preventing and/or treating relapse. The oral prednisone dose adjustment procedure is described in Section 6.8.1.3.

If the investigator considers it necessary, oral prednisone ≤0.3 mg/kg/day (or equivalent OCS) may be administered to participants during the period between their screening and baseline visits.

6.8.1.1. General Oral Prednisone Information

Information on the formulation, unit dose strength, sourcing, packaging, and labeling of oral prednisone is summarized in Table 5.

Investigators, study site staff, and participants must comply with package labeling instructions for proper oral prednisone storage and handling.

During each on-site visit, study site staff will provide the participant with a supply of daily oral prednisone doses (or equivalent OCS) sufficient to last until the participant's next on-site visit. Participants will return any used and unused doses to the study site at their next on-site visit.

6.8.1.2. Oral Prednisone Dosing and Treatment Compliance

Participants will take oral prednisone (or equivalent OCS) daily at the dose directed by the investigator.

Participants will be provided a diary to record daily intake of each oral prednisone dose. The participant will bring their completed diary with them to every on-site visit so that staff can review the dosing record; during home visits, the participant will share their diary information with site staff.

If a participant misses one or more oral prednisone doses, they must contact the investigator. The missed doses must not be "made up"; rather, the participant will resume taking the daily oral prednisone dosage prescribed by the investigator, unless they have had a change in BP disease status that warrants dose adjustment (Section 6.8.1.3).

6.8.1.3. Oral Prednisone Dose Adjustment Regimen (Based on BP Disease Assessment)

Participants will receive IMP with concurrent OCS therapy. The recommended OCS dosing regimen is described below and displayed in Table 7.

The investigator should not deviate from the concurrent oral prednisone dosing regimen, except in matters where the safety of the participant may be compromised. After taking appropriate action to ensure the safety of the participants, such concerns should be documented and communicated to the sponsor's medical monitor and designee within 24 hours of the event.

For OCS doses not listed in Table 7, minimum and maximum recommended doses are provided. For participants with body weights of <45 kg or ≥110 kg, the investigator should propose OCS doses and inform the medical monitor to ensure consistency within the study.

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

- All participants will begin the study by taking oral prednisone 0.5 mg/kg/day starting at baseline (week 0; day 1).
- If the participant has not achieved CDA within 1-3 weeks of treatment with oral prednisone 0.5 mg/kg/day, then the dosage may be increased to 0.75 mg/kg/day for up to an additional 3 weeks. This period may be extended by 1 additional week (based on clinical judgment) to achieve CDA with an oral prednisone dosage of either 0.75 mg/kg/day or 1 mg/kg/day.

- A participant will be considered as a treatment failure if they do not achieve CDA after receiving the IMP with the prednisone dosing regimen described above. In case of treatment failure, IMP will be permanently discontinued (Section 7.1.1). Under these circumstances, the participant will be considered a nonresponder (Section 9.3.2).
- When CDA is achieved, the oral prednisone dosing regimen is adjusted as follows:
  - After CDA has been sustained for ≥2 weeks, the dose tapering schedule begins with the next lower oral prednisone dosage as listed in Table 7. 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.
  - For participants who achieved CDA on oral prednisone 0.5 mg/kg/day, the tapering steps are 0.3, 0.2, 0.15, and 0.1 mg/kg/day. For participants who required a dose increase to 0.75 or 1.0 mg/kg/day to achieve CDA, the oral prednisone dosage must first be tapered down to 0.5 mg/kg/day before proceeding to 0.3, 0.2, 0.15, and 0.1 mg/kg/day as shown in Table 7.
  - 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 after the start of OCS tapering (ie, after CDA has been sustained for ≥2 weeks) 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 can be resumed after CDA has been sustained for at least 2 weeks on this increased dose.
  - If CDA is not achieved, the participant should resume the initial oral prednisone dosage of 0.5 mg/kg/day.
  - The participant must resume weekly on-site visits until CDA returns.

For concurrent oral methylprednisolone equivalent doses, refer to Table 16.

For home study visits that occur between mandatory on-site visits, the investigator will call the participant once weekly to review the participant's BP disease status and current oral prednisone (or equivalent) dosing regimen (Section 8.1.4).

Table 7: Concurrent Oral Prednisone Equivalent Doses (in mg) Based on Participant Body Weight

Oral prednisone dose level	Body weight category[a]													
	<45 kg	≥45 to <50 kg	≥50 to <55 kg	≥55 to <60 kg	≥60 to <65 kg	≥65 to <70 kg	≥70 to <75 kg	≥75 to <80 kg	≥80 to <85 kg	≥85 to <90 kg	≥90 to <95 kg	≥95 to <100 kg	≥100 to <105 kg	≥105 to <110 kg	≥110 kg
	Minimum recommended daily OCS doses	Daily OCS doses[b]													Maximum recommended daily OCS doses
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
Starting dose: 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 prednisone equivalent dose)
Notes: 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.

[a] Body weight should be rounded to the nearest whole number.
[b] The investigator should not deviate from the concurrent oral prednisone dosing regimen as specified in the table, except in matters where the safety of the participant may be compromised.

6.8.2. Prohibited Medications and Therapy During the Study

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

- Any systemic treatment for BP (except concurrent OCS), including but not limited to immunosuppressants, IVIg, SCIg, immunoadsorption, anti-CD20 biologics, tetracyclines with or without nicotinamide, dapsone, and IV or IM corticosteroids
- TCS (use must be discontinued before baseline)
- Any other biologic agent or experimental/study IMP
- Live or live-attenuated vaccines
- Complementary therapies, including traditional Chinese medicines, herbs, or procedures (eg, acupuncture), as assessed by the investigator

As discussed in Section 6.8.3, some of these treatments can be administered as rescue therapy if the participant discontinues IMP.

6.8.3. Rescue Therapy

Participants will discontinue IMP and may start rescue therapy if any of the following occur:

- The participant fails treatment with IMP (defined in Section 4.1.3)
- The participant relapses twice
- The participant presents with steroid toxicity (or any severe AE determined by the investigator to be related to OCS therapy)

Participants reporting any of the events mentioned above will permanently discontinue IMP (Section 7.1.1).

Rescue therapy may include OCS, TCS, conventional immunosuppressants (eg, azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil), tetracyclines with or without nicotinamide, dapsone, or IVIg. As described in Section 6.8.2, these treatments are permitted as rescue therapy following discontinuation of IMP.

7. IMP DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or the entire study is described in Appendix 1 (Section 10.1.11).

7.1. IMP Discontinuation

7.1.1. Permanent Discontinuation

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

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

Participants who permanently discontinue IMP will be encouraged to remain in the study and attend mandatory on-site visits as specified in the SoA (Table 1). If the participant cannot attend these visits for any reason, the study site will perform an early study discontinuation (ESD) visit and safety follow-up visits as specified in the SoA (Table 1).

Unless consent from the study has been withdrawn, the participant will attend an early treatment discontinuation (ETD) visit. Study sites will attempt to perform the ETD visit within 7 days after the participant's final IMP administration. After the ETD, the participant will continue participation in the study through the rest of the 36-week treatment period and may receive rescue therapy (defined in Section 6.8.3). At week 36, the participant will complete the EoTP visit assessments (Table 1). If the participant meets rollover eligibility requirements (described in the ARGX-113-2010 protocol) at the end of the EoTP visit, they will be invited to immediately enroll in the OLE study ARGX-113-2010. If the participant does not meet rollover eligibility requirements or chooses not to enroll in the OLE study, they will participate in the 7-week treatment-free follow-up period. Refer to the SoA (Table 1) for data to be collected at the time of discontinuation of IMP and follow-up and for any other evaluations that need to be completed.

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

- Participant becomes pregnant or intends to become pregnant (refer to Section 8.4.6).
- 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.
- Unblinding occurred.
- Participant exhibits any of the conditions outlined in Section 6.8.3. In these cases, participant may start rescue therapy.
- 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 the IMP.
- The participant develops any of the following, based on the sponsor's determination of relatedness:

  - Any treatment-emergent adverse event (TEAE) of Common Terminology Criteria for Adverse Events (CTCAE) severity grade 4 that is 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
- The participant develops any malignancy, either new or recurrent, other than basal cell carcinoma of the skin, regardless of relatedness.

7.1.2. Temporary Discontinuation

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

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

- Any SAE considered related to IMP by the sponsor
- Clinically significant active infection considered related to the IMP by the sponsor
- Any of the following liver chemistry laboratory results:
  - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values >8 times the upper limit of its normal reference range (×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 (INR) >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)

  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 IMP (eg, viral hepatitis, preexisting or acute liver disease, or toxicity related to concomitant medications other than IMP). If the event is considered by the investigator to be related to the IMP, IMP 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.

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.

If possible, an ESD visit should be conducted at the time the participant is withdrawn from the study (Table 1). Study sites should make every effort to perform the ESD visit within 7 days of the participant's last IMP dose. At the conclusion of the ESD visit, the participant will be asked if they will participate in the 7-week treatment-free follow-up period. A comment must be added to the source records to note if the participant accepts or rejects to perform the ESD visit and/or the treatment-free follow-up period. If the participant chooses not to participate in the treatment-free follow-up period, they will be permanently discontinued from IMP and the study at that time.

Participants withdrawn from the study will be ineligible to roll over to the OLE study (ARGX-113-2010).

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 cannot be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for 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 and/or should 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 (where 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 should be documented in the participant's medical record.

- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.
- Site staff, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get IMP. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor staff will not be involved in any attempts to collect vital status information.

8. STUDY ASSESSMENTS AND PROCEDURES

General Note – COVID-19 Considerations: Operational considerations due to the COVID-19 pandemic are provided in Section 10.14. The sponsor or the investigator may implement alternate strategies for participant visits, assessments, medication distribution, and monitoring resulting from COVID-19 concerns and/or restrictions per local health authority/ethics requirements.

8.1. General Considerations

8.1.1. General

- Study procedures and their timing are summarized in the SoA (Table 1). Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- From signing of the ICF until the last study-related activity, all AEs, concomitant medications, and procedures must be recorded on the eCRF.
- Safety/laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded staff until the study has been unblinded.

8.1.2. Screening Period

- Screening eligibility assessments, including their timing and the duration of the screening period, are listed in the SoA (Table 1). Screening assessments can only be performed after the participant has provided informed consent (by signing the ICF).
- All screening evaluations must be completed and reviewed before enrollment to confirm that potential participants meet all eligibility criteria.
- The investigator will record the details of all participants who are screened for the study, and then confirm eligibility for each or record the reasons for screening failure, as applicable.
- At screening, total IgG serum levels will always be measured in a central laboratory. The eligibility assessment can be based on central or local laboratory samples taken at screening or historical laboratory results from samples taken up to 7 days before screening (exclusion criterion 14A).
- A serological confirmation of BP diagnosis must be available using a positive IIF, CLEIA, or ELISA result according to local practice (inclusion criterion 3). The presence of anti-BP180 and anti-BP230 antibodies will also always be evaluated centrally by ELISA. In case serology methods are not available locally, the central laboratory result will be used for assessment of eligibility. The eligibility assessment may also be based on historical laboratory results from local samples taken up to 7 days before screening.

- The first day of the screening period is the day of the screening visit (the date of first screening visit is defined by the date of first screening procedure after signing the ICF).

8.1.3. Treatment and Follow-Up Periods

- Each participant should attend each study visit on the designated days (Table 1). There is a permissible visit window of ±2 days during the treatment period and ±3 days during the treatment-free follow-up period.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue IMP. Additionally, an independent unblinded DSMB may review all unblinded safety data on a regular basis as specified in Section 10.1.5.
- Participants who received IMP throughout the entire the 36-week treatment period will complete the EoTP visit assessments (Table 1) at week 36.
- Participants who discontinue IMP early will complete an ETD visit (Table 1), may begin rescue therapy (Section 6.8.3), continue their treatment period visits as scheduled, and then complete the EoTP assessments (Table 1) at week 36.
- Participants who withdraw consent or are permanently discontinued from the study will complete an ESD visit (Table 1); details for the study discontinuation procedures are provided in Section 7.2.
- Participants who complete the EoTP visit and choose not to enroll in the OLE study ARGX-113-2010 will complete the treatment-free follow-up period visits at weeks 39 and 43 (Table 1).

8.1.4. Home Study Visits

For other weekly visits as indicated in the SoA (Table 1), a home nurse or qualified site staff may travel to the participant's home to conduct visits or meet the participant at a convenient alternative location. Home nurse is either a nurse from the study site or a nurse from a commercial nursing vendor who is delegated by the investigator.
For home study visits, the investigator will call the participant within 48 hours before IMP administration to elicit AEs and participant's general well-being, and review the current BP disease status and OCS dosing regimen. The investigator will check with the participant if they have new lesions, transient or nontransient. If any new lesions are reported, the participant should visit the clinic for an unscheduled appointment (refer to Section 8.1.5).

8.1.5. Unscheduled Visits

In case of suspected new lesions as reported by the participant, or other issues requiring site staff intervention, such as notable weight changes, participants should come to the clinic for an unscheduled (UNS) visit for disease assessment. The investigator will decide which assessments to conduct based on the purpose of the unscheduled visit (Table 1). In case of relapse, IGA-BP, BPDAI, and Itch NRS assessments must be performed and participants should return to weekly

on-site visits until CDA is achieved again. At the UNS visits, blood samples for PK will only be collected if IMP is administered.

8.2. Efficacy and Quality of Life Assessments

Planned time points for all efficacy and QoL assessments are presented in the SoA (Table 1).

8.2.1. Efficacy Assessments

8.2.1.1. Assessment of BP Disease Status and OCS Dose Monitoring

The efficacy of treatment will be assessed by the investigator, who will assess the BP disease status (CDA, PR, CR, relapse, treatment failure) of the participant according to the definitions/criteria presented in Section 4.1.3. The investigator will also record the daily OCS dose administered to the participant since the last visit, adjust the daily OCS dose (taper, stop, re-initiate, or increase) based on the participant's BP disease status, and record treatment failures during on-site visits. For details on reviewing the current BP disease status and OCS dosing regimen for home study visits occurring between mandatory on-site visits, refer to Section 8.1.4.

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 (Section 10.6). The IGA-BP is a new assessment tool that was developed in 2021 by medical experts in the field of AIBDs, and it is currently being used (along with the BPDAI) in other clinical studies of therapies for BP. The IGA categorizes the severity of BP on a numerical scale of 0 (clear) to 4 (severe).

8.2.1.3. Bullous Pemphigoid Disease Area Index

In addition to the IGA-BP, BP disease activity will also be assessed by the investigator using the BPDAI[2] (Section 10.7). 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.[2,22]

8.2.1.4. Itch Numerical Rating Scale

Pruritic symptoms of BP will be indicated by the participant on the Itch NRS (Section 10.8), recording an average and a worst score for itch suffered within the past 24 hours.

8.2.2. Quality of Life (QoL) Assessments

Participants will complete the following PRO assessments of their QoL at the time points listed in the SoA (Table 1):

- EuroQol 5-dimension 5-level Scale (EQ-5D-5L; Section 10.9): 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 now has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems.

- Dermatology Life Quality Index (DLQI)[36] (Section 10.10): 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."
- Autoimmune Bullous Disease Quality of Life Index (ABQoL) questionnaire[37] (Section 10.11): the ABQoL was developed and validated for determining the impact of AIBDs and their therapies on the daily life of patients. It is a series of 17 questions concerning the participant's perceptions of how AIBD is affecting their daily lives, including comfort, hygiene, eating/drinking, appearance, social interactions, sexual activity, and employment.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 1). Safety measures will be assessed before IMP administration unless otherwise stated.

8.3.1. Physical Examinations

Physical examinations will be performed at the time points indicated in the SoA (Table 1).

A physical examination will include, at a minimum, an assessment of general appearance, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal condition, extremities, abdomen, breast, and cardiovascular, respiratory, neurological, and genital/rectal systems. Any signs related to the natural history of BP are not to be reported as physical abnormalities.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Abnormalities in physical examination at screening will be reported as medical history on the eCRF. At all other study visits, new clinically significant abnormal or worsened preexisting conditions will be reported as an AE.

8.3.2. Height and Weight

Height and weight will be measured at screening, and body mass index (BMI) will be calculated accordingly. Weight will be measured again at the time points indicated in the SoA (Table 1). Height and weight will also be measured without shoes, attired in light clothing.

8.3.3. Vital Signs

The assessment of vital signs (supine blood pressure, heart rate, and body temperature) will be performed at the time points indicated in the SoA (Table 1) and should be completed predose at visits when IMP is administered.

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

It is recommended that the method used to measure the body temperature of the participant at screening (eg, orally, tympanic, rectal, axillary, skin, temporal) should be the same method used for the participant at both on-site and home visits throughout the study.

Abnormalities in vital sign measurements at screening will be reported as medical history on the eCRF. At all other study visits, new clinically significant abnormal or worsened pre-existing vital sign abnormalities will be reported as an AE.

8.3.4. Electrocardiograms

ECGs will be performed at the time points indicated in the SoA (Table 1) and should be completed predose at visits when IMP is administered.

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.

Abnormalities in ECG at screening will be reported as medical history on the eCRF. At all other study visits, new clinically significant abnormal or worsened pre-existing ECG abnormalities will be reported as AEs.

8.3.5. Medical and Surgical History

All significant findings, surgeries, and pre-existing conditions (including allergies, if any) present at screening must be reported on the relevant medical history/current medical conditions page of the eCRF, including start and end dates, if known.

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

Details collected as a part of the medical history must include, but are not limited to, all previous treatment/therapy taken for BP, including start and end dates, if known.

All available vaccination history will be recorded as part of the participant's prior medication for vaccinations received in the past, or concomitant medication for vaccinations received during the study as described in the SoA (Table 1). Any vaccination information the participant, or his/her caregiver can remember should be recorded on the eCRF (with the brand name of the vaccine and date of vaccination, if possible).

8.3.6. Clinical Safety Laboratory Tests

8.3.6.1. Standard Blood and Urine Laboratory Tests

Blood and urine samples will be collected at the time points indicated in the SoA (Table 1) and analyzed at a laboratory for determination of clinical chemistry, hematology, coagulation, urinalysis, and serology (eg, viral marker testing); the parameters for each analysis are listed in Section 10.2.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the 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.

The details of sample collection, handling, storage, and transportation of the samples will be described in the laboratory manual.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 60 days after the last dose of IMP should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

- If such values do not return to normal/baseline within a period of time considered reasonable by the investigator, the etiology should be identified, and the sponsor notified.
- All protocol-required laboratory tests (as defined in Section 10.2) must be conducted in accordance with the laboratory manual and the SoA (Table 1).
- If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, AE or SAE), then the results must be recorded on the AE or SAE form.

8.3.6.2. Substudy (at Selected Sites) – Vaccination Response

Sites will collect all available vaccination history from study participants.

Selected sites may collect additional blood samples for additional/optional/future vaccination research. Such research may include (but not be limited to) the following:

1. Measurement of historical protective antibody titers in serum
2. Humoral (serum) responses to vaccinations received during the study
3. Cellular (peripheral blood mononuclear cells [PBMCs]) responses to vaccinations received during the study

These samples will only be collected from participants who have provided additional consent for the procedure, at the visits identified in the SoA (Table 1). Note: if the 12- and 24-week postvaccination samples cannot be taken during the treatment period (Table 1), then a postvaccination sample can be taken at the last participation time point in this study (eg, the ESD or F2 visit) or in the OLE study (ARGX-113-2010), as applicable.

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

8.3.6.3. Use and Storage of Blood Samples

Blood samples that are collected at the screening visit 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 procedures are performed.

Any samples remaining after the laboratory analyses as defined in the protocol have been completed may be stored for up to 15 years after the end of the study, in the laboratory or long-term storage designated by the sponsor or research partners worldwide, for future additional medical, academic, or scientific research to address any scientific questions related to efgartigimod, FcRn biology, or BP, unless this would not be allowed according to local regulations or the participant would not have agreed.

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.

In this study, some measures able to mitigate the occurrence of infections are required, and other precautionary measures optimizing the prevention of infections are recommended. For these reasons, the following actions are excluded for study entry:

- The administration of live or live-attenuated vaccines (eg, measles, mumps, rubella, rotavirus, smallpox, chickenpox, yellow fever) within the 4-week period before baseline visit or during the study (Section 6.8.2).
- Participants with a clinically significant active infection that is not sufficiently resolved before baseline in the investigator's opinion (exclusion criterion 5C).
- Participants who tested positive for an active viral infection at screening with HBV, HCV, and HIV (exclusion criterion 13A).
- Participants with total IgG serum levels <4 g/L at screening (exclusion criterion 14A).

The following measures are highly recommended before and during the study:

- To initiate or renew administration of non-live, inactivated, polysaccharide or recombinant vaccines (eg, tetanus, hepatitis A, hepatitis B, shingles) in participants susceptible to enter the study, at least 4 weeks before baseline visit.
- To vaccinate participants who are especially prone to or with an history of respiratory infections against Pneumococcus or Streptococcus pneumoniae.
- To vaccinate participants with seasonal vaccines (eg, influenza virus), especially those susceptible to enter the study in the winter months.
- To screen for possible infections (eg, respiratory, skin, mouth, eyes, nose and throat, genitals) and, if appropriate, initiate antibiotic treatment before baseline visit.
- To 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 discretion of the investigator and if it is administered at least 48 hours predose or 48 hours postdose of the IMP.

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.

All available vaccination history and 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. Pregnancy Testing

- WOCBP (Section 10.4.1) will be tested for pregnancy by serum at screening. Urine tests for pregnancy will occur at the time points specified in the SoA (Section 1.3).
- Pregnancy testing in WOCBP will be conducted at the end of relevant systemic exposure (ie, at the safety follow-up visits).
- 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 to 12 months after the baby's birth.

8.3.9. Additional Safety Assessment – the Glucocorticoid Toxicity Index

As an additional assessment of the impact of glucocorticoid morbidity, the GTI v2.0 will be assessed at the visits listed in the SoA (Table 1). 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 long-term tolerability of glucocorticoids during their prolonged use during clinical practice.[39]

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

- The Composite-GTI (C-GTI), which serves as a primary instrument intended to capture toxicities that are likely due to glucocorticoid exposure. The C-GTI has 9 functional domains: BMI, 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, because it is typically excluded from studies <1 year in duration, because bone densitometry is not sufficiently reliable in measuring changes over shorter durations.[39]

  Two analytical scores are generated from the weighted C-GTI items: the Cumulative Worsening Score (CWS) and the AIS. The CWS is designed to assess cumulative glucocorticoid toxicity, while the AIS can be used to assess whether a new therapy is effective in reducing glucocorticoid toxicity over time. Together, the CWS and AIS provide complementary information about the ability of an investigational agent to reduce overall glucocorticoid toxicity.
- The Specific List of the GTI (GTI-SL) captures well-known glucocorticoid-related side effects. This non-weighted instrument provides additional information for the domains

most affected by glucocorticoid use during the participant's course of treatment. It comprises 11 domains (9 of which are shared in common with the C-GTI) and 23 items.

Note: for the reason mentioned above, the GTI-SL item covering bone mineral density decrease (part of the Bone Health domain; Table 15) will not be used in this study.

The tabular components of the modified GTI are presented in Section 10.12.

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 8.4.7.

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).The method of reporting AESIs is provided in Section 8.4.7.

8.4.1. Time Period and Frequency for Collecting Information on AEs, SAEs, and AESIs

All AEs, SAEs, and AESIs will be collected from the signing of the ICF until the last follow-up visit at the time points specified in the SoA (Table 1).

Medical occurrences that begin before the start of IMP but after obtaining informed consent will be recorded as non-treatment-emergent AEs; these will not be included in safety analyses.

All SAEs and AESIs will be recorded and reported to the sponsor or designee immediately; under no circumstance should the reporting time exceed 24 hours (Section 10.3.4).
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 conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and they consider the event to be reasonably related to the IMP or study participation, the investigator must promptly notify the sponsor.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are described in Section 10.3.

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

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts.

All AEs observed from the moment the participant signs the ICF must be followed through resolution until one of the following occurs:

- The participant's last study visit
- The participant is lost to follow-up
- The participant withdraws consent

Resolution means that the participant has returned to a baseline state of health, or the investigator does not expect any further improvement or worsening of the AE.

Every effort should be made to follow all AEs and SAEs that are considered to be related to IMP or study procedures until an outcome can be reported. If the participant is lost to follow-up, all AEs will be categorized based on the investigator's last assessment.

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

All pregnancies reported during the study should be followed until pregnancy outcome (Section 8.4.6).

For SAEs, AESIs (Section 8.4.7), nonserious AEs, and pregnancies, the sponsor's designee may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (eg, from hospital discharge summaries, consultant reports, or autopsy reports) to perform an independent medical assessment of the reported case.

Further information on follow-up procedures is provided in Section 10.3.

8.4.4. Reporting of AEs and SAEs

All AEs that occur during the study, from signing of the ICF until the EoTP or the last follow-up visit, are to be recorded on the appropriate AE pages (either "serious" or "nonserious") of the eCRF. The investigator should complete all the details requested, including date of onset, time of onset, stop date (when applicable), stop time (when applicable), severity, action taken, outcome, and relationship to IMP, to corticosteroid (non-IMP) use, and to study procedures. Each event should be recorded separately on the eCRF.

Any SAE, including death due to any cause, which occurs during this study after the signing of the ICF, whether or not related to the IMP, must be reported immediately (within 24 hours of the study site's knowledge of the event). Further information on follow-up procedures is provided in Section 8.4.3 and Section 10.3.

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

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

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

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

8.4.5. 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 then file it along with the efgartigimod IB and will notify the IRB/IEC, if appropriate according to local requirements.

The sponsor (or designee) is responsible for reporting suspected unexpected serious adverse reactions (SUSARs) to the relevant regulatory authorities and IECs/IRBs per applicable regulatory requirements. The sponsor (or designee) is also responsible to forward SUSAR reports to all investigators involved in the study, who will be required to report these SUSARs to their respective IECs/IRBs, per their local regulatory requirements.

8.4.6. Pregnancy

- If pregnancy is reported, the investigator will record the pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the pregnancy in the female participant or the female partner of the male participant. Contact details are provided in Serious Adverse Event Reporting.
- The participant and pregnant female partner, if consented (Section 10.1.3), will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate and forward it to the sponsor.
- While pregnancy itself is not considered an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported accordingly.
- Any poststudy pregnancy-related SAE considered reasonably related by the investigator to IMP will be reported to the sponsor as described in Section 8.4.4.

- Any female participant who becomes pregnant during the study will discontinue IMP.

8.4.7. Adverse Events of Special Interest

An AESI is an event of scientific and medical concern specific to the sponsor's product or program. Ongoing monitoring and rapid communication by the investigator to the sponsor or designee could be appropriate. An AESI can be serious or nonserious, related or not related to the IMP or study procedures.

Efgartigimod treatment leads to reduced IgG levels. Because low IgG levels are associated with increased infection risks, events in the MedDRA System Organ Class (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/infestation
- Any confirmatory procedure, culture, or urgent medical intervention

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

8.4.7.1. Risk Mitigation for COVID-19 and Other Significant Infections

All candidates with clinically significant active infection that is not sufficiently resolved before baseline in the investigator's opinion, recent surgeries, and/or serious diseases will be excluded from study participation (exclusion criteria 5C, 6A, 9, and 13A). Additionally, IMP administration will be interrupted for any participant who contracts a clinically significant infection during the study; IMP administration will resume when the participant is considered healthy enough receive IMP.

A COVID-19 test is performed at screening if required per local regulations (Table 1); candidates who test positive will be excluded from taking part in the study. Additionally, participants who test positive for COVID-19 or report COVID-19 symptoms at any point during the study will have both IMP administration and site visits interrupted until it is considered safe to resume both (Section 10.14). If a participant contracts COVID-19, the event is recorded and reported as an AESI (Section 8.4.7).

Refer to Section 10.14 for operational considerations for COVID-19 risk mitigation.

8.4.8. AEs of Clinical Interest

8.4.8.1. 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, infusion/injection-related reactions can occur during or after administrations. Overall, the frequency of injection-related reactions in clinical studies has been low.

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

8.4.8.2. 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

Blood samples for PK analysis will be collected from each participant as described in the SoA (Table 1). Samples will be collected predose on IMP administration visits (within ≤2 hours before IMP administration) and any time if no IMP is administered. During unscheduled visits, blood samples for PK will be collected only if IMP is administered.

In part A only, 1 additional PK sample will be collected from at least 28 participants on day 10 (±1 day; should be collected at least 2 days after the second IMP dose is administered at week 1).

Efgartigimod serum concentrations will be determined using a validated assay.

The actual date and time of collection of each blood sample will be recorded in the requisition form. If no sample is taken, the reason will be recorded in the relevant section of the eCRF.

8.6. Pharmacodynamics

Blood samples will be collected for the determination of PD markers (total IgG serum levels, anti-BP180 and anti-BP230 antibodies, and [redacted]) as described in the SoA (Table 1). Total IgG serum levels, anti-BP180 and anti-BP230 antibodies, and [redacted] will be quantified at a central laboratory, and results will only be reported to investigative sites or other site staff at screening, to maintain study blind.

For baseline and all postbaseline PD assessment time points (Table 1), sample collection will be performed predose at IMP administration visits (within ≤2 hours before IMP administration). PD markers will be determined using validated assays.

The actual date and time of collection of these blood samples will be recorded in the requisition form. If no sample is taken, the reason will be recorded in the relevant section of the eCRF.

PD blood samples that are collected at the screening visit may be used for methodology validation and/or for future research purposes (Section 8.3.6.3). Such use of these samples

is only permitted after obtaining consent from the participant; this is described further in the ARGX-113-2009 ICF.

8.7. Genetics

Not applicable to ARGX-113-2009.

8.8. Biomarkers

Not applicable to ARGX-113-2009.

8.9. Immunogenicity Assessments

Blood samples will be collected to assess the serum levels of antidrug antibodies (ADA) against efgartigimod and plasma levels of antibodies against rHuPH20 as indicated in the SoA (Table 1). Samples will be collected predose on IMP administration visits (within ≤2 hours before IMP administration).

All samples will be analyzed in a 3-tiered approach using validated immunogenicity methods. First, all samples will be evaluated in a screening assay (tier 1) and scored as positive or negative. Second, screened positive samples will be evaluated in a confirmatory assay to assess the specificity of the immunogenicity response. The samples will be scored as confirmed positive or confirmed negative. Samples confirmed positive in tier 2 will be further analyzed in a titration assay to characterize the magnitude of the antibody response and a neutralizing antibody (NAb) assay to assess the antibodies for neutralizing activity.

The actual date and time of collection of these blood samples will be recorded in the requisition form. If no sample is taken, the reason will be recorded in the relevant section of the eCRF.

Immunogenicity blood samples that are collected at the screening visit will only be used for methodology validation and/or for future research purposes (Section 8.3.6.3). Such use of these samples is only permitted after obtaining consent from the participant; this is described further in the ARGX-113-2009 ICF.

8.10. Imaging Substudy

A photography substudy will be performed at selected study sites. In this substudy, site staff will take photographs of bullous lesions located at various anatomical regions of participants per the discretion of the investigator. As a guidance, time points of baseline, CDA, CR, and relapse are indicated; however, photographs may also be taken at intermediate time points.

Photography is generally accepted as a routine practice for documenting dermatological conditions in medicine. Participants will be requested to provide consent for any use that will be made of the image and for sharing anonymized pictures with the sponsor.

8.11. Health Economics OR Medical Resource Utilization and Health Economics

Not applicable to ARGX-113-2009.

9. STATISTICAL CONSIDERATIONS

The SAP will be finalized before the interim and final database lock of part A and the final database lock of part B, and it will include a more technical and detailed description of the statistical analyses described in this section. The below paragraphs contain the main general features of the statistical analysis.

9.1. Statistical Hypotheses

Part A:

The main goal of part A is to determine whether efgartigimod PH20 SC is effective in the treatment of participants with BP via assessment of the study's primary endpoint: the proportion of participants who are in CR while receiving efgartigimod PH20 SC or placebo and have been off OCS therapy for ≥8 weeks at week 36. Thus, the null hypothesis to be tested in relation to the primary endpoint of part A is as follows:

- Null hypothesis: efgartigimod PH20 SC is not different from placebo with respect to the achievement of CR while receiving efgartigimod PH20 SC or placebo and having been off OCS therapy for ≥8 weeks at week 36.

Part B:

The primary objective of part B is to demonstrate that efgartigimod PH20 SC is superior to placebo in achieving CR while receiving efgartigimod PH20 SC or placebo and having been off OCS therapy for ≥8 weeks at week 36. Thus, the null hypothesis to be tested in relation to the primary estimand (part B) is as follows:

- Null hypothesis: efgartigimod PH20 SC is not different from placebo with respect to the achievement of CR while receiving efgartigimod PH20 SC or placebo and having been off OCS therapy for ≥8 weeks at week 36.

The null hypotheses corresponding to the estimands for the proposed key secondary endpoints of part B (Table 4) are as follows:

1. Efgartigimod PH20 SC is not different from placebo with respect to the cumulative dose of OCS from baseline to week 36.
2. Efgartigimod PH20 SC is not different from placebo with respect to the proportion of participants who achieve an IGA-BP score of 0 while receiving efgartigimod PH20 SC or placebo and have been off OCS therapy for ≥8 weeks at week 36.
3. Efgartigimod PH20 SC is not different from placebo with respect to the proportion of participants who achieve CDA while receiving efgartigimod PH20 SC or placebo and remained free of relapse through week 36.
4. Efgartigimod PH20 SC is not different from placebo with respect to the proportion of participants in CR while receiving efgartigimod PH20 SC or placebo and receiving minimal OCS therapy for ≥8 weeks at week 36. (Minimal OCS therapy is defined as ≤0.1 mg/kg/day of prednisone or an equivalent dose of another OCS].)
5. Efgartigimod PH20 SC is not different from placebo with respect to changes from baseline in the 24-hour average itch score from the Itch NRS.

9.1.1. Multiplicity Adjustment

For part B of the study, the statistical comparisons for the primary endpoint and the key secondary endpoints will be carried out in the hierarchical order as indicated above. However, after interim analysis of part A data, another multiplicity adjustment testing strategy (eg, Holm's multiplicity adjustment) might be put forward if appropriate. The proposed hierarchical approach implies that statistically significant results for the comparison in the higher rank (primary, then ranked key secondary variables) are required to initiate the testing of the next comparison in the lower rank. Because a fixed-sequence procedure is used, each comparison will be tested at a significance level of 0.05 and an overall alpha level of 0.05 will be preserved.

9.2. Analysis Sets

Table 8 lists and defines the analysis sets to be applied in this study.

Table 8: Analysis Sets for ARGX-113-2009

Participant Analysis Set	Description
Full analysis set	All randomized participants. Participants will be included in the analyses according to the study arms to which they were randomized.
Safety analysis set	All randomized participants who received at least 1 dose of IMP. Participants will be analyzed according to the intervention they actually received.
Per protocol analysis set	All full analysis set participants who did not have a major protocol deviation impacting the efficacy results. The determination of the per protocol population will be finalized and documented before database lock and unblinding.

IMP=investigational medicinal product

The full analysis set is used to analyze endpoints related to the efficacy objectives and the safety analysis set is used to analyze the endpoints and assessments related to safety. Sensitivity analysis for efficacy will be performed in the per protocol analysis set.

9.3. Statistical Analyses

9.3.1. General Considerations

In general, data collected will be listed, together with derived variables. Descriptive statistical methods will be used to analyze safety and efficacy data. Summaries will generally be provided by treatment assignment and overall.

Summaries for continuous measures will include the number of observations (n), mean, SE, median, minimum and maximum. For categorical variables, summaries will include sample size, frequencies, and percentages.

The baseline value will be the last assessment before the first administration of IMP.

All study visits will be recalculated based on actual dates and will be referred to as "analysis visits" which will be used in the statistical analyses. The rules for calculating the analysis visits will be documented in the SAP. Rules for imputing partial dates or missing dates will also be documented in the SAP.

9.3.2. Primary Endpoint/Estimand Analysis

The estimand framework for analysis of the primary endpoint applies only to part B of this study.

- Population: adult participants with newly diagnosed or relapsing BP, regardless of whether the participant is naïve to treatment or has previously received treatment. Participants will be receiving concurrent therapy of oral prednisone (or equivalent OCS); therefore, candidates who have a known contraindication to OCS will be excluded from study participation (exclusion criterion 4).
- Variable: proportion of participants who are in CR while receiving efgartigimod PH20 SC or placebo and have been off OCS therapy for ≥8 weeks at week 36.
- Main intercurrent events (ICE):
    1. Intercurrent treatments before week 36
        a. Immunosuppressants or dapsone at a therapeutic dose for at least 4 weeks
        b. IVIg/SCIg at an immunomodulating dose (at least 1 g/kg/month)
        c. Tetracyclines at therapeutic dose for at least 2 weeks
        d. Rituximab or anti-CD20 biologic, at least 1 infusion
        e. Plasma exchange or immunoadsorption, at least 1 procedure
        f. IV or IM corticosteroids administered in the following conditions:
            - At least 1 administration, any dose, from week 28 to 36 (ie, during the 8-week period required to confirm CR off OCS therapy)
            - At any time before week 28 in any of the 3 following situations:
                - More than 60 mg/day of prednisone or prednisone equivalent dose for 3 consecutive days
                - More than 40 mg/day of prednisone or prednisone equivalent dose for 4 consecutive days
                - More than 7 days in total
        g. Any interventional study drugs under development for BP
        h. Very potent TCS with a weekly dose >20 g for 1 week
    2. Discontinuation of IMP before week 36 due to lack of efficacy

Population-level summary: the odds ratio (95% confidence interval [CI]) under efgartigimod PH20 SC in combination with concurrent OCS therapy versus placebo in combination with concurrent OCS therapy.

Handling of main ICEs: a composite strategy approach will be taken to address both main ICEs. This implies that participants who take intercurrent treatments and participants who discontinue IMP due to lack of efficacy will be considered nonresponders for the primary endpoint analysis.

Handling of missing data:

- Missing data for reason of 1 of the main ICEs will be handled as described above.
- If CR information is missing for the primary endpoint, the participant will be considered a nonresponder. Further details on other imputation techniques for missing CR information will be provided in the SAP.
- Details on handling other missing data will also be provided in the SAP.

Final analysis model: the proportion of participants with BP who are in CR while receiving efgartigimod PH20 SC or placebo and have been off OCS therapy for ≥8 weeks at week 36 will be tested using a Cochran-Mantel-Haenszel (CMH) test stratified for the 2 stratification factors of disease history (newly diagnosed versus relapsing) and disease severity (moderate versus severe). The odds ratio will be provided, along with the 95% CI and 2-sided p-value.

Supplementary analyses: to facilitate interpretation of the estimated treatment effect in the primary analysis, supplementary analyses will be conducted on the supportive estimand where the main ICEs are handled differently (eg, by using the hypothetical or treatment policy strategy instead of composite strategy). Details will be provided in the SAP.

9.3.3. Secondary Endpoints Analysis

9.3.3.1. Analysis of Secondary Efficacy Endpoints (Part B Only)

For part B, there are 5 proposed key secondary endpoints subject to alpha control:

1. Cumulative dose of OCS from baseline to week 36.
2. Proportion of participants who achieve an IGA-BP score of 0 while receiving efgartigimod PH20 SC or placebo and have been off OCS therapy for ≥8 weeks at week 36.
3. Proportion of participants who achieve CDA while receiving efgartigimod PH20 SC or placebo and remain free of relapse through week 36.
4. Proportion of participants who are in CR while receiving efgartigimod PH20 SC or placebo and have been receiving minimal OCS therapy for ≥8 weeks at week 36.
5. Changes from baseline in the 24-hour average itch score from the Itch NRS.

Details on how to deal with the main ICEs for the proposed key secondary endpoints will be provided in the SAP.

The first proposed key secondary endpoint—cumulative dose of OCS from baseline to week 36— will be analyzed in the form of a normalized cumulative OCS dose (NCOD), normalizing by weight and by number of days in study and will be denoted as NCOD.

For the NCOD endpoint, the analysis of covariance (ANCOVA) model will be used to compare both study arms. The model will include treatment and the stratification variables will be considered as factors. Other secondary efficacy endpoints will be analyzed in a similar fashion, as described below:

- Cumulative OCS dose at the time the participant exhibits CDA, CR, and CR while receiving efgartigimod PH20 SC or placebo and receiving minimal OCS therapy for ≥8 weeks
- CR/PR while receiving efgartigimod PH20 SC or placebo and off OCS therapy for ≥8 weeks
- Relapse

In addition to using the measure NCOD for analyzing the cumulative dose of OCS use over the study duration, the term "cumulative OCS use (mg)" will be used and analyzed using descriptive statistics.

The second, third, and fourth proposed key secondary endpoints will be analyzed using a CMH test as specified for the primary endpoint. Other secondary efficacy endpoints that are expressed as responder proportions will be analyzed similarly.

The fifth proposed key secondary endpoint—changes from baseline in the 24-hour average itch score from the Itch NRS—is measured over time and will be analyzed using a mixed-effect model for repeated measures, and the least squares mean difference will be estimated at the prespecified time point.

Additional secondary efficacy endpoints (which are not subject to alpha control) are listed in Table 3 and Table 4; these have been selected to further characterize the efficacy of efgartigimod PH20 SC in participants with BP.

9.3.3.2. Analysis of Other Secondary Endpoints

Other secondary endpoints (which are not subject to alpha control) are listed in Table 3 and Table 4; these have been selected to evaluate other aspects of the effects of efgartigimod PH20 SC in participants with BP, including its safety/tolerability, health impact, QoL, PK/PD, and immunogenicity. Additionally, this study includes endpoints to evaluate whether participants (and/or their caregivers) can competently (self-)administer efgartigimod PH20 SC.

These endpoints are not subject to multiplicity correction, and their analyses are purely descriptive.

Time to CDA and CR will be tested using a stratified Gehan-Wilcoxon test. The other time to event endpoints will be tested using a stratified log-rank test.

All continuous secondary endpoints (such as the C-GTI and QoL instruments) will be analyzed using a mixed-effect model for repeated measures.

Descriptive statistics will be provided for self-administration training, PD (total IgG serum levels and the anti-BP180 and anti-BP230 antibodies), incidence of ADA and NAb against efgartigimod, and incidence of antibodies and NAb produced against rHuPH20. Data for efgartigimod serum concentrations will be summarized. Total IgG serum levels and autoantibody data will be summarized in absolute values, change from baseline, and percent reduction from baseline over time. Population PK/PD analysis may be performed based on the PK and PD data and reported separately.

9.3.3.3. Safety Analyses

Exposure to IMP will be summarized by study arm, separately.

Summaries of TEAEs, AESIs, SAEs and other safety parameters will be provided by study arm. AEs will be classified using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) classification system. AEs, AESIs, and SAEs will be listed corresponding to MedDRA SOC and preferred term (PT). Multiple occurrences of a single PT in a patient will be counted only once at the maximum severity/grade. Any AEs with missing severity or relationship to IMP will be classified as severe and treatment-related, respectively. All AEs will be summarized by relatedness to IMP. Any AEs leading to death or discontinuation of IMP will also be summarized.

All TEAEs, AESIs, and SAEs will be analyzed descriptively, all while acknowledging that the study population (older adult participants with moderate-to-severe BP) has a high mortality rate, a high incidence of existing comorbidities, and an increased risk of developing additional comorbid conditions.

Laboratory parameters, physical examinations, vital sign measurements, and ECG data will also be analyzed descriptively.

9.3.3.4. Exploratory Endpoint Analysis

The exploratory endpoint [redacted] will be analyzed descriptively in a manner similar to that defined for [redacted]

9.3.3.5. Other Analyses

Subgroup analyses of the primary endpoint and key secondary endpoints will be made to assess consistency of the intervention effect across subgroups.

If the number of participants is too small (less than [10%]) within a subgroup, then the subgroup categories may be redefined before unblinding the study.

Pooled analyses of parts A and B will be performed.

Details on the above statistical analyses will be provided in the SAP.

9.4. Interim Analysis (Part A)

An interim analysis will be performed during part A of the study. Results of the interim analysis will inform the sponsor's decision whether to continue part B of the study as currently designed, modify the sample size for part B, or discontinue the study (both parts A and B) due to lack of efficacy.

The part A interim analysis will be performed using data collected from all of its participants through the data cutoff time point (defined as the last participant in part A who reaches week 26). The interim analysis will focus on the primary endpoint (Table 3). However, the analysis of secondary endpoints may be considered. Further details on the scope of interim analysis and the rules governing adaptations will be included in the SAP.

Part A endpoints are listed in Table 3.

Note: Both part A and part B of the study are randomized and double-blinded; the details of the study blinding are described in Section 6.3. The sponsor will take all possible measures to ensure that blinding is maintained at the individual participant level while the part A interim analysis is being performed.

9.4.1. Futility Analysis

The target value (TV) of the part A futility analysis will be defined as the value corresponding to a treatment difference of [redacted]% between the efgartigimod PH20 SC and placebo arms. Similarly, the lower reference value (LRV) will be defined as the value corresponding to a treatment difference of [redacted]% between the 2 study arms.

The sponsor's decision to proceed with the study (versus a decision to stop the study) will be guided by the posterior density of the treatment effect on the study's primary endpoint as a nonbinding futility rule[40]; this rule will be compared with the aforementioned TV and LRV.

- The outcome will be considered favorable ("Go") when the treatment effect is >[redacted]% with a posterior probability of >80% and when the treatment effect is >[redacted]% with a posterior probability of >10%.
- The outcome will be considered inconclusive ("Consider") when the treatment effect is >10% with a posterior probability of <[redacted]% and when the treatment effect is >30% with a posterior probability of >[redacted]%.
- The outcome will be considered unfavorable ("Stop") when the treatment effect is >[redacted]% with a posterior probability of <[redacted]%.

Computer modeling simulations of this analysis—using sample sizes of 20 participants per study arm, fixing the response rate in the placebo arm at [redacted]%, and varying the efgartigimod PH20 SC response rate between [redacted] and [redacted]%—have displayed suitable operating characteristics: the probability of producing a favorable ("Go") outcome is high when the treatment effect is high (Figure 3).

Figure 3: Probabilities of Producing Favorable ("Go"), Inconclusive ("Consider"), and Unfavorable ("Stop") Outcomes for Part A Futility Analysis With a Sample Size of 20 Participants per Study Arm

EFG=efgartigimod

Figure 4 presents the decision matrix for favorable, inconclusive, and unfavorable outcomes based on the treatment differences observed during part A.

Figure 4: Decision Matrix for Favorable ("Go"), Inconclusive ("Consider"), and Unfavorable ("Stop") Outcomes Based on the Absolute Number of Responders in Part A Study Arms (Efgartigimod PH20 SC vs Placebo)

EFG=efgartigimod; efgartigimod PH20 SC=efgartigimod for SC administration coformulated with rHuPH20; placebo=placebo for SC administration coformulated with rHuPH20; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly)

Some examples of potential outcomes from this framework are listed below:

- The outcome will be considered favorable ("Go") if the [redacted] of the 20 participants in the efgartigimod PH20 SC study arm ([redacted]%) are responders versus [redacted] of the 20 participants in the placebo arm ([redacted]%).
- The outcome will be considered inconclusive ("Consider") if the [redacted] of the 20 participants in the efgartigimod PH20 SC study arm ([redacted]%) are responders versus [redacted] of the 20 participants in the placebo arm [redacted]%).
- The outcome will be considered unfavorable ("Stop") if the [redacted] of the 20 participants in the efgartigimod PH20 SC study arm ([redacted]%) are responders versus [redacted] of the 20 participants in the placebo arm [redacted]%).

Note: The potential outcome that is produced from this analysis (favorable, inconclusive, unfavorable) will be used for guidance purposes only. The ultimate decision to proceed with or stop the study will be based upon a review of all of the available data and proper judgment of clinical relevance of the observed outcomes.

9.5. Sample Size Determination

Part A will randomize 40 participants. No formal sample size calculation is performed for part A. The sample size calculation for part B is based on the following assumptions:

- The primary endpoint is the proportion of participants who are in CR while receiving efgartigimod PH20 SC and off OCS therapy for ≥8 weeks at week 36
- Percentages for sample size calculation:
  - efgartigimod PH20 SC: [redacted]%
  - placebo: [redacted]%
- 1:1 randomization
- Power: 90%
- Significance level: 5% (2-sided)

A binomial distribution was used to calculate the sample size using PASS 2021 software. Table 9 presents the number of participants needed in each arm.

Table 9: Calculation Matrix Applied to Determine the Appropriate Number of Participants in Study ARGX-113-2009

Percentages for Sample Size Calculation:		Efgartigimod				
		[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Placebo	[redacted]%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Assuming a clinically relevant difference of [redacted]% and an expectation to achieve the primary endpoint in [redacted]% of participants treated with efgartigimod PH20 SC, a total of 120 participants (rounding from the sample size of [redacted] participants, calculated using PASS software) randomized

to either the efgartigimod PH20 SC arm or the placebo arm in a 1:1 ratio will yield more than 90% power in a 2-sided test at the 5% significance level.

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 in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval before initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- Before signing the ICF, participants will be instructed not to participate in any other clinical study that involves an intervention or collection of data until the completion of the current study.
- The investigator or his/her representative will explain the following to the participant and answer all questions regarding the study: the nature of the study, its purpose, the procedures involved, the expected duration, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available, and the extent of maintaining confidentiality of the participant's records.
- The investigator or their representative will explain the nature of the study—including the risks and benefits—to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- 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.
- Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or data sets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent

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

Photography is generally accepted as routine practice for documenting dermatological conditions in medical practice. Photographs may be taken at baseline and at subsequent visits to document response and progression. Participants will be requested to provide consent for any use that will be made of the image and for sharing anonymized pictures with the sponsor.

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

10.1.5. Data and Safety Monitoring Board

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

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

10.1.6. Dissemination of Clinical Study Data

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

The investigator is responsible for maintaining source documents. These will be made available for verification by the sponsor's designee monitor at each monitoring visit. The investigator must submit an eCRF for each participant, regardless of duration of participation or administration of IMP (ie, an eCRF has to be submitted for screen failures as well). All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and participant number. Any personal information, including participant name, should be removed or rendered illegible to preserve data privacy.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on eCRFs unless transmitted to the sponsor (or its designee) electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

Guidance on completion of eCRFs will be provided in the Completion Guidelines Document.

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

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management

and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

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

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site 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.

10.1.7.1. Data Handling and Record Keeping

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

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

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

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

10.1.7.2. Quality Assurance Audit

Study processes, study sites (including, but not limited to site visits, central laboratories, vendors), the study database, and study documentation may be subject to quality assurance audit during the course of the study by the sponsor or sponsor's designee on behalf of sponsor. In addition, inspections may be conducted by regulatory bodies at their discretion.
Such audits/inspections can occur at any time during or after completion of the study.

10.1.7.3. Quality Control

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

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

- Investigator meetings
- Central laboratories for clinical laboratory parameters
- Site initiation visit
- Routine site monitoring
- Ongoing site communication and training
- Ongoing oversight by sponsor's designee of safety parameters and adherence to selection criteria
- Eligibility review by sponsor's designee and medical monitors
- Data management quality control checks
- Continuous data acquisition and cleaning
- Quality control check of the clinical study report (CSR)
- To avoid interobserver variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all efficacy and safety evaluations.

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

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

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered on the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site 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.

10.1.9. Monitoring

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

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

- Data are authentic, accurate, and complete
- Safety and rights of participants are being protected
- The study is conducted in accordance with the currently approved protocol, any other study agreements, and all applicable regulatory requirements.

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

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

The sponsor's designee will perform an eCRF review, source document verification (wherever allowed per local regulations), and source document review.

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

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

10.1.10. Data Management

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

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

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Only if requested per local regulations, no data collection or source data verification will be performed on race and ethnicity. Source documents are all documents used by the investigator or hospital that relate to the participant's medical history, that verify the existence of the participant, the inclusion and exclusion criteria,

and all records covering the participant's participation in the study. They can include laboratory notes, ECG results, memoranda, pharmacy dispensing records, participant files, etc. The eCRFs should be completed by the investigator or a qualified designee from the site as soon as the data are available.

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

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

Data will also be provided by third party vendors, such as the results generated by the central laboratories, ECG reader, etc. These data will need to be reconciled with the data recorded on the eCRF before it can be merged with the eCRF data into the clinical database. The sponsor's designee will provide a data management plan detailing this reconciliation.

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

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

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

10.1.11. Study and Site Start and Closure

10.1.11.1. General Considerations

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

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.

10.1.11.2. Site Closure

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

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

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

Study sites can also be closed for any reason by the IRB/IEC. The sponsor may close individual study sites prematurely for reasons such as poor protocol compliance or unsatisfactory recruitment of participants.

10.1.11.3. Study Closure

The sponsor can halt the study and conduct a review of safety data if any of the following occur during either part A or B:

- 2 or more participants have safety findings that are considered unacceptable for the study population
- 2 or more study participants have the same (or similar) severe AE that is considered to be related or possibly related to the IMP

In both of the cases noted above, the study may resume (with resumption of IMP administration) following the conclusion of a safety data review and a favorable recommendation by the DSMB.

Additionally, the sponsor can halt the study for any other reason.

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

The study can also be terminated by the regulatory authority for any reason.

10.1.12. Investigator Obligations

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

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

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

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

10.1.13. Protocol Signatures

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

10.1.14. Publication Policy

All information regarding efgartigimod PH20 SC supplied by the sponsor to the investigator and all data generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The results of the study will be reported in a CSR.

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

The results of this study may be published or presented at scientific meetings. Any manuscript, abstract or other publication, presentation of results, or information arising in connection with the study must be prepared in conjunction with the sponsor after the study has been analyzed and reported and must be submitted to the sponsor for review and comment before submission for publication or presentation. This allows the sponsor to protect proprietary information and to provide comments. Study participant identifiers will not be used in the publication of results.

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 in line with International Committee of Medical Journal Editors criteria authorship requirements, based on scientific input and recruitment efforts.

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

10.2. Appendix 2: Clinical Laboratory Tests

- The tests listed in Table 10 will be performed as described in the laboratory manual.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory test report.
- Retesting during screening to assess eligibility may be performed at a local laboratory.

Table 10: Protocol-Required Laboratory Tests

Laboratory Test	Parameters		
Hematology	RBC count platelet count hemoglobin hematocrit	RBC indices: MCV MCH % reticulocytes	WBC count with differential: neutrophils eosinophils lymphocytes basophils monocytes
Clinical chemistry[a]	ALT AST ALP albumin[b] bilirubin (total and direct) BUN	calcium creatinine CRP GGT glucose glycosylated hemoglobin (HbA1c) potassium	sodium total protein[b] 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	Highly sensitive serum hCG pregnancy serum test at screening and urine test at other time points (as needed for women of childbearing potential, defined in Section 10.4.1)[c]		
Specialty laboratory tests	aPTT	INR	
Other screening tests	COVID-19 test (performed if required per local regulations) Tuberculosis QuantiFERON (or another regionally-approved IGRA test that has similar validity [eg, T-SPOT][d]) Serology for HBV, HCV, HIV (exclusion criterion 13A and Section 8.3.7)		

ALP=alkaline phosphatase; ALT/SGPT=alanine aminotransferase/serum glutamic pyruvic transaminase; aPTT=activated partial thromboplastin time; AST/SGOT=aspartate aminotransferase/serum glutamic oxaloacetic transaminase; BUN=blood urea nitrogen; CRP=C-reactive protein; CT=computerized tomography; GGT=gamma-glutamyl transferase; hCG=human chorionic gonadotropin; HBV=hepatitis type B; HCV=hepatitis type C; HDL=high-density lipoprotein; IEC=Independent Ethics Committee; IGRA=interferon gamma release assay;

INR=international normalized ratio; IRB=Institutional Review Board; LDL=low-density lipoprotein; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; WBC=white blood cell

[a] Blood for clinical chemistry testing will be sampled from nonfasted participants.

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

[c] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

[d] Additional testing (such as chest CT scan or X-ray) may be performed at the investigator's discretion to confirm whether the participant has an active tuberculosis infection.

10.2.1. Other Screening Tests

10.2.1.1. COVID-19

COVID-19 testing will be performed at screening if required according to local regulations; individuals with positive test results are excluded from taking part in the study (exclusion criterion 6A).

Additional COVID-19 testing recommendations/guidelines are presented in Section 10.14.

10.2.1.2. QuantiFERON-TB, IGRA Test and Testing for Active Tuberculosis Infection

A QuantiFERON-TB (or another regionally-approved IGRA test that has similar validity [such as the T-SPOT]) can be measured in the central laboratory for each participant at screening to determine whether they have antibodies against *Mycobacterium tuberculosis*. The assessment can be based on central or local laboratory samples taken at screening. Additional testing (such as a chest computerized tomography [CT] scan or X-ray) may be performed at the investigator's discretion to determine whether the participant has an active TB infection.

10.2.1.3. Hepatitis B Virus

Participants with an active acute or chronic hepatitis B viral infection at screening cannot be enrolled in the study.

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

Table 11: Interpretation of Hepatitis B Serological Test Results

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

anti-HBc=total hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus

[a]This decision will be made by a medical doctor with sufficient experience in hepatology or infectious disease. Additional tests (eg, HBV viral load) may be required to determine the status of the participant.

10.2.1.4. Hepatitis C Virus

Participants with an active acute or chronic hepatitis C viral infection at screening cannot be enrolled in the study. The hepatitis c virus antibody serologic test will be used to identify an active hepatitis C viral infection as indicated in Table 12.

Table 12: Interpretation of the Hepatitis C Antibody Test

HCV Ab Test Result	Interpretation
Positive	The patient cannot be enrolled in the study because the test results indicate an active acute or chronic HCV infection unless associated with a negative HCV RNA test.

HCV=hepatitis C virus; HCV Ab=hepatitis C virus antibody; RNA=ribonucleic acid

10.2.1.5. Human Immunodeficiency Virus

Participants who are HIV positive and do not have an AIDS-defining condition or a CD4 count ≥200 cells/mm^3 at screening can be enrolled in the study if they are adequately treated with antiviral therapy (Table 13). Participants who are HIV positive and have an AIDS-defining condition or a CD4 count <200 cells/mm^3 at screening cannot be enrolled in the study. The following are considered AIDS-defining conditions:

- Cytomegalovirus retinitis with loss of vision
- Pneumocystis jiroveci pneumonia
- Chronic intestinal cryptosporidiosis
- Mycobacterium tuberculosis (pulmonary or extrapulmonary)
- HIV-related encephalopathy
- Invasive cervical cancer

Table 13: Interpretation of HIV Test Results

HIV test result	Clinical condition/ CD4 Count/viral load	Interpretation
Positive	AIDS-defining condition is present or CD4 count <200 cells/mm^3	Test results and clinical conditions or CD4 count confirm AIDS diagnosis, which is exclusionary
	Viral load >200 copies/mm^3 despite participant receiving antiretroviral therapy	Participant ineligible because the antiretroviral therapy is not adequate
	Viral load <200 copies/mm^3 but participant not receiving antiretroviral therapy	Participant ineligible because not receiving antiretroviral therapy

AIDS=acquired immune deficiency syndrome; HIV=human immunodeficiency virus

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 may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either IMP or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> to be Collected as AEs
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless 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:

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted 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 should be considered serious.
- Hospitalization for elective treatment of a preexisting condition that did not worsen from screening will not be collected as an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include events of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.
- Suspected transmission of any infectious agent via the IMP will also be treated as an SAE.

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

AE and SAE Recording

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

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Severity

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

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

The grade refers to the severity of the AE. If a particular AE's severity is not specifically graded by the guidance document, the investigator is to use the general NCI CTCAE definitions of grade 1 through grade 5 following his or her best medical judgment, using the following general guideline:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) (eg, preparing meals, shopping for groceries or clothes, using the telephone).
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
- Grade 4: Life-threatening consequences or urgent intervention indicated.
- Grade 5: Death related to AE.

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

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe. Grade 4 and 5 AEs are always assessed as serious (ie, SAE).

Assessment of Causality

- The investigator is obligated to assess the relationship between IMP and each occurrence of each AE/SAE as **related** or **not related**. The investigator will use clinical judgment to determine whether there is reasonable possibility that the IMP caused the AE.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IMP administration, will be considered and investigated.
- **Related** means that the AE cannot be explained by the participant's medical condition, other therapies, or an accident. The temporal relationship between the AE and IMP administration is compelling and/or follows a known or suspected response pattern concerning that IMP.
- **Not related** means that the AE can be readily explained by other factors such as the participant's underlying medical condition, concomitant therapy, or accident. No plausible temporal or biologic relationship exists between the IMP and the AE.
- The investigator will also consult the investigator's brochure (IB) and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that they have reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always assess causality for every event before the initial transmission of the SAE data.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

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

10.3.4. 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 should check that all entered data are consistent.
- An alert email for the SAE/AESI report on the eCRF will then automatically be sent by email to the sponsor's designee safety mailbox via the EDC system.
- The paper SAE report form should 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 woman is considered to be of childbearing potential (WOCBP) unless she is either:

a. Postmenopausal: A postmenopausal state is defined by continuous amenorrhea for at least 1 year without an alternative medical cause with 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; therefore, an FSH test to confirm a postmenopausal state is not considered valid. In a case such as this, the postmenopausal state will need to be assessed by the investigator.
b. Surgically sterilized: Women who have had a documented permanent sterilization procedure (eg, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy)

10.4.2. Contraception Guidance

10.4.2.1. Female Contraception for Women of Childbearing Potential

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

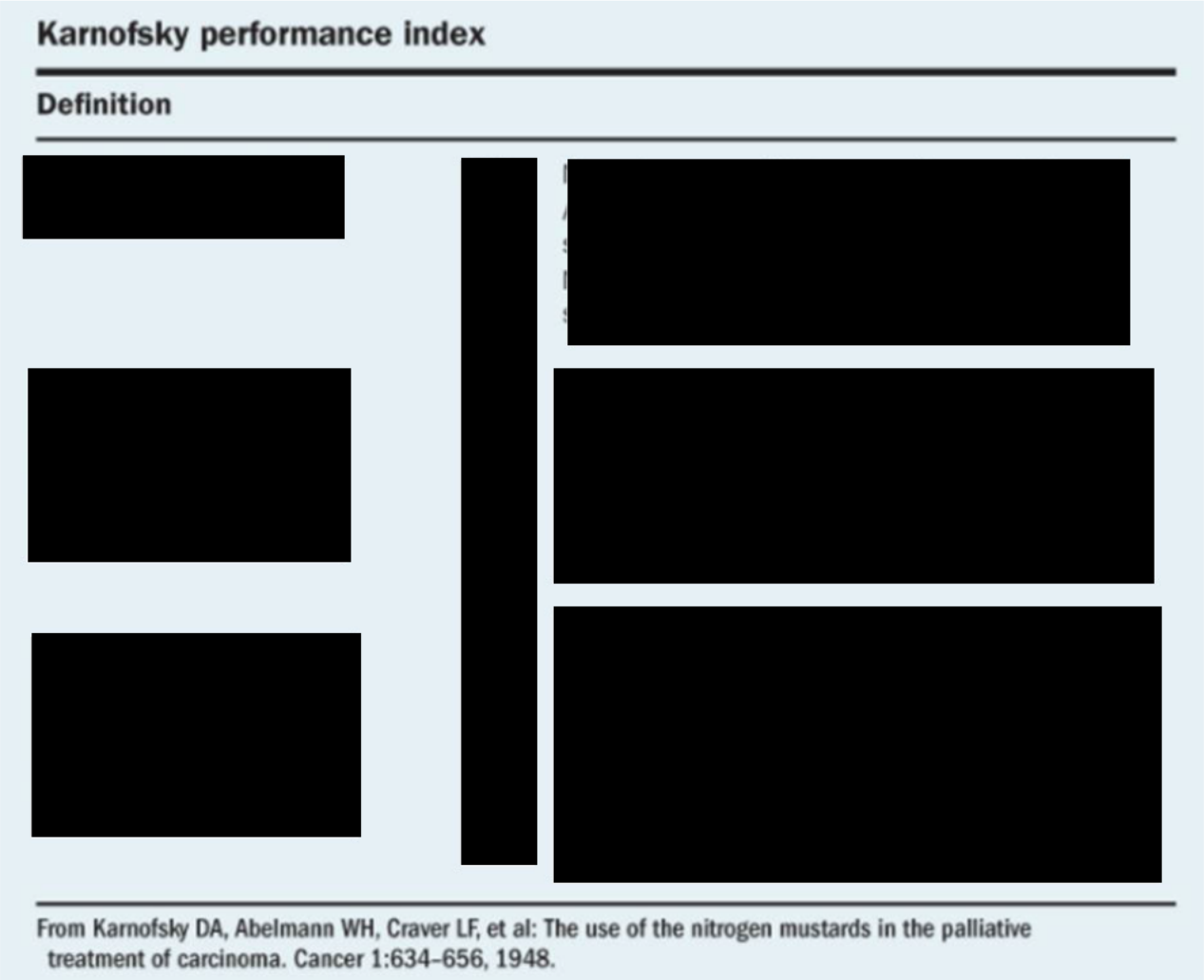
1. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    a. Oral
    b. Intravaginal
    c. Transdermal
2. Progestogen-only hormonal contraception associated with inhibition of ovulation:
    a. Oral
    b. Injectable
    c. Implantable
3. Intrauterine device (IUD)
4. Intrauterine hormone-releasing system (IUS)
5. Bilateral tubal occlusion
6. Vasectomized partner
7. Sexual abstinence: a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the IMP. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant
8. Progestogen-only oral hormonal contraception in which inhibition of ovulation is not the primary mode of action
    a. Oral
    b. Injectable
    c. Implantable

9. Male or female condom with or without spermicide
10. Cap, diaphragm, or sponge with spermicide

10.4.2.2. Male Contraception

No male contraception is required.

10.5. Appendix 5: The Karnofsky Performance Index



Karnofsky performance index

Definition

[redacted]

From Karnofsky DA, Abelmann WH, Craver LF, et al: The use of the nitrogen mustards in the palliative treatment of carcinoma. Cancer 1:634–656, 1948.

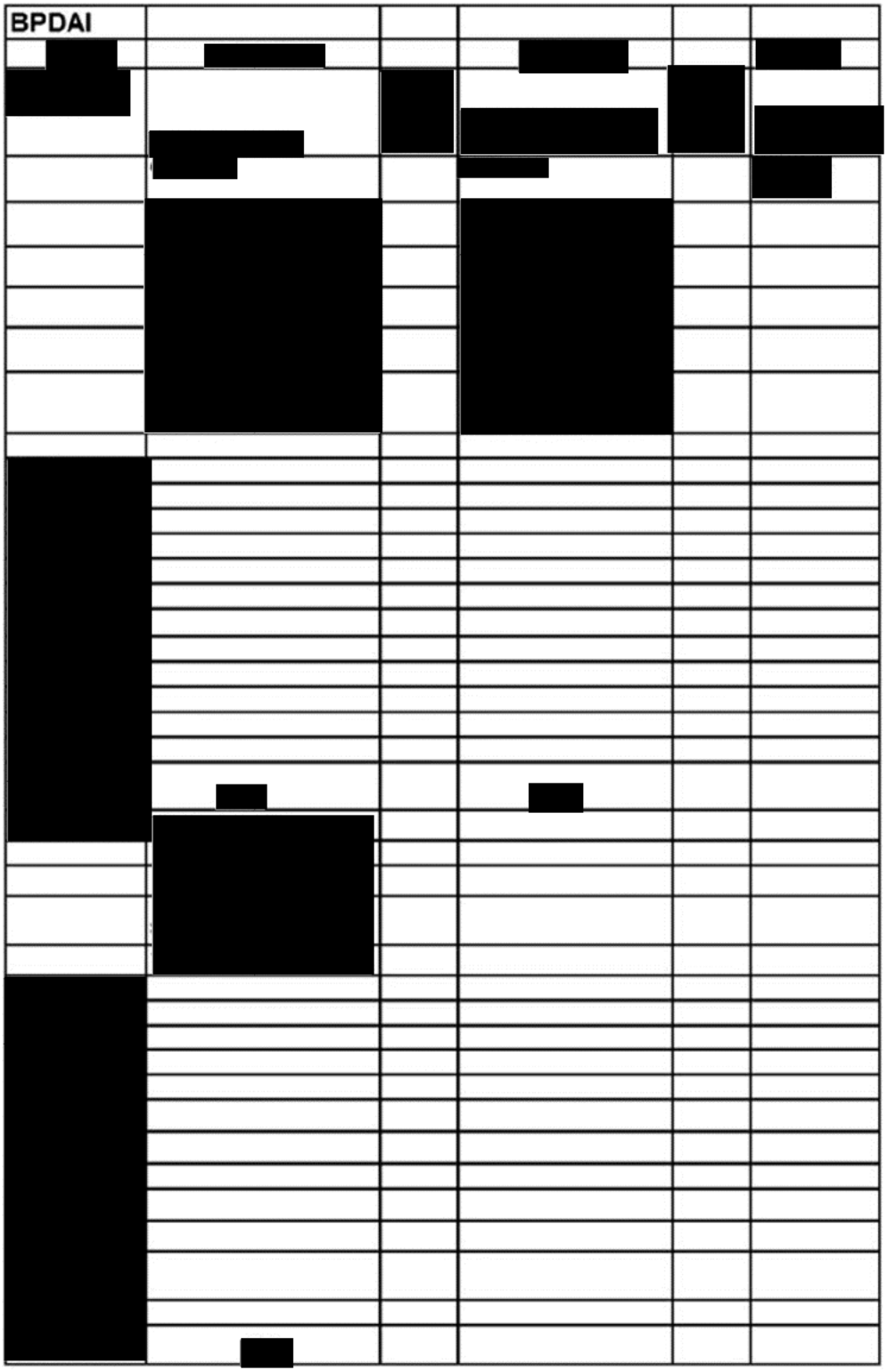
10.6. Appendix 6: Investigator Global Assessment of Bullous Pemphigoid (IGA-BP)

It is not necessary that all characteristics under morphological descriptors be present to meet criteria for an IGA score.

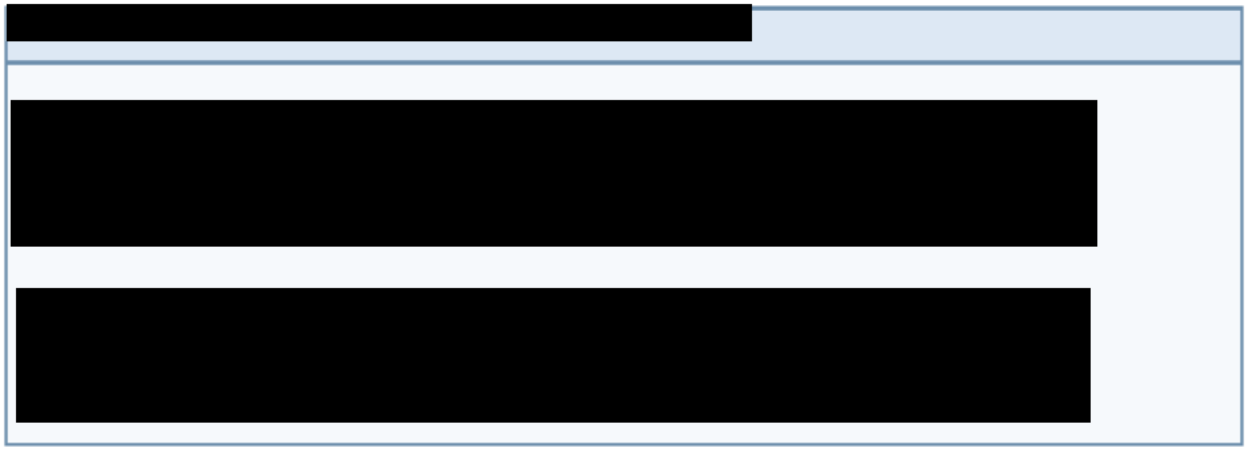
Score	*Morphological Descriptors
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

10.7. Appendix 7: Bullous Pemphigoid Disease Area Index (BPDAI) Questionnaire

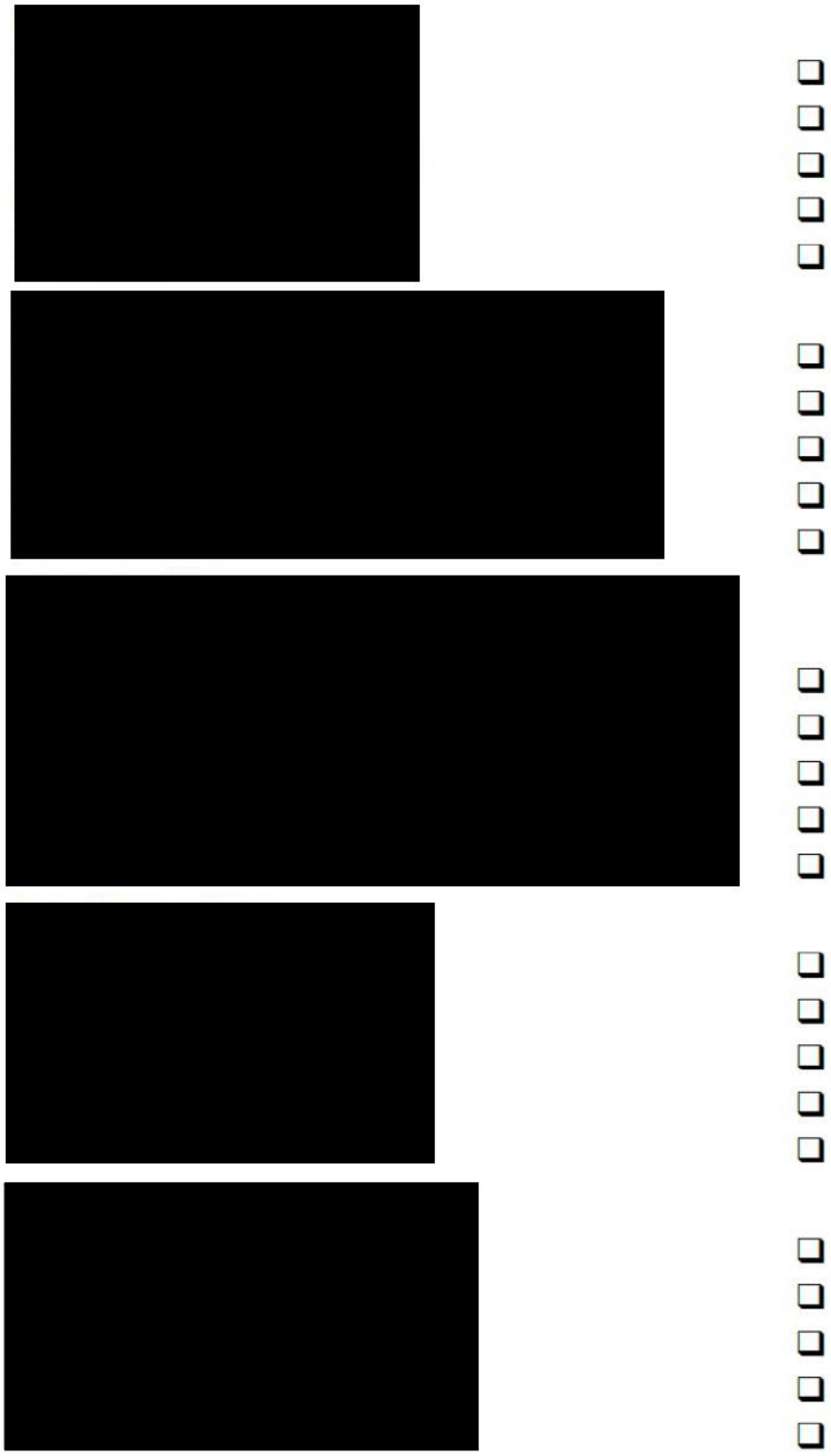


10.8. Appendix 8: The Itch Numerical Rating Scale (Itch NRS)



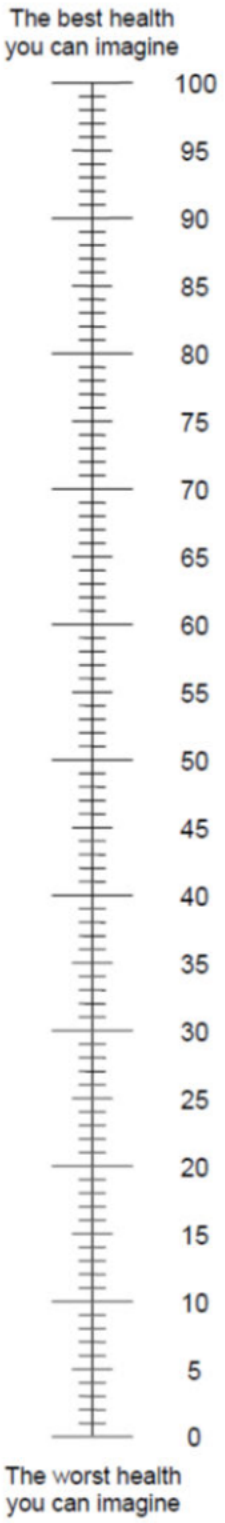
10.9. Appendix 9: The EuroQol 5-Dimension 5-Level (EQ-5D-5L)

[redacted]

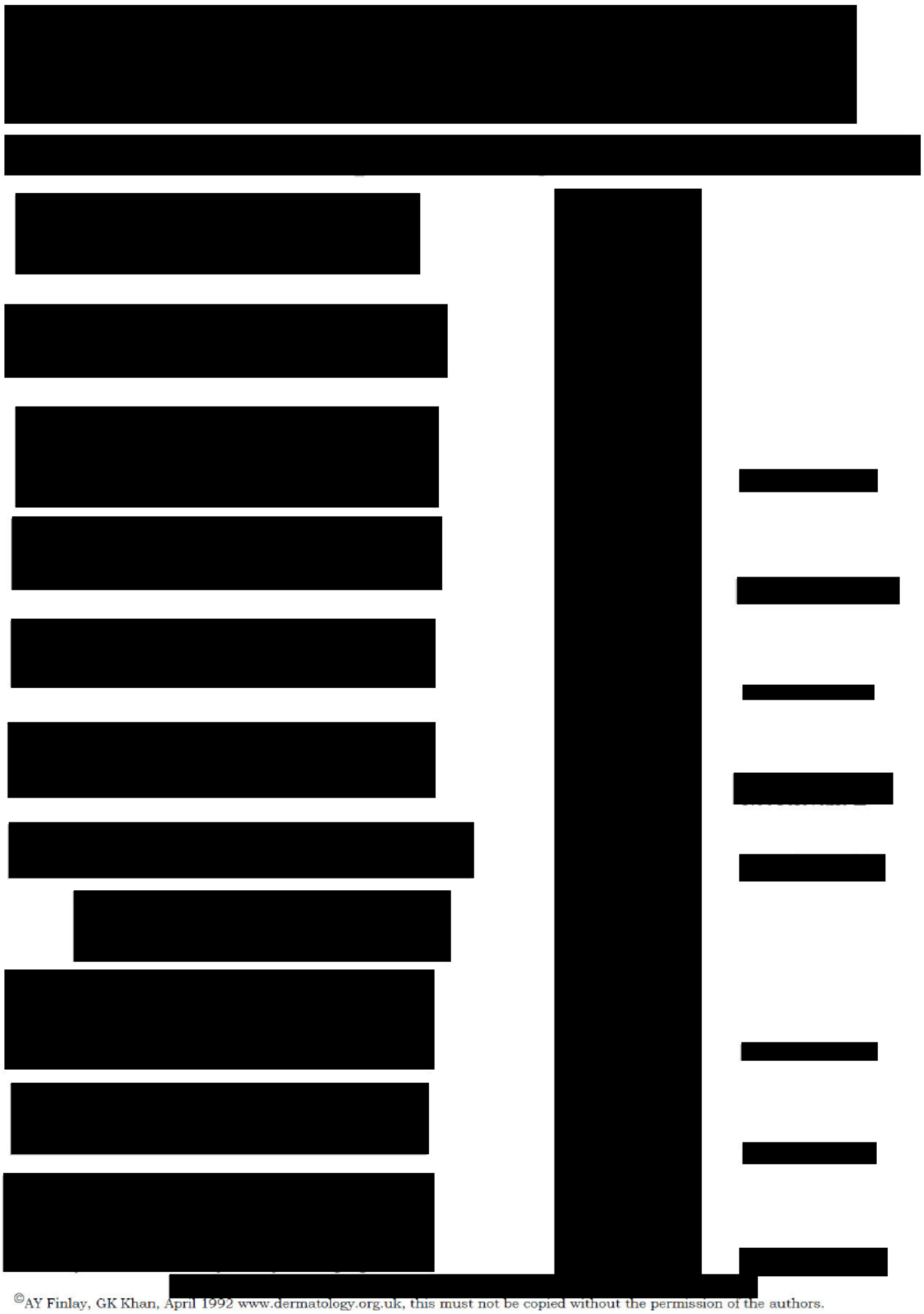


[redacted]

YOUR HEALTH TODAY = ☐



10.10. Appendix 10: Dermatology Life Quality Index (DLQI)



10.11. Appendix 11: Autoimmune Bullous Disease Quality of Life (ABQoL) Questionnaire

[redacted]

Thank you for taking the time to complete this questionnaire

10.12. Appendix 12: The Glucocorticoid Toxicity Index

Table 14: GTI 2.0 Composite Index (Adapted for ARGX-113-2009)

Domain	Score
[redacted]	

Table 14: GTI 2.0 Composite Index (Adapted for ARGX-113-2009) (Continued)

Domain	Score
[redacted]	[redacted]

Source: Adapted from McDowell et al. 2021.[39]
BMI=body mass index; GTI=Glucocorticoid Toxicity Index; HbA1c=glycated hemoglobin; LDL=low-density lipoprotein; NP=neuropsychiatric

Table 15: GTI 2.0 Specific List (Adapted for ARGX-113-2009)

Domain Item	At Baseline or Before	New Since Baseline
[redacted]		

Table 15: GTI 2.0 Specific List (Adapted for ARGX-113-2009) (Continued)

Domain Item	At Baseline or Before	New Since Baseline
[redacted]		

Source: Adapted from McDowell et al. 2021.[39]
BMI-body mass index; GTI=Glucocorticoid Toxicity Index
[a] For the reasons described in Section 8.3.9, bone mineral density will not be assessed in ARGX-113-2009. Therefore, the bone health parameter "bone mineral density decrease >6%" has been removed from this list.

10.13. Appendix 13: 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.

10.13.1. Japan

A Japanese patient is defined as a patient who was born in Japan and currently lives in Japan with Japanese nationality, has not lived outside of Japan for a total of >10 years, and whose parents and 4 grandparents are Japanese.

10.13.2. China

PD and immunogenicity blood samples that are collected from participants in China at screening 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 Human Genetic Resources Administration of China (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 6.8.1.3). For concurrent oral methylprednisolone dose adjustment regimen, refer to Table 16.

Table 16: Concurrent Oral Methylprednisolone Equivalent Doses (in mg) Based on Participant Body Weight

Oral prednisone dose level	Body weight category[a]													
	<45 kg	≥45 to <50 kg	≥50 to <55 kg	≥55 to <60 kg	≥60 to <65 kg	≥65 to <70 kg	≥70 to <75 kg	≥75 to <80 kg	≥80 to <85 kg	≥85 to <90 kg	≥90 to <95 kg	≥95 to <100 kg	≥100 to <105 kg	≥105 to <110 kg	≥110 kg
	Minimum recommended daily methylprednisolone doses	Daily methylprednisolone doses[b]													Maximum recommended daily methylprednisolone doses
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
Starting dose: 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
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 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.

[a] Body weight should be rounded to the nearest whole number.

[b] The investigator should not deviate from the recommended concurrent oral methylprednisolone dosing regimen, except in matters where the safety of the participant may be compromised.

10.14. Appendix 14: Operational Considerations for COVID-19 Risk Mitigation

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

This appendix is intended for use only if unforeseen changes in the COVID-19 pandemic lead to new restrictions at the site, or if new risks for participants or site staff prevent them from attending visits at the site. The sponsor/designee and the study site must agree to the duration of these changes.

10.14.1. Testing for COVID-19

Additional testing for COVID-19 beyond what is listed in the SoA (Table 1) is not required during the study. However, it is recommended that participants who develop COVID-19 symptoms be tested, and the results be reported for the study.

During the pandemic, the site staff should contact participants before each visit to inquire about COVID-19 symptoms (eg, fever, cough, sneezing, loss of taste/smell, difficulties breathing/chest tightness) and exposure to determine if it is safe for the participant to proceed with the visit as planned. If a participant tests positive for SARS-CoV-2 or has symptoms of COVID-19, they should not return to the site for visits (nor should home nurses visit the participant's home for home visits) until the investigator determines it is safe to return to normal study visit procedures, based on local regulations and guidance from the site staff.

Critical Parameters to Be Collected During the Study

All assessments should be performed as indicated in the SoA (Table 1). If assessments cannot be performed due to the COVID-19 pandemic, the following critical parameters must be collected: all AE reporting, injection site reactions, IMP administration, questionnaires, and safety laboratory assessments from the first visit through the end of study.

10.14.2. Study Protocol Changes

If the COVID-19 pandemic results in significant participant discontinuation, the sites may increase the recruitment of potential participants to replace the lost participants.

Critical Parameters to Be Collected During the Study

All assessments should be performed as indicated in the SoA (Table 1) if possible. In the event that some assessments cannot be performed due to the COVID-19 pandemic, the following critical parameters must be collected: all AE reporting, injection site reactions, IMP administration, OCS dose adjustment, disease assessment, and safety laboratory assessments from the first visit through the end of treatment.

10.14.3. Mandatory Site Visits

All visits that are designated as mandatory on-site visits (baseline [week 0] and weeks 1-4, 8, 12, 16, 20, 24, 26, 28, 32, 36, 39, and 43) must be performed at the site. If adaptations are required due to the COVID-19 pandemic, the following visits should be performed at the site if possible:

- Screening visit
- Baseline/day 1 [**Note**: Participants cannot be randomized to either of the study arms unless this visit occurs on-site]
- EoTP/ETD/ESD visits

During the COVID-19 pandemic, other study visits designated as mandatory on-site visits (weeks 1-4, every fourth weekly visit thereafter through week 36, and weeks 26, 39, and 43; [Table 1]) may be performed at the participant's home (or an alternate convenient location). Such home visits will include sample collections as described in Table 17.

A home nurse will travel to the participant's home to conduct these visit (or the participant will go to the alternate convenient location). The investigator will talk to the participant via an audio or video interview to elicit AEs and concomitant medications, as well as the general well-being of the participant. The investigator will also perform efficacy assessments using an audio or video interview with the participant. These assessments (via audio/video interview) will be conducted before the home nurse administers IMP.

The division of tasks between the investigator and home nurse are indicated in Table 17.
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- or caregiver-supported administration, provided that the participant or caregiver has completed the training and have been determined competent. Such an exception will require concurrent sponsor and investigator approval on a case-by-case basis.

Table 17: Scheme for Study Visits Performed at Home During a COVID-19 Pandemic

Critical Assessment	Performed By:	Method of Assessment
Updates/addenda to original informed consent (other than those conducted at screening and baseline visits)	Investigator	Audio or video interview
Disease assessment (CDA, PR, CR, relapse, treatment failure)[a]	Investigator	Audio or video interview
Adverse events	Investigator	Audio or video interview
Concomitant medications	Investigator	Audio or video interview
OCS dose adjustment evaluation	Investigator	Audio or video interview
Vital sign measurements	Home nurse[b]	In person at participant's home[c]
Blood collection (for safety assessments only)	Home nurse[b]	In person at participant's home[c]
Urine collection (for safety assessments only)	Home nurse[b]	In person at participant's home[c]
IMP administration	Home nurse[b]	In person at participant's home[c]

BP=bullous pemphigoid; CDA=control of disease activity; CR=complete remission; ICF=informed consent form; IMP=investigational medicinal product; OCS=oral corticosteroids (prednisone or equivalent); PR=partial remission.
[a] Refer to Section 4.1.3 for BP disease terminology definitions.
[b] The home nurse is either a nurse from the study site or a nurse from a commercial nursing vendor who is delegated by the investigator.
[c] Or at an alternate convenient location for the participant.

10.15. Appendix 15: Protocol Amendment History

Protocol Version 3.0, Amendment 2 (27 Mar 2023)

This amendment of the ARGX-113-2009 protocol is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for This Amendment

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

In addition, the changes implemented in the UK-specific protocol v2.1 – UK are included in this protocol amendment. Country-specific requirements are indicated in Section 10.13.

The major changes from protocol version 2.0 to protocol version 3.0 are summarized in the following table. Minor editorial changes, including the correction of typographical errors and formatting inconsistencies, are not summarized in the table.

Section number/ Section title	Description of change	Brief rationale for change
7. IMP Discontinuation and Participant Discontinuation/ Withdrawal	This section was revised to encourage participants who permanently discontinue IMP to remain in the study, but only attend mandatory on-site visits. The circumstances that result in IMP discontinuation and study withdrawal were revised.	Health authority requested updates. Changes reduce the burden on the participants.
9.5. Sample Size Determination	A clarification of the difference between the calculated and actual sample sizes was added.	Health authority requested update.
1.3. Schedule of Activities (SoA)	The visits at weeks 8 and 16 may also be performed at home, by qualified site staff, for a participant who has achieved CDA. In these cases, collection of the PK, PD, immunogenicity blood samples, and weight measurements are not required.	Revisions reduce the burden on participants.
	Participants who discontinue IMP must now only attend mandatory on-site visits.	

Section number/ Section title	Description of change	Brief rationale for change
1.3. Schedule of Activities (SoA) 8.5. Pharmacokinetics	On day 10 in part A of the study, at least 28 participants, rather than all participants, are required to have an additional PK sample collected.	Revision reduces the burden on participants. Data from at least 28 participants is sufficient to characterize anticipated peak concentrations after the second administration of efgartigimod PH20 SC.
6.8.3. Rescue Therapy	IVIg is added as a new option for rescue therapy.	IVIg is a nonimmunosuppressive treatment option for participants who permanently discontinue IMP under conditions described in the section.
1.3. Schedule of Activities (SoA) 2.3. Benefit/Risk Assessment 6.4. Study Intervention Compliance	The length of safety monitoring after on-site IMP administration was revised to at least 30 minutes.	Revision aligns with the current efgartigimod IB.
2.3.1, Table 2: Potential Risks and Mitigation Strategies for ARGX-113-2009, Infusion/injection-related reactions	The frequency of infusion/injection-related reactions in the studies was added. In addition, it was clarified that pretreatment, to prevent an infusion/injection-related reaction, is not required.	Revision aligns with the current efgartigimod IB.
2.3.1, Table 2: Potential Risks and Mitigation Strategies for ARGX-113-2009, Injection site reactions	Injection site reactions were added as a potential clinically significant risk.	Injection site reactions are now defined as adverse events of clinical interest that need to be monitored.
2.3.1, Table 2: Potential Risks and Mitigation Strategies for ARGX-113-2009	Language on the potential risk of teratogenicity/fetotoxicity was deleted.	Reproductive toxicity studies with efgartigimod did not show a teratogenic effect in rat or rabbit, nor did it adversely affect male and female fertility or the reproductive and developmental performance in rats.

Section number/ Section title	Description of change	Brief rationale for change
		However, the measures to exclude pregnant or lactating females and those who intend to become pregnant during the study, as well as the immediate discontinuation of IMP use in case of pregnancy, remain unchanged.
2.3.1, Table 2: Potential Risks and Mitigation Strategies for ARGX-113-2009	Language on potential risk of first-time administration of efgartigimod PH20 SC to participants with BP was deleted.	This is an inherent risk associated with any clinical study investigating an IMP for the first time in a new patient population. Applicable laws, regulations, and guidelines (Section 10.1.1) are being followed to minimize this risk.
2.3, Table 2: Potential Risks and Mitigation Strategies for ARGX-113-2009	The section title was changed from “Immune modulation leading to increased infection risk” to “Serious infection.” The mitigation strategy was rephrased. Recommendations for additional mitigation measures before and during the study (Section 8.3.7) are listed. The potential clinically significant risk of “Susceptibility to infection” was deleted, as this risk is covered under “Serious infection.”	Revisions improve comprehension.

Section number/ Section title	Description of change	Brief rationale for change
5.2. Exclusion Criteria 2.3.1., Table 2: Potential Risks and Mitigation Strategies for ARGX-113-2009 8.3.7. Infections and Vaccinations	Participants with latent infections are excluded from the study. Exclusion criterion 5 was revised accordingly and renumbered as 5B.	Because the mechanism of action of efgartigimod involves reducing IgG levels, there is a potential risk of reactivating the infection in participants.
5.2. Exclusion Criteria	Exclusion criterion 7, which was renumbered as 7A, was revised to exclude potential participants with any medical condition, that in the opinion of the investigator would interfere with an accurate assessment of clinical symptoms of BP, putting the participant at undue risk, or prevent participants from complying with protocol requirements.	Revision ensures the safety of the participant and the integrity of the collected data.
5.2. Exclusion Criteria 10.2.1.5. Human Immunodeficiency Virus Table 13: Interpretation of HIV Test Results	Exclusion criterion 13, which was renumbered as 13A, now includes participants who are HIV positive and not adequately treated with antiviral therapy.	Because the mechanism of action of efgartigimod involves reducing IgG levels, there is a potential risk of infection or other complications in participants.
5.2. Exclusion Criteria 8.3.7. Infections and Vaccinations	Participants with total IgG serum levels of 4-6 g/L at screening are now by default eligible to participate in the study. Exclusion criterion 14 was revised accordingly and renumbered as 14A.	Based on emerging data from studies with efgartigimod in other indications, the sponsor has decided that treatment with efgartigimod is safe for any participant with total IgG serum levels ≥4 g/L at screening.
5.2. Exclusion Criteria	Exclusion criterion 15, which was renumbered as 15A, was revised to clarify that the investigator has decision-making power.	Clarification reduces the risk of protocol deviations.
5.2. Exclusion Criteria 8.3.7. Infections and Vaccinations	Participants who have received a live or live-attenuated vaccine <4 weeks before the baseline visit	Because the mechanism of action of efgartigimod involves reducing IgG levels, and safety

Section number/ Section title	Description of change	Brief rationale for change
	are excluded from the study (exclusion criterion 17).	of immunization with live or live-attenuated vaccines was not studied.
5.2. Exclusion Criteria	Participants who are enrolled in another interventional clinical study are excluded from this study (exclusion criterion 18).	Participants enrolled in other clinical studies could confound the study results.
5.2. Exclusion Criteria	Participants with severe renal impairment at screening are excluded from this study (exclusion criterion 19).	Due to limited data in patients with severe renal impairment, a conservative approach was taken to exclude patients with severe renal impairment from clinicals studies with efgartigimod. No new signal has been identified and the known safety profile of efgartigimod remain unchanged.
8.1.2. Screening Period	This section was revised to emphasize that the eligibility of potential participants is at the discretion of the investigator and does not require confirmation from the sponsor.	The investigator determines the eligibility of the participants to ensure GCP compliance.
	The paragraph was revised to clarify that the eligibility assessment for total IgG serum levels can be based on both central and **local** laboratory results obtained at screening. In addition, eligibility assessment for total IgG serum levels and anti-BP 180 and anti-BP230 antibodies can be based on historical laboratory results from local samples taken up to 7 days before screening.	Revision allows for faster availability of screening results.

Section number/ Section title	Description of change	Brief rationale for change
8.2.1.1. Assessment of BP Disease Status and OCS Dose Monitoring 1.3. Schedule of Activities (SoA)	A time window for the investigator's weekly call to the participant was added: within 48 hours before the IMP administration during the home visits. Text was added to specify that the investigator must check with the participant if they have new lesions. If the participant reports any new lesions, they are instructed to visit the clinic for an unscheduled appointment.	Revision ensures that new lesions are detected as soon as possible.
8.4.8. AEs of Clinical Interest 8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting	Events that are not considered to be AESIs but still require attention or special monitoring will be reported.	Revision aligns with the current efgartigimod IB.
9.3.2. Primary Endpoint/ Estimand Analysis	IV or IM corticosteroids administered before week 36 are only considered intercurrent treatments if administered under specific conditions. These conditions are specified in the protocol.	Revision supports accurate determination of the primary endpoint.
10.2., Table 10: Protocol-Required Laboratory Tests	CRP and GGT have been added to the list of clinical chemistry parameters.	CRP, an inflammatory marker, is used to assess the participant's response to treatment and the severity of the disease. GGT, a liver enzyme, is used to monitor for the potential of treatment-associated liver damage because of IgG deposits.
10.2., Table 10: Protocol-Required Laboratory Tests	Footnote b was added: study sites are no longer provided with albumin and total protein results in real time. The investigator will receive an alert if results are	Revision protects data integrity in double-blinded efgartigimod studies.

Section number/ Section title	Description of change	Brief rationale for change
	outside of the normal range, to allow for appropriate safety follow-up.	
Section 10.4.2.2. Male Contraception 2.3.1. Risk Assessment 5.1. Inclusion Criteria	Male contraception is no longer required. Inclusion criterion 6 was revised accordingly and renumbered as 6B.	Revision aligns with the current efgartigimod IB. Reproductive toxicology studies did not show any effect on male reproductive potential.
10.13.2., Table 16: Concurrent Oral Methylprednisolone Equivalent Doses (in mg) Based on Participant Body Weight 6.8.1.3.Oral Prednisone Dose Adjustment Regimen (Based on BP Disease Assessment)	A table with recommendations on the concurrent oral methylprednisolone dosing regimen was added.	In some countries, methylprednisolone is used instead of prednisone; therefore, recommendations are provided for methylprednisolone, in line with what was presented for prednisone.
6.8.1.3. Oral Prednisone Dose Adjustment Regimen (Based on BP Disease Assessment) 6.8.1.3; Table 7: Concurrent Oral Prednisone Equivalent Doses (in mg) Based on Participant Body Weight	Text clarifies that for participants with body weights of <45 kg or ≥110 kg, the investigator should propose OCS doses and inform the medical monitor, to ensure consistency within the study. The minimum and maximum recommended doses for participants with body weights <45 kg and ≥110 kg, respectively, were included in Table 7.	Revisions provide additional, specific information for study site staff.
	Text clarifies that participants will be considered a treatment failure if they do not achieve CDA after receiving IMP with the described escalated prednisone dosing regimen, rather than the prednisone dosing regimen only.	Revision reduces the risk of wrongly identifying the participant as treatment failure.
	The tapering step of 0.15 mg/kg/day was included in the	Correction as described in the Administrative Letter dated 13 Oct 2022.

Section number/ Section title	Description of change	Brief rationale for change
	table but was missing from the text.	
6.8.2. Prohibited Medications and Therapy During the Study	It is clarified that OCS is allowed, however, IV or IM corticosteroids are not permitted during the study.	Revisions provide explicit guidance.
4.1.3. Bullous Pemphigoid Disease Status Terminology to Be Used in the Study	The definition of complete remission was revised.	Revision ensures an accurate evaluation of CR endpoint.
4.1.3. Bullous Pemphigoid Disease Status Terminology to Be Used in the Study	The definition of relapse was aligned with consensus terminology.	Revision aligns with the publication of Murrell et al. which aims to improve consistent reporting of clinical outcomes.
1.3. Schedule of Activities (SoA)	Footnote b was revised to add that home administration of IMP is not permitted until week 5.	Revision provides explicit guidance.
1.3. Schedule of Activities (SoA) 8.1.5. Unscheduled Visits	Footnote f was revised to explain in what situations an unscheduled visit may be performed (including a notable weight change) and that the investigator will decide which assessments should be conducted during the unscheduled visits.	Revision provides additional, specific information for study site staff.
1.3. Schedule of Activities (SoA)	Footnote j was added to allow weight measurements when “other weekly visits” occur on-site.	Measuring weight may allow for adjustment of concurrent prednisone (or equivalent) dose.
8.1.4. Home Study Visits	The section was added to clarify what happens during other weekly visits at home.	Revision provides additional, specific information for study staff.
8.1.3. Treatment and Follow-Up Periods	The sentence stating that all participants will complete the EoTP visit at week 36 was removed.	Participants who withdrew or who permanently discontinued the study should not complete an EoTP visit.
10.14.4.,Table 17: Scheme for Study Visits Performed at	The title of Table 17 was revised to focus on home visits during a COVID-19 pandemic.	Clarifications reduce the risk of protocol deviations.

Section number/ Section title	Description of change	Brief rationale for change
Home During the COVID-19 Pandemic	The baseline in row 1 was incorrectly indicated as being week 1. This was corrected to week 0. The definition of home nurse was added.	
2.3.1., Table 2: Potential Risks and Mitigation Strategies for ARGX-113-2009, Infusion/injection-related reactions	Mitigation measures for risks of infusion/injection-related reactions when IMP is administered at home was deleted.	The risk of infusion/injection-related reactions is not higher in home administrations; no additional mitigations are needed.
2.3.1., Table 2: Potential Risks and Mitigation Strategies for ARGX-113-2009, Potential complications from exposure OCS	The increase of OCS doses based on clinical status of participant is removed as a mitigation measure for complications from exposure to OCS. In addition, the table was revised to include a more concise phrasing of the mitigation strategy for potential complications from exposure.	The rapid tapering of OCS is a mitigation measure for potential complications from OCS exposure; however, increasing OCS doses is not a mitigation measure. In addition, revision provides additional, specific information for study site staff.
5.1. Inclusion Criteria	Inclusion criterion 2, which was renumbered as 2B, was revised to clarify that participants must have reached the local legal age of consent at the time of signing the ICF.	Criterion was revised to comply with local requirements.
5.4. Screen Failures	The section was revised to distinguish between retesting and rescreening participants who fail the initial screening.	Revision provides additional, specific information for site staff.
6.1., Table 5: Study Interventions	Table 5 was revised to include the IMP name and description, and to correct the descriptions of dose formulation and unit dose strength.	Correction.
6.8. Concomitant Therapy	The text was revised to clarify that participants must maintain a	Clarification reduces the risk of protocol deviations.

Section number/ Section title	Description of change	Brief rationale for change
	stable regimen of medication throughout the study and that herbal supplements also include Chinese traditional medicine.	
8.6 Pharmacodynamics	Protocol is revised to clarify that total IgG serum levels, anti-BP 180 and anti-BP 230 antibodies, and [redacted] are quantified at a central laboratory, and results will only be reported to investigative sites or other site staff at screening to maintain study blind.	Clarification reduces the risk of protocol deviations.
2. Introduction 2.3. Benefit/Risk Assessment	The 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.
3.1, Table 3: Part A Objectives and Endpoints 3.2, Table 4: Part B Objectives and Endpoints	The endpoints to evaluate the PD and immunogenicity of efgartigimod PH20 SC in participants with BP were rephrased.	Endpoints were not changed. Revision ensures correct interpretation of endpoints.
9.3.3.2. Analysis of Other Secondary Endpoints	Text is added to clarify that population PK/PD analysis may be performed based on PK and PD data and reported separately.	Information added for completeness.
6.3.1. Emergency Unblinding	Revision emphasizes that the sponsor must be notified within 24 hours if emergency unblinding occurred.	Clarification reduces the risk of protocol deviations.

Protocol Version 2.0, Amendment 1 (10 May 2022)

This amendment of the ARGX-113-2009 protocol is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for This Amendment

The primary rationale for this amendment is to modify both the primary and several secondary endpoints of the study per recommendations by the US Food and Drug Administration (FDA) in their 03 Feb 2022 "Study May Proceed" letter to the sponsor.

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

Section Number/ Section Title	Description of Change	Brief Rationale for Change
SIGNATURE OF SPONSOR	[redacted], MD, PhD is now the sponsor signatory for this protocol.	Effective 01 Apr 2022, Dr. [redacted] became the sponsor's chief medical officer.
Throughout document	The text of the primary endpoint, key secondary endpoints 2, 3, and 4, and several other secondary endpoints was modified to state that these endpoints will be assessed while the participants are "…receiving efgartigimod PH20 SC or placebo…."	The endpoint text was modified to clarify that, throughout the study, participants will receive investigational medicinal product (IMP), while concurrent OCS therapy dosages will be adjusted (tapered or increased) throughout the study based on the participant's disease status.
1.1. Synopsis Other sections impacted by this change: • Tables 3 and 4 • Sections 4.1.1, 4.2.4.1, 4.2.4.2, 9.1, 9.3, 9.3.2, and 9.3.3	The primary endpoint was changed: "Proportion of participants who are in CR while receiving efgartigimod PH20 SC or placebo and have been off OCS therapy for ≥8 weeks at week 36." Key secondary endpoint #4 was changed: "Proportion of participants who are in CR while receiving efgartigimod PH20 SC or placebo and have been receiving minimal OCS therapy for ≥8 weeks at week 36. (Minimal OCS therapy is defined as ≤0.1 mg/kg/day of prednisone [or an equivalent dose of another OCS].)"	The positions of these 2 endpoints were switched based on an FDA recommendation.

Section Number/ Section Title	Description of Change	Brief Rationale for Change
1.1. Synopsis Other sections impacted by this change: • Tables 3 and 4 • Sections 4.2.4.2, 9.1, and 9.3.3	Key secondary endpoint #2 was changed: "Proportion of participants who achieve an IGA-BP score of 0 while receiving efgartigimod PH20 SC or placebo and have been off OCS therapy for ≥8 weeks at week 36."	The endpoint was changed based on an FDA recommendation.
1.1. Synopsis Other sections impacted by this change: • Tables 3 and 4 • Sections 4.2.4.2, 9.1, and 9.3.3	The phrase "to week 36" was deleted from key secondary endpoint #5: "Changes from baseline in the 24-hour average itch score from the Itch Numerical Rating Scale (Itch NRS)."	The endpoint was changed to clarify that the study will assess changes (from baseline) in this Itch NRS score throughout the 36-week treatment period.
Table 1–Schedule of Activities (SoA) Other sections impacted by this change: • Exclusion criterion 6 • Sections 8, 8.4.7.1, 10.2.1.1, 10.14, and 10.14.1 • Table 10	The requirement of a SARS-CoV-2 nasopharyngeal swab test was removed; COVID-19 tests will be performed if required per local regulations Sections 8 and 10.14 were modified to loosen the study's previous restrictions and requirements for COVID-19 risk mitigation procedures, and instead allow the sponsor and investigator to implement alternate operational strategies for COVID-19 concerns per local health authority and ethics requirements.	The text was modified to align COVID-19 testing and mitigation strategies/procedures with local regulations and requirements.
Table 1–Schedule of Activities (SoA) Other sections impacted by this change: • Sections 4.1.2 and 8.3.6.1 • Table 10	The "specialty laboratory tests" assessment has been removed. Additionally, the specialty lipid panel test parameters apolipoprotein B, D-dimer, fibrinogen, lipoprotein A, and von Willebrand factor have been removed.	These specialty tests were deleted because no lipid safety signals have been observed in efgartigimod studies to date.
2–Introduction	The third paragraph after the bulleted list was revised: "Efgartigimod PH20 SC or placebo will be administered once weekly throughout the 36-week treatment period. All participants will also receive concurrent therapy with OCS: oral prednisone at a starting dosage of	This text was modified to explicitly state that participants will be administered investigational medicinal product (IMP: efgartigimod PH20 SC or placebo) throughout the entire 36-week treatment period.

Section Number/ Section Title	Description of Change	Brief Rationale for Change
	0.5 mg/kg/day (or an alternate OCS of equivalent dose strength) at baseline. The OCS dosage will be adjusted according to each participant's BP disease status throughout the study."	
2.3, Table 2–Potential Risks and Mitigation Strategies for ARGX-113-2009 Immunomodulation section	The section title was changed from "Immunomodulation, potentially leading to increased infection risk" to "Immune modulation leading to increased infection risk." Under Summary of Data/Rationale for Risk, the following paragraph was deleted: "EFG treatment may be associated with a small increase in the frequency of infections. However, infections observed in other indications were mild and responded to treatment. No opportunistic infections have been observed with EFG." Under Mitigation Strategy, the first paragraph was modified to state that participants with active or chronic infections, recent surgeries, and/or serious diseases will be excluded.	This text was modified to reflect currently available information regarding the potential effects of efgartigimod on immune modulation.
2.3, Table 2–Potential Risks and Mitigation Strategies for ARGX-113-2009, Injection-/infusion-related reactions section	The following paragraph was deleted from the Summary of Data/Rationale for Risk column: "At this time, no drug hypersensitivity or anaphylactic reactions have been reported among those treated with either EFG IV or EFG PH20 SC in clinical studies of other indications."	The paragraph was deleted because it is no longer applicable.
2.3, Table 2–Potential Risks and Mitigation Strategies for ARGX-113-2009 Other sections impacted by this change: • Inclusion criteria 6a and 6b, Exclusion criterion 16 • Sections 10.4.1 and 10.4.2.1	Contraception requirements and sperm donation restrictions for study participants have been updated.	Guidance on contraception has been updated following results of nonclinical reproductive toxicity studies.

Section Number/ Section Title	Description of Change	Brief Rationale for Change
3, Table 3–Part A Objectives and Endpoints Other sections impacted by this change: • Table 4	The phrase "to week 36" was deleted from the secondary endpoint assessing changes from baseline in the Bullous Pemphigoid Disease Area Index (BPDAI); now this endpoint reads as follows: "Changes from baseline in the BPDAI activity score."	This change clarifies that the study will assess changes (from baseline) in the BPDAI activity score throughout the 36-week treatment period.
3, Table 3–Part A Objectives and Endpoints Other sections impacted by this change: • Table 4	The endpoints for the quality-of-life (QoL) assessments were modified to clarify that the scores obtained from all 3 will be evaluated "over time."	The text was modified to clarify that the study will assess changes in EQ-5D-5L, DLQI, and ABQoL scores throughout the 36-week treatment period.
4.2.2–Rationale for the Selection of the Participant Population • Inclusion criterion 2	The conditional definition of adulthood in Japan (≥20 years of age) was changed.	Effective 01 Apr 2022, the official age of adulthood in Japan was changed from 20 years of age to 18 years of age.
4.2.4.1–Rationale for the Selection of Study Endpoints, Primary Endpoint	This section was modified to describe the rationale for the study's new primary endpoint: "Proportion of participants who are in CR while receiving efgartigimod PH20 SC or placebo and have been off OCS therapy for ≥8 weeks at week 36."	Section 4.2.4.1 was modified to describe the rationale for the selection of the new primary endpoint.
4.2.5–Rationale for the Selection of Study Assessments	This section was modified to include additional information about the IGA-BP and BPDAI scales.	This text was modified to provide additional, clarifying information for these 2 assessment scales.
5.2–Exclusion Criteria Other sections impacted by this change: • Section 8.4.7.1	Exclusion criterion 5 was changed to read: "Active or chronic infection at screening." Section 8.4.7.1 was modified to indicate that participants with active or chronic infections, recent surgeries, and/or serious diseases will be excluded from study participation.	This text was modified to reflect the latest information available regarding the potential effects of efgartigimod on immune modulation.
5.5–Criteria for Temporarily Delaying Study Participation Other sections impacted by this change:	Topical corticosteroids (TCS) were added to the list of BP treatments that must be discontinued before beginning study participation.	This text was modified to provide explicit guidance and instructions about TCS treatment.

Section Number/ Section Title	Description of Change	Brief Rationale for Change
• Section 6.8.2	Section 6.8.2 now indicates that topical corticosteroid treatment must be discontinued before baseline.	
6.3–Measures to Minimize Bias: Randomization and Blinding	The fourth paragraph was revised to specify the stratification method for participants who are randomized in part B of the study.	This text was modified to provide additional information on the participant stratification method.
6.3–Measures to Minimize Bias: Randomization and Blinding	Additional information clarifying which study team members will have access to IMP treatment assignment information.	New text provides more information on blinding/unblinding of study personnel to IMP treatment assignment information.
6.8.1.3–Oral Prednisone Dose Adjustment Regimen (Based on BP Disease Assessment)	Additional instructional text was included to describe OCS tapering once the participant achieves CDA.	This text was modified to provide additional, specific information for study site personnel.
6.8.1.3, Table 7–Concurrent Oral Prednisone Equivalent Doses (in mg) Based on Participant Body Weight	A new version of this table has replaced the old version.	The new version of the table provides more specific guidance about appropriate/acceptable oral prednisone doses (adjusted for participant body weight) during OCS tapering and escalation schedules.
7.1.2–QTcF Interval Prolongation Stopping Criteria	The entire section describing QTcF interval prolongation stopping criteria was deleted.	The section was deleted because results from clinical studies of efgartigimod have shown no evidence of any cardiac effects or any effects on ECG parameters.
7.2–Participant Discontinuation/ Withdrawal From the Study	The following bulletpoints were added to the subsection describing reasons for early discontinuation from the study: "The participant's general health worsens to an extent warranting study discontinuation per the investigator" "The participant is receiving any rescue therapy regimen other than those permitted (Section 6.8.3)"	This section was modified per recommendations from the German regulatory authority (Germany's Federal Institute for Vaccines and Biomedicines).
8.4–Adverse Events, Serious Adverse Events, and Other Safety Reporting	The beginning of Section 8.4 has been modified to refer to Section 10.3 for additional guidelines on AEs and SAEs, as well as guidance on completing and transmitting SAE reports. Section 8.4.7 has been revised to note that any AE categorized in the MedDRA system	This text was modified per new guidance from the sponsor's Global Patient Safety (GPS) department.

Section Number/ Section Title	Description of Change	Brief Rationale for Change
Other sections impacted by this change: • Sections 8.4.7 and 10.3	organ class of "Infections and Infestations" is considered an adverse event of special interest (AESI). This section now includes additional guidance about the information that should be collected when a participant has an AESI. In Section 10.3, the subsection titled "Definition of Unsolicited and Solicited AE" has been deleted. Also, Section 10.3.2 has been revised to delete "is a suspected transmission of any infectious agent via an authorized medicinal product" from the definition of SAE.	
9–Statistical Considerations	The first paragraph of this section has been deleted.	This text was deleted because the information contained in the paragraph is better suited to the study's statistical analysis plan (SAP).
Table 8–Analysis Sets for ARGX-113-2009	The description of the "per protocol analysis set" has been revised.	This text was revised for clarity.
9.3.3.1–Analysis of Secondary Efficacy Endpoints (Part B Only)	The formula for calculating the normalized cumulative oral corticosteroid dose (NCOD) has been removed.	The formula was removed because an updated NCOD calculation formula will be provided in the ARGX-113-2009 statistical analysis plan (SAP).
9.3.3.1–Analysis of Secondary Efficacy Endpoints (Part B Only)	The descriptions of the analytical methods to be applied to the second, third, and fourth proposed key secondary endpoints have been consolidated into a single paragraph.	The paragraph was revised for clarity and brevity.
9.3.3.3–Safety Analyses	The following statement was added as the section's third paragraph: "All TEAEs, AESIs, and SAEs will be analyzed descriptively, all while acknowledging that the study population (elderly participants with moderate-to-severe BP) has a high mortality rate, a high incidence of existing comorbidities, and an increased risk of developing additional comorbid conditions."	The text was added per new guidance from the sponsor's GPS department.
9.4–Interim Analysis (Part A)	The section has been revised to reflect that any of the endpoints described for part A may be assessed at week 26 as part of the study's interim analysis, and that the endpoints to be analyzed for interim analysis have yet to be selected.	This text was revised based on an FDA recommendation.

Section Number/ Section Title	Description of Change	Brief Rationale for Change
10.1.11–Study and Site Start and Closure	Information has been added outlining specific criteria for temporarily halting and permanently stopping the study; additionally, site and study closure criteria are described separately.	This section was revised based on an FDA recommendation.
Table 10–Protocol-Required Laboratory Tests	Bilirubin (total and direct) has been added to the list of clinical chemistry parameters. Activated partial thromboplastin time and international normalized ratio have been added to the list of specialty laboratory tests.	The table was updated to comply with the latest version of the argenx efgartigimod protocol template.
10.6–Investigator Global Assessment of Bullous Pemphigoid (IGA-BP)	The previous version of the IGA-BP has been replaced with an updated version that clarifies participant scoring assessments.	This section was updated because a newer version of the assessment scale was developed after the original protocol was approved.

11. REFERENCES

1. Schmidt E, Obe K, Brocker E, Zillikens D. Serum levels of autoantibodies to BP180 correlate with disease activity in patients with bullous pemphigoid. *Arch Dermatol*. 2000;136(2):174-178.
2. Masmoudi W, Vaillant M, Vassileva S, et al. International validation of the Bullous Pemphigoid Disease Area Index severity score and calculation of cutoff values for defining mild, moderate, and severe types of bullous pemphigoid. *Br J Dermatol*. 2021;184(6):1106-1112.
3. Amagai M, Ikeda S, Hashimoto T, et al. A randomized double-blind trial of intravenous immunoglobin for bullous pemphigoid. *J Dermatol Sci*. 2017;85(2):77-84.
4. Kasperkiewicz M, Schulze F, Meier M, et al. Treatment of bullous pemphigoid with adjuvant immunoadsorption: a case series. *J Am Acad Dermatol*. 2014;71(5):1018-1020.
5. Jafari SMS, Gadaldi K, Feldmeyer L, Yawalkar N, Borradori L, Schlapbach C. Effects of omalizumab on FcεRI and IgE expression in lesional skin of bullous pemphigoid. *Front Immunol*. 2019;10:1919.
6. Kridin K, Ludwig RJ. The growing incidence of bullous pemphigoid: overview and potential explanations. *Front Med*. 2018;220.
7. Wertenteil S, Garg A, Strunk A, Alloo A. Prevalence estimates for pemphigoid in the United States: a sex-adjusted and age-adjusted population analysis. *J Am Acad Dermatol*. 2019;80(3):655-659.
8. Tedbirt B, Gillibert A, Andrieu E, et al. Mixed individual-aggregate data on all-cause mortality in bullous pemphigoid: a meta-analysis. *JAMA Dermatol*. 2021;157(4):421-430.
9. Joly P, Roujeau J, Benichou J, et al. A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. *N Engl J Med*. 2002;346(5):321-327.
10. Wojnarowska F, Kirtschig G, Highet AS, Venning VA, Khumalo NP. British Association of Dermatologists. Guidelines for the management of bullous pemphigoid. *Br J Dermatol*. 2002;147(2):214-221.
11. Hull CM, McKenna JK, Zone JJ. Topical corticosteroids and bullous pemphigoid. *Arch Dermatol*. 2003;139(2):225-226.
12. Guillaume JC, Vaillant L, Bernard P, et al. Controlled trial of azathioprine and plasma exchange in addition to prednisolone in the treatment of bullous pemphigoid. *Arch Dermatol*. 1993;129(1):49-53.
13. Harman KE, Black MM. High-dose intravenous immune globulin for the treatment of autoimmune blistering diseases: an evaluation of its use in 14 cases. *Br J Dermatol*. 1999;140(5):865-874.
14. Ahmed AR. Intravenous immunoglobulin therapy for patients with bullous pemphigoid unresponsive to conventional immunosuppressive treatment. *J Am Acad Dermatol*. 2001;45(6):825-835.

15. Kremer N, Snast I, Cohen ES, et al. Rituximab and omalizumab for the treatment of bullous pemphigoid: a systematic review of the literature. *Am J Clin Dermatol*. 2019;20(2):209-216.
16. Polansky M, Eisenstadt R, DeGrazia T, Zhao X, Liu Y, Feldman R. Rituximab therapy in patients with bullous pemphigoid: a retrospective study of 20 patients. *J Am Acad Dermatol*. 2019;81(1):179-186.
17. Bouscarat F, Chosidow O, Picard-Dahan C, et al. Treatment of bullous pemphigoid with dapsone: retrospective study of thirty-six cases. *J Am Acad Dermatol*. 1996;34(4):683-684.
18. Williams HC, Wojnarowska F, Kirtschig G, et al. Doxycycline versus prednisolone as an initial treatment strategy for bullous pemphigoid: a pragmatic, non-inferiority, randomised controlled trial. *Lancet*. 2017;389(10079):1630-1638.
19. Bernard P, Antonicelli F. Bullous pemphigoid: a review of its diagnosis, associations, and treatment. *Am J Clin Dermatol*. 2017;18(4):513-528.
20. Witte M, Zillikens D, Schmidt E. Diagnosis of autoimmune blistering diseases. *Front Med*. 2018;5:296.
21. Di Lernia V, Casanova D, Goldust M, Ricci C. Pemphigus vulgaris and bullous pemphigoid: update on diagnosis and treatment. *Derm Pract Concept*. 2020;10(3):e2020050.
22. Murrell D, Daniel B, Joly P, et al. Definitions and outcome measures for bullous pemphigoid: recommendations by an international panel of experts. *J Amer Acad Dermatol*. 2012;66(3):479-485.
23. Bernard P, Bedane C, Prost C, Ingen-Housz-Oro S, Joly P. Bullous pemphigoid: guidelines for the diagnosis and treatment. Centres de reference des maladies bulleuses auto-immunes. Societe Francaise de Dermatologie. *Ann Dermatol Venereol*. 2011;138(3):247-251.
24. Feliciani C, Joly P, Jonkman M, et al. Management of bullous pemphigoid: the European Dermatology Forum consensus in collaboration with the European Academy of Dermatology and Venereology. *Br J Dermatol*. 2015;172(4):867-877.
25. Schmidt E, Sticherling M, Sardy M, et al. S2k guidelines for the treatment of pemphigus vulgaris/foliaceus and bullous pemphigoid: 2019 update. *J Dtsch Dermatol Ges*. 2020;18(5):516-526.
26. Ujiie H, Iwata H, Yamagami J, et al. Japanese guidelines for the management of pemphigoid (including epidermolysis bullosa acquisita). *J Dermatol*. 2019;46(12):1102-1135.
27. Joly P, Roujeau J, Benichou J, et al. A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. *N Engl J Med*. 2002;346(5):321-327.
28. Hull CM, McKenna JK, Zone JJ. Topical corticosteroids and bullous pemphigoid. *Arch Dermatol*. 2003;139(2):225-226.

29. Bernard P, Charneux J. Bullous pemphigoid: a review. *Ann Dermatol Venereol*. 2011;138(3):173-181.
30. Bernard P, Reguiai Z, Tancrede-Bohin E, et al. Risk factors for relapse in patients with bullous pemphigoid in clinical remission: a multicenter, prospective, cohort study. *Arch Dermatol*. 2009;145(5):537-542.
31. Wang Y, Mao X, Wang Y, et al. Relapse of bullous pemphigoid: an update on this stubborn clinical problem. *Ann Med*. 2018;50(3):234-239.
32. Phan N, Blome C, Fritz F, et al. Assessment of pruritus intensity: prospective study on validity and reliability of the visual analogue scale, numerical rating scale, and verbal rating scale in 471 patients with chronic pruritus. *Acta Derm Venereol*. 2012;92(5):502-507.
33. Verweyen E, Stander S, Keritz K, et al. Validation of a comprehensive set of pruritus assessment instruments: the Chronic Pruritus Tools Questionnaire PRURITOOLS. *Acta Derm Venereol*. 2019;99(7):657-663.
34. Storck M, Sandmann S, Bruland P, et al. Pruritus intensity scales across Europe: a prospective validation study. *J Eur Acad Dermatol Venereol*. 2021;35(5):1176-1185.
35. The EuroQol Group. *The EQ-5D-5L: About the version.* Accessed: 19 Feb 2024. https://euroqol.org/information-and-support/euroqol-instruments/eq-5d-5l/
36. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI): a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994;19(3)210-216.
37. Sebaratnam DF, Hanna AM, Chee SN, et al. Development of a quality-of-life instrument for autoimmune bullous disease: the Autoimmune Bullous Disease Quality of Life questionnaire. *JAMA Dermatol*. 2013;149(10):1186-1191.
38. Centers for Disease Control (CDC). *Interpretation of hepatitis B serologic test results.* Accessed: 19 Feb 2024. https://www.cdc.gov/hepatitis/hbv/interpretationOfHepBSerologicResults.htm
39. McDowell PJ, Stone JH, Zhang Y, et al. Quantification of glucocorticoid-associated morbidity in severe asthma using the Glucocorticoid Toxicity Index. *J Allergy Clin Immunol*. 2021;9(1):365-372.
40. Frewer P, Mitchell P, Watkins C, Matcham J. Decision-making in early clinical drug development. *Pharm Stat*. 2016;15(3):255-263.

Signature Page for VV-TMF-87341 v2.0

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

Signature Page for VV-TMF-87341 v2.0