Clinical Trial Protocol

Protocol Title:	An Open-Label, Multicenter, Follow-up Trial of ARGX-113-1904 to Evaluate the Safety, Tolerability, and Efficacy of Efgartigimod PH20 SC in Patients With Pemphigus (ADDRESS+)
Protocol Number:	ARGX-113-1905
Version Number:	3.0 (Amendment 2)
Compound:	Efgartigimod (ARGX-113)
Investigational Medicinal Product:	Efgartigimod PH20 SC (efgartigimod coformulated with recombinant human hyaluronidase PH20 [rHuPH20] for subcutaneous [SC] administration)
Trial Phase:	3
Sponsor Name:	argenx BV
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Regulatory Agency Identifier Number(s):	IND: 146526 EudraCT: 2020-002917-16
Date and Version:	05 September 2022, Version 3.0

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Confidentiality Statement

Notification: Possible Adaptations of Protocol During the COVID-19 Pandemic

The aim of ARGX-113-1905 is to investigate a new subcutaneous (SC) treatment option for participants with pemphigus. This SC treatment consisting of efgartigimod coformulated with recombinant human hyaluronidase PH20 (rHuPH20) (called efgartigimod PH20 SC) could offer clinically significant benefits to pemphigus participants.

The sponsor (argenx BV) has performed a critical assessment of the use of efgartigimod during the COVID-19 pandemic. Following careful evaluation, the risk/benefit profile of efgartigimod has not changed in the context of this pandemic. This decision was made based on efgartigimod's mechanism of action, the safety data generated to date, and provisions made in all clinical trials with efgartigimod for safety reporting and withholding treatment upon evidence of infection. This assessment will be reviewed regularly to consider new information about the pandemic and the ongoing, continuous assessment of adverse events (AEs) reported during argenx BV clinical trials.

Due to the COVID-19 pandemic, it may not be possible to perform all assessments as planned for this trial (at the site, at the times indicated in the Schedule of Activities [SoA] in Section 1.3, or both).

In order to provide participants with pemphigus the opportunity to continue the trial during the COVID-19 pandemic, an appendix with possible adaptations to ARGX-113-1905 has been developed. This appendix describes a minimum number of assessments required to guarantee the safety and wellbeing of participants during the trial, to secure the collection of the critical parameters for analysis, and to account for the possibility of efgartigimod administration in the participant's home. This appendix is included in Section 10.11 (Appendix 11) of this protocol.

Signature of Sponsor

Protocol Title: An Open-Label, Multicenter, Follow-up Trial of ARGX-113-1904 to Evaluate the Safety, Tolerability, and Efficacy of Efgartigimod PH20 SC in Patients With Pemphigus (ADDRESS+)

Protocol Number: ARGX-113-1905

Acronym: ADDRESS+

Sponsor Representative:

[redacted], MD, PhD
Chief Medical Officer

Date

SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: An Open-Label, Multicenter, Follow-up Trial of ARGX-113-1904 to Evaluate the Safety, Tolerability, and Efficacy of Efgartigimod PH20 SC in Patients With Pemphigus (ADDRESS+)

PROTOCOL NO: ARGX-113-1905

This protocol is a confidential document of argenx BV. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from argenx BV.

Instructions to the investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the site in which the trial will be conducted. Return the signed original copy to the local representative of your sponsor's designated contract research organization (CRO).

I have read this protocol in its entirety and agree to conduct the trial accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Site: _____

_____

_____

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date of Issue**
Protocol Version 3.0 (v3.0), Amendment 2	05 Sep 2022
Protocol Version 2.0 (v2.0), Amendment 1	05 Feb 2021
Protocol Version 1.0 (v1.0)	12 Aug 2020

Amendment 2 (05 Sep 2022)

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

Overall Rationale for the Amendment:

The major changes from v2.0 to v3.0 of this protocol are summarized in the following table. Note that several of the identified changes were previously defined in an administrative letter for the protocol. Text that is formatted with a ~~strikethrough line~~ identifies protocol content that has been deleted, while text that is formatted in ***boldfaced italics*** identifies content that has been added. Minor editorial changes—including the correction of typographical errors, formatting inconsistencies, and wording choices—are not summarized in this table.

Summary of Changes Between Protocol Version 2.0 and Protocol Version 3.0

Section	Description of Change	Brief Rationale
Sponsor's Medical Contact	[redacted], MD, PhD is now the sponsor's medical contact for this study.	Updated to reflect the sponsor's current medical contact
Signature of Sponsor	[redacted], MD, PhD is now the sponsor signatory for this protocol.	Updated to reflect the sponsor's current chief medical officer
1.1. Synopsis	The upper limit of participants who can enter the trial ("up to 150") has been deleted.	Removed because the antecedent study ARGX-113-1904 has reopened enrollment, and participants who complete this study will be invited to roll over into ARGX-113-1905. Thus, the total number of participants may exceed 150.
3. OBJECTIVES AND ENDPOINTS Other sections impacted by this change: 1.1. Synopsis	"Anti-drug antibodies (ADA) to efgartigimod (serum levels)" was updated to:	Updated for accuracy

Section	Description of Change	Brief Rationale
	"Incidence and prevalence of antidrug antibodies (ADA) against efgartigimod (serum levels)"	
4.1. Overall Design Other sections impacted by this change: 1.1. Synopsis Section 1.3., Table 1 and Table 2: Schedule of Activities 6.5.1. Concomitant Pemphigus Therapy Appendix 11, Table 8 and Table 9: Modified Schedule of Activities During COVID-19 Pandemic	Item 1 in the list of clinical status categories at the end-of-study (EoS) of ARGX-113-1904 has been revised to "…CRmin or CRoff ***and are currently not in flare*** will be observed every 4 weeks…."	Revised to provide clear directives to investigators and site personnel about this group of participants who enter ARGX-113-1905
4.1. Overall Design Other sections impacted by this change: 1.1. Synopsis 6.5.1. Concomitant Pemphigus Therapy	Item 4 in the list of clinical status categories at the EoS of ARGX-113-1904 has been revised to "…absence of DC with oral prednisone 1.5 mg/kg/day for a minimum of 3 weeks, ***participants who roll over due to prednisone-related SAE who have not achieved DC***, or flare between DC and achieving CRmin that is not controlled by 2 dose levels ***of OCS*** above the dose…."	Revised to provide clear directives to investigators and site personnel about this group of participants who enter ARGX-113-1905
4.1. Overall Design Other sections impacted by this change: 1.1. Synopsis 6.5.1. Concomitant Pemphigus Therapy	The instructions for tapering oral prednisone doses were clarified for: (1) participants who achieve DC with oral prednisone doses ≤0.5 mg/kg qd; (2) participants who achieve DC with oral prednisone doses >0.5 mg/kg qd or after having their oral prednisone dose escalated.	Modified to provide clear instructions to investigators and site personnel about appropriate prednisone dose tapering based on the participant's dose at the time they achieve DC
4.1. Overall Design Other sections impacted by this change 1.1. Synopsis 4.2. Scientific Rationale for Trial Design 6.5.1. Concomitant Pemphigus Therapy 10.9. Appendix 9: Definition of Terms	A note has been added to clarify that, when 10 mg/day oral prednisone is reached in ARGX-113-1904 or ARGX-113-1905, this dose level must be maintained for 8 weeks until CRmin has been achieved.	Modified to clarify the definition/characterization of CRmin in the study
Section 1.3., Table 1: Schedule of Activities Other sections impacted by this change: 8. TRIAL ASSESSMENTS AND PROCEDURES Appendix 11, Table 8: Modified Schedule of Activities During COVID-19 Pandemic	• The time point for the EoT visit has been corrected. • The timing of visits and sample collection has been clarified (Section 8 and Tables 1 and 8, footnotes g, l, and n).	Incorporated changes from an administrative letter dated 28 Oct 2021
Section 1.3., Table 1 and Table 2: Schedule of Activities Other sections impacted by this change: 8. TRIAL ASSESSMENTS AND	The assessments to be performed during an unscheduled visit in case of new lesions, flare, AEs, or other safety reasons have been clarified.	Revised for accuracy

Section	Description of Change	Brief Rationale
PROCEDURES Appendix 11, Table 8 and Table 9: Modified Schedule of Activities During COVID-19 Pandemic	A new table (Table 5) has been added in Section 8. TRIAL ASSESSMENTS AND PROCEDURES to outline the assessments to be performed during an unscheduled visit.	
Section 1.3., Table 1: Schedule of Activities Other sections impacted by this change: Appendix 11, Table 8: Modified Schedule of Activities During COVID-19 Pandemic	The footnote reference for anti-Dsg-1 and anti-Dsg-3 antibody assessments was removed. These assessments need to be performed as indicated in the SoA, regardless of whether the participant is receiving treatment with efgartigimod PH20 SC.	Corrected for consistency
Section 1.3., Table 1: Schedule of Activities Other sections impacted by this change: Appendix 11, Table 8: Modified Schedule of Activities During COVID-19 Pandemic	Footnotes l and n were clarified to state that scheduled PK and PD samples are to be taken 4 weeks after CRmin even if a participant achieved CRmin in ARGX-113-1904. Similarly, blood samples for immunogenicity are to be taken 4 and 8 weeks after CRmin even if a participant achieved CRmin during ARGX-113-1904.	Revised for accuracy
Section 1.3., Table 1 and Table 2: Schedule of Activities Other sections impacted by this change: 8.8.2. Immunological Profiling Appendix 11, Table 8 and Table 9: Modified Schedule of Activities During COVID-19 Pandemic	The timing of samples for lymphocyte populations were updated for long-term immunological profiling. Samples will be taken at selected sites only: Sample collection is optional at on-site visits at W13 (±2 weeks), W26 (±2 weeks), W39 (±2 weeks), W52 (±2 weeks) or EoT/ET, and EoS, and it is mandatory at on-site visits at W52 (±2 weeks) or EoT/ET and EoS for participants in CRmin or CRoff.	Updated to obtain long-term immunological profiling samples from participants in CRmin and CRoff
Section 1.3., Table 1 and Table 2: Schedule of Activities Other sections impacted by this change: Appendix 11, Table 8 and Table 9: Modified Schedule of Activities During COVID-19 Pandemic	An X was added in the column 'lymphocyte populations' at V1 (at rollover) in line with other assessments scheduled at rollover and listed in the ARGX-113-1904 protocol at EoS/ED visit.	Added for accuracy
Section 1.3., Table 2: Schedule of Activities Other sections impacted by this change: Appendix 11, Table 9: Modified Schedule of Activities During COVID-19 Pandemic	• Footnotes l and r were adjusted to refer to the EoS visit (instead of W60), because some participants will complete the study at W56. • Footnote m was modified to specify the timing of pregnancy tests: "A urine pregnancy test will be performed locally ~~and~~ at least once every 4 weeks, ***at CR, and as of CR again every 4 weeks at on-site visits***."	Revised for accuracy

Section	Description of Change	Brief Rationale
Section 1.3., Table 2: Schedule of Activities Other sections impacted by this change: 8. TRIAL ASSESSMENTS AND PROCEDURES Appendix 11, Table 9: Modified Schedule of Activities During COVID-19 Pandemic	• An X was added in the column 'On-site visits every 4 weeks until W52 – After CRmin until W52' for PK samples, which should also be taken 4 weeks after CRmin (or at the next on-site visit), per footnote o. • The immunogenicity sampling adheres to footnote q; thus, "every 2 weeks" was deleted in the table. • Footnotes b and c were modified to provide additional clarification about when the participant can begin receiving IMP at home visits. • Footnotes l, o, q, r, and s were revised to clarify the timing of visits and sample collection. • Footnote l was added in the row heading for Vaccination antibodies	Incorporated changes from an administrative letter issued 28 Oct 2021
2.3.1.Risk Assessment Other sections impacted by this change: 2.3.2. Benefit Assessment 8.4.8. Adverse Events of Special Interest	The summary of the phase 2 study ARGX-113-1701 data was updated based on the final CSR.	Updated based on a newly available final CSR for ARGX-113-1701
5.1. Inclusion Criteria	3A.i: Male participants must agree to use an acceptable method of contraception (as described in Section 10.4.2.2) ~~and not donate sperm~~ from signing the informed consent form (ICF) until the ~~end~~***last dose*** of the ~~study~~***study drug***.	Guidance on contraception and sperm donation has been updated based on results from nonclinical reproductive toxicity studies
5.1. Inclusion Criteria Other sections impacted by this change: Appendix 4: Section 10.4.2.1. Female Contraception for Women of Childbearing Potential	3A.ii. • agree to use a highly effective or acceptable contraception method (as described in Section 10.4.2.1), which should be maintained at minimum until ~~90 days~~ after the last dose of IMP Women of childbearing potential (WOCBP) must use a highly effective or acceptable contraception method, which should be maintained at minimum until ~~90 days~~ after the last dose of IMP.	
5.2. Exclusion Criteria Other sections impacted by this change: Appendix 4: Section 10.4.3. Collection of Pregnancy Information	1A. Pregnant and lactating women and those intending to become pregnant during the trial ~~or within 90 days after the last administration of IMP~~. Male participants will be instructed by the ICF to immediately inform the investigator if their partner becomes pregnant during the trial ~~or up to 90 days~~	

Section	Description of Change	Brief Rationale
	~~after they received the last dose of study drug~~. The investigator will collect pregnancy information on any female participant who becomes pregnant during the period of administration of IMP ~~and up to 90 days after the participant received the last IMP~~.	
5.1. Inclusion Criteria	The reference to a serum pregnancy test at screening was removed from inclusion criterion 3A.ii.	Revised for accuracy (Screening is not applicable in this study.)
6.2. Preparation/Handling/Storage/ Accountability Other sections impacted by this change: 1.1. Synopsis 4.1. Overall Design 6.5.1. Concomitant Pemphigus Therapy	Clarifications were added to indicate that more detail regarding the proper transport, storage, preparation, and administration of IMP is provided in the home guide.	Modified to provide additional information about the IMP home guide
8. TRIAL ASSESSMENTS AND PROCEDURES: Treatment Period	The fourth paragraph of this section was revised to clarify the minimum duration that participants who had treatment failure during ARGX-113-1904 or flare after CRmin must continue on-site visits before they are permitted to begin home visits.	Revised to provide clear directives to investigators and site personnel about scheduling home visits for these groups of participants
8.3.8. Injection Site Reactions	Injection site reactions (ISRs) will be monitored throughout the study. Section 8.3.8. Injection Site Reactions, includes information about ISRs observed during studies with efgartigimod PH20 SC. The following specific instructions for monitoring ISRs were added: ***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 rHuPH20 and administered SC. The most frequently reported injection site reaction AEs are injection site erythema, injection site pain, and injection site swelling. Most are nonserious and mild (CTCAE grade 1) and do not lead to disruption in IMP administration.*** ***Any injection site reaction will be reported as an AE (Section 10.3.3). Certain types of local reactions could***	Updated for alignment across efgartigimod PH20 SC open-label extension study protocols regarding the monitoring of ISRs

Section	Description of Change	Brief Rationale
	be photographed and shared with the sponsor for review and assessment. ***As a routine precaution, participants should be trained or observed closely by a trained health care professional for any potential injection site reaction.***	
8.4.1. Time Period and Frequency for Collecting AE and SAE Information	All SAEs ***and AESIs*** will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3.3 ***and Section 10.3.4.***	Revised for accuracy and to clarify how and when AESIs must be reported (within 24 hours)
Appendix 3: Section 10.3.4. Reporting of SAEs and AESIs	The following text: All SAEs will be recorded on the paper SAE report form and the AE form on the eCRF. The investigator or designated site staff should check that all entered data are consistent. An alert email for the SAE report in the eCRF will then automatically be sent by email to the sponsor's designated CRO safety mailbox via the EDC system. The paper SAE report form should be faxed or emailed to the sponsor's designated CRO (see Safety Mailbox/Fax details on the title page of this protocol). Has been replaced with: • All SAEs and AESIs will be recorded on the AE form of the eCRF. SAEs will also be recorded on the paper SAE report form. • The investigator or designated site staff will ensure all entered data are consistent. • An email alert for the SAE and AESI reports on the eCRF will automatically be sent to the sponsor's/designee's safety mailbox via the electronic data capturing (eDC) system. • The paper SAE report form will be faxed or emailed to the sponsor/designee (see Safety Mailbox/Fax details on page 2 of this protocol).	

Section	Description of Change	Brief Rationale
8.4.8. Adverse Events of Special Interest	The text and Table 6 of this section have been updated to include the final results from ARGX-113-1701. The section previously included *interim* results from ARGX-113-1701.	Updated to provide the results from the final ARGX-113-1701 CSR
8.6. Pharmacodynamics	The second paragraph of this section now includes the following sentence: ***IgG subtype analyses may be limited to a representative portion of study participants.***	Updated to account for the possibility that an upper limit will be placed on these analyses
8.7. Immunogenicity	The second paragraph of this section has been revised to provide specific details about the 3-tiered approach that is used for immunogenicity analysis.	Revised following consultation with the sponsor's Bioanalytics department
10.2. Appendix 2: Table 7: Protocol-Required Laboratory Assessments Other sections impacted by this change 8.3.6. Clinical Safety Laboratory Assessments All Schedule of Activities Tables (ie, Tables 1, 2, 8, and 9)	The urinalysis assessments that will be assessed and the relevant footnotes in all SoAs have been updated.	Revised to eliminate urinalysis parameters that are not required
Appendix 3: Section 10.3.4. Reporting of SAEs and AESIs	Revised to update the SAE ***and AESI*** information that must be reported via the eDC system.	Updated to include current requirements for data entry on the eDC system
10.5. Appendix 5: Administrative Structure	Information was updated for several contract research organizations that are performing analytical, sample storage, and data storage services for this study.	Updated to reflect current information
10.11. Appendix 11: Possible Adaptations of Trial Protocol During COVID-19 Pandemic: Mandatory Site Visits and Allowed Home Visits	Instructions were added about vital sign measurements, blood/urine collection, and IMP administration when a home nurse cannot be identified or cannot travel to a participant's home for a home visit.	Revised for accuracy

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

An Open-Label, Multicenter, Follow-up Trial of ARGX-113-1904 to Evaluate the Safety, Tolerability, and Efficacy of Efgartigimod PH20 SC in Patients With Pemphigus (ADDRESS+)

Brief Title:

Open-label follow-up trial of ARGX-113-1904

Indication:

Pemphigus

Trial Sites/Countries:

Global, multicenter trial using the same sites and countries as the antecedent trial ARGX-113-1904

Target Population:

Adult patients with moderate to severe pemphigus vulgaris (PV) or pemphigus foliaceus (PF) who participated in ARGX-113-1904 and roll over to ARGX-113-1905

Investigational Medicinal Product (IMP), Dose, and Mode of Administration:

Efgartigimod PH20 SC will be administered either weekly 1000 mg or [redacted] mg on [redacted] and [redacted] followed by weekly 1000 mg with treatment being stopped upon achieving complete remission on minimal therapy (CRmin).

Rationale:

Pemphigus is a chronic disease and patients under treatment experience intermittent episodes of clinical remission and flare. The mainstays of therapy in PV are systemic corticosteroids and rituximab. Corticosteroids rapidly affect PV symptoms (3 to 4 weeks), but must be administered at high daily doses (eg, oral prednisone 1 to 1.5 mg/kg) to attain effectiveness. At such high doses, the well-known cumulative toxicities common to corticosteroid treatment occur frequently; using short courses at the lowest possible dosage, by tapering gradually while keeping the disease in remission, is the therapeutic goal. Recently, rituximab has been approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of pemphigus in adults with moderate to severe PV. When administered as adjunctive treatment to a short course of prednisone, rituximab, while having a relatively late onset of action, has been shown to induce a higher rate of remission after 1 or 2 years, and a longer duration of remission than prednisone alone; however, administration of rituximab

intravenous (IV) frequently results in infusion-related reactions (IRRs) and adverse events (AEs), which may be of late onset.

An innovative drug is needed for the treatment of PV and PF that has a fast onset of action (eg, early disease control [DC, defined as the absence of new lesions and the start of healing of established lesions], complete clinical remission [CR, defined as the absence of new lesions and complete healing of established lesions] within weeks), a strong prednisone sparing effect, and a favorable safety profile. The late onset of action of rituximab is well-documented in the literature: in a meta-analysis reviewing 30 studies, DC was achieved by a mean of 7 to 8 weeks and CRmin by a mean of 6.5 months.

The antecedent trial ARGX-113-1904 intends to demonstrate that efgartigimod PH20 SC with an add-on therapy of oral prednisone at low doses would be a possible treatment modality for PV and PF that could lead to early disease remission at minimal prednisone dose. This trial has a treatment period of up to 30 weeks and provides a tailored dose regimen for participants by stopping investigational medicinal product (IMP) administration upon achieving CRmin (defined as the absence of new lesions and complete healing of established lesions while the participant receives minimal prednisone therapy of ≤10 mg/day for at least 2 months [8 weeks]). *Note: when 10 mg/day is reached in ARGX-113-1904 or ARGX-113-1905, this dose level must be maintained for 8 weeks until CRmin has been achieved.*

This trial provides extension of efgartigimod PH20 SC treatment and retreatment options for participants who have been randomized to the efgartigimod PH20 SC treatment arm in ARGX-113-1904, and the first treatment of efgartigimod PH20 SC and retreatment options for participants who had been randomized to the placebo arm in ARGX-113-1904.

At the blinded rollover from ARGX-113-1904 into ARGX-113-1905, participants may be in different clinical stages of treatment. Participants may have achieved CRmin, participants may have achieved CR without meeting the minimal therapy criterion, participants may have achieved DC or end of consolidation (EoC, the time at which no new lesions have developed for a minimum of 2 weeks and approximately 80% of lesions have healed) without having achieved CR, participants may have had treatment failure or a flare after having achieved CRmin.

ARGX-113-1905 evaluates the ability to (further) taper prednisone therapy and achieve CR off therapy (CRoff), the ability to achieve CR and CRmin for participants who have not yet achieved CRmin, and the ability to treat flare; and assesses patient outcome measures and the safety, PD, PK, and immunogenicity of efgartigimod PH20 SC over the duration of the trial.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the safety of treatment, extended treatment, and retreatment with efgartigimod PH20 SC in participants with PV or PF	• Incidence and severity of treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), and serious adverse events (SAEs) by system organ class (SOC) and preferred term (PT) • Vital sign measurements, physical examinations, electrocardiograms (ECGs), and clinical laboratory safety evaluations
Secondary	
• To evaluate the efficacy of efgartigimod PH20 SC treatment in PV and PF	• Proportion of PV participants who achieve CRmin • Proportion of PV and PF participants who achieve CRmin • Time to DC • Time to CR • Time to CRmin • Time to CRoff • Time to flare • Rate of treatment failure • Rate of flare • Cumulative prednisone dose over the trial • Pemphigus Disease Area Index (PDAI) at each visit
• To assess the health impact of glucocorticoid (GC) use in participants with PV or PF	• Composite Glucocorticoid Toxicity Index (C-GTI) comprising the Aggregate Improvement Score (AIS) and the Cumulative Worsening Score (CWS)
• To evaluate the effects of efgartigimod PH20 SC on quality of life (QoL) in participants with PV or PF	• EuroQol 5-Dimension 5-Level (EQ-5D-5L) score • Autoimmune Bullous Disease Quality of Life (ABQOL) score
• To evaluate the pharmacokinetics (PK) of efgartigimod PH20 SC in participants with PV or PF	• Efgartigimod serum concentrations
• To evaluate the PD of efgartigimod PH20 SC in participants with PV or PF	• Total IgG and subtype (IgG1, IgG2, IgG3, IgG4) serum levels

Objectives	Endpoints
	• Anti-desmoglein (Dsg)-1 and -3 autoantibodies serum levels
• To evaluate the immunogenicity of efgartigimod in participants with PV or PF	• Incidence and prevalence of antidrug antibodies (ADA) against efgartigimod (serum levels)
• To explore feasibility of self-administration of efgartigimod PH20 SC	• Percentage of participants who performed self-administration • Percentage of caregivers who administered the injection to the participant • Number of visits needed for the participant or caregiver to be competent to start administering efgartigimod PH20 SC • Frequency of self- or caregiver-supported administration at home
Exploratory	
• To evaluate the disease-specific genetic background and effects of efgartigimod PH20 SC on the serological and immunological profiles of participants with PV or PF	• Anti-Dsg-1 and -3 autoantibody subtypes and autoantibody reactivity to Dsg domains and other antigens • Lymphocyte dynamic changes
• To evaluate the immunogenicity of rHuPH20 in participants with PV or PF	• Antibodies produced against recombinant human hyaluronidase (rHuPH20) (plasma levels)

Overall Design

This is a prospective, multicenter, open-label extension (OLE) trial on the efficacy, safety, patient outcome measures, tolerability, immunogenicity, PK, and PD of efgartigimod PH20 SC in adult PV or PF participants, who participated in the antecedent trial ARGX-113-1904.

Participants at the end of study (EoS) visit or early discontinuation (ED) visit in ARGX-113-1904 will be given the option to enroll into ARGX-113-1905 after confirmation of eligibility while retaining the blinding of ARGX-113-1904. For each participant, the date of the baseline visit in ARGX-113-1905 will be the same as the date of the EoS/ED visit in ARGX-113-1904.

At baseline, participants will be treated according to their clinical status at EoS of ARGX-113-1904, as follows:

1. Participants who have achieved CRmin or CRoff and are currently not in flare will be observed every 4 weeks through on-site visits without efgartigimod PH20 SC treatment. In participants who have achieved CRmin (oral prednisone ≤10 mg per day for 2 months [8 weeks]), prednisone tapering may be pursued upon investigator's judgment until participants achieve CRoff.
2. Participants in CR who have not achieved CRmin will receive weekly efgartigimod PH20 SC administrations of 1000 mg while continuing the add-on therapy of oral prednisone until CRmin is achieved. Prednisone tapering may be pursued upon investigator's judgment until participants achieve CRoff. Participants will be treated through on-site visits or through home visits with an on-site visit once every 4 weeks.
3. Participants who have achieved DC but not CR will receive weekly on-site administrations of 1000 mg efgartigimod PH20 SC with an add-on therapy of oral prednisone (Table 4) until CR has been achieved, and then will continue to receive weekly efgartigimod PH20 SC administrations of 1000 mg until CRmin is achieved either on site or through home visits with an on-site visit once every 4 weeks.
4. Participants under certain conditions of treatment failure as defined below or participants with flare after having achieved CRmin, may roll over prematurely into ARGX-113-1905 and will be treated with efgartigimod PH20 SC at a dose of [redacted] mg on [redacted] and [redacted] followed by weekly administrations of 1000 mg with an add-on therapy of oral prednisone until CRmin.

   The following types of treatment failure are considered here:

   - absence of DC with oral prednisone 1.5 mg/kg/day for a minimum of 3 weeks
   - participants who roll over due to prednisone-related SAE who have not achieved DC, or
   - flare between DC and achieving CRmin that is not controlled by 2 dose levels of OCS above the dose at which the flare is observed and that is at least 0.3 mg/kg/day (Table 4)

   In the absence of DC, participants will receive prednisone at the starting dose of 1.5 mg/kg/day. In case of uncontrolled flare before CRmin, participants will receive, as starting dose, the last dose from ARGX-113-1904. In case of flare after CRmin, participants will receive a prednisone dose in line with the severity of the flare, with the recommendation of a minimum of 0.3 mg/kg/day when the flare is of mild severity (PDAI activity score <15) and of 0.5 mg/kg/day when the flare is moderate to severe (PDAI activity score ≥15). Dosing of efgartigimod PH20 SC will be done during on-site visits or home visits according to the Schedule of Activities (SoA) in Table 2.
5. Participants who developed a prednisone-related SAE may prematurely roll over into ARGX-113-1905 and may be treated with efgartigimod PH20 SC through on-site or home visits according to the clinical statuses as described above. Concomitant prednisone

will be considered to fit the clinical statuses as described above if compatible with the nature and severity of the SAE, with a lower dose to no concomitant prednisone being considered otherwise.

Participants or their caregivers (a person of legal age that the participant proposes to perform the administrations) may also self-administer efgartigimod PH20 SC after they have successfully completed self-administration training (in ARGX-113-1904 with at least 1 refresher training in ARGX-113-1905 or during ARGX-113-1905). All participants and/or their caregivers will receive a home guide for transport, storage, preparation, and administration of the IMP.

At any postbaseline visit before DC is achieved, the prednisone dose will be adjusted by incrementing dosage according to clinical judgment, with the recommendation to increase by 1 or more steps (Table 4) in case of disease progression or insufficient clinical change. To facilitate common judgments among investigators, recommendations for assessment of disease progression and insufficient clinical change are:

- Disease progression: increase of at least 5 in PDAI activity score compared to baseline score, observed at any postbaseline visit before DC
- Insufficient clinical change: the absence of DC after 3 to 4 weeks of the participant being treated at the starting baseline prednisone dose or after 3 to 4 weeks of any new incremented dose of prednisone

The recommendations of the prednisone dose escalation are:

- Stepwise escalation of daily prednisone dose by 1 or more steps according to clinical judgment in case of disease progression
- Adjustment by incrementing dosage by 1 step in case of insufficient clinical change
- Possible further escalation from the previous step by 1 or more steps, according to clinical judgment and under the same recommendation as above
- Maximum escalation to 1.5 mg/kg qd for 3 weeks

If DC is not attained after a minimum of 3 weeks of the participant receiving oral prednisone 1.5 mg/kg qd, then the participant will be considered a treatment failure and will be withdrawn from the trial.

For participants who achieve DC at a starting dose of 0.5 mg/kg qd or lower, the prednisone dose will be maintained at that starting dose qd until CR and 2 weeks thereafter, or EoC and 4 weeks thereafter, after which tapering will be initiated. For participants achieving DC with an escalated prednisone dose (ie, >0.5 mg/kg qd), that dose will be maintained until 2 weeks after achieving DC and then will be tapered (Table 4) in increments of 0.25 mg/kg every 2 weeks until the starting dose is achieved. This starting dose will be maintained until a sustained CR is achieved for 2 weeks after which further tapering will be initiated, or prednisone tapering below 0.5 mg/kg qd may be initiated in case of sustained EoC for 4 weeks. Further tapering will be performed thereafter, as long as CR or EoC are sustained. Each new tapered prednisone dose until 20 mg/day must be maintained for 2 weeks. Then, the prednisone dose is further tapered by 2.5 mg/day per week. When 10 mg/day is reached, this dose level will be maintained for at least 8 weeks until CRmin is achieved. The prednisone dose can then be further tapered to reach CRoff according to the clinical judgment of the investigator.

At visits when at least 1 new lesion is observed or established lesions remain extensive without being defined as a flare (ie, the appearance of 3 or more new lesions in a 4-week period that do not heal spontaneously within 1 week, or by the extension of established lesions in a participant who had achieved DC), the prednisone dose will be maintained or may be increased, according to clinical judgment. If the lesion resolves, tapering of the prednisone dose will be pursued as planned.

In case of flare in the period between DC and CRmin, the prednisone dose will be increased to achieve DC again. If the flare occurs after CR, and IMP was administered at home by a nurse, the participant will resume weekly on-site visits until he/she achieves CR again. Participants who are not controlled by a dose of OCS that is 2 dose levels above the dose at which the flare is observed and that is at least 0.3 mg/kg/day (Table 4) will be managed according to clinical judgment (ie, either receive a further increased prednisone dose or be withdrawn from the trial). Withdrawal of participants with a flare before CRmin will be defined as treatment failure.

In case of flare after having achieved CRmin (ie, while being off efgartigimod treatment), participants will be immediately treated/retreated with a new cycle of efgartigimod PH20 SC. The first day of new efgartigimod treatment will define a new baseline for assessments of outcomes (DC, CR, etc) and prednisone escalation or tapering schedule.

In the new treatment cycle, participants will be administered efgartigimod PH20 SC at a weekly dose of [redacted] mg for the first [redacted] weeks, followed by weekly administrations of 1000 mg until CRmin. Oral prednisone will be administered at a dose chosen according to clinical judgment, with the recommendation of 0.3 mg/kg qd in the case of mild flare (PDAI activity score <15) and 0.5 mg/kg qd in the case of moderate to severe flare (PDAI activity score ≥15). The treatment goal of a new treatment cycle is to first achieve DC again and therefore these participants will be treated accordingly (refer to Table 2 for the corresponding SoA).

A new treatment cycle of efgartigimod PH20 SC can be initiated in eligible participants until week 44. In participants requiring a new treatment cycle of efgartigimod PH20 SC between weeks 45 and 49, the initiation will be optional and based on clinical judgment and participant consent. A new efgartigimod treatment cycle will not be permitted after week 49 to ensure a minimum of 4 weeks of efgartigimod treatment/cycle.

Except for oral prednisone, no other systemic therapies (eg, immunosuppressants, IVIg, immunoadsorption, anti-CD20 biologics) will be permitted during the trial.

Trial procedures will be performed per the SoA as detailed in Section 1.3 and Section 10.11.

Disclosure Statement: ARGX-113-1905 is an open-label, multicenter, follow-up trial of ARGX-113-1904 to evaluate safety, tolerability, and efficacy of fixed doses of efgartigimod PH20 SC in participants with pemphigus.

Number of Participants: All participants who were randomized into ARGX-113-1904 will be eligible to roll over to ARGX-113-1905.

Intervention Groups and Duration: Up to 60 weeks for participants who receive IMP administrations up to week 52 and with a follow-up period of up to 8 weeks after the last IMP administration.

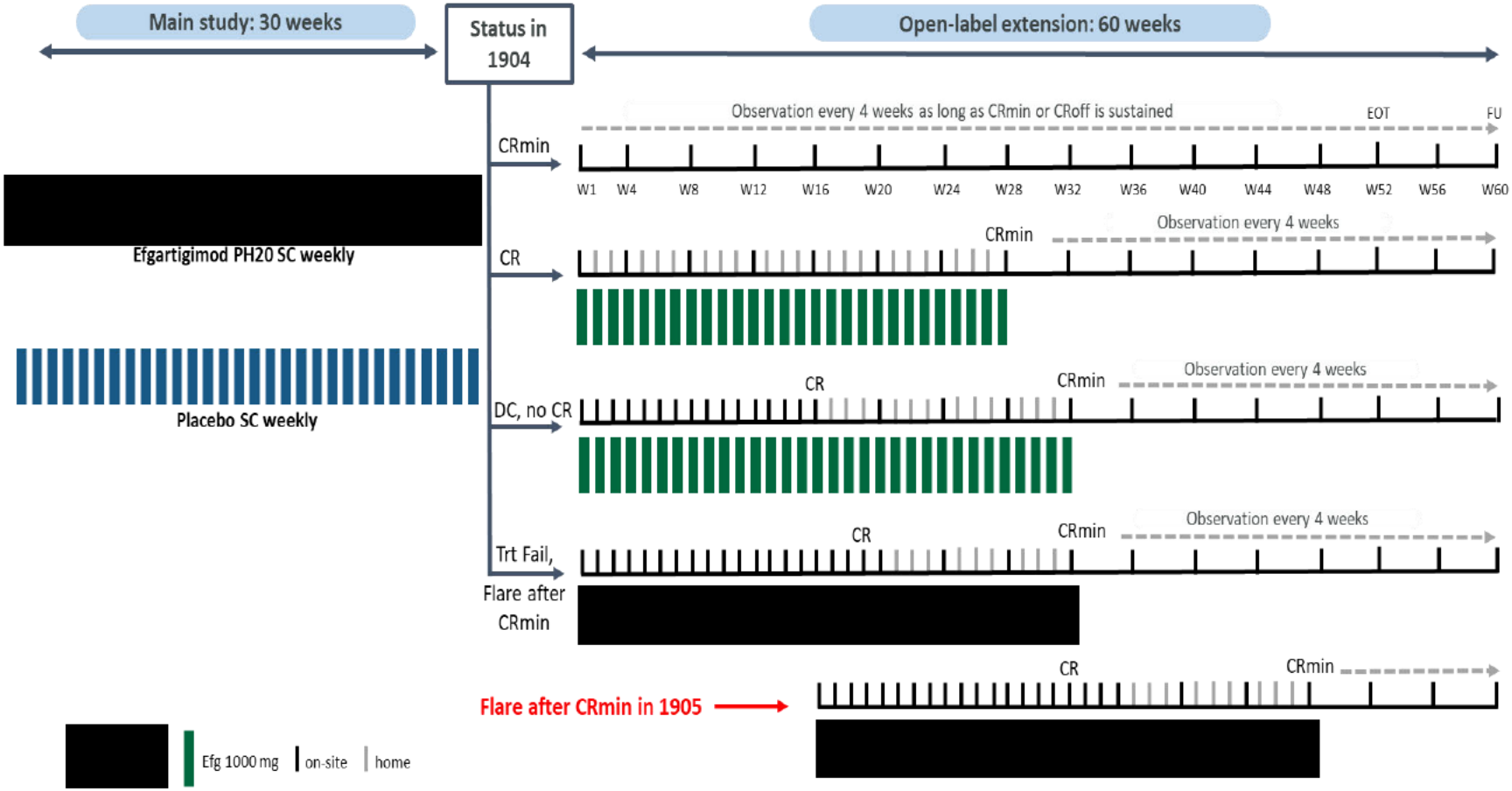
Data Safety Monitoring Board: Yes (Section 10.1.5.1)

Definitions:

- **Complete clinical remission (CR):** the absence of new lesions and complete healing of established lesions (except for postinflammatory hyperpigmentation or erythema from resolving lesions).
- **Complete remission on minimal therapy (CRmin):** the absence of new and established lesions completely healed while the participant is receiving prednisone therapy at ≤10 mg/day for at least 2 months (8 weeks). *Note: when 10 mg/day is reached in ARGX-113-1904 or ARGX-113-1905, this dose level must be maintained for 8 weeks until CRmin has been achieved.*
- **Complete remission off therapy (CRoff):** the absence of new and established lesions completely healed while the participant is receiving no prednisone therapy for at least 2 months (8 weeks).
- **Disease control (DC):** the absence of new lesions and the start of healing of established lesions.
- **Disease progression:** an increase of ≥5 points in the PDAI activity score, observed at any postbaseline visit before DC.
- **End of consolidation (EoC):** the time at which no new lesions have developed for a minimum of 2 weeks and approximately 80% of lesions have healed.
- **Flare:** the appearance of 3 or more new lesions in a 4-week period that do not heal spontaneously within 1 week or the extension of established lesions, in a participant who had achieved DC.
- **Insufficient clinical change:** the absence of DC after 3 to 4 weeks of the participant being treated at the starting baseline dose or after 3 to 4 weeks of any new incremented dose of prednisone.
- **Transient and persistent lesions:** the appearance of new lesions that do not qualify as flare will be recorded as new transient or new persistent lesions. Transient new lesions are defined as the presence of new lesions that heal within 1 week. Persistent new lesions are defined as the presence of new lesions that last more than 1 week.
- **Treatment failure:** the absence of DC with oral prednisone 1.5 mg/kg/day for a minimum of 3 weeks, or flare before CRmin resulting in withdrawal of the participant.

1.2. Schema

Figure 1: ARGX-113-1905 Trial Design



CR=complete clinical remission; CRmin=complete remission on minimal therapy; CRoff=complete remission off therapy; DC=disease control; Efg=efgartigimod PH20 SC; EoT=end of treatment; FU=follow-up; SC=subcutaneous; Trt Fail=treatment failure; W=week

1.3. Schedule of Activities

Table 1: Schedule of Activities for ARGX-113-1905 for Participants in CR, CR on Minimal Therapy, and CR off Therapy at Rollover From ARGX-113-1904

Trial period	**Open-label extension**														**UNS[b]**	**Follow-up**	
Visit number	**V1 Roll over[a]**	**V1 + 4 weeks**	**V1 + 8 weeks**	**V1 + 12 weeks**	**V1 + 16 weeks**	**V1 + 20 weeks**	**V1 +24 weeks**	**V1 + 28 weeks**	**V1 + 32 weeks**	**V1 + 36 weeks**	**V1 + 40 weeks**	**V1 + 44 weeks**	**V1 + 48 weeks**	**V1 +51 weeks EoT/ET**		**Safety follow-up 1 EoT/ET + 4 weeks[c]**	**Safety follow-up 2 EoT/ET + 8 weeks EoS[c]**
Assessment/procedure	**±0 days**	**±2 days[d]**														**±3 days[d]**	**±3 days[d]**
Informed consent	X																
Inclusion/exclusion criteria	X																
Weight[e]	X						X[e]							X			
ECG[f,g]	X			X			X			X			X	X		X	X
Physical examination and vital signs[f,h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[f,i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X	X
Urine pregnancy test[f,j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X	X
Vaccination antibodies[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X	X
Blood sampling																	
• clinical chemistry and hematology[f,k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X	X
• anti-Dsg-1 and anti-Dsg-3 antibodies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X	X

Trial period	**Open-label extension**														**UNS**[b]	**Follow-up**	
Visit number	**V1 Roll over**[a]	**V1 + 4 weeks**	**V1 + 8 weeks**	**V1 + 12 weeks**	**V1 + 16 weeks**	**V1 + 20 weeks**	**V1 +24 weeks**	**V1 + 28 weeks**	**V1 + 32 weeks**	**V1 + 36 weeks**	**V1 + 40 weeks**	**V1 + 44 weeks**	**V1 + 48 weeks**	**V1 +51 weeks EoT/ET**		**Safety follow-up 1 EoT/ET + 4 weeks**[c]	**Safety follow-up 2 EoT/ET + 8 weeks EoS**[c]
Assessment/procedure	**±0 days**	**±2 days**[d]														**±3 days**[d]	**±3 days**[d]
• PK[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b,m]	X	X
• Total IgG and IgG subtypes[f,l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X	X
• immunogenicity[f,n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
• IgG autoantibody subtypes and specificity[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X	X
PDAI[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ABQOL[f,o]	X	at CRmin (or the next on-site visit)												X			
EQ-5D-5L[f,o]	X	at CRmin (or the next on-site visit)												X			
Disease assessment[f,p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lymphocyte populations (at selected sites)[q]	X			X			X				X			X		X	X
GTI	X						X[r]							X[r]			
IMP self-administration training[s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Efgartigimod PH20 SC[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Prednisone taper[u]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Trial period	**Open-label extension**														**UNS[b]**	**Follow-up**	
Visit number	**V1 Roll over[a]**	**V1 + 4 weeks**	**V1 + 8 weeks**	**V1 + 12 weeks**	**V1 + 16 weeks**	**V1 + 20 weeks**	**V1 +24 weeks**	**V1 + 28 weeks**	**V1 + 32 weeks**	**V1 + 36 weeks**	**V1 + 40 weeks**	**V1 + 44 weeks**	**V1 + 48 weeks**	**V1 +51 weeks EoT/ET**		**Safety follow-up 1 EoT/ET + 4 weeks[c]**	**Safety follow-up 2 EoT/ET + 8 weeks EoS[c]**
Assessment/procedure	**±0 days**	**±2 days[d]**														**±3 days[d]**	**±3 days[d]**
Concomitant therapies/procedures	Continuous monitoring																
AE monitoring	Continuous monitoring																

ABQOL=Autoimmune Bullous Disease Quality of Life; AE=adverse events; ALT=alanine aminotransferase; ALP=alkaline phosphatase; AST=aspartate aminotransferase; BMI=body mass index; BUN=blood urea nitrogen; CR=complete clinical remission; CRmin=CR on minimal therapy; CRP=C-reactive protein; DC=disease control; Dsg=desmoglein; ECG=electrocardiogram; EoC=end of consolidation; EoS=end of study; EoT=end of treatment; EQ-5D-5L=EuroQol 5-dimension 5-level scale; ET=early termination; GGT=gamma-glutamyl transferase; GTI=Glucocorticoid Toxicity Index; IgG=immunoglobulin type G; IMP=investigational medicinal product; LDH=lactate dehydrogenase; LDL-C=low-density lipoprotein cholesterol; MCV=mean corpuscular volume; NAb=neutralizing antibody; PDAI=Pemphigus Disease Area Index; PD=pharmacodynamic; PK=pharmacokinetics; QTcF=Fridericia corrected QT interval; rHuPH20=recombinant human hyaluronidase PH20; RBC=red blood cells; SC=subcutaneous(ly); UNS=unscheduled visit; W=week; WBC=white blood cells; V=visit at site

[a] For participants who roll over from ARGX-113-1904 to ARGX-113-1905, the baseline visit will occur for these participants at the same visit as the EoS/ED visit in study ARGX-113-1904. All assessments will be performed before IMP administration.

[b] In case of suspected new lesions as reported by the participants, AEs, flare, or other safety reasons, participants should come to the clinic. This may require an unscheduled visit. Depending on the reason for the visit, different assessments need to be performed. Refer to Section 8 for more information. Participants with new lesions or flare after achieving CR should return to weekly on-site visits. Participants with flare who had achieved CRmin or CRoff should switch to the visit schedule outlined in Table 2.

[c] Follow-up 1 will be the EoS visit for participants who ended treatment before W49 or 4 weeks before ET. Both follow-up visits will be required only for participants who continue to receive efgartigimod PH20 SC for at least 1 visit between W49 and W52 or during the last 4 weeks before ET.

[d] Study visit windows are ±2 days during the treatment period and ±3 days for the follow-up visits.

[e] Weight will be measured and BMI will be calculated accordingly, at the rollover visit, at W26 (or the next on-site visit if W26 does not coincide with an on-site visit) and W52. Weight will also be measured if there has been an obvious change since the last measurement.

[f] Assessment or procedure will be completed predose at visits when IMP is administered.

[g] The ECG will be recorded at baseline, every 3 months while receiving efgartigimod PH20 SC treatment, at CRmin (or the next on-site visit if CRmin is achieved during a week without an on-site visit), and at EoS. The ECG (heart rate, PR, QT, and QRS interval) will be read centrally, and QTcF and QTcB will be calculated. The ECG will be recorded only at baseline and EoS in participants not receiving efgartigimod. Additional ECGs may be performed at the discretion of the investigator during unscheduled visits.

[h] A complete physical examination will be performed at each on-site visit. Vital sign measurements include systolic and diastolic blood pressure, heart rate, and body temperature.

[i] Urinalysis will be performed by dipstick method and will include specific gravity, pH, protein, glucose, ketones, blood, bilirubin, urobilinogen, nitrite, leukocyte esterase, and microscopic examination (if blood or protein is abnormal).

[j] A urine pregnancy test will be performed locally and at least once every 4 weeks.

[k] Clinical blood laboratory tests will include hematology and blood chemistry at all visits. The hematology profile includes hemoglobin, hematocrit, MCV, RBC count, platelet count, and WBC count with differential. The blood chemistry profile includes sodium, potassium, calcium, HbA1c, creatinine, creatinine clearance, BUN, ALT, AST, total bilirubin, GGT, CRP, ALP, LDH, LDL-C, uric acid, total protein, and albumin.

[l] PK and PD (total IgG and IgG subtypes) samples will be taken every 4 weeks as long as the participant is receiving efgartigimod PH20 SC treatment (until CRmin or the next on-site visit) and 4 weeks after CRmin (or the next on-site visit; this also applies if the participant achieved CRmin in ARGX-113-1904) or EoT. Blood samples will be taken predose (within 2 hours before the start of IMP administration during visits when IMP is administered).

[m] At unscheduled visits, blood samples for PK will only be taken if IMP is administered.

[n] Blood samples will be taken to test for immunogenicity to efgartigimod in serum and rHuPH20 in plasma every 4 weeks while the participant is receiving efgartigimod PH20 SC treatment (until CRmin or the next on-site visit) and 4 and 8 weeks after CRmin (or the next 2 on-site visits; this also applies if the participant achieved CRmin in ARGX-113-1904) or EoT. NAb will be tested for all confirmed positive immunogenicity samples.

[o] Questionnaires are to be completed before any other assessment.

[p] Disease assessment parameters include DC, EoC, CR, CRmin, CRoff, flare, and treatment failure. Participants who have achieved CR and have new lesions should come to the clinic for an unscheduled visit for disease assessment.

[q] Samples for lymphocyte populations will be taken at selected sites only: optionally at on-site visits at W13 (±2 weeks), W26 (±2 weeks), W39 (±2 weeks), W52 (±2 weeks) or EoT/ET and EoS, and mandatory at on-site visits at W52 (±2 weeks) or EoT/ET and EoS for participants in CRmin or CRoff.

[r] The GTI assessment will be performed at visit 1, W26 (or the next on-site visit), and W52.

[s] Participants and/or their caregivers will be invited to receive at least 1 refresher training for self-administration, or caregiver-supported administration of IMP. Training will continue until deemed successfully completed by authorized staff.

[t] Efgartigimod PH20 SC will be administered weekly at a dose of 1000 mg until CRmin. For IMP administrations between the scheduled site visits, the participant can choose between self-administration (if training successfully completed), home nurse visits, or return to the trial site for the SC injection only. Participants who have achieved CRmin or CRoff and are currently not in flare will be observed every 4 weeks without any further IMP administration until flare or EoS. Only for on-site visits and home nurse visits, participants should be followed up for safety monitoring for at least 1 hour after the first IMP administration, or followed by 15 minutes of observation for subsequent administrations and released according to their clinical status. The last planned IMP administration is at W52. If the participant withdraws from the study, efgartigimod PH20 SC will not be administered.

[u] Prednisone dose tapering will begin 2 weeks after achieving CR or 4 weeks after sustained EoC (thus, no new lesions have developed for a minimum of 6 weeks and approximately 80% or more of lesions have healed).

Table 2: Schedule of Activities for ARGX-113-1905 for Participants Not in CR at Rollover From ARGX-113-1904, or Participants With Flare after CRmin or CRoff in ARGX-113-1905

Trial period	Open-label extension					EoT/ET	UNS[d]	Follow-up	
	V1[a]	Observational visits	IMP admin only visit	Observational visits		EoT/ET		Follow-up	
Visit Number		Weekly on-site visits until CR[b]	Weekly home or on-site visits until CRmin[c]	On-site visits every 4 weeks until CRmin	On-site visits every 4 weeks until W52	W52		Safety follow-up 1	Safety follow-up 2
Trial Week	Rollover[a]	V1 + 7x	CR until CRmin	CR until CRmin	After CRmin until W52	W52		EoT/ET + 4 weeks[e]	EoT/ET + 8 weeks EoS[e]
Assessment/Procedure	±0 days	±2 days[f]				±2 days		±3 days[f]	
Informed consent	X								
Inclusion/exclusion criteria	X								
Weight[g]	X	X[g]		X[g]	X[g]	X			
ECG[h,i]	X	X		X	X	X		X	X
Physical examination and vital signs[i,j]	X	X		X	X	X	X	X	X
Urinalysis[i,k,l]	X	X		X	X	X	X[d]	X	X
Urine pregnancy test[i,m]	X	X		X	X	X	X[d]	X	X
Vaccination antibodies[i,l]	X	X		X	X	X	X[d]	X	X
Blood sampling									
• Clinical chemistry and hematology[i,l,n]	X	X		X	X	X	X[d]	X	X
• anti-Dsg-1 and anti-Dsg-3 antibodies[i,l]	X	X		X	X	X	X[d]	X	X

Trial period	Open-label extension					EoT/ET	UNS[d]	Follow-up	
	V1[a]	Observational visits	IMP admin only visit	Observational visits		EoT/ET		Follow-up	
Visit Number		Weekly on-site visits until CR[b]	Weekly home or on-site visits until CRmin[c]	On-site visits every 4 weeks until CRmin	On-site visits every 4 weeks until W52	W52		Safety follow-up 1	Safety follow-up 2
Trial Week	Rollover[a]	V1 + 7x	CR until CRmin	CR until CRmin	After CRmin until W52	W52		EoT/ET + 4 weeks[e]	EoT/ET + 8 weeks EoS[e]
Assessment/Procedure	±0 days	±2 days[f]				±2 days		±3 days[f]	
• PK[i,o]	X	X		X	X[o]	X	X[d,p]	X	X
• Total IgG and IgG subtypes[i,o]	X	X		X	X	X	X[d]	X	X
• immunogenicity[i,q]	X	X		X	X	X		X	X
• IgG autoantibody subtypes and specificity[i]	X	X[r]		X	X	X	X[d]	X	X
PDAI[i]	X	X		X	X	X	X	X	X
ABQOL[i,s,t]	X	X[s]		X[s]	X[s]	X			
EQ-5D-5L[i,s,t]	X	X[s]		X[s]	X[s]	X			
Disease assessment[i,u]	X	X		X	X	X	X	X	X
Photography (at selected sites)[v]	X	X[v]				X	X[d,v]		
Lymphocyte populations (at selected sites)[w]	X	X[w]		X[w]	X[w]	X[w]		X	X
GTI[x]	X	X[x]		X[x]	X[x]	X			
IMP self-administration training[y]	X	X	X	X	X	X			

Trial period	Open-label extension					EoT/ET	UNS[d]	Follow-up	
	V1[a]	Observational visits	IMP admin only visit	Observational visits		EoT/ET		Follow-up	
Visit Number		Weekly on-site visits until CR[b]	Weekly home or on-site visits until CRmin[c]	On-site visits every 4 weeks until CRmin	On-site visits every 4 weeks until W52	W52		Safety follow-up 1	Safety follow-up 2
Trial Week	Rollover[a]	V1 + 7x	CR until CRmin	CR until CRmin	After CRmin until W52	W52		EoT/ET + 4 weeks[e]	EoT/ET + 8 weeks EoS[e]
Assessment/Procedure	±0 days	±2 days[f]				±2 days		±3 days[f]	
Efgartigimod PH20 SC[z]	X[z]	X[z]	X	X		X	X		
Prednisone taper[aa]	X	X		X	X	X	X		
Concomitant therapies/ procedures	Continuous monitoring								
AE monitoring	Continuous monitoring								

ABQOL=Autoimmune Bullous Disease Quality of Life; AE=adverse event; ALT=alanine aminotransferase; ALP=alkaline phosphatase; AST=aspartate aminotransferase; BMI=body mass index; BUN=blood urea nitrogen; CR=complete clinical remission; CRmin=CR on minimal therapy; CRP=C-reactive protein; DC=disease control; Dsg=desmoglein; ECG=electrocardiogram; EoC=end of consolidation; EoS=end of study; EoT=end of treatment; EQ-5D-5L=EuroQol 5-dimension 5-level scale; ET=early termination; GGT=gamma-glutamyl transferase; GTI=Glucocorticoid Toxicity Index; IgG=immunoglobulin type G; IMP=investigational medicinal product; LDH=lactate dehydrogenase; MCV=mean corpuscular volume; NAb=neutralizing antibody; PD=pharmacodynamic; PDAI=Pemphigus Disease Area Index; PK=pharmacokinetics; QTcF=Fridericia corrected QT interval; rHuPH20=recombinant human hyaluronidase PH20; RBC=red blood cells; SC=subcutaneous(ly); UNS=unscheduled visit; V=visit at site; V1 + 7x=visit 1 + 7 times x with 'x' being the weeks post V1 (eg, V1 + 7x3 is the visit at W3 [21 days post visit 1]); W=week; WBC=white blood cells

[a] For participants who roll over from ARGX-113-1904 to ARGX-113-1905, the baseline visit will occur at the EoS/ED visit of ARGX-113-1904. All assessments are performed before IMP administration.

[b] A minimum of 6 on-site visits (rollover (V1) to W6 or start of retreatment +5 weeks) is required before switching to home administrations, even if CR is reported earlier.

[c] Home visits are allowed once a participant achieves CR but not before W7 or not before the start of retreatment +6 weeks. The investigator should call the participant every 2 weeks until CRmin to confirm the participant is still in CR and to determine the prednisone tapering schedule.

[d] In case of suspected new lesions as reported by the participant, AEs, flare, or other safety reasons, the participant should come to the clinic. This may require an unscheduled visit. Depending on the reason for the visit, different assessments need to be performed. Refer to Section 8 for more information.

[e] Follow-up 1 will be the EoS visit for participants who ended treatment before W49, or 4 weeks before ET. Both follow-up visits will be required only for participants who continue to receive efgartigimod PH20 SC for at least 1 visit between W49 and W52, or during the last 4 weeks before ET.

[f] Study visit windows are ±2 days during the treatment period and ±3 days for the follow-up visits.

[g] Weight will be measured and BMI will be calculated accordingly, at the rollover visit, at W26 (or the next on-site visit if W26 does not coincide with an on-site visit) and W52. Weight will also be measured if there has been an obvious change since the last measurement.

[h] The ECG will be recorded at baseline, at the start of retreatment and every 3 months (or the next on-site visit) while receiving efgartigimod PH20 SC treatment, at CRmin (or the next on-site visit if CRmin is achieved during a week without an on-site visit), and EoS. The ECG (heart rate, PR, QT, and QRS interval) will be read centrally, and QTcF and QTcB will be calculated. Additional ECGs may be performed at the discretion of the investigator during unscheduled visits.

[i] Assessment or procedure will be completed predose at visits when IMP is administered.

[j] A complete physical examination will be performed at each on-site visit. Vital sign measurements include systolic and diastolic blood pressure, heart rate, and body temperature.

[k] Urinalysis will be performed by dipstick method and will include specific gravity, pH, protein, glucose, ketones, blood, bilirubin, urobilinogen, nitrite, leukocyte esterase, and microscopic examination (if blood or protein is abnormal).

[l] Samples will be taken every week from rollover (V1) to W9 or start of retreatment +8 weeks, and then every 4 weeks and at the visit when CR is observed. Once CR is achieved, samples will be taken every 4 weeks at on-site visits until EoS. For participants achieving CR between rollover (V1) and W6 or the start of retreatment +5 weeks, samples will be taken weekly from rollover (V1) to W6 or start of retreatment +5 weeks, and then every 4 weeks during on-site visits until EoS.

[m] A urine pregnancy test will be performed locally at least once every 4 weeks, at CR, and as of CR again every 4 weeks at on-site visits.

[n] Clinical blood laboratory tests will include hematology and blood chemistry at all visits. The hematology profile includes hemoglobin, hematocrit, MCV, RBC count, platelet count, WBC count with differential. The blood chemistry profile includes sodium, potassium, calcium, HbA1c, creatinine, creatinine clearance, BUN, ALT, AST, total bilirubin, GGT, CRP, ALP, LDH, low-density lipoprotein cholesterol (LDL-C), uric acid, total protein, and albumin.

[o] PK and PD (total IgG and IgG subtypes) samples will be taken every 4 weeks, at CR, and as of CR again every 4 weeks at on-site visits, as long as the participant is receiving efgartigimod PH20 SC treatment (until CRmin or the next on-site visit if CRmin is achieved during a week without an on-site visit), and 4 weeks after CRmin (or the next on-site visit) or EoT. Blood will be taken predose (within 2 hours before the start of IMP administration during visits when IMP is administered).

[p] Blood will be taken for PK assessment predose (within 2 hours before the start of IMP administration during visits when IMP is administered). At UNS visits, blood samples for PK analysis will be taken only if IMP is administered.

[q] Blood will be taken to test for immunogenicity to efgartigimod in serum and to rHuPH20 in plasma every 4 weeks, at CR, and as of CR every 4 weeks at on-site visits while the participant is receiving efgartigimod PH20 SC treatment (until CRmin or the next on-site visit if CRmin is achieved during a week without an on-site visit), and 4 and 8 weeks after CRmin (or the next 2 on-site visits) or EoT. NAb will be tested for all confirmed positive immunogenicity samples.

[r] Blood will be taken every 4 weeks and at the visit when CR is observed for IgG autoantibody subtypes and specificity. Once CR is achieved, samples will be taken every 4 weeks at on-site visits until EoS.

[s] The ABQOL and EQ-5D-5L will be administered at the start of retreatment, when achieving CRmin (or at the next on-site visit if CRmin is achieved during a week without an on-site visit), and at EoT/W52 only.

[t] Questionnaires are to be completed before any other assessment.

[u] Disease assessment parameters include DC, EoC, CR, CRmin, CRoff, flare, and treatment failure. Participants who have achieved CR and have new lesions should come to the clinic for a UNS visit for disease assessment.

[v] Pictures of different anatomical regions may be taken per judgment of the investigator. As a guidance, time points of baseline, DC, CR and flare are indicated. Pictures may also be taken at intermediate time points.

[w] Samples for lymphocyte populations will be taken at selected sites only: optionally at on-site visits at W13 (±2 weeks), W26 (±2 weeks), W39 (±2 weeks), W52 (±2 weeks) or EoT/ET and EoS, and mandatory at on-site visits at W52 (±2 weeks) or EoT/ET and EoS for participants in CRmin or CRoff.

[x] The GTI assessment will be performed at visit 1, W26 (or the next on-site visit) and W52.

[y] Participants and/or their caregivers will be invited to receive at least 1 refresher training for self-administration, or caregiver-supported administration of IMP. Training will continue until deemed successfully completed by authorized staff.

[z] Efgartigimod PH20 SC will be administered subcutaneously weekly at a dose of 1000 mg until CRmin. In case of treatment failure in ARGX-113-1904, or flare while not receiving efgartigimod therapy, efgartigimod PH20 SC will be administered on [redacted] at a dose of [redacted]mg, followed by weekly SC administrations of 1000 mg until CRmin. For IMP administrations between the scheduled visits (after achieving CR), the participant can choose between self-administration (if training successfully completed), home nurse visits or return to the trial site for the SC injection only. Participants who have achieved CRmin or CRoff and are currently not in flare will be observed every 4 weeks without any further IMP administration until flare or EoS. Only for on-site visits and home nurse visits, participants should be followed up for safety monitoring for at least 1 hour after the first administration, or followed by 15 minutes of observation for subsequent administrations for safety monitoring and released according to their clinical status. The last planned IMP administration is at W52. If the participant withdraws from the study, efgartigimod PH20 SC will not be administered.

[aa] Prednisone dose tapering will begin 2 weeks after achieving CR or 4 weeks after sustained EoC (thus, no new lesions have developed for a minimum of 6 weeks and approximately 80% or more of lesions have healed).

2. INTRODUCTION

This is a prospective, multicenter, open-label extension (OLE) trial on the efficacy, safety, patient outcome measures, tolerability, immunogenicity, PK, and PD of efgartigimod PH20 SC in adult PV or PF participants, who participated in the antecedent trial ARGX-113-1904.

2.1. Trial Rationale

Pemphigus is a chronic disease and patients under treatment experience intermittent episodes of clinical remission and flare. The mainstays of therapy in PV are systemic corticosteroids and rituximab. Corticosteroids rapidly affect PV symptoms (3 to 4 weeks), but must be administered at high daily doses (eg, oral prednisone 1 to 1.5 mg/kg) to attain effectiveness. At such high doses, the well-known cumulative toxicities common to corticosteroid treatment occur frequently, and using short courses at the lowest possible dosage by tapering gradually while keeping the disease in remission is the therapeutic goal. Recently, rituximab, a monoclonal antibody binding the CD20 antigen on, and depleting, B-lymphocytes, has been approved in adults with moderate to severe PV. When administered as adjunctive treatment to a short course of prednisone, rituximab, while having a relatively late onset of action, was shown to induce a higher rate of remission after 1 or 2 years, and a longer duration of remission than prednisone alone; however, administration of rituximab IV frequently results in infusion-related reactions (IRRs) and adverse events (AEs), which may be of late onset.

An innovative drug is needed for the treatment of PV and PF that has a fast onset of action (eg, early disease control [DC, defined as the absence of new lesions and the start of healing of established lesions], complete clinical remission [CR, defined as the absence of new lesions and complete healing of established lesions] within weeks), a strong prednisone sparing effect, and a favorable safety profile.

The antecedent trial ARGX-113-1904 intends to demonstrate that efgartigimod PH20 SC with an add-on therapy of low doses of oral prednisone is a possible treatment modality for PV and PF which leads to early disease remission at minimal prednisone dose. The trial has a treatment phase of up to 30 weeks, and provides a tailored dose regimen for participants by stopping investigational medicinal product (IMP) administration upon achieving complete remission on minimal therapy (CRmin, defined as the absence of new lesions and complete healing of established lesions while the participant is receiving minimal prednisone therapy of ≤10 mg/day for at least 2 months [8 weeks]). *Note: when 10 mg/day is reached in ARGX-113-1904 or ARGX-113-1905, this dose level must be maintained for 8 weeks until CRmin has been achieved.*

ARGX-113-1905 provides efgartigimod PH20 SC extended treatment and retreatment options for participants who were randomized to the efgartigimod PH20 SC treatment arm in ARGX-113-1904, and provides first efgartigimod PH20 SC treatment and retreatment options for participants who were randomized to the placebo treatment arm in ARGX-113-1904.

At blinded rollover from ARGX-113-1904 into ARGX-113-1905, participants may be in different clinical stages: participants may have achieved CRmin; participants may have achieved

CR without meeting the minimal therapy criterion; participants may have achieved DC or EoC (the time at which no new lesions have developed for a minimum of 2 weeks and approximately 80% of lesions have healed) without having achieved CR; participants may have had treatment failure or a flare after having achieved CRmin.

ARGX-113-1905 evaluates the ability to (further) taper prednisone therapy and achieve CRoff (CRoff defined as the absence of new and established lesions completely healed while the participant is receiving no prednisone therapy for at least 2 months [8 weeks]), the ability to achieve CR and CRmin for participants who had not yet achieved CRmin, and the ability to treat flare; and assesses participant outcome measures and the safety, PD, PK, and immunogenicity of efgartigimod PH20 SC over the duration of the trial.

2.2. Background

PV and PF (also called superficial pemphigus) are 2 close entities belonging to the heterogenous group of autoimmune skin blistering diseases, and clinically characterized by mucosal erosions (PV) and cutaneous blisters (PV and PF). PV is caused by IgG autoantibodies against the desmosomal proteins, desmoglein-3 (Dsg-3) and/or Dsg-1, on epidermal keratinocytes. Because the binding of the antibodies (which are predominantly of the IgG4 subtype and therefore do not activate complement) to the extracellular domain of Dsg is sufficient to cause loss of keratinocyte adhesion and blister formation, they generate directly the clinical manifestations of PV. Dsg-3 is expressed throughout the epidermis of the skin and the mucosa, whereas Dsg-1 prevails in the superficial layer of the skin and is absent in the mucosa. Accordingly, mucosal PV lesions are mostly induced by anti-Dsg-3 antibodies, whereas cutaneous PV lesions are triggered by both anti-Dsg-3 and anti-Dsg-1 antibodies. Interestingly, disease activity has been shown to be closely correlated with serum levels of antibodies against Dsg-1 and, to a lesser extent, Dsg-3.[28,29] PF is caused by antibodies against Dsg-1 that is expressed in the superficial layer of the epidermis and, therefore, involves the skin only. Two forms have been described: the non-endemic form, and the endemic form (also called “fogo selvagem”). Fogo selvagem has been observed in the Amazonian region, where a non-infectious protein (LJM11) residing in the salivary glands of the sand fly (*Lutzomyia longipalpis*) was suggested to cause a cross-reaction with Dsg-1.[22] Otherwise, endemic and non-endemic PF share the same clinical, histological and immunological findings. Like in PV, anti-Dsg-1 autoantibodies are directly pathogenic.

Both PV and PF are rare. The incidence of PV is variable, with a higher frequency along the Mediterranean border. Its annual incidence ranges from 0.8/million in Finland, to around 1.5/million in France, 4 to 5/million in Italy, up to 8/million in Greece, and 16/million in Israel.[1] It is sporadic and affects patients in their middle age, of both sexes. PF is even less common in North America and Europe (10%-15% of the pemphigus cases).

Both conditions are chronic and intractable, with life-threatening potential. Clinically, PV presents as a mucosal-dominant, mucocutaneous or, less commonly, solely cutaneous type. Patients frequently shift from 1 type to another, typically from mucosal type at the beginning of the disease to become mucocutaneous later on. Mucocutaneous type tends to be a more severe disease, whereas diagnostic delay is common in the mucosal type. Although it may affect a wider range of age, its peak frequency ranges between 50 and 60 years of age. Women are slightly

overrepresented in the PV population, in which the female-predominant thyroid diseases and rheumatoid arthritis are associated.[2]

Typically, lesions begin in the oral mucosa and might then extend to other mucosal areas and the skin. Mucosal involvement consists of flaccid blisters that rapidly rupture, leaving painful erosions. Mucosal lesions may also affect the pharynx, upper larynx, esophagus, nose and eyes, and genitals. They are usually associated with significant impairments, including difficulties of eating and swallowing, of having sexual intercourses, etc. They frequently lead to weight loss, malnutrition and alteration of QoL. Cutaneous lesions are featured by flaccid blisters and erosions that easily ooze and become superinfected (crusty lesions). Although any skin area may be involved, lesions predominate in the head, upper trunk and groin. They are painful, especially in the folds. At examination, the epidermis can be detached when the finger rubs the skin at the periphery of the lesions (Nikolsky sign), which is highly indicative of PV diagnosis.

Diagnosis of PV follows an algorithm of different tools, which should be performed in the presence of clinical manifestations suggestive of the disease. They include histology, direct immunofluorescence (DIF), and the evidence of autoantibodies against Dsg-3 and/or Dsg-1 in serum either through indirect immunofluorescence (IIF) or enzyme-linked immunosorbent assay (ELISA) tests. Histopathology shows suprabasal acantholysis (keratinocytes floating in blister fluid). Acantholysis is highly suggestive of PV, as it is not seen in other autoimmune blistering diseases such as bullous pemphigoid (BP), but the diagnosis should be confirmed by the characteristic deposition of IgG and/or complement on the cell surface of keratinocytes by DIF. DIF is considered today as the gold standard investigation for diagnosis. However, IIF and/or ELISA are necessary to confirm the diagnosis. Commercial ELISA assays are available for quantitative measurement of Dsg-1 and Dsg-3 autoantibodies in serum. They potentially offer advantages over IIF, such as increased sensitivity (>90%), but are not helpful for excluding other self-antigens and AIBDs. Therefore, IIF and ELISA may be considered complementary in the diagnostic investigation of PV. Taken together, the international guidelines recommend making diagnosis of PV in patients with indicative clinical signs, confirmed by histopathology, positive DIF, and positive IIF and/or ELISA.[5]

PV is a chronic disease, with no tendency of spontaneous improvement. On the contrary, the disease worsens progressively and has a mortality rate 3 times higher than in the general population when untreated.[3] Under treatment, the disease usually evolves in periods of remission and flare. Eventually, it takes many years for achieving a definite cure. As treatments are part of the co-morbidity factors that are related to their high rate of serious side effects, the mortality is still high and severe infections remain today the main cause of death.[4]

Because Dsg-1 is expressed in the superficial portion of the epidermis, PF participants present with itchy, scaly and crusted erosions of the cutaneous tissue. Blisters are uncommonly seen, owing to their superficial nature and easy rupture. Another clinical variant may be the development of squamous and crusty lesions on the face, scalp, chest and inter-scapular areas (“seborrheic pemphigus”). In more severe forms, desquamative erythroderma may be observed in almost all of the skin surface. PF diagnosis follows the investigational tools that are used in PV. At histology, a cleft in the subcorneal or the superficial granular layer can be seen. DIF shows the intercellular deposition of IgG within the epidermis, and the IIF reveals the presence

of serum autoantibodies against intercellular components of the skin. ELISA tests quantify the positive level of anti-Dsg-1 antibodies in serum, whereas the search for anti-Dsg-3 antibodies is negative.

Like PV, PF does not tend to amend spontaneously. Treatment is always needed, with the aim at healing existing lesions and preventing the appearance of new lesions as soon as possible.

Basic and clinical research has led to a better understanding of the mechanisms of pemphigus diseases and novel therapies have been developed. Nonetheless, long diagnostic delay and suboptimal treatment are important concerns in pemphigus diseases. As described above, a drug with a faster onset of action is needed so that quicker DC can be achieved in combination with low starting doses of corticosteroids (eg, prednisone at 0.5 mg/kg per day), and CR can be attained and maintained while the participant reaches rapidly minimal corticosteroid dose (prednisone ≤10 mg/day) or even no concomitant treatment (off prednisone therapy).

The therapeutic management of participants with pemphigus is very challenging. Its primary principles are to promptly stop the occurrence of new blisters and then achieve CR and to minimize the side effects of systemic corticosteroids. Corticosteroids have indeed a high cumulative toxicity in these chronic diseases, which must be mitigated by reducing their amount and duration of exposure as much as possible. Secondarily, the objective of the treatments is to prevent the development of new lesions either on minimal corticosteroid therapy, or even without any treatment. For this purpose, participants must be managed by referral centers, where they can be monitored carefully by experienced dermatologists. In many participants, a multi-disciplinary approach is necessary, including specialists in oral medicine, ophthalmologists and gynecologists when mucosal lesions are present. To help the practitioners in the therapeutic management of pemphigus participants, consensual definitions of the most important clinical endpoints among national and international experts, [14] as well as regular guidelines for the diagnosis and treatment of these diseases are available.[9,10,14,23] In addition, validated scales for monitoring disease activity and extension (eg, Pemphigus Disease Area Index [PDAI], Autoimmune Bullous Skin Disorder Intensity Score [ABSIS]) have been established.[13,24] The specific scale Autoimmune Bullous Disease Quality of Life (ABQOL) was developed and validated for ascertaining the impact of the disease and its therapies on the patient's daily life.[19]

According to the most recent international guideline,[5] corticosteroids remain a first-line therapy in pemphigus. They are the most rapidly acting treatment known today, ie, DC achieved in about 3 weeks (no new lesions, established lesions starting to heal) when used at effective dose.[6,7,8] Oral prednisone is the most commonly used corticosteroid. The starting oral prednisone dose is high, ranging from 1 to 2 mg/kg daily, and may be reduced (0.5–1 mg/kg per day) if combined with rituximab or immunosuppressants. If DC is not achieved after 3 to 4 weeks at the latest, the prednisone dose must be increased. In patients with very active disease, intravenous bolus of corticosteroids (eg, methylprednisolone) may be preferred, especially at the treatment initiation.

Tapering of oral prednisone is initiated as soon as DC is achieved or up to the end of the consolidation (EoC) phase. EoC is defined as the absence of new lesions for at least 2 weeks and approximately 80% of established lesions healed. The duration of the consolidation period varies greatly between patients, mucosal erosions and extensive cutaneous lesions tending to be late to heal. The goal of the EoC phase is to reach CR (no new lesions, all established lesions

completely healed) and, at the same time, reach a minimal effective dose of prednisone (10 mg per day or less for at least 2 months), or even stop prednisone (off therapy), in order to prevent side effects. Unfortunately, this double objective is hard to achieve, and a majority of patients flare under a tapered dose of prednisone. In a prospective study, 64% of patients with PV who were treated with prednisone could achieve a first complete remission on minimal dose after 12 months.[25] Flare occurred frequently, ie, in 45% of the cases within 6 months. Finally, the common course of PV is one of episodes of flare and transient remission, and it takes several years of prednisone treatment before achieving permanent remission. In 1 study, 36% of patients with PV were treated with prednisone or equivalent for at least 10 years. [26] Meanwhile, the risk of corticosteroid-related side effects increased with treatment duration (osteoporosis, diabetes, hypertension, Cushing syndrome, cataract, glaucoma, infections, etc).[27] Accordingly, most patients with PV need adjuvant therapies (eg, rituximab, immunosuppressants) to maintain them under remission and reduce the cumulative prednisone dose.

The recent approval of rituximab in PV adults has dramatically changed the mainstay of therapy of the disease, and is now approved as a first-line therapy in association with prednisone for moderate and severe cases. Rituximab is primarily used in patients with refractory PV who do not respond well to other treatments. However, the lack of long-lasting remission and great number of SAEs associated with prednisone and immunosuppressants has led researchers to develop alternative first-line treatments. Rituximab as second-line and third-line treatment (1 to 2 g per cycle) was shown to a induce long-term remission at a high rate, which could not be achieved by any other treatment (75% remission rate in PV after 1 year[9]). Flare rates after rituximab therapy ranged between 25% after 1 year up to 80% in long-term follow-up. Recent evidence has shown the efficacy of a first cycle of rituximab (2 g) as first-line treatment followed by new cycles (0.5 g) after 12 months and 18 months, in combination with lower doses of prednisone (0.5 to 1 mg/kg per day according to disease severity[10]). Using this first-line regimen, a higher proportion of complete remission after 2 years, ie, 89%, was demonstrated. Flare cases were observed to be also lower (24% after 2 years), a majority occurring within 6 to 12 months after the first cycle. A strong prednisone sparing effect, ie, by about two-thirds, was demonstrated.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks of both efgartigimod and rHuPH20 may be found in the latest editions of the Investigator's Brochures (IBs).

2.3.1. Risk Assessment

In clinical studies to date, efgartigimod has been well-tolerated in both healthy adult participants and in those with pemphigus, myasthenia gravis (MG), and primary immune thrombocytopenia (ITP). The majority of treatment-emergent adverse events (TEAEs) were considered to be mild (grade 1) in severity.

In the phase 2 study ARGX-113-1701 in participants with pemphigus, 5 severe (grade 3) TEAEs were reported, 3 of which were assessed as not related to the drug (syncope, pneumonia, and tibia fracture) and the remaining 2 TEAEs of tooth infection and blood creatine phosphokinase (CPK) increased were assessed by the investigator to be possibly related to the IMP. Out of these

5 severe TEAEs, no action was taken on the drug dose for 3 participants; drug was withdrawn from the participant who had nonrelated grade 3 pneumonia; and the dose was interrupted for the participant who reported possibly related blood CPK increase. The most commonly reported TEAEs were nasopharyngitis, diarrhea, and headache, reported in 4 participants (11.8%) participants each. The most frequently reported treatment-related TEAE was influenza-like illness, which occurred in 3 (8.8%) participants in total.

In the phase 2 trial ARGX-113-1602 in participants with MG, no grade ≥3 TEAEs were reported and no TEAE led to discontinuation from treatment or from the study. The most common TEAE was headache, reported in 4 of 12 participants (33%) treated with efgartigimod 10 mg/kg and 3 of 12 participants (25%) who received placebo. Additionally, in a randomized, double-blinded, placebo-controlled, phase 3 trial in participants with MG (ARGX-113-1704), 65 (77.4%) participants in the efgartigimod group and 70 (84.3%) participants in the placebo group reported ≥1 TEAE. Most TEAEs were of mild or moderate severity. TEAEs of grade 3 or 4 severity were reported with similar frequencies (efgartigimod: 9 [10.7%] participants; placebo: 8 [9.6%] participants). Treatment-emergent SAEs were reported in 4 (4.8%) participants in the efgartigimod and 7 (8.4%) participants in the placebo group. No deaths occurred during the study. TEAEs that led to discontinuation of IMP were reported in 3 (3.6%) participants in each treatment group.

In the phase 2 trial ARGX-113-1603 in participants with ITP, 1 TEAE of thrombocytopenia grade 4 was reported, which was considered unrelated to treatment, but led to treatment discontinuation. Injection site hematoma was the most commonly reported TEAE, reported in 3 of 13 participants (23.1%) in the efgartigimod 5 mg/kg group and in 2 of 13 participants (15.4%) in the efgartigimod 10 mg/kg group. Headache was reported in 1 of 13 participants (7.7%) treated with efgartigimod 5 mg/kg, and 2 of 12 participants (16.7%) who received placebo.

The only clinically relevant laboratory findings, observed after repeated administration of efgartigimod 10 mg/kg, were decreased monocyte count (reported for 1 participant with MG) and abnormal differential white blood cell count in individual healthy participants after administration of a single dose of 25 and 50 mg/kg efgartigimod, which was associated with decreased CD8, CD3, CD56, CD4, and CD19 lymphocyte levels. All events were short-lasting and resolved within 2 to 4 days. An increase in C-reactive protein was reported in individual healthy participants administered a single dose of 25 and 50 mg/kg efgartigimod. All events resolved within 3 to 6 days and were, in general, not associated with signs of fever or serious infections.

In nonclinical toxicology trials repeated administration of 100 mg/kg (15 infusions, every 2 days) efgartigimod was associated with reversible Kupffer cell hypertrophy/hyperplasia in rat, as well as hepatic cytoplasmic alterations and degeneration, and diffuse mixed inflammatory cell infiltrates (correlating with alanine aminotransferase [ALT] increase) in cynomolgus monkey. The former most likely relates to a reaction to the foreign protein in the rodent and the latter could be linked to endotoxins that were present in the test article batch used for the study. No such observations were made in a 6-month chronic dosing trial where cynomolgus monkeys were administered 100 mg/kg efgartigimod IV once a week. In both healthy participants

and in those with MG or ITP, no clinically significant changes were observed in liver enzyme levels (including ALT and aspartate aminotransferase), serum lipids, or electrolytes (including potassium).

No clinically significant changes in vital signs and/or ECG findings have been observed in clinical trials to date.

Safety for use during pregnancy has not been established. Therefore, efgartigimod should not be administered to pregnant or lactating women. However, reproductive toxicity studies in rat and rabbit showed that efgartigimod elicited no signs of maternal toxicity or teratogenic effects up to the high IV dose of 100 mg/kg/day and did not adversely affect male and female fertility, or the reproductive and developmental performance in rat following repeated IV injections at 100 mg/kg/day.

rHuPH20, used in both the efgartigimod and placebo preparations, is a permeation (diffusion) enhancer with a well-characterized nonclinical and clinical safety profile that allows the rapid delivery of large volumes of fluid and/or co-administered drugs subcutaneously. In clinical studies, the subcutaneous administration of rHuPH20 in combination with other substances was well-tolerated. Most AEs were mild, transient injection site reactions, including erythema, pain, bruising, pruritus, burning, tenderness, edema, induration, irritation, paresthesia, numbness, and rash. Moderate injection site reactions, which have occurred less frequently, include burning, erythema, pain, and numbness. Mild-to-moderate headache was also commonly reported. Many AEs in these trials were related to the co-administered drug or have been associated with the rapid introduction of a relatively large volume of fluid in the subcutaneous space. rHuPH20 is coformulated or co-administered with several products in the US and EU (eg, Herceptin® SC, MabThera® SC, HyQvia®, and Darzalex Faspro™).

In the phase 1 trial ARGX-113-1901, overall, single-dose SC administration of 750 mg, 1250 mg, 1750 mg, or 10 mg/kg efgartigimod comixed with 2000 U/mL rHuPH20 was well-tolerated by all participants. No deaths, serious adverse events (SAEs), or TEAEs leading to discontinuation were reported. The most frequently reported TEAEs were injection site reactions, most of which were considered related to the IMP. A total of 27 TEAEs reported in 20 (60.6%) participants were considered by the investigator to be related to the IMP. All related TEAEs were reported as mild in severity, except for 1 related TEAE (injection site erythema) which was reported as moderate in severity. Dose-related effects were observed. All participants recovered from their TEAEs by the end of the study, except for 1 participant who had a TEAE of dizziness. There were no clinically relevant findings with respect to clinical laboratory, vital signs, ECGs, or full-body physical examination. Targeted physical examination showed that a total of 19 participants (57.6%) had 1 or more abnormalities at the injection site (including erythema, bruising, pain, discoloration, pruritus, swelling, and hematoma), which were reported as TEAEs. The percentage of participants with 1 or more abnormalities at the injection site appeared to increase with increasing SC doses of efgartigimod comixed with rHuPH20.

2.3.2. Benefit Assessment

Efgartigimod has been shown to effectively reduce IgG antibodies and improve clinical outcomes in several clinical trials of healthy participants and those with pemphigus, MG, or ITP.

In the phase 2 trial ARGX-113-1701 in participants with pemphigus, the efficacy of efgartigimod is supported by pharmacodynamic effects (effects on IgG and anti-Dsg-1 and -3 autoantibodies) and the effects on the clinical activity (PDAI) and clinical outcomes of the disease (DC and CR). The drug had a fast onset of action by sharply reducing the serum levels of autoantibodies. Autoantibody reduction was correlated with a rapid decrease of the disease activity (PDAI), and was associated with an early achievement of DC and CR. Participants achieved DC with or without concomitant prednisone, while participants achieved CR when efgartigimod administration was combined with low-dose prednisone. Flare was prevented when efgartigimod was given at weekly intervals, before and after DC or CR.

In Dec 2021, the FDA approved efgartigimod for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor antibody (AChR-Ab) seropositive. In the phase 2 trial (ARGX-113-1602) of gMG participants, 4 weekly IV infusions of 10 mg/kg efgartigimod led to statistically significant improvements in clinical scales and were well tolerated.[11] Additionally, in a randomized, double-blinded, placebo-controlled, phase 3 trial in participants with MG (ARGX-113-1704), the primary endpoint was met: the percentage of AChR-Ab seropositive participants who, after the first treatment cycle, had reduction of ≥2 points on the Myasthenia Gravis Activities of Daily Living (MG-ADL) total score compared to study entry baseline for ≥4 consecutive weeks, with the first ≥2-point reduction observed no later than 1 week after the last IMP infusion. Participants who met this criterion were considered MG-ADL responders. In the AChR-Ab seropositive population, there was a statistically significantly higher proportion of MG-ADL responders in the efgartigimod group (67.7%) than in the placebo group (29.7%) ($p<0.001$; logistic regression, 2-sided exact p-value) in cycle 1.

In a phase 2 trial of patients with ITP (ARGX-113-1603), efgartigimod resulted in a rapid and marked reduction of IgG antibodies (maximum mean reduction of 65%) and of all IgG subtypes.[12] Additionally, efgartigimod was associated with an increase in platelet counts in more participants than occurred in the placebo group, with greater numerical separation from placebo as the platelet count threshold stringency was increased. Additional post hoc analyses further supported these observations, showing a longer duration of clinically meaningful effect and statistically significantly more active-treated participants achieving a platelet count of $\geq 50 \times 10^9$/L for more than 10 cumulative days compared to the placebo group.

Efgartigimod PH20 SC (the same formulation used in pemphigus studies) is also under investigation in an ongoing phase 2 trial in patients with chronic inflammatory demyelinating polyneuropathy (CIDP) (ARGX-113-1802).

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the efficacy and safety data collected up to date, the benefit-risk assessment supports further testing of efgartigimod PH20 SC in participants with pemphigus.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the safety of treatment, extended treatment, and retreatment with efgartigimod PH20 SC in participants with PV or PF	• Incidence and severity of treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), and serious adverse events (SAEs) by system organ class (SOC) and preferred term (PT) • Vital sign measurements, physical examinations, electrocardiograms (ECGs), and clinical laboratory safety evaluations
Secondary	
• To evaluate the efficacy of efgartigimod PH20 SC treatment in PV and PF	• Proportion of PV participants who achieve CRmin • Proportion of PV and PF participants who achieve CRmin • Time to DC • Time to CR • Time to CRmin • Time to CRoff • Time to flare • Rate of treatment failure • Rate of flare • Cumulative prednisone dose over the trial • Pemphigus Disease Area Index (PDAI) at each visit
• To assess the health impact of glucocorticoid (GC) use in participants with PV or PF	• Composite Glucocorticoid Toxicity Index (C-GTI) comprising the Aggregate Improvement Score (AIS) and the Cumulative Worsening Score (CWS)
• To evaluate the effects of efgartigimod PH20 SC on quality of life (QoL) in participants with PV or PF	• EuroQol 5-Dimension 5-Level (EQ-5D-5L) score • Autoimmune Bullous Disease Quality of Life (ABQOL) score
• To evaluate the pharmacokinetics (PK) of efgartigimod PH20 SC in participants with PV or PF	• Efgartigimod serum concentrations
• To evaluate the PD of efgartigimod PH20 SC in participants with PV or PF	• Total IgG and subtype (IgG1, IgG2, IgG3, IgG4) serum levels • Anti-Dsg-1 and -3 autoantibodies serum levels

Objectives	Endpoints
• To evaluate the immunogenicity of efgartigimod in participants with PV or PF	• Incidence and prevalence of antidrug antibodies (ADA) against efgartigimod (serum levels)
• To explore feasibility of self-administration of efgartigimod PH20 SC	• Percentage of participants who performed self-administration • Percentage of caregivers who administered the injection to the participant • Number of visits needed for the participant or caregiver to be competent to start administering efgartigimod PH20 SC • Frequency of self- or caregiver-supported administration at home
Exploratory	
• To evaluate the disease-specific genetic background and effects of efgartigimod PH20 SC on the serological and immunological profiles of participants with PV or PF	• Anti-Dsg-1 and -3 autoantibody subclasses and autoantibody reactivity to Dsg domains and other antigens • Lymphocyte dynamic changes
• To evaluate the immunogenicity of rHuPH20 in participants with PV or PF	• Immunogenicity to rHuPH20 (plasma levels)

4. TRIAL DESIGN

4.1. Overall Design

This is a prospective, multicenter, OLE trial on the efficacy, safety, patient outcome measures, tolerability, immunogenicity, PK, and PD of efgartigimod PH20 SC in adult PV or PF participants, who participated in the antecedent trial ARGX-113-1904.

Participants at the EoS visit or ED visit in ARGX-113-1904 will be given the option to enroll into ARGX-113-1905 after confirmation of eligibility while retaining the blinding of ARGX-113-1904. For each participant, the date of the baseline visit in ARGX-113-1905 will be the same as the date of the EoS/ED visit in ARGX-113-1904.

At baseline, participants will be treated according to their clinical status at EoS of ARGX-113-1904, as follows:

1. Participants who have achieved CRmin or CRoff and are currently not in flare will be observed every 4 weeks through on-site visits without efgartigimod PH20 SC treatment. In participants who have achieved CRmin (oral prednisone ≤10 mg per day for 2 months [8 weeks]), prednisone tapering may be pursued upon investigator's judgment until participants achieve CRoff.
2. Participants in CR who have not achieved CRmin will receive weekly efgartigimod PH20 SC administrations of 1000 mg while continuing the add-on therapy of oral prednisone until CRmin is achieved. Prednisone tapering may be pursued upon investigator's judgment until participants achieve CRoff. Participants will be treated through on-site visits, or through home visits with an on-site visit once every 4 weeks.
3. Participants who have achieved DC but not CR will receive weekly on-site administrations of 1000 mg efgartigimod PH20 SC with an add-on therapy of oral prednisone (Table 4) until CR has been achieved, and then will continue to receive weekly efgartigimod PH20 SC administrations of 1000 mg until CRmin is achieved either on site or through home visits with an on-site visit once every 4 weeks.
4. Participants under certain conditions of treatment failure as defined below or participants with flare after having achieved CRmin, may roll over prematurely into ARGX-113-1905 and will be treated with efgartigimod PH20 SC at a dose of [redacted] mg on [redacted] followed by weekly administrations of 1000 mg with an add-on therapy of oral prednisone until CRmin.

   The following types of treatment failure are considered here:

   - absence of DC with oral prednisone 1.5 mg/kg/day for a minimum of 3 weeks
   - participants who roll over due to prednisone-related SAE who have not achieved DC, or
   - flare between DC and achieving CRmin that is not controlled by 2 dose levels of OCS above the dose at which the flare is observed and that is at least 0.3 mg/kg/day (Table 4)

In the absence of DC, participants will receive prednisone at the starting dose of 1.5 mg/kg/day. In case of uncontrolled flare before CRmin, participants will receive, as starting dose, the last dose from ARGX-113-1904. In case of flare after CRmin, participants will receive a prednisone dose in line with the severity of the flare, with the recommendation of a minimum of 0.3 mg/kg/day when the flare is of mild severity (PDAI activity score <15) and of 0.5 mg/kg/day when the flare is moderate to severe (PDAI activity score ≥15). Dosing of efgartigimod PH20 SC will be done during on-site visits or home visits according to Table 2.

5. Participants who developed a prednisone-related SAE may prematurely roll over into ARGX-113-1905 and may be treated with efgartigimod PH20 SC through on-site or home visits according to the clinical statuses as described above. Concomitant prednisone will be considered to fit the clinical statuses as described above as far as compatible with the nature and severity of the SAE, with a lower dose to no concomitant prednisone being considered otherwise.

Participants or their caregivers (a person of legal age that the participant proposes to perform the administrations) may self-administer efgartigimod PH20 SC after they have successfully completed self-administration training (in ARGX-113-1904 with at least 1 refresher training in OLE trial ARGX-113-1905, or during ARGX-113-1905). All participants and/or their caregivers will receive a home guide for transport, storage, preparation, and administration of the IMP.

At any postbaseline visit before DC is achieved, the prednisone dose will be adjusted by incrementing dosage according to clinical judgment, with the recommendation to increase by 1 or more steps (Table 4) in case of disease progression or insufficient clinical change. To facilitate common judgments among investigators, recommendations for assessment of disease progression and insufficient clinical change are:

- Disease progression: increase of at least 5 in PDAI activity score compared to baseline score, observed at any postbaseline visit before DC
- Insufficient clinical change: the absence of DC after 3 to 4 weeks of the participant being treated at the starting baseline prednisone dose or after 3 to 4 weeks of any new incremented dose of prednisone

The recommendations of the prednisone dose escalation are:

- Stepwise escalation of daily prednisone dose by 1 or more steps according to clinical judgment in case of disease progression
- Adjustment by incrementing dosage by 1 step in case of insufficient clinical change
- Possible further escalation from the previous step by 1 or more steps, according to clinical judgment and under the same recommendation as above
- Maximum escalation to 1.5 mg/kg qd for 3 weeks

If DC is not attained after a minimum of 3 weeks of the participant receiving oral prednisone 1.5 mg/kg qd, then the participant will be considered a treatment failure and will be withdrawn from the trial.

For participants who achieve DC at the starting dose of 0.5 mg/kg qd or lower, the prednisone dose will be maintained at that starting dose qd until CR and 2 weeks thereafter, or EoC and 4 weeks thereafter, after which tapering will be initiated. For participants achieving DC with an escalated prednisone dose (ie, >0.5 mg/kg qd), that dose will be maintained until 2 weeks after achieving DC and then will be tapered (Table 4) in increments of 0.25 mg/kg every 2 weeks until the starting dose is achieved. This starting dose will be maintained until a sustained CR is achieved for 2 weeks, after which further tapering will be initiated, or prednisone tapering below 0.5 mg/kg qd may be initiated in case of sustained EoC for 4 weeks. Further tapering will be performed thereafter, as long as CR or EoC are sustained. Each new tapered prednisone dose until 20 mg/day must be maintained for 2 weeks. Then, the prednisone dose is further tapered by 2.5 mg/day per week. When 10 mg/day is reached, this dose level will be maintained for at least 8 weeks until CRmin is achieved. The prednisone dose can then be further tapered to reach CRoff according to the clinical judgment of the investigator.

At visits when at least 1 new lesion is observed or established lesions remain extensive without being defined as a flare (ie, the appearance of 3 or more new lesions in a 4-week period that do not heal spontaneously within 1 week, or by the extension of established lesions in a participant who had achieved DC), the prednisone dose will be maintained or may be increased, according to clinical judgment. If the lesion resolves, tapering of the prednisone dose will be pursued as planned.

In case of flare in the period between DC and CRmin, the prednisone dose will be increased to achieve DC again. If the flare occurs after CR and IMP was administered at home by a nurse, the participant will resume weekly on-site visits until he/she achieves CR again. Participants who are not controlled by a dose of OCS that is 2 dose levels above the dose at which the flare is observed and that is at least 0.3 mg/kg/day (Table 4) will be managed according to clinical judgment ie, either receive a further increased prednisone dose or be withdrawn from the trial. Withdrawal of participants with a flare before CRmin will be defined as treatment failure.

In case of flare after having achieved CRmin (ie, while being off efgartigimod treatment), participants will be immediately treated/retreated with a new cycle of efgartigimod PH20 SC. The first day of new efgartigimod treatment will define a new baseline for assessments of outcomes (DC, CR, etc) and prednisone escalation or tapering schedule.

In the new treatment cycle, participants will be administered efgartigimod PH20 SC at a weekly dose of [redacted] mg for the first[redacted], followed by weekly SC administrations of 1000 mg until CRmin. Oral prednisone will be administered at a dose chosen according to clinical judgment, with the recommendation of 0.3 mg/kg qd in the case of mild flare (PDAI activity score <15) and 0.5 mg/kg qd in the case of moderate to severe flare (PDAI activity score ≥15). The treatment goal of a new treatment cycle is to first achieve DC again and therefore these participants will be treated accordingly (Table 2).

A new treatment cycle of efgartigimod PH20 SC can be initiated in eligible participants until week 44. In participants requiring a new treatment cycle of efgartigimod PH20 SC between weeks 45 and 49, the initiation will be optional and based on clinical judgment and participant consent. A new efgartigimod treatment cycle will not be permitted after week 49 to ensure a minimum of 4 weeks of efgartigimod treatment/cycle.

Except for oral prednisone, no other systemic therapies (eg, immunosuppressants, IVIg, immunoadsorption, anti-CD20 biologics) will be permitted during the trial.

Trial procedures will be performed per the SoA as detailed in Section 1.3 and Section 10.11.

4.2. Scientific Rationale for Trial Design

Pemphigus is a chronic disease and patients under treatment have intermittent episodes of clinical remission and flare. The mainstays of therapy in PV are systemic corticosteroids and rituximab. Corticosteroids rapidly affect PV symptoms (3–4 weeks), but must be administered at high daily doses (eg, oral prednisone 1–1.5 mg/kg) to attain effectiveness. At such high doses, the well-known cumulative toxicities common to corticosteroid treatment occur frequently, and using short courses at the lowest possible dosage by tapering gradually while keeping the disease in remission is the therapeutic goal. Recently, rituximab has been approved in adults with moderate to severe PV. When administered as adjunctive treatment to a short course of prednisone, rituximab, while having a relatively late onset of action, was shown to induce a higher rate of remission after 1 or 2 years, and a longer duration of remission than prednisone alone; however, administration of rituximab IV frequently results in IRRs and AEs, which may be of late onset.

An innovative drug is needed for the treatment of PV and PF that has a fast onset of action (eg, early DC, CR within weeks), a strong prednisone sparing effect, and a favorable safety profile.

Antecedent trial ARGX-113-1904 intends to demonstrate that efgartigimod PH20 SC with an add-on therapy of low doses of oral prednisone is a possible treatment modality for PV and PF which leads to early disease remission at minimal prednisone dose. The trial has a treatment phase of up to 30 weeks, and provides a tailored dose regimen for participants by stopping IMP administration upon achieving CRmin (defined as the absence of new lesions and complete healing of established lesions while the participant is receiving minimal prednisone therapy of ≤10 mg/day for at least 2 months [8 weeks]). *Note: when 10 mg/day is reached in ARGX-113-1904 or ARGX-113-1905, this dose level must be maintained for 8 weeks until CRmin has been achieved*.

Study ARGX-113-1905 provides efgartigimod PH20 SC extended and retreatment options for participants who were randomized to the efgartigimod PH20 SC treatment arm in ARGX-113-1904, and provides first treatment and retreatment options for participants who were randomized to the placebo treatment arm in study ARGX-113-1904.

At blinded rollover from ARGX-113-1904 into ARGX-113-1905 participants may be in different clinical stages. Participants may have achieved CRmin, participants may have achieved CR without meeting the minimal therapy criterion, participants may have achieved DC or EoC (the time at which no new lesions have developed for a minimum of 2 weeks and approximately 80% of lesions have healed) without having achieved CR, participants may have had treatment failure or a flare after having achieved CRmin.

ARGX-113-1905 evaluates the ability to (further) taper prednisone therapy and achieve CRoff, the ability to achieve CR and CRmin for participants who had not yet achieved CRmin, and the

ability to treat flare; and assesses patient outcome measures and the safety, PD, PK, and immunogenicity of efgartigimod PH20 SC over the duration of the trial. Duration of CR, time to CRoff and the effects of retreatment by the study drug will be specifically evaluated during the trial.

4.3. Justification for Dose

SC administration is highly preferred over an IV formulation for patients with pemphigus, given the expected need for weekly administration over prolonged durations. Therefore, efgartigimod with rHuPH20 will be administered SC weekly until CRmin; retreatment may be initiated in case of flare after having achieved CRmin. To achieve a fast PD effect and clinical response a dose of [redacted] mg will be administered in the first [redacted], followed by weekly doses of 1000 mg to maintain the PD effect and related clinical response.

Active pemphigus is seen by most clinicians as a disease that requires urgent control. Signs of activity include the extension of the lesions (eg, mucosal lesions becoming mucocutaneous in PV) and the sharp increase in anti-Dsg serum levels. In such circumstances, respiratory infections related to lesions of the mouth or throat as well as skin infections are frequent. Infections are today the first cause of mortality in pemphigus. The exposure to non-targeted immunosuppressive therapies such as high doses of corticosteroids and immunosuppressants is a co-morbidity factor.

ARGX-113-1701 showed that efgartigimod treatment resulted in a rapid DC with or without associated prednisone, as well as complete remission associated with low to intermediate prednisone doses (0.25 to 0.5 mg/kg per day).

In view of the severity of the disease a fast onset of action is desirable. Therefore, the proposed dose regimen for this trial starts with a dose that achieves close to maximal IgG reduction within 2 weeks with a goal of a reduction in time to a clinically relevant improvement. Subsequently, a lower weekly dose is expected to maintain improvement in this population.

As pathogenic IgGs are key to the pathophysiology of pemphigus, the selected doses and dose regimen target a nearly maximal PD effect (ie, reduction of pathogenic IgGs). Considering the chronic nature of pemphigus, where patients are typically treated chronically for years with corticosteroids or immunosuppressants, the dosing regimen of a weekly regimen reflects the need for chronic treatment to keep suppressing pathogenic IgGs.

Results from the phase 1 study in healthy participants, phase 2 studies of participants with MG, ITP, and pemphigus, and PK/PD modeling analysis indicate that a dose of 10 mg/kg efgartigimod, administered weekly (q7d) through IV infusion achieved close to maximal IgG reduction, resulted in a reduction of pathogenic autoantibodies, and was associated with clinical efficacy in in participants with MG, ITP, and pemphigus. Furthermore, this dose was considered safe and well-tolerated in all populations. The PK and PD profile of efgartigimod appeared to be similar in all investigated populations so far. Therefore, a flat SC dose resulting in a similar PD effect as achieved with 10 mg/kg weekly IV administration is targeted as a maintenance dose for patients with pemphigus.

PK and PD data from ARGX-113-1901 (which investigated different efgartigimod PH20 SC doses) were used for a population PK/PD analysis to find an efgartigimod PH20 SC dose that results in a similar PD effect compared to efgartigimod 10 mg/kg IV. Simulations were performed to include parameter uncertainty. Outcome measures investigating comparable effects on IgG levels as the 10 mg/kg IV dosed weekly, include area under the effect-time curve days 22 to 29, maximal IgG reduction between day 22 and 29, and trough IgG reduction at day 29.

To maximize the probability of clinical improvement, both the median values and the 90% confidence interval (CI) ranges of the PD outcome parameters were considered in the dose selection. A SC dose was selected for which the predicted median value on each of the 3 outcome parameters has at least reached the median value of the IV dosing, and for which the lower limits of the 90% CI are predicted to fall within the lower limits of the IgG reduction of 10 mg/kg IV dosing. A dose of 1000 mg efgartigimod PH20 SC meets all these requirements.

Based on these simulations, a weekly dose of 1000 mg efgartigimod PH20 SC is selected as the maintenance dose for this trial. The predicted IgG reduction with weekly 1000 mg efgartigimod PH20 SC doses is comparable to that of 10 mg/kg IV efgartigimod.

As pemphigus is a chronic disease, current therapies require chronic administration. In this trial, efgartigimod with rHuPH20 will be administered via the SC route in a flat dose in a new highly concentrated formulation, which may be more convenient for patients with pemphigus.

In order to allow for a convenient SC administration with efgartigimod to achieve the targeted exposure and PD effect, efgartigimod will be coformulated with rHuPH20. This compound is being used in co-formulations with approved therapeutic antibodies to facilitate SC injection with volumes larger than 2 mL. The use of rHuPH20 in combination with other therapeutic proteins typically increases the absorption rate of these proteins, albeit to different extents. Increased rate of absorption of efgartigimod by rHuPH20 is expected to increase the overall exposure to efgartigimod after SC administration allowing administration of a SC dose in an acceptable volume and duration of administration that targets an exposure that results in a close to the maximal PD effect.

A [redacted] mg efgartigimod to be administered as [redacted] SC injections coformulated with rHuPH20 has been selected for this trial. This dose is anticipated to achieve close to maximal IgG reduction within [redacted] as achieved by 1000 mg SC at steady state.

4.4. End of Study Definition

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

A participant is considered to have completed the study if he/she has completed all periods of the study including the EoT/ET visit and any follow-up visits (if applicable).

5. TRIAL POPULATION

Protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted. Participants who do not meet all the inclusion criteria or who have any of the exclusion criteria will not be eligible to receive any study medication.

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

5.1. Inclusion Criteria

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

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

2. The participant participated in ARGX-113-1904 and completed the study or has the defined criteria for rollover.

3A. Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical trials and:

   i. Male participants:

      – Male participants must agree to use an acceptable method of contraception (as described in Section 10.4.2.2) from signing the informed consent form (ICF) until the last dose of the study drug.

   ii. Female participants:

      – Women of childbearing potential (WOCBP as defined in Section 10.4.1) must:

         - have a negative urine pregnancy test at baseline before the IMP can be administered

         - agree to use a highly effective or acceptable contraception method (as described in Section 10.4.2.1), which should be maintained at minimum until after the last dose of IMP

5.2. Exclusion Criteria

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

1A. Pregnant and lactating women and those intending to become pregnant during the trial

2. Participants with clinical evidence of other significant serious disease or participants who recently underwent or have planned a major surgery during the period of the trial, or any other condition in the opinion of the investigator, that could confound the results of the trial or put the participant at undue risk

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

5.3. Lifestyle Considerations

No lifestyle restrictions are required.

5.4. Screen Failures

Not applicable in this long-term extension trial.

6. TRIAL INTERVENTION

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

6.1. Trial Intervention(s) Administered

A list of trial interventions is presented in Table 3. Fixed doses of SC IMP will be administered on body sites spared of any cutaneous pemphigus lesions, the abdomen being used as preferred site. If the abdomen is affected by lesions, optional sites (the thighs and the arms) may be chosen.

Refer to the Pharmacy Manual and preparation guide for further details. Additionally, participants may receive oral prednisone (or equivalent such as prednisolone) as concomitant therapy (refer to Section 6.5.1).

Table 3: Trial Interventions

Intervention	Efgartigimod PH20 SC	Prednisone (or equivalent)
Type	Biologic	Non-IMP
Dose formulation	Efgartigimod 165 mg/mL or 180 mg/mL + 2000 U/mL rHuPH20 solution for SC injection to be dosed at a fixed dose of 1000 mg per injection	Prednisone/prednisolone tablets for oral administration
Unit dose strength(s)	165 mg/mL or 180 mg/mL	Prednisone 1 mg, 5 mg, 10 mg, 20 mg, 50 mg Prednisolone 5 mg
Dosage level(s)	Weekly 1000 mg administrations until CRmin, for participants in DC or CR at rollover from ARGX-113-1904. [redacted] mg administered in separate sites on [redacted] followed by weekly 1000 mg administrations until CRmin, for participants under treatment failure in ARGX-113-1904, or participants starting a new treatment cycle.	Refer to Section 6.5.1
Route of administration	Abdominal SC injection(s); preferred site[a]	Oral administration
Use	Investigational drug	Non-IMP or concomitant therapy
IMP	IMP	Non-IMP
Sourcing	Provided by the sponsor to the trial site	Provided by the sponsor to the trial site, or sourced locally
Packaging and labeling	The IMP will be provided in glass vials. Each glass vial will be labeled as required per country requirement	Non-IMP will be provided in the commercial package and labeled as required per country requirement, or as magistral preparation upon prescription by the investigator

CR=complete clinical remission; CRmin=complete remission on minimal therapy; DC=disease control; IMP=investigational medicinal product; SC=subcutaneous

[a] IMP will be administered on body sites spared of any cutaneous pemphigus lesions, the abdomen being used as preferred site. If the abdomen is affected by lesions, optional sites (thighs or arms) may be chosen.

Efgartigimod PH20 SC will be provided in a vial at a concentration of 165 mg/mL or 180 mg/mL (new concentration) for efgartigimod and 2000 U/mL for rHuPH20. Each dose of efgartigimod PH20 SC will include 1000 mg efgartigimod. Note that there will be a transition period during which both formulations of efgartigimod PH20 SC (with efgartigimod at a concentration of 165 mg/mL or 180 mg/mL) will be used. After this transition period, all participants will receive the efgartigimod PH20 SC formulation with efgartigimod at the higher concentration of 180 mg/mL. The formulation with the higher concentration of efgartigimod (180 mg/mL) reduces the dosing volume for each SC injection.

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Preparation

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

Efgartigimod PH20 SC will be manufactured in accordance with Good Manufacturing Practice regulations. Refer to the Pharmacy Manual for information about IMP preparation, including the volume of efgartigimod PH20 SC to be administered. Instructions on preparation and administration of IMP will be included in the on-site guide and home guide.

6.2.2. Handling

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IMP received and any discrepancies are reported and resolved before use of efgartigimod PH20 SC.

Only participants enrolled in the trial may receive efgartigimod PH20 SC and only authorized and trained site staff may supply or administer efgartigimod PH20 SC. Participants or their caregivers may also self-administer efgartigimod PH20 SC after they have successfully completed self-administration training (in ARGX-113-1904 with at least 1 refresher training in trial ARGX-113-1905 or training during ARGX-113-1905). All participants and/or their caregivers will receive a home guide for transport, storage, preparation, and administration of the IMP.

6.2.3. Storage

Efgartigimod PH20 SC will be supplied to the pharmacy or substitute at the investigational site by and under the responsibility of the sponsor's designated IMP supply vendor, who will also provide the investigator with the certificate of analysis, certificate of conformity, and European Union qualified person release documents.

Efgartigimod PH20 SC must be stored refrigerated (2 °C to 8 °C or 35 °F to 46 °F) in its secondary packaging, should not be exposed to freezing temperatures, should not be shaken, and should be protected from direct sunlight during storage at the clinical site.

The investigator (or his/her designee) is responsible for the correct and safe storage of efgartigimod PH20 SC assigned to the clinical site, in a locked, secure storage facility with access limited to those individuals authorized to dispense efgartigimod PH20 SC and maintained within the appropriate temperature ranges.

Further guidance and information for the final disposition of unused efgartigimod PH20 SC are provided in the Pharmacy Manual.

For home administrations, the participant (or caregiver) is responsible for the correct storage of the IMP at home. Participants will receive a home guide for transport, storage, preparation, and administration.

6.2.4. Accountability

The investigator, institution, or the head of the medical institution (where applicable) is responsible for efgartigimod PH20 SC accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Detailed instructions on accountability of efgartigimod PH20 will be included in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

ARGX-113-1905 is open-label. No trial team members from the investigating staff, the sponsor (except the sponsor's clinical trial supplies team in ARGX-113-1904), and the sponsor's designated CRO (except the specialty laboratories responsible for PK, PD, and immunogenicity analysis), will have access to the information related to IMP treatment assigned in ARGX113-1904 until after database lock for ARGX-113-1904.

The blinding of PK, PD, and immunogenicity data for ARGX-113-1905 will be maintained until database lock of the main trial ARGX-113-1904.

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

6.4. Trial Intervention Compliance

The participants are dosed by qualified approved personnel. They will receive efgartigimod PH20 SC directly from the investigator or designee, under medical supervision. Participants or their caregivers will be invited to receive training in self-administration or caregiver-supported administration, respectively, and will be permitted to perform administration of the IMP after they have successfully completed training (in ARGX-113-1904 with at least 1 refresher training in trial ARGX-113-1905 or training during ARGX-113-1905). The date and time of each dose administered at the site will be recorded in the source documents and recorded in the electronic case report form (eCRF). In the case of home administration, the home nurse will record the date and time of each dose administered in the source documents for recording on the eCRF.

The investigator should promote treatment compliance by stating that compliance is necessary for the participant's safety and the validity of the trial. The prescribed dose, timing, and mode of administration cannot be changed. All dates, start and end time of efgartigimod PH20 SC administration, and any deviations from the intended regimen must be recorded on the eCRF.

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

Site personnel will be informed of medication errors to ensure accuracy going forward. The sponsor's designated CRO monitor's report will include details of any missed doses, medication errors (Section 6.4.3), treatment or scheduling errors, and the associated explanations. It will be evaluated if these medication errors will be reported as protocol deviations in the clinical database. All supplies and pharmacy documentation must be made available throughout the trial for the sponsor's designated CRO monitor to review.

6.4.1. Handling Missed Doses of the Investigational Medicinal Product

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

6.4.2. Protocol Deviations

The investigator should not implement any deviation from, or changes to the approved protocol without agreement of the sponsor, and before review and documented approval of an amendment from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) and regulatory authority per local regulation, except where necessary to eliminate an immediate hazard to trial participants, or when the change involves only logistical or administrative aspects of the trial (eg, change of telephone numbers, etc). The investigator (or designee) should document and explain any deviation from the approved protocol.

6.4.3. Treatment of Overdose

For this trial, a variation of more than 10% of the amount of efgartigimod 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 which was assigned to that participant per the protocol.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately
- Closely monitor the participant for any AE/SAE and laboratory abnormalities
- Document the quantity of the excess dose as well as the duration of the overdose on the eCRF

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

6.5. Concomitant Therapy

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

6.5.1. Concomitant Pemphigus Therapy

At baseline, participants will be treated according to their clinical status at EoS of ARGX-113-1904, as follows:

1. Participants who have achieved CRmin or CRoff and are currently not in flare will be observed every 4 weeks through on-site visits without efgartigimod PH20 SC treatment. In participants who have achieved CRmin (oral prednisone ≤10 mg per day for 2 months [8 weeks]), prednisone tapering may be pursued upon investigator's judgment until participants achieve CRoff.

2. Participants in CR who have not achieved CRmin will receive weekly efgartigimod PH20 SC administrations of 1000 mg while continuing the add-on therapy of oral prednisone until CRmin is achieved. Prednisone tapering may be pursued upon investigator's judgment until participants achieve CRoff. Participants will be treated through on-site visits, or through home visits with an on-site visit once every 4 weeks.

3. Participants who have achieved DC but not CR will receive weekly on-site administrations of 1000 mg efgartigimod PH20 SC with an add-on therapy of oral prednisone (Table 4) until CR has been achieved, and then will continue to receive weekly efgartigimod PH20 SC administrations of 1000 mg until CRmin is achieved either on site or through home visits with an on-site visit once every 4 weeks.

4. Participants under certain conditions of treatment failure as defined below or participants with flare after having achieved CRmin, may roll over prematurely into ARGX-113-1905 and will be treated with efgartigimod PH20 SC at a dose of [redacted] on [redacted] followed by weekly administrations of 1000 mg with an add-on therapy of oral prednisone until CRmin.

   The following types of treatment failure are considered here:

   - absence of DC with oral prednisone 1.5 mg/kg/day for a minimum of 3 weeks
   - participants who roll over due to prednisone-related SAE who have not achieved DC, or
   - flare between DC and achieving CRmin that is not controlled by 2 dose levels of OCS above the dose at which the flare is observed and that is at least 0.3 mg/kg/day (Table 4)

   In the absence of DC, participants will receive prednisone at the starting dose of 1.5 mg/kg/day. In case of uncontrolled flare before CRmin, participants will receive, as starting dose, the last dose from ARGX-113-1904. In case of flare after CRmin, participants will receive a prednisone dose in line with the severity of the flare, with the recommendation of a minimum of 0.3 mg/kg/day when the flare is of mild severity (PDAI activity score <15) and of 0.5 mg/kg/day when the flare is moderate to severe (PDAI activity score ≥15). Dosing of efgartigimod PH20 SC will be done during on-site visits or home visits according to Table 2.

5. Participants who developed a prednisone-related SAE may prematurely roll over into ARGX-113-1905 and may be treated with efgartigimod PH20 SC through on-site or home visits according to the clinical statuses as described above. Concomitant prednisone will be considered to fit the clinical statuses as described above if compatible with the nature and severity of the SAE, with a lower dose to no concomitant prednisone being considered otherwise.

Participants or their caregivers (a person of legal age that the participant proposes to perform the administrations) may also self-administer efgartigimod PH20 SC after they have successfully completed self-administration training (in ARGX-113-1904 with at least 1 refresher training in ARGX-113-1905 or during ARGX-113-1905). All participants and/or their caregivers will receive a home guide for transport, storage, preparation, and administration of the IMP.

At any postbaseline visit before DC is achieved, the prednisone dose will be adjusted by incrementing dosage according to clinical judgment, with the recommendation to increase by 1 or more steps (Table 4) in case of disease progression or insufficient clinical change. To facilitate common judgments among investigators, recommendations for assessment of disease progression and insufficient clinical change are:

- Disease progression: increase of at least 5 in PDAI activity score compared to baseline score, observed at any postbaseline visit before DC
- Insufficient clinical change: the absence of DC after 3 to 4 weeks of the participant being treated at the starting baseline prednisone dose or after 3 to 4 weeks of any new incremented dose of prednisone

The recommendations of the prednisone dose escalation are:

- Stepwise escalation of daily prednisone dose by 1 or more steps according to clinical judgment in case of disease progression
- Adjustment by incrementing dosage by 1 step according to clinical judgment in case of insufficient clinical change
- Possible further escalation from the previous step by 1 or more steps, according to clinical judgment and under the same recommendation as above
- Maximum escalation to 1.5 mg/kg qd for 3 weeks

If, after a minimum of 3 weeks of oral prednisone at 1.5 mg/kg qd, DC is not attained, then the participant will be considered a treatment failure, and be withdrawn from the trial.

For participants who achieve DC at a starting dose of 0.5 mg/kg qd or lower, the prednisone dose will be maintained at that starting dose qd until CR and 2 weeks thereafter, or EoC and 4 weeks thereafter, after which tapering will be initiated. For participants achieving DC with an escalated prednisone dose (ie, >0.5 mg/kg qd), that dose will be maintained until 2 weeks after achieving DC and then will be tapered in increments of 0.25 mg/kg (Table 4) every 2 weeks until the starting dose is achieved. Then the starting dose will be maintained until a sustained CR is achieved for 2 weeks after which further tapering will be initiated, or prednisone tapering below 0.5 mg/kg qd may be initiated in case of sustained EoC (defined as the time at which no new lesions have developed for a minimum of 2 weeks and approximately 80% of lesions have healed) for 4 weeks. Further tapering will be performed thereafter, as long as CR or EoC are

sustained. The rules for tapering are shown in Table 4. Each new tapered prednisone dose until 20 mg/day must be maintained for 2 weeks. Then, the prednisone dose is further tapered by 2.5 mg/day per week. When 10 mg/day is reached, this dose level will be maintained for at least 8 weeks until CRmin is achieved. The prednisone dose can then be further tapered to reach CRoff according to the clinical judgment of the investigator,.

At visits when at least 1 new lesion is observed or established lesions remain extensive without being defined as a flare (ie, the appearance of 3 or more new lesions in a 4-week period that do not heal spontaneously within 1 week, or by the extension of established lesions in a participant who had achieved DC), the prednisone dose will be maintained or may be increased, according to clinical judgment. If the lesion resolves, tapering of the prednisone dose will be pursued as planned.

In case of flare in the period between DC and CRmin, the prednisone dose will be increased to achieve DC again. If the flare occurs after CR and IMP was administered at home by a nurse, the participant will resume weekly on-site visits until he/she achieves CR again. Participants who are not controlled by a dose of OCS that is 2 dose levels above the dose at which the flare is observed and that is at least 0.3 mg/kg/day (Table 4), will be managed according to clinical judgment, ie, either receive a further increased prednisone dose or be withdrawn from the trial. Withdrawal of participants with a flare before CRmin will be defined as treatment failure.

In case of flare after having achieved CRmin and thus while being off efgartigimod treatment, participants will be immediately treated/retreated with a new cycle of efgartigimod PH20 SC. The first day of new efgartigimod treatment will define a new baseline for assessments of outcomes (DC, CR, etc) and prednisone escalation or tapering schedule.

In the new treatment cycle, participants will be administered efgartigimod PH20 SC at a dose of [redacted] for the firs[redacted] followed by weekly administrations of 1000 mg until CRmin. Oral prednisone will be administered at a dose chosen according to clinical judgment, with the recommendation of 0.3 mg/kg qd in the case of mild flare (PDAI activity score <15) and 0.5 mg/kg qd in the case of moderate to severe flare (PDAI activity score ≥15). The treatment goal of a new treatment cycle is to first achieve DC again and therefore these participants will be treated accordingly (Table 2).

Except for oral prednisone, no other systemic therapies (eg, immunosuppressants, IVIg, immunoadsorption, anti-CD20 biologics) will be permitted during the trial.

Additionally, the following treatments may be used during the trial:

- Skin-directed topical corticosteroids
- Skin-directed topical antibiotics, antiseptics and moisturizers
- Buccal and mucosa-directed corticosteroids, antiseptics and anesthetics
- Analgesics
- Usual treatments associated with intake of oral corticosteroids (eg, vitamin D, calcium, KCl, bisphosphonates) are intended to be used according to standard of care and current guidelines
- Non-live/non-attenuated vaccinations, and seasonal vaccinations (eg, influenza)

Table 4: Concomitant Prednisone Equivalent Doses (in mg) by Body Weight

Daily prednisone dose	Participant body weight (±2.5 kg)[a]										Tapering frequency
	50 kg (47.5-52.4)	**55 kg (52.5-57.4)**	**60 kg (57.5-62.4)**	**65 kg (62.5-67.4)**	**70 kg (67.5-72.4)**	**75 kg (72.5-77.4)**	**80 kg (77.5-82.4)**	**85 kg (82.5-87.4)**	**90 kg (87.5-92.4)**	**95 kg (92.5-97.4)**	**100 kg (97.5-102.5)**	
1.5 mg/kg	75 mg	80 mg	90 mg	95 mg	105 mg	110 mg	120 mg	125mg	135 mg	140 mg	150 mg	Tapering every 2 weeks
1.25 mg/kg	60 mg	70 mg	75 mg	80 mg	85 mg	95 mg	100 mg	105 mg	110 mg	120 mg	125 mg	
1 mg/kg	50 mg	55 mg	60 mg	65 mg	70 mg	75 mg	80 mg	85 mg	90 mg	95 mg	100 mg	
0.75 mg/kg	35 mg	40 mg	45 mg	50 mg	50 mg	55 mg	60 mg	65 mg	65 mg	70 mg	75 mg	
0.5 mg/kg	25 mg	25 mg	30 mg	30 mg	35 mg	35 mg	40 mg	40 mg	45 mg	45 mg	50 mg	
0.3 mg/kg or 20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	25 mg	25 mg	25 mg	30 mg	30 mg	
0.2 mg/kg or 20 mg	Skip	Skip	Skip	Skip	Skip	Skip	20 mg	20 mg	20 mg	20 mg	20 mg	
<20 mg/day												
17.5 mg/day	17.5 mg	17.5 mg	17.5 mg	17.5 mg	17.5 mg	17.5 mg	17.5 mg	17.5 mg	17.5 mg	17.5 mg	17.5 mg	Tapering every week
15 mg/day	15 mg	15 mg	15 mg	15 mg	15 mg	15 mg	15 mg	15 mg	15 mg	15 mg	15 mg	
12.5 mg/day	12.5 mg	12.5 mg	12.5 mg	12.5 mg	12.5 mg	12.5 mg	12.5 mg	12.5 mg	12.5 mg	12.5 mg	12.5 mg	
10 mg/day	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg	

[a] Body weight should be rounded to the nearest whole number. For body weights not covered by the table (ie, <47.5 kg and >102.5 kg), the prednisone equivalent doses can be based on the indicated daily prednisone dose per kg body weight. The proposed doses should be confirmed by the medical monitor.

6.5.2. Prohibited Medications and Therapy During the Trial

The following medications or treatments are not permitted during the trial:

- Any monoclonal antibody (including rituximab or another anti-CD20 biologic)
- Intravenous methylprednisolone and any other corticosteroid by the parenteral route
- Sulfasalazine
- Tetracyclines
- Nicotinamide at doses above the recommended dietary allowance (RDA)/dietary reference intake (DRI)
  - Nicotinamide doses at or below RDA/ DRI from oral supplements are allowed
- Plasmapheresis/plasma exchange
- Immunoadsorption
- IVIg
- Vaccination with live/attenuated vaccines (eg, measles, mumps, rubella, rotavirus, smallpox, chickenpox, yellow fever)
- Conventional immunosuppressants (eg, azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil) or dapsone
- Other investigational drug

6.6. Dose Modification

Not applicable

6.7. Intervention After the End of the Trial

After a participant has completed the trial or has withdrawn/discontinued early, the usual treatment will be administered, if required, according to the trial site's standard of care and generally accepted medical practice depending on the participant's individual needs.

7. DISCONTINUATION OF TRIAL INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Trial Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. Participants who discontinue the trial early, will complete all the assessments listed for the end of treatment visit as in the SoA (Section 1.3) and will be followed up for 8 weeks for ongoing safety and efficacy monitoring after the last dose of IMP.

7.2. Participant Discontinuation/Withdrawal From the Trial

A participant may withdraw from the trial at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

At the time of withdrawal from the trial, if possible, an early termination visit (equivalent to EoT visit) should be conducted, as shown in the SoA (Section 1.3). Refer to the SoA for data to be collected at the time of trial discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be offered to enter the 8-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 EoT visit and/or the follow-up period.

If the participant withdraws consent, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the trial, he or she may request destruction of any samples taken and not tested, and the investigator must notify the sponsor immediately and document this in the site trial records.

Reasons for early discontinuation from the trial include:

- It is in the participant's best interest – discussion with the medical monitor of the CRO and the sponsor's medical director is encouraged before discontinuation
- The participant experiences a severe AE or SAE, or a clinically significant change in a laboratory test, if the investigator deems discontinuation appropriate
- The participant becomes pregnant, which requires follow-up until delivery of the baby
- The participant has active PV or PF disease as judged by the investigator, notably despite prednisone escalation
- Physician decision
- If allergic angioedema or other serious hypersensitivity reactions such as anaphylaxis or anaphylactoid reactions occurs. Administration of IMP should be discontinued immediately, and appropriate therapy initiated

7.3. Lost to Follow-Up

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

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

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

Discontinuation of specific sites or of the trial as a whole are described in Section 10.1.

8. TRIAL ASSESSMENTS AND PROCEDURES

Trial procedures and their timing are summarized in the SoA (Section 1.3). Adherence to the trial requirements, including those specified in the SoA, is essential and required for trial conduct.

When a protocol-required procedure cannot be performed, the investigator will document the reason, and any corrective and preventive actions that were taken to ensure that the normal processes are adhered to in source documents. The trial team should be informed of these incidents in a timely manner. This will be considered a protocol deviation and will be recorded accordingly.

Treatment Period

Each participant should attend each trial visit on the designated days. There is a permissible visit window of ±2 days during the treatment period.

From signing of the informed consent form until the last trial-related activity, all AEs that occur and all concomitant medications that are taken and procedures performed, whether allowed or not, during the trial are to be recorded on the appropriate pages on the eCRF.

Immediate safety concerns should be discussed first with the CRO's medical monitor and then 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.

For participants who had treatment failure in ARGX-113-1904 or a flare after CRmin, a minimum of 6 on-site visits (rollover [V1] to W6 or start of retreatment +5 weeks) are required before switching to home administrations, even if CR is achieved earlier. Home visits are allowed once a participant achieves CR but not before week 7 or start of retreatment +6 weeks. The investigator should call the participant every 2 weeks until CRmin to confirm the participant is still in CR and determine the safety status, clinical status (eg, new lesions), and prednisone tapering schedule.

During the IMP treatment period, all assessments and procedures have to be performed before the start of the IMP administration, except for the continuous assessment of AEs (Section 8.4), and the recording of concomitant therapy and procedures (Section 8.3.5).

At all visits, the efficacy and QoL assessments should be performed first, before any other trial-specific procedure with the only exception of obtaining informed consent at baseline. The EQ-5D-5L and ABQOL should be performed before all other efficacy assessments (Section 8.2).

Unscheduled Visits

In case of suspected new lesions as reported by the participant, AEs, flare, or other safety reasons, participants should come to the clinic. This may require an unscheduled visit or can coincide with a planned observational or IMP administration-only visit. At this visit assessments need to be performed as follows:

- Assessments as specified in Table 5

  Note: In case of new lesions or flare, the assessments indicated with an "" in Table 5 should be performed only once at the visit where the new lesions or the flare are/is confirmed. The assessments with an "*" should not be repeated at subsequent visits (even if more new lesions develop at these subsequent visits or the flare is sustained) unless when the subsequent visits coincide with planned observational or IMP administration-only visits and the assessments are to be performed for those visits per the SoA (Section 1.3).*

- Assessments as specified for the planned observational or IMP-administration-only visit, if applicable

In case the participant was in CR when the new lesions/flare was observed: the planned weekly IMP-only or observational visits should be performed on site (home visits are not allowed) for disease assessment and PDAI until CR is reached again.

In case the participant was in CRmin or CRoff at the time of the new lesions: the participant should return for weekly on-site visits for disease assessment and PDAI until CR is reached again. This will require unscheduled visits or can coincide with planned observational visits. In case flare is confirmed, participants need to switch to the visit schedule outlined in Table 2 or if they entered ARG-113-1905 per Table 2, will be immediately retreated with a new cycle of efgartigimod PH20 SC. The first day of new efgartigimod treatment will define a new baseline for assessments of outcomes (DC, CR, etc) and prednisone escalation or tapering schedule.

Table 5: Assessments to be Performed During an Unscheduled Visit[a]

Assessment	Unscheduled visit – any reason other than new lesions or flare	Unscheduled visit – new lesions	Unscheduled visit – flare
Physical examination & vital signs	X	X*	X*
PDAI	X	X	X
Disease assessment	X	X	X
Urinalysis	X		
Urine pregnancy	X		
Blood sample for PK	Only if IMP is administered	Only if IMP is administered	Only if IMP is administered
Clinical chemistry & hematology	At the discretion of the investigator	At the discretion of the investigator	At the discretion of the investigator
Anti-Dsg-1 and anti-Dsg-3 antibodies			X*
Vaccination antibodies			X*
Total IgG (no IgG subtypes)	X		
IgG autoantibody subtypes and cytokines			X*
Photography (at selected sites)	Per the judgment of the investigator	Per the judgment of the investigator	Per the judgment of the investigator

Assessment	Unscheduled visit – any reason other than new lesions or flare	Unscheduled visit – new lesions	Unscheduled visit – flare
IMP administration	If the visit coincides with a planned IMP-administration only visit	If the visit coincides with a planned IMP-administration only visit	If the visit coincides with a planned IMP-administration only visit
Prednisone taper	X	X	X
AE monitoring	X	X	X
Concomitant therapies	X	X	X

[a] The unscheduled visit can coincide with a planned observational or IMP administration-only visit.

Treatment-Free Follow-Up Period

Participants who reach week 52 or discontinue early will enter the treatment-free follow-up period of 8 weeks. Week 60 follow-up visit will only be required for those participants who were still receiving efgartigimod for at least 1 visit between week 49 and week 52. For participants who ended treatment before week 49, week 56 will be the end of study visit. There is a permissible visit window of ±3 days during the follow-up period.

8.1. Demography

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

8.2. Efficacy Assessments

The efficacy of the IMP will be assessed at on-site and home visits by the investigator, assessing the following: PDAI, DC, EoC, CR, CRmin, CRoff, and flare. The investigator will record the daily prednisone dose since the last visit, and treatment failures at on-site visits. For home visits, the investigator should call the participant every 2 weeks until CRmin is achieved to confirm the participant is still in CR.

Additionally, the clinical activity of pemphigus will be assessed using the PDAI (Section 10.6), which has been developed by the International Pemphigus Committee.[13,14] It is an evaluation tool able to capture the extent of the disease on the skin and mucosa. It is a validated system, which was found to be reproducible, reliable in the inter-rater assessment, and correlates with the global physician impression of extent. It is more sensitive than another developed scale, called ABSIS, especially in the pemphigus population with mild-to-moderate intensity. The PDAI has a possible score ranging from 0 to 263. Participants of mild severity distribute between PDAI activity scores of 1 to 15, those with moderate severity range from 15 to 44, and participants with severe disease have a PDAI activity score of ≥45.

8.3. Safety Assessments

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

8.3.1. Physical Examinations

Physical examinations will be performed at the time points indicated in the SoA (Section 1.3).

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

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

At all trial visits, new clinically significant abnormal or worsened preexisting conditions will be reported as an AE.

8.3.2. Height and Weight

Weight will be measured and body mass index (BMI) will be calculated accordingly, at the rollover visit, at W26 (or the next on-site visit if W26 does not coincide with an on-site visit) and W52. Weight will be remeasured if there has been an obvious change in weight since the last measurement. For the assessment of weight, participants will be required to remove their shoes and wear light indoor 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 (Section 1.3) 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 rest.

It is recommended that the method used to measure body temperature (eg, orally, tympanic, rectal, axillary, skin, temporal) at screening is maintained throughout the trial for each participant.

At all trial visits, new clinically significant abnormal or worsened preexisting vital sign abnormalities will be reported as an AE.

8.3.4. Electrocardiography

ECGs will be performed at the time points indicated in the SoA (Section 1.3) and should be completed predose at visits when IMP is administered.

ECGs will be acquired according to instructions provided by a centralized ECG reading facility where the ECGs will be centrally assessed. At a minimum, interval data (PR, QT, QTcF [Fridericia corrected QT interval], and QRS intervals), ventricular rate, and overall interpretation will be recorded for each ECG. Data will be transferred electronically for inclusion in the database.

At all trial visits, new clinically significant abnormal or worsened preexisting ECG abnormalities will be reported as an AE.

8.3.5. Medical and Surgical History

Medical and surgical history will not be collected for this trial. All data regarding medical and surgical history for participants rolling into ARGX-113-1905 will come from the ARGX-113-1904 database.

8.3.6. Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, hematology, urinalysis, and serology (ie, viral testing) will be collected and analyzed at a central lab as indicated in the SoA (Section 1.3) and Section 10.2. The urine sample for the pregnancy test will be analyzed locally.

On days that IMP is administered, blood for laboratory assessments should be collected before dosing.

Additional safety samples may be collected if clinically indicated, at the discretion of the investigator.

The estimated total maximum blood volume needed for a participant during the trial (when completing the trial) is approximately 770 mL for the entire duration of the study (or up to 1056 mL for participants participating in the immunological profiling).

For all female participants of childbearing potential, a urine pregnancy test will be conducted and analyzed locally at the site at the visits specified in the SoA (Section 1.3).

Clinical laboratory tests will be reviewed for results of potential clinical significance at all time points throughout the trial. The investigator will evaluate any change in laboratory values. If the investigator determines a laboratory abnormality to be clinically significant, it will be considered as a laboratory AE, however, if the abnormal laboratory value is consistent with a current diagnosis, it may be documented accordingly without being reported as AE.

The details of sampling, handling, storage, and transportation of the samples will be described in the laboratory manual (refer to Section 10.5 for the addresses of the laboratories used for sample analyses).

All laboratory tests with values considered clinically significantly abnormal during participation in the trial should be recorded as an AE and 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 judged reasonable by the investigator, then the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.3.6.1. Vaccination Antibodies Testing

Serum samples collected at visits according to the SoA (Section 1.3) may be used to analyze vaccination antibodies and response to vaccines possibly given during the trial, if applicable. Data from testing of vaccination antibodies will not be part of the clinical database and will be described in a separate report.

8.3.6.2. Storage of Blood Samples in the Trial

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

In addition, blood samples may be used to validate methods to measure efgartigimod, antibodies, and biomarkers, as well as used for vaccination antibody testing and any other additional research interests.

8.3.7. Infections and Vaccinations

Patients with pemphigus are prone to developing infections, including those of the bronchi (bronchitis) and the lung (pneumonia), resulting from the mucosal pemphigus lesions of the upper respiratory tract, infections of the mouth and ear-nose-throat (ENT) system, superinfections of the skin, and infections of the genital and urinary tract. Concomitant and historical treatments by non-targeted therapies (corticosteroids, immunosuppressants) or targeted therapies (rituximab) are co-morbidity factors able to trigger or aggravate these infections.

In this trial, some measures able to mitigate the occurrence of infections are required, and other precautionary measures optimizing the prevention of infections are recommended.

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

- To initiate or renew administration of non-live, inactivated, polysaccharide or recombinant vaccines (eg, tetanus, hepatitis A, hepatitis B, shingles)

- To vaccinate participants who are especially prone to or with a history of respiratory infections against *Pneumococcus* or *Streptococcus pneumoniae*

- To vaccinate participants with seasonal vaccines (eg, influenza virus), especially those susceptible to enter the trial in the winter months

- To screen for possible infections (eg, respiratory, skin, mouth, eyes, nose and throat, genitals) and, if appropriate, initiate antibiotic treatment

- To provide participants suffering from recurrent episodes of herpes simplex or herpes zoster with antiviral treatment throughout the trial treatment

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 medical monitor of the CRO and, subsequently, the sponsor's medical monitor.

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. 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 rHuPH20 and administered SC. The most frequently reported injection site reaction AEs are injection site erythema, injection site pain, and injection site swelling. Most are nonserious and mild (CTCAE grade 1) and do not lead to disruption in IMP administration.

Any injection site reaction will be reported as an AE (Section 10.3.3). Certain types of local reactions could be photographed and shared with the sponsor for review and assessment.

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

8.3.9. Suicidal Ideation and Behavior Risk Monitoring

Not applicable.

8.3.10. Additional Safety Assessment

As an additional assessment of the impact of glucocorticoid morbidity, the Glucocorticoid Toxicity Index (GTI) will be used. It is a complementary scoring system to the overall report of AEs that are judged as 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.

The original version of the GTI (GTI 1.0) has been developed as a prospective tool to assess the impact of glucocorticoid morbidity.[20] Its optimal use is in prospective, randomized, controlled-clinical trials in which glucocorticoids are administered chronically, but the GTI has also been employed in real-world applications. In this trial, the GTI 2.0 will be used.[21] In this new version, the weights derived in the initial GTI validation study are used to generate 2 scores from the composite GTI (C-GTI), ie, the Cumulative Worsening Score (CWS) and the Aggregate Improvement Score (AIS). These scores and their rationales are briefly outlined below. For the sake of simplicity, we use the term "GTI" below to refer to the GTI 2.0 instrument that will be used in this trial.

The GTI is composed of 2 components:

- The C-GTI, which serves as a primary instrument intended to capture common glucocorticoid toxicities (ie, toxicities that are likely due to glucocorticoid exposure and sensitive to cumulative doses over the period of 6 months to 3 years), has 9 functional domains (specifically: BMI, glucose control, blood pressure, lipid metabolism, bone mineral density, muscle strength, skin toxicity, neuropsychiatric effects, and infection). Each of the domains contains 3 to 4 weighted items that correspond to varying degrees of glucocorticoid toxicity within their respective domain. Among the 9 GTI domains, bone mineral density is excluded if the GTI will be measured at intervals shorter than 1 year, because bone densitometry is not sufficiently reliable in measuring changes at shorter intervals. Therefore, in the context of the ARGX-113-1904 trial with a maximum duration of 30 weeks, the index is truncated by removing the "bone mineral density" domain. Development of the GTI beyond the original validation work has suggested 2 approaches to analysis. These approaches provide complementary information about the ability of an investigational agent to reduce GC toxicity and also optimize the granularity with which the GTI captures the GC toxicity. The CWS is designed to assess cumulative GC toxicity, regardless of whether the toxicity has lasting effects or is transient. New toxicities that occur are added, but toxicities that appear to resolve on follow-up are not removed. Thus, the CWS serves as a lasting record of GC toxicity observed, and can only increase or remain the same over time. In the case of the presence of some GC toxicity at baseline, the AIS can be used to establish that a new therapy is effective at diminishing any baseline GC toxicity over time. With the AIS, toxicities can be removed if improvement occurs, and added if worsening occurs. If toxicities present at baseline or occurring during the trial resolve over the course of follow-up, then that improvement is reflected in a negative score for that item during the interval. Both the CWS and the AIS are calculated for each interval, and then the interval scores are summed.

- The complementary GTI Specific List (GTI-SL) captures well-known glucocorticoid-related side effects. It is not weighted, and provides additional information in the domains most affected by glucocorticoid use during an individual's treatment course. It comprises 11 domains (including 9 shared in common with the C-GTI) and 23 items. In this study, the item "major decrease in bone mineral density" will be excluded as bone matter density will not be assessed, and 22 items will be used.

The GTI with its 2 components (C-GTI and GTI-SL) are located in Section 10.12.

8.4. Adverse Events and Serious Adverse Events

Definitions of AE and SAE are provided in Section 10.3 as well as guidelines for assessing causality and relationship to IMP.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following

up AEs that are serious, considered related to the trial intervention or trial procedures, or that caused the participant to discontinue IMP and/or the trial (refer to Section 7).

An unexpected AE is any adverse drug event, which is not listed in the reference safety information in the current IB or is not listed at the specificity or intensity that has been observed.

Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE.

Each AE is to be evaluated for duration, severity (using the Common Terminology Criteria for Adverse Events [CTCAE Version 5.0]), seriousness, and causal relationship to the IMP or trial procedures. The action taken with the investigational drug and the outcome of the event must also be recorded.

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

All AEs and SAEs will be collected from the signing of ICF until end of treatment or the last follow-up visit at the time points specified in the SoA (Section 1.3).

All SAEs and AESIs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3.3 and 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 AE or SAE after the conclusion of trial participation. However, if the investigator learns of any SAE, including a death due to any cause, at any time after a participant has been discharged from the trial, and the investigator considers the event to be reasonably related to the trial intervention, to corticosteroid (non-IMP) use, or to trial participation, then 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 provided in Section 10.3.3.

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

8.4.3. Reporting of AEs and SAEs

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

Any SAE, including death due to any cause, which occurs during this trial after signature of the ICF, whether or not related to the IMP, must be reported immediately (within 24 hours of the trial site's knowledge of the event). Further information on follow-up procedures is provided in Section 8.4.4 and Section 10.3.3.

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 as well as 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 trial visit are to be collected and reported in the safety database, and all efforts should be made to follow-up until resolution.

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

8.4.4. Follow-up of AEs and SAEs

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

Any AEs observed from signing the ICF to the last trial-related activity will be followed up until resolution, until the participant is lost to follow-up, or until the participant withdraws consent (as defined in Section 7). Resolution means that the participant has returned to a baseline state of health or the investigator does not expect any further improvement or worsening of the AE.

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

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

All pregnancies reported during the trial should be followed until pregnancy outcome (Section 10.4).

For SAEs, AESIs (Section 8.4.8), 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) in order to perform an independent medical assessment of the reported case.

Further information on follow-up procedures is provided in Section 10.3.3.

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 a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

The sponsor (or its designee) will be responsible for reporting Suspected Unexpected Serious Adverse Reactions (SUSARs) to the relevant regulatory authorities and IEC/IRB, per applicable regulatory requirements. The sponsor (or its designee) will also be 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 a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) who is pregnant (Section 10.4).

While pregnancy itself is not considered to be 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 as such.

The participant/pregnant female partner 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 the information will be forwarded to the sponsor.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.5. While the investigator is not obligated to actively seek this information in former study participants/pregnant female partner, the investigator may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.4.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as Reportable AEs or SAEs for the Trial

Not applicable.

8.4.8. Adverse Events of Special Interest

An AESI (serious or nonserious, related or not related) is an event of scientific and medical concern specific to the sponsor's product or program (eg, an underlying condition being investigated, a mechanism of action/potential immunosuppression). Further characterizing information will be collected on the eCRF. This event could be expected due to the natural progression of the underlying disease, disorder, or condition of the participant(s) and the participant's predisposing risk factor profile including concomitant medications.

Efgartigimod treatment induces reductions in IgG levels, and there is a potential risk for infections associated with low IgG levels. Moreover, due to the nature of underlying disease, Pemphigus patients are more prone to infections; therefore, infections are considered as AESI in this trial.

The characteristics of infections in the phase 2 trial ARGX-113-1701 with efgartigimod in pemphigus patients are summarized in Table 6. A total of 32 TEAEs related to infections were reported in 21 (61.8%) participants; among them, 7 events in 5 (14.7%) patients were assessed as probably or possibly related to efgartigimod, and the remaining 25 events were assessed as not or unlikely related to efgartigimod.

Table 6: ARGX-113-1701 Summary of Treatment-emergent Adverse Events in the Infections and Infestations System Organ Class by Preferred Term – Safety Analysis Set

	Efgartigimod (10 mg/kg IV) (N=19) **n (%) e**	Efgartigimod (25 mg/kg IV) (N=15) **n (%) e**	Overall (N=34) **n (%) e**
Participants with at least 1 TEAE	**16 (84.2) 60**	**13 (86.7) 61**	**29 (85.3) 121**
Infections and infestations	**11 (57.9) 15**	**10 (66.7) 17**	**21 (61.8) 32**
Nasopharyngitis	0	4 (26.7) 4	4 (11.8) 4
Urinary tract infection	1 (5.3) 2	2 (13.3) 2	3 (8.8) 4
Rhinitis	0	2 (13.3) 3	2 (5.9) 3
Bronchitis	2 (10.5) 2	0	2 (5.9) 2
Gastroenteritis	1 (5.3) 1	1 (6.7) 1	2 (5.9) 2
Impetigo	1 (5.3) 1	1 (6.7) 1	2 (5.9) 2
Pustule	1 (5.3) 2	0	1 (2.9) 2
Bacteriuria	1 (5.3) 1	0	1 (2.9) 1
Candida infection	0	1 (6.7) 1	1 (2.9) 1
Conjunctivitis	1 (5.3) 1	0	1 (2.9) 1
Folliculitis	0	1 (6.7) 1	1 (2.9) 1
Oral herpes	1 (5.3) 1	0	1 (2.9) 1

	Efgartigimod (10 mg/kg IV) (N=19) **n (%) e**	Efgartigimod (25 mg/kg IV) (N=15) **n (%) e**	Overall (N=34) **n (%) e**
Pneumonia	1 (5.3) 1	0	1 (2.9) 1
Pulpitis dental	0	1 (6.7) 1	1 (2.9) 1
Respiratory tract infection	1 (5.3) 1	0	1 (2.9) 1
Sialoadenitis	1 (5.3) 1	0	1 (2.9) 1
Skin infection	0	1 (6.7) 1	1 (2.9) 1
Tonsillitis	1 (5.3) 1	0	1 (2.9) 1
Tooth infection	0	1 (6.7) 1	1 (2.9) 1
Upper respiratory tract infection	0	1 (6.7) 1	1 (2.9) 1

Source: ARGX-113-1701 CSR Table 14.3.1.2
TEAE=treatment-emergent adverse events; IV=intravenous; N/n=number of participants; e=number of events
Notes: Percentages are based on the number of participants in the Safety Analysis Set. Adverse event terms are coded by system organ class and preferred term using MedDRA version 23.1

No causal factor related to the mechanism of action of efgartigimod (eg, severe hypogammaglobulinemia) could be identified. However, it is important to mention that the trial does not include a comparative arm (ie, placebo control) to better assess the relationship to the drug; thus, the contribution of a drug that reduces serum IgG levels cannot be excluded.

8.4.9. Infusion-Related Reactions

Per the current efgartigimod IB, IRRs are defined as AEs within the standardized Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQs) for hypersensitivity, anaphylactic reaction, and extravasation (excluding implant); all broad search applied; and all AEs that occurred within 48 hours of an infusion.

In the phase 2 trial ARGX-113-1701 in pemphigus, efgartigimod IV infusions have resulted in only 1 case of grade 1 urticaria, which was assessed as an IRR.

8.4.10. Injection Site Reactions

Efgartigimod comixed with rHuPH20 in single-dose SC administrations was well-tolerated in healthy participants with frequently reported mild injection site reactions, including erythema, pain, bruising, pruritus, burning, tenderness, edema, induration, irritation, paresthesia, numbness, and rash. Injection site reactions observed after SC administration in this study will be reported as an AE.

8.5. Pharmacokinetics

Blood samples for PK will be collected from each participant as presented in the SoA (Section 1.3). Sampling will be done predose on IMP administration visits (within 2 hours before IMP).

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

Concentrations of efgartigimod will be determined using a validated assay.

8.6. Pharmacodynamics

Blood samples for the determination of the PD markers (total IgG, IgG subtypes [IgG1, IgG2, IgG3, and IgG4]) and anti-Dsg-1 and anti-Dsg-3 autoantibodies will be collected as indicated in the SoA (Section 1.3). Sampling will be done predose on IMP administration visits (within 2 hours before IMP).

These PD markers will be determined using validated assays. IgG subtype analyses may be limited to a representative portion of study participants.

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

8.7. Immunogenicity Assessments

Blood samples to test for an immunogenic response against efgartigimod and rHuPH20 will be collected as indicated in the SoA (Section 1.3). Sampling will occur predose on IMP administration visits.

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 positive or negative. Second, screened positive samples will be evaluated in a confirmatory assay (tier 2) to assess the specificity of the immunogenicity response. The samples will be scored 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 (tier 3).

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

8.8. Exploratory Research

8.8.1. IgG Autoantibody Subtype and Specificity Study

Pemphigus is an autoimmune blistering disease caused by IgG autoantibodies against adhesion proteins. These autoantibodies are characteristically directed against Dsg-1 and Dsg-3, and predominantly of the IgG4 subtype.[15] Despite this, serum concentrations of anti-Dsg autoantibodies do not always correlate with the disease activity, the anti-Dsg-1/3 autoantibody profile does not always match the clinical phenotype of skin and mucosal involvement when taking into account the relative expression patterns of Dsg-1 and Dsg-3 in skin and mucosa, and there is evidence of synergy of anti-Dsg and non-Dsg antibodies in pemphigus. [5,15,16]

Efgartigimod, an FcRn inhibitor that gives a targeted reduction of IgG antibodies of all subtypes,[18] has been evaluated in the treatment of patients with MG,[11] ITP,[12] and pemphigus (ARGX-113-1701).

The objective of the IgG autoantibody subtype and specificity research in this trial is to link serological profiles (ie, beyond the overall IgG reactivity toward Dsg-1 and/or Dsg-3 whole extracellular domains) with clinical observations.

Blood samples for this exploratory research will be collected as indicated in the SoA (Section 1.3).

8.8.2. Immunological Profiling

Immunological profiling in the antecedent study ARGX-113-1904 aims to comprehensively evaluate the impact of efgartigimod on immune parameters to confirm the drug mode of action, illuminate previously unappreciated pathways and targets impacted by therapy, and define molecular and cellular biomarkers associated with treatment response. Analysis in ARGX1131905 is restricted to specific analysis of lymphocyte populations in selected sites and a limited number of participants for long-term follow-up. Additionally, all patients in CRmin or CRoff will be sampled for lymphocyte populations at on-site visits at W52 (±2 weeks) or EoT/ET and EoS.

Blood samples will be collected as indicated in the SoA (Section 1.3).

8.9. Imaging

For illustrative purposes, pictures of different anatomical regions may be taken at selected sites per judgment of the investigator. As a guidance, time points of baseline, DC, CR, and flare are indicated. Pictures may also be taken at intermediate time points.

Photography is generally accepted as routine practice for documenting dermatological conditions in medical practice. Photographs will be taken only at baseline for participants not in CR or with a flare 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.

8.10. Medical Resource Utilization and Health Economics

Refer to Section 8.11.

8.11. Quality of Life and Patient-Reported Outcomes

The participant will complete the patient-reported outcome instrument (EQ-5D-5L) and the QoL questionnaire (ABQOL) as indicated in the SoA (Section 1.3).

EQ-5D-5L: EQ-5D (5-level version) is a standardized measure of health status developed by the EuroQoL Group in order to provide a simple, generic measure of health for clinical and economic appraisal (Section 10.7). 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. The respondent is asked to indicate his/her health state by ticking (or placing a cross)

in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number expressing the level selected for that dimension. A unique health state is defined by combining 1 level from each of the 5 dimensions. A total of 3125 possible health states is defined in this way. Each state is referred to in terms of a 5-digit code. For example, state 11111 indicates no problems on any of the 5 dimensions, while state 12345 indicates no problems with mobility, slight problems with washing or dressing, moderate problems with doing usual activities, severe pain or discomfort and extreme anxiety or depression.

ABQOL: The ABQOL scale was developed and validated for ascertaining the impact of pemphigus and its therapies on the daily life of the patient (refer to Section 10.8).[19]

9. STATISTICAL CONSIDERATIONS

The statistical analyses will be performed by the sponsor's designated CRO using statistical analysis systems SAS® (SAS Institute, Cary, NC, US) version 9.4 or higher, and the software package R, if applicable. The standard operating procedures (SOPs) and work instructions of the sponsor's designated CRO will be used as the default methodology if not otherwise specified.

9.1. Statistical Methods

9.1.1. Statistical Methods and Plan

A detailed and comprehensive Statistical Analysis Plan (SAP) will be written and signed off before the interim and final analysis database lock. Minor changes to the statistical methods set out in this protocol do not require a protocol amendment, but will be documented (as changes from the protocol) in the SAP and in the trial report(s). The below paragraphs contain the main general features of the statistical analysis. More details will be provided as needed in the SAP. Although this is an open-label trial, the blinding of PK, PD, and immunogenicity data for ARGX-113-1905 will be maintained until after database lock of ARGX-113-1904. A summary of the plan is described below.

All comparisons of endpoints between prior treatment groups will be purely descriptive.

9.1.2. Safety (Primary Endpoints)

All clinical safety outcomes will be reported using descriptive statistics in the form of summary tables. Wherever it is suitable, respective graphical displays will be presented along with the summary tables. The main safety primary endpoints will be summaries from the following sections of each endpoint.

- Incidence and severity of:
  - TEAEs
  - AESIs
  - SAEs
- Vital signs and physical examination
- ECG
- Clinical laboratory test results (hematology, clinical chemistry, urinalysis)

9.1.3. Secondary Endpoints

All efficacy endpoints will be evaluated descriptively and presented as summary tables on following efficacy secondary endpoints. 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.

Efficacy Endpoints

- Proportion of participants with PV who achieve CRmin
- Proportion of participants with PV and PF who achieve CRmin
- Time to DC
- Time to CR
- Time to CRmin
- Time to CRoff
- Time to flare
- Rate of treatment failure
- Rate of flare
- Cumulative prednisone dose over the trial
- PDAI at each visit

Health-related Quality of Life

- ABQOL score
- EuroQol 5-Dimension 5-Level (EQ-5D-5L) Scale

Treatment Self-administration

- Percentage of participants who performed self-administration
- Percentage of caregivers who administered the injection to the participant
- Number of visits needed for the participant or caregiver to be competent to start administering efgartigimod PH20 SC
- Frequency of self- or caregiver-supported administration at home

Additionally, the health impact of glucocorticoid (GC) use in participants with PV or PF will be assessed using C-GTI and GTI-SL.

9.1.4. Pharmacodynamics, Pharmacokinetics, and Immunogenicity

Descriptive statistics will be provided for efgartigimod serum concentrations, PD levels (total IgG and subtypes), anti-Dsg1 and anti-Dsg3, and immunogenicity.

9.2. Statistical Hypotheses

Not applicable. There is no specific statistical hypothesis that will be tested in this open-label study.

9.3. Sample Size Determination

Not applicable for this OLE trial.

9.4. Populations for Analysis

The following populations are defined:

Population	Description
Safety set	All participants who received at least 1 dose, or part of a dose, of IMP
Rollover set	All participants who rolled over from the ARGX-113-1904 study

The safety set is used for safety analysis (except for the analysis of C-GTI and GTI-SL). In general, the rollover set is used for efficacy evaluation (according to the treatment the participant was randomized to in the ARGX-113-1904 study). All details on the specific analysis of an endpoint in a specific population will be provided in the SAP.

9.5. Statistical Analyses

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

9.5.1. General Considerations

The baseline value for study ARGX-113-1905 will be the value at the last visit in ARGX-113-1904.

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

9.5.2. Participant Disposition

Participant disposition will be summarized in a table. It will include the number of participants enrolled previously on placebo and efgartigimod in ARGX-113-1904, who received IMP treatment, completed the trial, as well as the number of early discontinuations from IMP treatment and trial, with reasons for discontinuation from IMP or trial. Summaries will be provided for the overall trial period and, where relevant, by previous treatment group.

9.5.3. Analysis Sets and Protocol Deviations

The number of participants for the analysis set will be presented as described in Section 9.4.

Major protocol deviations, by previous treatment group in ARGX-113-1904, will be summarized in a table and presented in a listing.

9.5.4. Demographic and Baseline Characteristics, and Concomitant Medication

Participant demographic and baseline characteristic data, including prior and concomitant therapies will be summarized using standard summary statistics (Section 9.1) and listed.

9.5.5. Primary Endpoint(s)

Exposures to IMP and prednisone will be summarized. The safety analysis will be analyzed overall but also by status at entry into ARGX-113-1905.

Summaries of TEAEs and other safety parameters will be provided by treatment group. Summary statistics will be presented for all other safety endpoints including vital signs, physical examinations, laboratory values and ECGs.

AEs will be classified using the latest version of the MedDRA classification system. AEs and AESIs will be listed corresponding to SOC and MedDRA PT. Multiple occurrences of a single PT in a participant 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. Clinically significant laboratory abnormalities will be summarized descriptively.

9.5.6. Secondary Endpoints

All secondary endpoints will be presented with descriptive summary statistics. All data collected will be listed, together with derived variables. Graphical displays will show efficacy variables over time.

Descriptive statistical methods will be used to analyze all secondary efficacy data. In addition, summaries for certain subgroups if defined will also be presented. For time to event endpoints, survival curves will be estimated using the Kaplan-Meier time to event method. Summary statistics and summary plots will be presented for all other endpoints including other endpoints including CWS and AIS (as components of C-GTI) and the complementary GTI-SL, QoL, PK, PD, immunogenicity, and self-administration. More details for the analysis of the endpoints will be described in the SAP.

Analyses will not only refer to the baseline of ARGX-113-1905, but the baseline of ARGX1131904 will be used for specific analysis as stated in the SAP for this OLE trial.

More detailed descriptions will be presented in the SAP of the study.

9.5.7. Other Endpoints

Results from the exploratory research will not be part of the clinical database and will be described in a separate report.

9.5.8. Missing Data Handling

Details on handling missing data will be provided in the SAP.

9.6. Interim Analyses

Interim analyses may be performed in support of potential regulatory authority interactions.

9.7. Data Safety Monitoring Board

Refer to Section 10.1.5.

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 of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, 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 trial is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial 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 (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

The sponsor will fund the study as outlined in the clinical study agreement.

The sponsor will obtain adequate global/local insurance for the study participants including the study participants for the required duration of time.

The sponsor maintains an insurance coverage for this study in accordance with the laws and regulations of the countries in which the study is performed. Liability and insurance provisions for this study are specified in the investigator's contract. The terms and conditions will apply as specified in the policy document.

10.1.3. Informed Consent Process

Before signing the ICF, the study 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.

Any participant who provides informed consent is being assigned a unique participant ID via the IRT system.

The investigator or his/her representative will explain the following to the participant and answer all questions regarding the trial: the nature of the 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.

Participants must be informed that their participation is voluntary, that they may withdraw from the study at any time, and that withdrawal of consent will not affect their subsequent medical treatment or relationship with the treating physician.

Participants will be required to sign a statement of informed consent, after receipt of detailed information on the study, that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

The ICF will be used to explain the potential risks and benefits of study participation to the participant in simple terms before the participant is screened.

A separate ICF will be issued in case of pregnancy of a female partner of a male participant.

The ICF contains a statement that the consent is freely given.

All participant information and ICFs must be available in the local and vernacular languages required at the site and include participant information sheets/brochures that outline the study procedures. All ICF(s) must be signed and dated by the participant.

Confirmation of a participant's informed consent must also be documented in the participant's medical record before any study-related procedure under this protocol, including screening tests and assessments. The authorized person obtaining the informed consent must also sign the ICF.

The investigator is responsible for ensuring that the informed consent is obtained from each participant and for obtaining the appropriate signatures and dates on the informed consent

document before the performance of any protocol procedures and before the administration of IMP.

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

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

10.1.4. Data Protection

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

The participant 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 personnel 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 will be taken only at baseline for participants not in CR or with a flare 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. Committees Structure

10.1.5.1. Data 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 DSMB may unblind the data collected during ARGX-113-1904, for the sake of the participant's safety in the study.

The objective of the DSMB will be to review all unblinded safety data (including the overall number of participants treated up to that point, rates, and participant-level details) and the evaluation of IgG. The planning and frequency of the meetings will be detailed in a DSMB charter. In addition, ad hoc meetings can be requested at any time during the 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, agreed with the DSMB members and the sponsor. The DSMB charter will also define and document the content of the safety summaries and general procedures (including communications).

10.1.6. Dissemination of Clinical Study Data

The sponsor or 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 level of protection. 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 designated CRO monitor at each monitoring visit. The investigator must submit an eCRF for each participant, regardless of duration of participation or administration of IMP. 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 printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered on the eCRF. Only if requested per local regulations, no source data verification will be performed on race and ethnicity.

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 (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, CROs).

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.7.1. Data Handling and Record Keeping

It is the investigator's responsibility to maintain essential study documents (records and documents pertaining to the conduct of this study and the distribution of IMP, including regulatory documents, eCRFs, signed participant ICFs, laboratory test results, IMP inventory records, source documents, relevant correspondence, AE reports, and all other supporting documentation) as required by the applicable national regulatory requirements. The study site 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 (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 BV.

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 (CRO or other vendor) on behalf of sponsor. In addition, inspections may be conducted by regulatory bodies at their discretion. Such audits/inspections can occur at any time during or after completion of the 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 designated CRO monitors of safety parameters and adherence to selection criteria
- Data management quality control checks
- Continuous data acquisition and cleaning
- Quality control check of the clinical 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 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 trial. Also, current medical records must be available.

Definition of what constitutes source data can be found in the source data agreement, defined per site and agreed upon between the CRO and the investigator.

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

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Monitoring

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

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

- Data are authentic, accurate, and complete
- Safety and rights of participants are being protected
- The 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 designated CRO monitor direct access to all relevant documents.

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

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

The source documentation agreement form describes the source data for the different data on the eCRF. This document should be completed and signed by the sponsor's designated CRO monitor and investigator, and should be filed in the investigator's 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 designated CRO monitor will conduct site closure activities with the investigator and site staff as appropriate, in accordance with applicable regulations, ICH GCP guidelines, and CRO/sponsor procedures.

10.1.10. Data Management

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

Case report forms are provided for each participant in electronic format (ie, eCRF). Data will be transcribed by the 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 CRO. Appropriate training and security measures will be completed by the investigator and all designated site staff before the study is 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 in 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 CRO will provide the details of the review process in a data management plan and a monitoring plan. Any change, including the issuing of queries, will be fully audit-trailed by the electronic data capture system, meaning the name of the person, time, and date stamp are captured, as well as the reason for change.

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

Adverse events, concomitant diseases, and 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 pemphigus therapy) will be classified according to active drug substance using the WHO drug dictionary (WHO DD). The generic name, the preferred name, and the WHO name will be assigned using the WHO DD thesaurus.

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

10.1.11. Study and Site Start and Closure

The study start date is the date 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.

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

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the 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 or at a site level by the IRB/IEC. The sponsor may close individual study sites prematurely for reasons such as poor protocol compliance or unsatisfactory recruitment of participants.

10.1.12. Investigator Obligations

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

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

The investigator is responsible for ensuring that all study site personnel, including subinvestigators, adhere to all applicable regulations and guidelines, including local laws and

regulations, regarding the study, both during and after study completion. The investigator is responsible for informing the IRB/IEC of the 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 which has been approved/given favorable opinion by the IRB/IEC, according to ICH GCP and applicable regulatory requirements. The investigator is ultimately responsible for the conduct of all aspects of the 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 as well as in 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 investigator will sign the protocol signature page and send a copy of the signed page to the sponsor or representative. By signing the protocol, the investigator confirms in writing that he/she has read, understands, and will strictly adhere to the 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 the investigator has not signed the protocol.

10.1.14. Publication Policy

All information regarding efgartigimod supplied by the sponsor to the investigator and all data generated as a result of this 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.

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. 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: Laboratory Tests

Table 7: Protocol-Required Laboratory Assessments

Hematology	Hemoglobin, hematocrit, mean corpuscular volume (MCV), red blood cell (RBC) count, platelet count, white blood cell (WBC) count with differential
Clinical chemistry	Sodium, potassium, calcium, HbA1c, creatinine, creatinine clearance, blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, gamma-glutamyl transferase (GGT), low-density lipoprotein cholesterol (LDL-C), C-reactive protein (CRP), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), uric acid, total protein, and albumin
Urinalysis	Specific gravity, pH, protein, glucose, ketones, blood, bilirubin, urobilinogen, nitrite, leukocyte esterase, and microscopic examination (if blood or protein is abnormal)
Pharmacokinetics	Serum levels of efgartigimod
Pharmacodynamic markers	Serum levels of total IgG and IgG subtypes (IgG1, IgG2, IgG3, and IgG4) and anti-Dsg-1 and anti-Dsg-3 autoantibodies
Immunogenicity	Serum levels of antidrug antibodies (ADA) to efgartigimod. Plasma levels of antibodies produced against recombinant human hyaluronidase (rHuPH20) to be tested in case of safety concerns.
Local evaluations	Urine pregnancy test

10.3. Appendix 3: Adverse Events: 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 study intervention, whether or not considered related to the study intervention. • Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definitions of Unsolicited and Solicited AEs
• An unsolicited adverse event is an adverse event that was not solicited using a Participant Diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs. • Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, or emergency room visit, or visit to/by a health care provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant's concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records. • Unsolicited AEs that are not medically attended nor perceived as a concern by participants will be collected during interview with the participants and by review of available medical records at the next visit. • Solicited AEs are predefined local at the injection site and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.

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 signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention 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 study intervention 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.

Events to Be Collected as AEs
• "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT to Be Collected as AEs
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • 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:
1. Results in death
2. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event will be considered as serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not collected as an AE.
4. 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 experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma

An SAE is defined as any untoward medical occurrence that, at any dose:
(eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
5. Is a congenital anomaly/birth defect
6. Other situations: Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

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 make an assessment of intensity for each AE and SAE reported during the study. All AEs observed will be graded using the National Cancer Institute (NCI) CTCAE version 5.0. The NCI CTCAE is a descriptive terminology, which can be utilized for AE reporting. A grading (severity) scale is provided for each AE term. 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. The CTCAE displays grades 1 through 5 with unique clinical descriptions of severity for each AE based on 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.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

Note: a semicolon indicates "or" within the description of the grades.

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

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

Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE, under 1 of the following categories.

- Not related: Events can be classified as "not related" if there is not a reasonable possibility that the IMP caused the AE.
- Unlikely related: An "unlikely" relationship suggests that only a remote connection exists between the IMP and the reported AE. Other conditions, including chronic illness, progression or expression of the disease state, or reaction to concomitant medication, appear to explain the reported AE.
- Possibly related: A "possible" relationship suggests that the association of the AE with the IMP is unknown; however, the AE is not reasonably supported by other conditions.
- Probably related: A "probable" relationship suggests that a reasonable temporal sequence of the AE with drug administration exists and, in the Investigator's clinical judgment, it is likely that a causal relationship exists between the drug administration and the AE, and other conditions (concurrent illness, progression or expression of disease state, or concomitant medication reactions) do not appear to explain the AE.
- Related: A "related" relationship suggests that the AE follows a reasonable temporal sequence from administration of IMP, it follows a known or expected response pattern to the IMP, and it cannot reasonably be explained by known characteristics of participant's clinical state.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.

For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator

Assessment of Causality
always make an assessment of 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 1 of the criteria used when determining regulatory reporting requirements. For final reporting purposes, the relationship will be converted into "Binary Determination" per the CIOMS. Unrelated and Unlikely will be merged into "Unrelated" and Related, Possible and Probable will be merged into "Related."

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 post-mortem 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 will ensure all entered data are consistent. • An email alert for the SAE and AESI reports on the eCRF will automatically be sent to the sponsor's/designee's safety mailbox via the eDC system. • The paper SAE report form will be faxed or emailed to the sponsor/designee (see Safety Mailbox/Fax details on page 2 of this protocol).

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions

10.4.1.1. Woman of Childbearing Potential

A woman is considered to be of childbearing potential 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. A historical pretreatment FSH measurement of >40 IU/L is accepted as proof of a postmenopausal state for women on hormone replacement therapy.

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 a highly effective or acceptable contraception method, which should be maintained at minimum until after the last dose of IMP.

The same type of hormonal contraception must have been received for at least 1 month before starting the study.

Highly effective methods of contraception are:

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

- Vasectomized partner
- Sexual abstinence

Acceptable methods of contraception are:

- Progestogen-only hormonal contraception in which inhibition of ovulation is not the primary mode of action
  - Oral
  - Injectable
  - Implantable
- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide

10.4.2.2. Male Contraception

An acceptable method of contraception is a condom.

10.4.3. Collection of Pregnancy Information

10.4.3.1. Male Participants With Partners Who Become Pregnant

- Male participants will be instructed by the ICF to immediately inform the investigator if their partner becomes pregnant during the trial.
- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this trial.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy and submitted via email or fax (refer to the Safety Mailbox/Fax details on page 2 of this protocol).
- The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- An investigator, who is contacted by the male participant or his pregnant partner, may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the physician and/or obstetrician.

10.4.3.2. Female Participants Who Become Pregnant

- A urine pregnancy test will be conducted and analyzed locally at the visits detailed in the SoA (Section 1.3).
- The investigator will collect pregnancy information on any female participant who becomes pregnant during the period of administration of IMP. The initial information will be recorded on the appropriate form and submitted to the sponsor and/or sponsor's designee within 24 hours of learning of a participant's pregnancy. The following actions will be performed:
  - The participant should immediately be discontinued from IMP treatment.
  - The participant should have the early termination assessments and enter the follow-up period.
  - All assessments for early termination (refer to Section 1.3) must be performed unless contraindicated by pregnancy (harmful to fetus) or unless the participant withdraws informed consent.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such. Any posttrial pregnancy-related SAE considered reasonably related to the IMP by the investigator will be reported to the sponsor as described in Section 8.4.5. While the investigator is not obligated to actively seek this information in former trial participants, he or she may learn of an SAE through spontaneous reporting.
- The investigator must update the participant with information currently known about potential risks and available treatment alternatives.
- If required by local regulations, the female participant will be requested to sign a separate pregnancy ICF.
- Full details will be recorded on a paper pregnancy report form and submitted via email or fax (refer to the Safety Mailbox/Fax details on page 2 of this protocol), and reporting details will be specified in the trial manual. The investigator will update the pregnancy report form with additional information as soon as the outcome of the pregnancy is known.
- If the outcome of the pregnancy is an SAE, then this must be additionally reported as an SAE on the appropriate SAE report form.

10.5. Appendix 5: Administrative Structure

Central Laboratories
Cerba Research NV Industriepark Zwijnaarde 3 B-9052 Gent Belgium
Analysis of Pharmacokinetics (PK) and Antidrug Antibodies (ADA)
LGC Newmarket Road Fordham Cambridgeshire CB7 5WW United Kingdom
Antibodies and Neutralizing Antibodies Against rHuPH20
Labcorp Bioanalytical Services LLC 8211 Scicor Drive, Suite B Indianapolis, IN 46214 US
Total IgG and IgG Subtypes
Pharmaceutical Product Development (PPD) Central Lab 2 Tesseneer Drive Highland Heights, KY 41076 US
Long-Term Storage of Pharmacokinetics-Pharmacodynamics (PK-PD) and Immunogenicity
Azenta Life Science Im Leuschnerpark 1b 64347 Griesheim Germany
Central ECG Reading
Clario 1818 Market Street, Suite 2600 Philadelphia, PA 19103 US
Trial Monitoring/Medical Monitoring
PPD Global Ltd. 11 Granta Park, Great Abington Cambridge, CB21 6GQ United Kingdom Phone: +44 1223 374100
Data Management and Biostatistics, and Coordination of Data Safety Monitoring Board
SGS Life Sciences (SGS LS), a division of SGS Belgium NV Generaal de Wittelaan 19A b5 B-2800 Mechelen Belgium
Urinalysis – India only
IQVIA RDS (India) Private Limited 301-A-2, Leela Business Park M.V. Road, Andheri (East) Mumbai 400059 India

10.6. Appendix 6: Pemphigus Disease Area Index (PDAI) Scoring System

Pemphigus Disease Area Index (PDAI)

Skin

Activity		Damage
Anatomical Location	Erosion/Blisters or new erythema	Post-inflammatory hyperpigmentation or erythema from resolving lesion
	0 absent **1** 1-3 lesions, up to one >2 cm in any diameter, none > 6 cm **2** 2-3 lesions, at least two > 2 cm diameter, none > 6cm **3** >3 lesions, none > 6 cm diameter **5** >3 lesions, and/or at least one >6 cm **10** >3 lesions, and/or at least one lesion >16 cm diameter or entire area — Number lesions if ≤ 3	**0** absent **1** present
Ears		
Nose		
Rest of the face		
Neck		
Chest		
Abdomen		
Back, buttocks		
Arms		
Hands		
Legs		
Feet		
Genitals		
Total skin	**/120**	**/12**

Scalp

Scalp	Erosion/Blisters or new erythema	Post-inflammatory hyperpigmentation or erythema from resolving lesion
	0 absent **1** in one quadrant **2** two quadrants **3** three quadrants **4** affects whole skull **10** at least one lesion > 6 cm	**0** absent **1** present
Total Scalp (0-10)	**/10**	**/1**

Mucous membrane

Anatomical Location	Erosion/Blisters	
	0 absent **1** 1 lesion **2** 2--3 lesions **5** >3 lesions or 2 lesions >2 cm **10** entire area	Number lesions if ≤ 3
Eyes		
Nose		
Buccal mucosa		
Hard palate		
Soft palate		
Upper gingiva		
Lower gingiva		
Tongue		
Floor of mouth		
Labial bucosa		
Posterior pharynx		
Anogenital		
Total Mucosa	**/120**	

Total Activity Score: ☐ **Total Damage Score** ☐

10.7. Appendix 7: EQ-5D-5L Scale

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

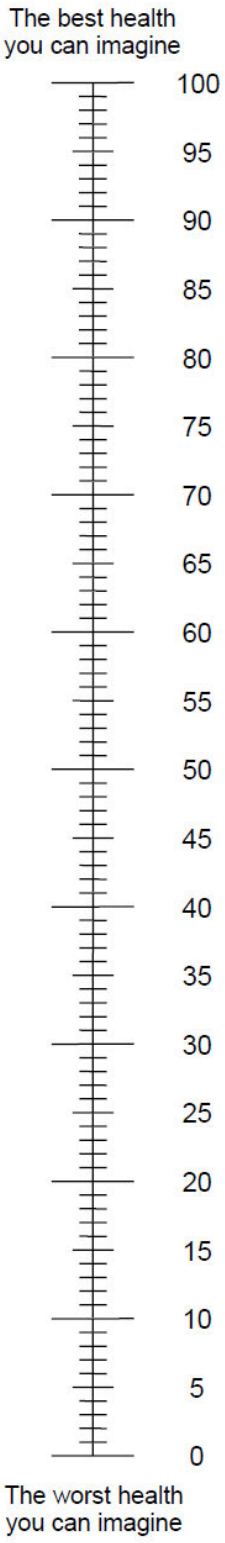
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



10.8. Appendix 8: Autoimmune Bullous Disease Quality of Life (ABQOL) Questionnaire

The following questions ask about the ways in which *blistering disease* affects your quality of life.

Please choose an option from the right hand column which most closely correlates to how you felt *within the last week*.

Please indicate the time started the survey: _____ AM/PM

1. In regards to your blistering disease, does your skin burn, sting or hurt in any way?	○ All the time ○ Sometimes ○ Occasionally ○ Never
2. In regards to your blistering disease, does your skin itch?	○ All the time ○ Sometimes ○ Occasionally ○ Never
3. Have you had to change your clothing because of your blistering disease?	○ I have to be very careful with how tight my clothing is and what materials they are made of – I have had to change what I wear all the time ○ I have had to change most of the things I wear ○ I have had to change some of the things I wear ○ I have never had to change what I wear
4. Do you notice your skin heals slowly?	○ I notice this all the time ○ I notice this sometimes ○ I notice this occasionally ○ I have never had this problem
5. Do you have difficulty bathing or showering because of your blistering disease?	○ All the time ○ Sometimes ○ Occasionally ○ Never

6. In regards to your blistering disease, does your mouth have erosions which are painful?	○ All the time ○ Sometimes ○ Occasionally ○ Never
7. In regards to your blistering disease, do your gums bleed easily?	○ All the time ○ Sometimes ○ Occasionally ○ Never
8. Does your blistering disease result in you having to avoid food or drinks that you enjoy?	○ I can no longer eat any of the foods I used to enjoy ○ I can eat some of the foods I enjoy ○ I can eat most of the foods I enjoy ○ I can eat anything I like
9. As a result of your blistering disease, are you embarrassed about your appearance?	○ All the time ○ Sometimes ○ Occasionally ○ Never
10. Do you feel depressed or angry because of your blistering disease?	○ All the time ○ Sometimes ○ Occasionally ○ Never
11. Do you feel anxious or cannot relax as a result of your blistering disease?	○ All the time ○ Sometimes ○ Occasionally ○ Never
12. Do you worry that friends and family find your blistering skin condition tiresome?	○ All the time ○ Sometimes ○ Occasionally ○ Never
13. Is your blistering disease causing sexual difficulties?	○ All the time ○ Sometimes ○ Occasionally ○ Never

14. Does your blistering disease affect relationships with friends or loved ones?	○ I have had to end a relationship because of my disease OR I cannot have a relationship because of my disease ○ Relationships are very difficult ○ Relationships are a little difficult ○ This has not affected my relationships
15. Does your blistering disease affect your social life?	○ I cannot go out to socialize any more ○ I can only go to some social events ○ I can go to most social events ○ My social life is not affected
16. Does your blistering disease affect your work or study?	○ Yes, I can no longer work or study ○ Yes, I find it difficult to work or study ○ Yes, it is a little harder than before to work or study ○ No, I am not affected **OR** this is not applicable
17. Do employers discriminate against you because of your blistering disease?	○ I cannot find a job due to my blistering disease ○ I have had to change jobs due to my blistering disease ○ I still have my job but it is more difficult than before ○ My employers are completely understanding **OR** this is not applicable

Please indicate the time finished the survey: _____ AM/PM

Thank you for taking the time to complete this questionnaire

10.9. Appendix 9: Definition of Terms

Complete clinical remission (CR):

The absence of new lesions and complete healing of established lesions (except for postinflammatory hyperpigmentation or erythema from resolving lesions).

Complete remission on minimal therapy (CRmin):

The absence of new and established lesions completely healed while the participant is receiving prednisone therapy at ≤10 mg/day for at least 2 months (8 weeks). *Note: when 10 mg/day is reached in ARGX-113-1904 or ARGX-113-1905, this dose level must be maintained for 8 weeks until CRmin has been achieved.*

Complete remission off therapy (CRoff):

The absence of new and established lesions completely healed while the participant is receiving no prednisone therapy for at least 2 months (8 weeks).

Council for International Organizations of Medical Sciences:

The CIOMS is an international, non-governmental, non-profit organization established jointly by the WHO and United Nations Educational, Scientific and Cultural Organization in 1949. They provide a set of ethical principles regarding human experimentations, including International Reporting of adverse drug reactions (ADRs) and International Reporting of Periodic Drug Safety Update Summaries.

The CIOMS form provides a standardized format for the reporting of suspected adverse reactions to any particular medicinal product and is the accepted and widely used format for reporting suspected ADR/suspected unexpected serious adverse reaction in clinical trials.

Contract research organization:

A person, or a group of persons (commercial, academic, or other), who, as an independent contractor with argenx BV, assume(s) 1 or more obligations of argenx BV, eg, development of a protocol, selection and/or monitoring of investigators, evaluation of reports, preparation of materials to be submitted to regulatory authorities.

Database lock:

An action taken to prevent further changes to a trial database. A database is locked after review, query resolution, data cleaning and determination that the database is ready for analysis.

Data Safety Monitoring Board (DSMB):

Independent group of experts that advises and whose responsibilities are to periodically review and evaluate the accumulated trial data for participant safety, trial conduct and progress and, when appropriate, efficacy, and to make recommendations to the sponsor concerning the continuation, modification or termination of the trial.

Disease control (DC):

The absence of new lesions and the start of healing of established lesions.

Disease progression:

Increase of ≥5 points in the PDAI activity score, observed at any postbaseline visit before DC.

Eligible:

Qualified for randomization into the trial based upon strict adherence to inclusion/exclusion criteria.

End of consolidation (EoC):

The time at which no new lesions have developed for a minimum of 2 weeks and approximately 80% of lesions have healed**.**

Flare:

Appearance of 3 or more new lesions in a 4-week period that do not heal spontaneously within 1 week, or the extension of established lesions, in a participant who had achieved DC.

Good Clinical Practice (GCP):

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial participants are protected (ICH E6 [R2]).

Institutional Review Board/Independent Ethics Committee (IRB/IEC):

An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and wellbeing of human participants involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving / providing favorable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial participants.

Informed consent/informed consent form:

A process by which a clinical investigation participant voluntarily confirms his or her willingness to participate in a particular clinical trial, after having been informed of all aspects of the trial that are relevant to the participant's decision to participate. Informed consent is documented by means of a dated and signed ICF.

Insufficient clinical change:

The absence of DC after 3 to 4 weeks of the participant being treated at the starting baseline dose or after 3 to 4 weeks of any new incremented dose of prednisone.

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH):

The ICH is a project that brings together the regulatory authorities of Europe, Japan, and the US, and experts from the pharmaceutical industry in the 3 regions to discuss scientific and technical aspects of pharmaceutical product registration.

Investigational medicinal product (IMP):

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Protocol amendment:

A written description of a change(s) to or formal clarification of a protocol.

Randomization:

Process of random attribution of treatment to participants in order to reduce bias of selection.

Transient and persistent lesions:

The appearance of new lesions that do not qualify as flare will be recorded as new transient or new persistent lesions. Transient new lesions are defined as the presence of new lesions that heal within 1 week. Persistent new lesions are defined as the presence of new lesions that last more than 1 week.

Treatment:

Term used throughout the clinical trial to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a trial participant.

Treatment failure:

The absence of DC with oral prednisone 1.5 mg/kg/day for a minimum of 3 weeks, or flare before CRmin resulting in withdrawal of the participant.

10.10. Appendix 10: Abbreviations

Abbreviation/Term	Expansion/Definition
ABQOL	Autoimmune Bullous Disease Quality of Life
ABSIS	Autoimmune Bullous Skin disorder Intensity Score
AChR-Ab	acetylcholine receptor–antibody
ADA	antidrug antibodies
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AIS	aggregate improvement score
ALT	alanine aminotransferase
ALP	alkaline phosphatase
BMI	body mass index
BSA	body surface area
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
C-GTI	Composite Glucocorticoid Toxicity Index
CI	confidence interval
CIDP	chronic inflammatory demyelinating polyneuropathy
CIOMS	Council for International Organizations of Medical Science
CPK	creatine phosphokinase
CR	complete clinical remission
CRmin	complete remission on minimal therapy
CRO	contract research organization
CRoff	complete remission off therapy
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
CWS	cumulative worsening score
DC	disease control
Dsg	desmoglein
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form

Abbreviation/Term	Expansion/Definition
ED	early discontinuation
ENT	ear-nose-throat
EoC	end of consolidation
EoS	end of study
EoT	end of treatment
EQ-5D-5L	EuroQol Five-Dimension Five-Level Scale
ET	early termination
EU	European Union
FcRn	neonatal crystallized fragment receptor
FSH	follicle-stimulating hormone
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GTI	Glucocorticoid Toxicity Index
GTI-SL	Glucocorticoid Toxicity Index Specific List
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	immunoglobulin gamma
IMP	investigational medicinal product
IND	investigational new drug
IRB	Institutional Review Board
IRR	infusion-related reaction
IRT	interactive response technology
ITP	immune thrombocytopenia
IV	intravenous
IVIg	IV immunoglobulin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MG	myasthenia gravis

Abbreviation/Term	Expansion/Definition
MG-ADL	Myasthenia Gravis Activities of Daily Living
NAb	neutralizing antibodies
OCS	oral corticosteroids
OLE	open-label extension
PD	pharmacodynamic
PDAI	Pemphigus Disease Area Index
PF	pemphigus foliaceus
PK	pharmacokinetics
PPD	Pharmaceutical Product Development
PPE	personal protective equipment
PT	preferred term
PV	pemphigus vulgaris
qd	daily
QoL	quality of life
QTcF	Fridericia corrected QT interval
rHuPH20	recombinant human hyaluronidase PH20
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SoA	schedule of activities
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
US	United States
WBC	white blood cell
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

10.11. Appendix 11: Possible Adaptations of Trial Protocol During COVID-19 Pandemic

Introduction

The aim of ARGX-113-1905 is to investigate a new subcutaneous (SC) treatment option for patients with pemphigus. This SC treatment consists of efgartigimod coformulated with recombinant human hyaluronidase PH20 (rHuPH20) (called efgartigimod PH20 SC) and could offer clinically significant benefits to those who have pemphigus.

argenx BV has performed a critical assessment of the use of efgartigimod during the COVID-19 pandemic. Based on the risk-benefit assessment, ARGX-113-1905 can be conducted; however, because of the pandemic, argenx BV acknowledges that considerable difficulties for participating centers to meet all previously planned assessments might occur (Section 1.3). Therefore, an appendix with possible adaptations to this trial has been developed. This appendix describes a minimum number of assessments required to guarantee the safety and wellbeing of the participants during the trial and to secure the collection of the critical parameters for analysis. It remains at the investigator's discretion to assess if it is in the best interest of the participant to participate/continue in the trial.

Note that a "home visit" as described in this appendix could also be a visit at an alternative convenient location.

Note that the home nurse, who will go to the participant in case of a home visit, could also be another qualified person to perform all tasks (eg, a physician). In addition, a home nurse can be qualified personnel from an alternative convenient location if the trial visit cannot be performed at the trial site.

During the COVID-19 pandemic, the 2 main goals of the study are to ensure the safety of the participant while simultaneously maintaining data collection.

<u>For participants with no suspected signs of COVID-19 or have tested negative</u>:

The administration of efgartigimod PH20 SC may continue, while the safety of the participants should be preserved. For participants who have no suspected signs of COVID-19 disease or are tested negative, there is no evidence that efgartigimod PH20 SC must be discontinued. In these participants, it is therefore recommended to make an individual benefit/risk assessment, which includes the participant's age, the co-morbidities (eg, obesity, respiratory and cardiovascular diseases, diabetes), the treatment history (eg, corticosteroids, immunosuppressants and rituximab) and the disease activity. The environmental conditions of containment for each participant are also to be considered. Based on this benefit/risk assessment, administration of efgartigimod PH20 SC may be pursued, postponed or discontinued.

<u>Data collection:</u>

It is important to continue collecting critical clinical trial data, for example, through telephone communication when trial site visits cannot be performed. The assessments deemed suitable for regular telephone consultation are questions on AEs, disease outcomes (DC, CR, flare) and compliance for prednisone intake and its dose. Prednisone dose must be adapted according to the study protocol.

POSSIBLE ADAPTATIONS TO ARGX-113-1905 TRIAL PROTOCOL DURING COVID-19 PANDEMIC

Implementation of this Appendix

- Implementation for all sites includes social distancing, personal protective equipment (PPE), and a telephone call before each trial visit for checking of COVID-19 symptoms.
- The adaptations to the visits and procedures described in this appendix that are acceptable alternatives to the main protocol procedures should only to be implemented in exceptional cases and after approval of the sponsor and/or CRO. Approval will be granted based on the possibility of the participant to go to the site and per local and/or hospital regulations.

The appendix is intended for countries and/or sites in geographical areas where COVID-19 has affected trial sites' workload, severe movement restrictions have been imposed, or when there is a risk to participants/trial staff if attending trial sites for trial visits. The initial duration of the implementation of this appendix will be agreed and can be extended based on the local epidemic status.

When a (home) visit is performed under this COVID-19 appendix, it should be documented as a COVID-19 (home) visit on the eCRF for the applicable visit.

Testing for COVID-19

Additional testing for COVID-19 beyond that mandated by relevant local authorities is not required at the start of the study. However, argenx BV recommends participants who develop symptoms of COVID-19 during the trial to be tested.

Protecting Home Nurse and Site Staff From COVID-19

The home nurse and site staff as well as qualified personnel from an alternative convenient location. Staff should apply appropriate social distancing and use personal protection equipment according to the local hospital and governmental regulations/recommendations; see also below.

Participants With COVID-19 (Either a Positive Test or With Symptoms [Suspicion of COVID-19 Infection])

Participants with a COVID-19 infection should not enter the trial. In case a participant develops a COVID-19 infection when he/she is in the trial, the following applies.

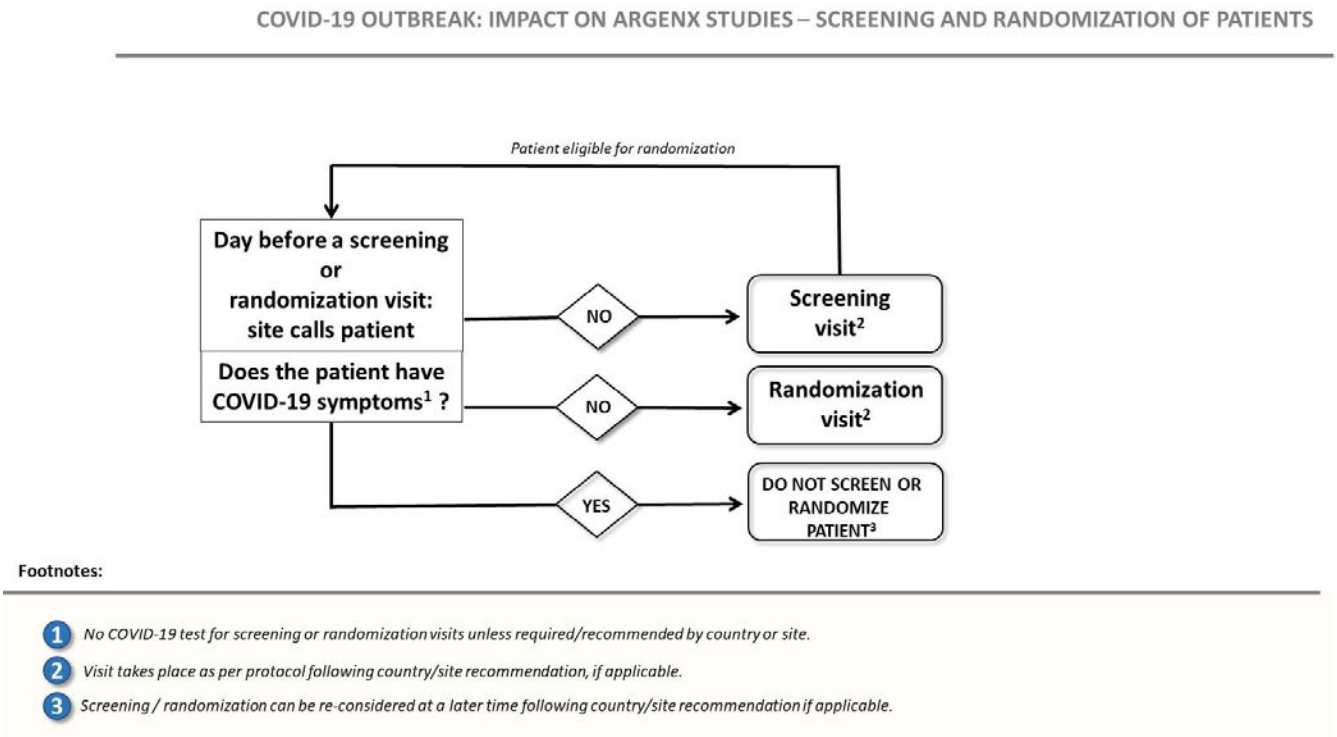
The instructions to manage an infection that are in the main protocol are also applicable in case of an infection with COVID-19 (ie, it will be considered an AESI similar to all infections). Treatment should be interrupted until the participant is considered recovered from COVID-19 (according to the local recommendations).

During the pandemic, the trial site staff should contact participants before each visit to inquire about COVID-19 symptoms and exposure using the flow charts below and make a decision on proceeding or postponing the visit according to the following flow charts.

The following symptoms should be specifically addressed during that phone call: fever, cough, sneezing, loss of taste/smell, difficulties breathing/chest tightness.

The impact of the COVID-19 pandemic on argenx BV clinical trials is outlined in Figure 2.

Figure 2: Impact of COVID-19 Pandemic on argenx BV Clinical Trials



Participants with symptoms of COVID-19 infection will be treated for this infection as guided by the local health care system. Participants will be monitored by the trial site by telephone contact.

In case the participant will have to be in self-isolation for a longer period than 2 weeks, it will be discussed on a case-by-case basis with the sponsor and/or with the CRO whether the participant can remain in the trial.

Once a participant has recovered, they can continue the trial and receive trial medication, provided that they have not received/are not receiving prohibited medication (Section 6.5.2).

Critical Parameters to Be Collected During the Trial

Please note that, if feasible, all assessments, including those that are not critical (ie, indicated as assessments that are not mandatory in the SoA in Section 1.3) should be performed.

The critical parameters which are mandatory to be collected during the trial, are summarized below:

Eligibility • ICF • Participation in ARGX-113-1904 • Other parameters to confirm eligibility (refer to Section 5.1 and Section 5.2)	**Efficacy** • Disease assessment (DC, EoC, CR, flare) • Monitoring of prednisone dosage
Safety • AEs • Safety labs	**IMP** • Administration • Accountability

During the COVID-19 pandemic, the collection of these critical parameters is specified in the Schedule of Activities (SoA) in Section 1.3 and Table 8 and Table 9.

- The evaluation of eligibility for the trial will be as described in the main protocol. The screening visit must be performed at the trial site (see below).
- For the evaluation of efficacy, safety, and for the IMP administration and accountability, certain modifications compared to the main protocol are allowed in this protocol compared to the main protocol (see below).

Mandatory Site Visits and Allowed Home Visits

In order to collect the critical parameters of the trial, certain visits have to be performed at the site and other visits can be at home*:

- Rollover Visit

The rollover visit has to be be performed at the study site. If it is not possible to go to the study site for these baseline visits due to the COVID-19 situation, the sponsor or CRO have to be contacted as soon as possible to discuss viable options.

- Start of retreatment in case of flare after CRmin (while being off efgartigimod therapy)

Confirmation of flare and start of retreatment has to be performed at the trial site. If it is not possible to go to the trial site due to the COVID-19 situation, retreatment should not be initiated.

- Other Trial Visits

During the COVID-19 pandemic, study visits after the rollover visit or start of retreatment will be done at home, including blood and urine collection. A home nurse will travel to the participant's home to conduct this visit (or the participant will go to an alternative convenient location). The investigator will talk to the participant via an audio or video interview to elicit AEs, concomitant medications, and their general wellbeing; the investigator will also perform efficacy assessments via the audio/video interview. The assessments via an audio or video interview will be conducted before the home nurse administers the trial medication. The division of tasks between the investigator and home nurse are indicated in the scheme below. 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, and IMP will be administered through self- or caregiver-supported administration, provided that the participant or caregiver has completed the training and has been deemed competent.

- Week 52/EoT/ET

The week 52/EoT/ET visit of the trial needs to be performed at the trial site. If it is not possible to go to the trial site for this visit due to the COVID-19 pandemic, the sponsor or CRO have to be contacted as soon as possible to discuss viable options.

*Note that a "home visit" as described in this appendix could also be a visit at an alternative convenient location.

Scheme for Home Visits[a]		
Critical assessments	**Performed by**	**Method of assessment**
• ICF (not initial ICF at screening, explained to participant) • Disease assessment (DC, CR, EoC, flare) • AEs • Concomitant medication (including prednisone dosage)	Investigator	Audio or video interview
• Vital signs • IMP administration • Blood sampling • Urine collection	Home nurse	In person at participant's home[a]

AEs=adverse events; CR=complete clinical remission; DC=disease control; EoC=end of consolidation; ICF=informed consent form; IMP=investigational medicinal product
[a] A "home visit" could also be a visit at an alternative convenient location.

Efficacy Assessments

- The critical efficacy assessments of the trial are:
  - Disease assessment (DC, CR, EoC, flare)
  - Monitoring of prednisone dosage

Safety Assessments

- Adverse event

During home visits, a telephone/video interview will be conducted by the treating physician or designee about possible AEs. Any suspected COVID-19 infection relevant signs or symptoms (including an abnormal laboratory findings) will be reported as an AE, with clear distinction whether it is a confirmed test positive COVID-19 infection or suspected infection if not tested.

- Vital signs

During home visits, vital signs (heart rate, body temperature, and blood pressure) will be measured by the home nurse at the beginning of the home visit and the results will be communicated to the treating physician. If pyrexia is detected, the home nurse should call the trial site immediately and await further instructions from the treating physician.

- Blood and urine sampling

During home visits, blood samples will be collected for clinical chemistry, hematology, anti-Dsg-1 and anti-Dsg-3 antibodies, PK, total IgG and IgG subtypes, and ADA every 4 weeks for participants in CR. For those who are not in CR at rollover or are starting retreatment, blood samples will be collected weekly until week 6 and then every 4 weeks until week 60. Additionally, urine samples will be collected for urinalysis using the same schedule, and urine pregnancy testing will be performed every 4 weeks.

- ECG

A local ECG machine from the site can be used in case equipment from the central ECG laboratory does not arrive at the site. A test transfer to the central ECG laboratory (eResearchTechnology [ERT]) with an anonymized test ECG is required. Requirement for the test ECG and test transfer are described in the user guide ("site upload tool quick guide") from ERT. Except for screening, an ECG is not considered as critical data at other visits and will not be done in case of a home visit.

Concomitant Medication

At the time of the home visit, the site treating physician will telephone/video interview the participant about concomitant medications, especially prednisone dosage. It will be documented whether concomitant medication is taken for a confirmed test positive COVID-19 infection or suspected infection (if not tested).

IMP Administration

IMP will be administered by authorized staff either at the site during scheduled visits or at home visits by a home nurse. In addition, participants or their caregivers may self-administer IMP after they have successfully completed self-administration training (in ARGX-113-1904 with at least 1 refresher training in ARGX-113-1905, or training during ARGX-113-1905).

Trial Endpoint

The criteria for the trial endpoint for a participant as described in the main protocol, also apply to this appendix.

Table 8: Modified Schedule of Activities During COVID-19 Pandemic for ARGX-113-1905 for Participants in CR, CR on Minimal Therapy, and CR off Therapy at Rollover From ARGX-113-1904

In the Schedule of Activities (SoA) tables for ARGX-113-1905 (see below), the mandatory assessments are indicated in red (**X**). The assessments that need to be performed only if feasible during the COVID-19 pandemic are indicated in black (X). At site visits, all assessments have to be performed (critical [**X**] and non-critical [X], if operationally feasible).

Trial period	**Open-label extension**														**UNS[b]**	**Follow-up**	
Visit number	**V1 Roll over[a]**	**V1 + 4 weeks**	**V1 + 8 weeks**	**V1 + 12 weeks**	**V1 + 16 weeks**	**V1 + 20 weeks**	**V1 +24 weeks**	**V1 + 28 weeks**	**V1 + 32 weeks**	**V1 + 36 weeks**	**V1 + 40 weeks**	**V1 + 44 weeks**	**V1 + 48 weeks**	**V1 +51weeks EoT/ET**		**Safety follow-up 1 EoT/ET + 4 weeks[c]**	**Safety follow-up 2 EoT/ET + 8 weeks EoS[c]**
Assessment/procedure	**±0 days**	**±2 days[d]**														**±3 days[d]**	**±3 days[d]**
Informed consent	X																
Inclusion/exclusion criteria	X																
Weight[e]	X						X[e]							X			
ECG[f,g]	X			X			X			X			X	X		X	X
Physical examination and vital signs[f,h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[f,i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X	X
Urine pregnancy test[f,j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X	X
Vaccination antibodies[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X	X
Blood sampling																	
• clinical chemistry and hematology[f,k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X	X

Trial period	**Open-label extension**														**UNS[b]**	**Follow-up**	
Visit number	**V1 Roll over[a]**	**V1 + 4 weeks**	**V1 + 8 weeks**	**V1 + 12 weeks**	**V1 + 16 weeks**	**V1 + 20 weeks**	**V1 +24 weeks**	**V1 + 28 weeks**	**V1 + 32 weeks**	**V1 + 36 weeks**	**V1 + 40 weeks**	**V1 + 44 weeks**	**V1 + 48 weeks**	**V1 +51weeks EoT/ET**		**Safety follow-up 1 EoT/ET + 4 weeks[c]**	**Safety follow-up 2 EoT/ET + 8 weeks EoS[c]**
Assessment/procedure	**±0 days**	**±2 days[d]**														**±3 days[d]**	**±3 days[d]**
• anti-Dsg-1 and anti-Dsg-3 antibodies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X	X
• PK[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b,m]	X	X
• Total IgG and IgG subtypes[f,l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X	X
• immunogenicity[f,n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
• IgG autoantibody subtypes and specificity[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[b]	X	X
PDAI[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ABQOL[f,o]	X	at CRmin (or the next on-site visit)												X			
EQ-5D-5L[f,o]	X	at CRmin (or the next on-site visit)												X			
Disease assessment[f,p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lymphocyte populations (at selected sites)[q]	X			X			X				X			X		X	X
GTI	X						X[r]							X[r]			
IMP self-administration training[s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Efgartigimod PH20 SC[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Trial period	**Open-label extension**														**UNS[b]**	**Follow-up**	
Visit number	**V1 Roll over[a]**	**V1 + 4 weeks**	**V1 + 8 weeks**	**V1 + 12 weeks**	**V1 + 16 weeks**	**V1 + 20 weeks**	**V1 +24 weeks**	**V1 + 28 weeks**	**V1 + 32 weeks**	**V1 + 36 weeks**	**V1 + 40 weeks**	**V1 + 44 weeks**	**V1 + 48 weeks**	**V1 +51weeks EoT/ET**		**Safety follow-up 1 EoT/ET + 4 weeks[c]**	**Safety follow-up 2 EoT/ET + 8 weeks EoS[c]**
Assessment/procedure	**±0 days**	**±2 days[d]**														**±3 days[d]**	**±3 days[d]**
Prednisone taper[u]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant therapies/procedures	Continuous monitoring																
AE monitoring	Continuous monitoring																

ABQOL=Autoimmune Bullous Disease Quality of Life; AE=adverse events; ALT=alanine aminotransferase; ALP=alkaline phosphatase; AST=aspartate aminotransferase; BMI=body mass index; BUN=blood urea nitrogen; CR=complete clinical remission; CRmin=CR on minimal therapy; CRP=C-reactive protein; DC=disease control; Dsg=desmoglein; ECG=electrocardiogram; EoC=end of consolidation; EoS=end of study; EoT=end of treatment; EQ-5D-5L=EuroQol 5-dimension 5-level scale; ET=early termination; GGT=gamma-glutamyl transferase; GTI=Glucocorticoid Toxicity Index; IgG=immunoglobulin type G; IMP=investigational medicinal product; LDH=lactate dehydrogenase; LDL-C=low-density lipoprotein cholesterol; MCV=mean corpuscular volume; NAb=neutralizing antibody; PDAI=Pemphigus Disease Area Index; PD=pharmacodynamic; PK=pharmacokinetics; QTcF=Fridericia corrected QT interval; rHuPH20=recombinant human hyaluronidase PH20; RBC=red blood cells; SC=subcutaneous(ly); UNS=unscheduled visit; W=week; WBC=white blood cells; V=visit at site

[a] For participants who roll over from ARGX-113-1904 to ARGX-113-1905, the baseline visit will occur for these participants at the same visit as the EoS/ED visit in study ARGX-113-1904. All assessments will be performed before IMP administration.

[b] In case of suspected new lesions as reported by the participants, AEs, flare, or other safety reasons, participants should come to the clinic. This may require an unscheduled visit. Depending on the reason for the visit, different assessments need to be performed. Refer to Section 8 for more information. Participants with new lesions or flare after achieving CR should return to weekly on-site visits. Participants with flare who had achieved CRmin or CRoff should switch to the visit schedule outlined in Table 9.

[c] Follow-up 1 will be the EoS visit for participants who ended treatment before W49 or 4 weeks before ET. Both follow-up visits will be required only for participants who continue to receive efgartigimod PH20 SC for at least 1 visit between W49 and W52 or during the last 4 weeks before ET.

[d] Study visit windows are ±2 days during the treatment period and ±3 days for the follow-up visits.

[e] Weight will be measured and BMI will be calculated accordingly, at the rollover visit, at W26 (or the next on-site visit if W26 does not coincide with an on-site visit) and W52. Weight will also be measured if there has been an obvious change since the last measurement.

[f] Assessment or procedure will be completed predose at visits when IMP is administered.

[g] The ECG will be recorded at baseline, every 3 months while receiving efgartigimod PH20 SC treatment, at CRmin (or the next on-site visit if CRmin is achieved during a week without an on-site visit), and at EoS. The ECG (heart rate, PR, QT, and QRS interval) will be read centrally, and QTcF and QTcB will be calculated. The ECG will be recorded only at baseline and EoS in participants not receiving efgartigimod. Additional ECGs may be performed at the discretion of the investigator during unscheduled visits.

[h] A complete physical examination will be performed at each on-site visit. Vital sign measurements include systolic and diastolic blood pressure, heart rate, and body temperature.

[i] Urinalysis will be performed by dipstick method and will include specific gravity, pH, protein, glucose, ketones, blood, bilirubin, urobilinogen, nitrite, leukocyte esterase, and microscopic examination (if blood or protein is abnormal).

[j] A urine pregnancy test will be performed locally and at least once every 4 weeks.

[k] Clinical blood laboratory tests will include hematology and blood chemistry at all visits. The hematology profile includes hemoglobin, hematocrit, MCV, RBC count, platelet count, and WBC count with differential. The blood chemistry profile includes sodium, potassium, calcium, HbA1c, creatinine, creatinine clearance, BUN, ALT, AST, total bilirubin, GGT, CRP, ALP, LDH, LDL-C, uric acid, total protein, and albumin.

[l] PK and PD (total IgG and IgG subtypes) samples will be taken every 4 weeks as long as the participant is receiving efgartigimod PH20 SC treatment (until CRmin or the next on-site visit) and 4 weeks after CRmin (or the next on-site visit; this also applies if the participant achieved CRmin in ARGX-113-1904) or EoT. Blood samples will be taken predose (within 2 hours before the start of IMP administration during visits when IMP is administered).

[m] At unscheduled visits, blood samples for PK will only be taken if IMP is administered.

[n] Blood samples will be taken to test for immunogenicity to efgartigimod in serum and rHuPH20 in plasma every 4 weeks while the participant is receiving efgartigimod PH20 SC treatment (until CRmin or the next on-site visit) and 4 and 8 weeks after CRmin (or the next 2 on-site visits; this also applies if the participant achieved CRmin in ARGX-113-1904) or EoT. NAb will be tested for all confirmed positive immunogenicity samples.

[o] Questionnaires are to be completed before any other assessment.

[p] Disease assessment parameters include DC, EoC, CR, CRmin, CRoff, flare, and treatment failure. Participants who have achieved CR and have new lesions should come to the clinic for an unscheduled visit for disease assessment.

[q] Samples for lymphocyte populations will be taken at selected sites only: optionally at on-site visits at W13 (±2 weeks), W26 (±2 weeks), W39 (±2 weeks), W52 (±2 weeks) or EoT/ET and EoS, and mandatory at on-site visits at W52 (±2 weeks) or EoT/ET and EoS for participants in CRmin or CRoff.

[r] The GTI assessment will be performed at visit 1, W26 (or the next on-site visit), and W52.

[s] Participants and/or their caregivers will be invited to receive at least 1 refresher training for self-administration, or caregiver-supported administration of IMP. Training will continue until deemed successfully completed by authorized staff.

[t] Efgartigimod PH20 SC will be administered weekly at a dose of 1000 mg until CRmin. For IMP administrations between the scheduled site visits, the participant can choose between self-administration (if training successfully completed), home nurse visits, or return to the trial site for the SC injection only. Participants who have achieved CRmin or CRoff and are currently not in flare will be observed every 4 weeks without any further IMP administration until flare or EoS. Only for on-site visits and home nurse visits, participants should be followed up for safety monitoring for at least 1 hour after the first IMP administration, or followed by 15 minutes of observation for subsequent administrations and released according to their clinical status. The last planned IMP administration is at W52. If the participant withdraws from the study, efgartigimod PH20 SC will not be administered.

[u] Prednisone dose tapering will begin 2 weeks after achieving CR or 4 weeks after sustained EoC (thus, no new lesions have developed for a minimum of 6 weeks and approximately 80% or more of lesions have healed).

Table 9: Modified Schedule of Activities During COVID-19 Pandemic for ARGX-113-1905 for Participants Not in CR at Rollover From ARGX-113-1904, or Participants With Flare after CRmin or CRoff in ARGX-113-1905

In the Schedule of Activities (SoA) tables for ARGX-113-1905 (see below), the mandatory assessments are indicated in red (**X**). The assessments that need to be performed only if feasible during the COVID-19 pandemic are indicated in black (X). At site visits, all assessments have to be performed (critical [**X**] and non-critical [X], if operationally feasible).

	Open-label extension							Follow-up	
Trial period	**V1**[a]	**Observational visits**	**IMP admin only visit**	**Observational visits**		**EoT/ET**	**UNS**[d]		
Visit number		**Weekly on-site visits until CR**[b]	**Weekly home or on-site visits until CRmin**[c]	**On-site visits every 4 weeks until CRmin**	**On-site visits every 4 weeks until W52**	**W52**		**Safety follow-up 1**	**Safety follow-up 2**
Trial week	**Rollover**[a]	**V1 + 7x**	**CR until CRmin**	**CR until CRmin**	**After CRmin until W52**	**W52**		**EoT/ET + 4 weeks**[e]	**EoT/ET + 8 weeks EoS**[e]
Assessment/procedure	**±0 days**	**±2 days**[f]				**±2 days**		**±3 days**[f]	
Informed consent	X								
Inclusion/exclusion criteria	X								
Weight[g]	X	X[g]		X[g]	X[g]	X			
ECG[h,i]	X	X		X	X	X		X	X
Physical examination and vital signs[i,j]	X	X		X	X	X	X	X	X
Urinalysis[i,k,l]	X	X		X	X	X	X[d]	X	X
Urine pregnancy test[i,m]	X	X		X	X	X	X[d]	X	X
Vaccination antibodies[i,l]	X	X		X	X	X	X[d]	X	X

Trial period	Open-label extension					EoT/ET	UNS[d]	Follow-up	
	V1[a]	Observational visits	IMP admin only visit	Observational visits		EoT/ET		Safety follow-up 1	Safety follow-up 2
Visit number		Weekly on-site visits until CR[b]	Weekly home or on-site visits until CRmin[c]	On-site visits every 4 weeks until CRmin	On-site visits every 4 weeks until W52	W52			
Trial week	Rollover[a]	V1 + 7x	CR until CRmin	CR until CRmin	After CRmin until W52	W52		EoT/ET + 4 weeks[e]	EoT/ET + 8 weeks EoS[e]
Assessment/procedure	±0 days	±2 days[f]				±2 days		±3 days[f]	
Blood sampling									
• Clinical chemistry and hematology[i,l,n]	X	X		X	X	X	X[d]	X	X
• anti-Dsg-1 and anti-Dsg-3 antibodies[i,l]	X	X		X	X	X	X[d]	X	X
• PK[i,o]	X	X		X	X[o]	X	X[d,p]	X	X
• Total IgG and IgG subtypes[i,o]	X	X		X	X	X	X[d]	X	X
• immunogenicity[i,q]	X	X		X	X	X		X	X
• IgG autoantibody subtypes and specificity[i]	X	X[r]		X	X	X	X[d]	X	X
PDAI[i]	X	X		X	X	X	X	X	X
ABQOL[i,s,t]	X	X[s]		X[s]	X[s]	X			
EQ-5D-5L[i,s,t]	X	X[s]		X[s]	X[s]	X			
Disease assessment[i,u]	X	X		X	X	X	X	X	X

Trial period	Open-label extension					EoT/ET	UNS[d]	Follow-up	
	V1[a]	Observational visits	IMP admin only visit	Observational visits		EoT/ET		Follow-up	
Visit number		Weekly on-site visits until CR[b]	Weekly home or on-site visits until CRmin[c]	On-site visits every 4 weeks until CRmin	On-site visits every 4 weeks until W52	W52		Safety follow-up 1	Safety follow-up 2
Trial week	Rollover[a]	V1 + 7x	CR until CRmin	CR until CRmin	After CRmin until W52	W52		EoT/ET + 4 weeks[e]	EoT/ET + 8 weeks EoS[e]
Assessment/procedure	±0 days	±2 days[f]				±2 days		±3 days[f]	
Photography (at selected sites)[v]	X	X[v]				X	X[d,v]		
Lymphocyte populations (at selected sites)[w]	X	X[w]		X[w]	X[w]	X[w]		X	X
GTI[x]	X	X[x]		X[x]	X[x]	X			
IMP self-administration training[y]	X	X	X	X	X	X			
Efgartigimod PH20 SC[z]	X[z]	X[z]	X	X		X	X		
Prednisone taper[aa]	X	X		X	X	X	X		
Concomitant therapies/ procedures	Continuous monitoring								
AE monitoring	Continuous monitoring								

ABQOL=Autoimmune Bullous Disease Quality of Life; AE=adverse event; ALT=alanine aminotransferase; ALP=alkaline phosphatase; AST=aspartate aminotransferase; BMI=body mass index; BUN=blood urea nitrogen; CR=complete clinical remission; CRmin=CR on minimal therapy; CRP=C-reactive protein; DC=disease control; Dsg=desmoglein; ECG=electrocardiogram; EoC=end of consolidation; EoS=end of study; EoT=end of treatment; EQ-5D-5L=EuroQol 5-dimension 5-level scale; ET=early termination; GGT=gamma-glutamyl transferase; GTI=Glucocorticoid Toxicity Index; IgG=immunoglobulin type G; IMP=investigational medicinal product; LDH=lactate dehydrogenase; MCV=mean corpuscular volume; NAb=neutralizing antibody; PD=Pharmacodynamic; PDAI=Pemphigus Disease Area Index; PK=pharmacokinetics; QTcF=Fridericia corrected QT interval; rHuPH20=recombinant human hyaluronidase PH20; RBC=red blood cells; SC=subcutaneous(ly); UNS=unscheduled visit; V=visit at site; V1 + 7x=visit 1 + 7 times x with 'x' being the weeks post V1 (eg, V1 + 7x3 is the visit at W3 [21 days post visit 1]); W=week; WBC=white blood cells

[a] For participants who roll over from ARGX-113-1904 to ARGX-113-1905, the baseline visit will occur at the EoS/ED visit of ARGX-113-1904. All assessments are performed before IMP administration.

[b] A minimum of 6 on-site visits (rollover (V1) to W6 or start of retreatment +5 weeks) is required before switching to home administrations, even if CR is reported earlier.

[c] Home visits are allowed once a participant achieves CR but not before W7 or not before the start of retreatment +6 weeks. The investigator should call the participant every 2 weeks until CRmin to confirm the participant is still in CR and to determine the prednisone tapering schedule.

[d] In case of suspected new lesions as reported by the participant, AEs, flare, or other safety reasons, the participant should come to the clinic. This may require an unscheduled visit. Depending on the reason for the visit, different assessments need to be performed. Refer to Section 8 for more information.

[e] Follow-up 1 will be the EoS visit for participants who ended treatment before W49, or 4 weeks before ET. Both follow-up visits will be required only for participants who continue to receive efgartigimod PH20 SC for at least 1 visit between W49 and W52, or during the last 4 weeks before ET.

[f] Study visit windows are ±2 days during the treatment period and ±3 days for the follow-up visits.

[g] Weight will be measured and BMI will be calculated accordingly, at the rollover visit, at W26 (or the next on-site visit if W26 does not coincide with an on-site visit) and W52. Weight will also be measured if there has been an obvious change since the last measurement.

[h] The ECG will be recorded at baseline, at the start of retreatment and every 3 months (or the next on-site visit) while receiving efgartigimod PH20 SC treatment, at CRmin (or the next on-site visit if CRmin is achieved during a week without an on-site visit), and EoS. The ECG (heart rate, PR, QT, and QRS interval) will be read centrally, and QTcF and QTcB will be calculated. Additional ECGs may be performed at the discretion of the investigator during unscheduled visits.

[i] Assessment or procedure will be completed predose at visits when IMP is administered.

[j] A complete physical examination will be performed at each on-site visit. Vital sign measurements include systolic and diastolic blood pressure, heart rate, and body temperature.

[k] Urinalysis will be performed by dipstick method and will include specific gravity, pH, protein, glucose, ketones, blood, bilirubin, urobilinogen, nitrite, leukocyte esterase, and microscopic examination (if blood or protein is abnormal).

[l] Samples will be taken every week from rollover (V1) to W9 or start of retreatment +8 weeks, and then every 4 weeks and at the visit when CR is observed. Once CR is achieved, samples will be taken every 4 weeks at on-site visits until EoS. For participants achieving CR between rollover (V1) and W6 or the start of retreatment +5 weeks, samples will be taken weekly from rollover (V1) to W6 or start of retreatment +5 weeks, and then every 4 weeks during on-site visits until EoS.

[m] A urine pregnancy test will be performed locally at least once every 4 weeks, at CR, and as of CR again every 4 weeks at on-site visits.

[n] Clinical blood laboratory tests will include hematology and blood chemistry at all visits. The hematology profile includes hemoglobin, hematocrit, MCV, RBC count, platelet count, WBC count with differential. The blood chemistry profile includes sodium, potassium, calcium, HbA1c, creatinine, creatinine clearance, BUN, ALT, AST, total bilirubin, GGT, CRP, ALP, LDH, low-density lipoprotein cholesterol (LDL-C), uric acid, total protein, and albumin.

[o] PK and PD (total IgG and IgG subtypes) samples will be taken every 4 weeks, at CR, and as of CR again every 4 weeks at on-site visits, as long as the participant is receiving efgartigimod PH20 SC treatment (until CRmin or the next on-site visit if CRmin is achieved during a week without an on-site visit), and 4 weeks after CRmin (or the next on-site visit) or EoT. Blood will be taken predose (within 2 hours before the start of IMP administration during visits when IMP is administered).

[p] Blood will be taken for PK assessment predose (within 2 hours before the start of IMP administration during visits when IMP is administered). At UNS visits, blood samples for PK analysis will be taken only if IMP is administered.

[q] Blood will be taken to test for immunogenicity to efgartigimod in serum and to rHuPH20 in plasma every 4 weeks, at CR, and as of CR every 4 weeks at on-site visits while the participant is receiving efgartigimod PH20 SC treatment (until CRmin or the next on-site visit if CRmin is achieved during a week without an on-site visit), and 4 and 8 weeks after CRmin (or the next 2 on-site visits) or EoT. NAb will be tested for all confirmed positive immunogenicity samples.

[r] Blood will be taken every 4 weeks and at the visit when CR is observed for IgG autoantibody subtypes and specificity. Once CR is achieved, samples will be taken every 4 weeks at on-site visits until EoS.

[s] The ABQOL and EQ-5D-5L will be administered at the start of retreatment, when achieving CRmin (or at the next on-site visit if CRmin is achieved during a week without an on-site visit), and at EoT/W52 only.

[t] Questionnaires are to be completed before any other assessment.

[u] Disease assessment parameters include DC, EoC, CR, CRmin, CRoff, flare, and treatment failure. Participants who have achieved CR and have new lesions should come to the clinic for a UNS visit for disease assessment.

[v] Pictures of different anatomical regions may be taken per judgment of the investigator. As a guidance, time points of baseline, DC, CR and flare are indicated. Pictures may also be taken at intermediate time points.

[w] Samples for lymphocyte populations will be taken at selected sites only: optionally at on-site visits at W13 (±2 weeks), W26 (±2 weeks), W39 (±2 weeks), W52 (±2 weeks) or EoT/ET and EoS, and mandatory at on-site visits at W52 (±2 weeks) or EoT/ET and EoS for participants in CRmin or CRoff.

[x] The GTI assessment will be performed at visit 1, W26 (or the next on-site visit) and W52.

[y] Participants and/or their caregivers will be invited to receive at least 1 refresher training for self-administration, or caregiver-supported administration of IMP. Training will continue until deemed successfully completed by authorized staff.

[z] Efgartigimod PH20 SC will be administered subcutaneously weekly at a dose of 1000 mg until CRmin. In case of treatment failure in ARGX-113-1904, or flare while not receiving efgartigimod therapy, efgartigimod PH20 SC will be administered on [redacted] mg, followed by weekly SC administrations of 1000 mg until CRmin. For IMP administrations between the scheduled visits (after achieving CR), the participant can choose between self-administration (if training successfully completed), home nurse visits or return to the trial site for the SC injection only. Participants who have achieved CRmin or CRoff and are currently not in flare will be observed every 4 weeks without any further IMP administration until flare or EoS. Only for on-site visits and home nurse visits, participants should be followed up for safety monitoring for at least 1 hour after the first administration, or followed by 15 minutes of observation for subsequent administrations for safety monitoring and released according to their clinical status. The last planned IMP administration is at W52. If the participant withdraws from the study, efgartigimod PH20 SC will not be administered.

[aa] Prednisone dose tapering will begin 2 weeks after achieving CR or 4 weeks after sustained EoC (thus, no new lesions have developed for a minimum of 6 weeks and approximately 80% or more of lesions have healed).

10.12. Appendix 12: Glucocorticoid Toxicity Index (GTI)

Table 10: Approach to Calculating the Baseline GTI 2.0 Score: Toxicities Assigned Weighted Scores from the C-GTI to Establish a Baseline GTI Score

Toxicity domain		Points
Body mass index (BMI)	BMI < 27	0
	BMI ≥ 27 but < 30	21
	BMI ≥ 30	36
Glucose metabolism	HgbA1c < 5.7	0
	HgbA1c < 5.7 but on medication	32
	HgbA1c ≥ 5.7	32
	HgbA1c ≥ 5.7 and on medication	44
	Diabetic retinopathy, nephropathy, or neuropathy (count only one)	44
Blood pressure	Normotensive: systolic ≤ 120 and diastolic ≤ 85 no medications	0
	Systolic ≤ 120 and diastolic ≤ 85 but on medications	19
	Systolic > 120 or diastolic > 85 on no medications	19
	Systolic > 120 or diastolic > 85 and on medications	44
	Hypertensive emergency or PRES (count only one)	44
Lipid metabolism	LDL ≤ target	0
	LDL ≤ target but on medications	10
	LDL > target on no medications	10
	LDL > target on treatment	30
Bone/tendon	Normal BMD or no known history of osteoporosis	0
	Osteoporosis	29
	Insufficiency fracture secondary to osteoporosis	29
	Osteonecrosis	29
	Tendon rupture while on corticosteroid	29
Glucocorticoid myopathy	No myopathy	0
	Minor glucocorticoid myopathy	9
	Moderate glucocorticoid myopathy	63
	Severe glucocorticoid myopathy	63
Skin	No skin toxicity	0
	*Minor skin toxicity (1 or more than 1 minor skin item)	8
	*Moderate skin toxicity (1 or more than 1 moderate skin item)	26
	*Severe skin toxicity (1 or more than 1 moderate skin item)	26
	*Select only 1 (minor, moderate, or severe)	
Neuropsychiatric	No neuropsychiatric toxicity	0
	*Minor (1 or more than 1 minor NP item: insomnia, mania, depression, cognitive)	11
	*Moderate (1 or more than 1 moderate NP item: insomnia, mania, depression, cognitive)	74
	*Severe (1 or more than 1 severe NP item: insomnia, mania, depression, cognitive)	74
	Psychosis	74
	Glucocorticoid-induced violence	74
	*Select only 1 (minor, moderate, or severe)	
Infection	No GTI-relevant infections within the prebaseline GTI interval of the study	0
	Oral or vaginal candidiasis or noncomplicated zoster (<grade 3) within the prebaseline GTI interval of the study	19
	Grade 3 or grade 4 infection within the pre-baseline GTI interval of the study	93
Ocular	Increased IOP	33
	Posterior subcapsular cataract	33
	Central serous retinopathy	33
Gastrointestinal	GI perf absence of NSAIDs	33
	PUD without *Helicobacter pylori*	33
Endocrine	Adrenal insufficiency	33

BMD, bone mineral density; *GI*, gastrointestinal; *GTI*, Glucocorticoid Toxicity Index; *HgbA1c*, glycated haemoglobin; *IOP*, intraocular pressure; *LDL*, low density lipoprotein; *NP*, neuropsychiatric; *NSAID*, nonsteroidal anti-inflammatory drug; *PRES*, posterior reversible encephalopathy syndrome; *PUD*, peptic ulcer disease.
*Minor: Acneiform rash (grades 1-2), easy bruising (grade 1), hirsutism (grade 1), atrophy/striae (grade 1), erosions/ulceration (grade 1). Moderate: Acneiform rash (grades 3), easy bruising (grade 2), hirsutism (grade 2), atrophy/striae (grade 2), erosions/tears/ulceration (grade 2). Severe: Acneiform rash (grade 4), atrophy/striae (grade 3), erosions/tear/ulceration (grade 3).

*Bone/tendon will not be scored as part of the C-GTI.

Table 11: Approach to Calculating the Changes in GTI 2.0 Score: Weighted Scores Assigned to Improvements or Worsenings in the C-GTI

	Domain	Score
1. Change in body weight (BMI)	Decrease by ≥5 BMI units	−36
	Decrease by >2 but <5 BMI units	−21
	No significant change (±2 BMI units)	0
	Increase of >2 to <5 BMI units	21
	Increase of 5 or more BMI units	36
2. Glucose metabolism	Improvement in HbA1c AND decrease in medication	−44
	Improvement in HbA1c OR decrease in medication	−32
	No significant change	0
	Increase in HbA1c OR increase in medication	32
	Increase in HbA1c AND increase in medication	44
3. Blood pressure (BP)	Improvement in BP AND decrease in medication	−44
	Improvement in BP OR decrease in medication	−19
	No significant change	0
	Increase in BP OR increase in medication	19
	Increase in BPAND increase in medication	44
4. Hyperlipidemia	Decrease in LDL AND decrease in medication	−30
	Decrease in LDL OR decrease in medication	−10
	No significant change	0
	Increase in LDL OR increase in medication	10
	Increase in LDL AND increase in medication	30
5. Bone health (BMD)	Increase in BMD (gain of more than 0.5)	−29
	No significant change in BMD (±0.5)	0
	Decrease in BMD (loss of more than 0.5)	29
6. Corticosteroid myopathy	Moderate weakness to none	−63
	Moderate-to-mild weakness	−54
	Mild weakness to none	−9
	No significant change	0
	None-to-mild weakness (without functional limitation)	9
	Mild-to-moderate weakness	54
	None-to-moderate weakness (with functional limitation)	63
7. Skin corticosteroid-related toxicity	Decrease in skin toxicity—moderate to none	−26
	Decrease in skin toxicity—moderate to mild	−18
	Decrease in skin toxicity—mild to none	−8
	No significant change	0
	Increase in skin toxicity—none to mild	8
	Increase in skin toxicity—mild to moderate	18
	Increase in skin toxicity—none to moderate	26
8. Neuropsychiatric—corticosteroid-related symptoms	Decrease in NP toxicity—moderate to none	−74
	Decrease in NP toxicity—moderate to mild	−63
	Decrease in NP toxicity—mild to none	−11
	No significant change	0
	Increase in NP toxicity—none to mild	11
	Increase in NP toxicity—mild to moderate	63
	Increase in NP toxicity—none to moderate	74
9. Infection	No infection	0
	Oral or vaginal candidiasis or uncomplicated zoster (<grade 3)	19
	Grade 3, 4, or 5 infection	93

BMD, bone mineral density; *GTI*, Glucocorticoid Toxicity Index; *HgbA1c*, glycated haemoglobin; *LDL*, low density lipoprotein; *NP*, neuropsychiatric.

*Bone health will not be scored as part of the C-GTI.

Table 12: GTI 2.0 Specific List: 11 Domains (9 of Which are Shared by the C-GTI) and 23 Unique Items

	At baseline or before	New since baseline
Body mass index (BMI)		
• An absolute increase in BMI of more than 8 units (and >24.9 kg/m^2)		
Blood pressure		
• Hypertensive emergency (see definition, below)		
• PRES (posterior reversible encephalopathy syndrome) (see definition, below)		
Endocrine		
• Symptomatic adrenal insufficiency		
Bone health		
• Osteonecrosis of one joint		
• Osteonecrosis of more than one joint		
• Bone mineral density decrease >6%		
• Insufficiency fracture		
• Insufficiency fracture in more than one bone		
Muscle and tendon		
• Severe glucocorticoid myopathy (see definition)		
• Tendon rupture		
• More than 1 tendon rupture		
Eye		
• Central serous retinopathy		
• New-onset or worsened elevation of intraocular pressure requiring treatment or change in treatment		
• Posterior subcapsular cataracts (or history of same)		
Infection		
• Grade 4 infection (see definition, below)		
• Grade 5 infection (death from infection)		
Glucose tolerance		
• Diabetic nephropathy		
• Diabetic neuropathy		
• Diabetic retinopathy		
Gastrointestinal tract		
• Gastrointestinal perforation (occurring in the absence of regular nonsteroidal anti-inflammatory drug use)		
• Peptic ulcer disease confirmed by endoscopy (excluding *Helicobacter pylori*)		
Skin		
• Severe skin toxicity (see definition, below)		
Neuropsychiatric		
• Psychosis, defined as hallucinations, delusions, or disorganized thought processes (occurring in the absence of mania, delirium, or depression)		
• Glucocorticoid-induced violence toward self or others		
Other glucocorticoid toxicities		
Please specify: _____		
_____		
_____		

GTI, Glucocorticoid Toxicity Index.

*Bone mineral density decreases >6% will not be reported.

GTI Supporting Information: Definitions

Glucocorticoid-induced myopathy definitions:

- Glucocorticoid myopathy is defined as mild symmetrical weakness of the proximal muscles and/or neck flexors associated with steroid therapy and NOT due to any other apparent cause. Muscle enzymes are typically within normal limits
- Minor/Mild and moderate severity myopathy are defined by a muscle strength of grade 4 on the standard Medical Research Council Rating scale
  - A 4 means weaker than normal but greater than antigravity strength against resistance.
  - "Minor" or "Mild" is mild weakness (Grade 4) that does NOT functionally limit the patient.
  - "Moderate" is mild weakness (Grade 4) that does impose functional limitations on the patient enough to interfere with normal daily activities.
  - Note that a person may have muscle weakness consistent with glucocorticoid-induced myopathy that is detectable on physical examination but the person is not aware of it or have any corresponding functional limitation. This would be classified as minor or mild.
- Severe glucocorticoid-induced myopathy, defined as a weakness of grade 3 or less (no more than antigravity strength and unable to overcome any resistance or any degree weaker), is included in the Specific List. People who are severely weak may have difficulty rising from a chair without assistance or other major functional limitations but the formal categorization should be based on the degree of weakness on strength testing

Severity of glucocorticoid toxicity to the skin:

- Manifestations to be considered:
  - Acneiform rash
  - Easy bruising
  - Hirsutism
  - Atrophy/striae
  - Erosions/tears/ulcerations

Table 13: Severity Categorization of Skin Manifestations by Grade

Minor/mild	Moderate	Severe (specific domain)
Acneiform rash (grades 1-2)	Acneiform rash (grade 3)	Acneiform rash (grade 4)
Easy bruising (grade 1)	Easy bruising (grade 2)	
Hirsutism (grade 1)	Hirsutism (grade 2)	
Atrophy/Striae (grade 1)	Atrophy/Striae (grade 2)	Atrophy/Striae (grade 3)
Erosions/Tears/Ulcerations (grade 1)	Erosions/Tears/Ulcerations (grade 2)	Erosions/Tears/Ulcerations (grade 3)

Skin definitions from the National Cancer Institute CTCAE:

- Acneiform rash
  - Grade 1: papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness.
  - Grade 2: papules and/or pustules covering 10 to 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL; papules and/or pustules covering > 30% BSA with or without mild symptoms.
  - Grade 3: papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated.
  - Grade 4: life-threatening consequences; papules and/or pustules covering any percent of BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated.
- Easy bruising
  - Grade 1: localized or in a dependent area
  - Grade 2: generalized
- Hirsutism: In women, an increase in length, thickness, or density of hair in a male distribution
  - Grade 1: hirsutism that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair.
  - Grade 2: hirsutism that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychological impact.

- Atrophy/striae
  - Grade 1: covering <10% BSA; OR associated with telangiectasias or changes in skin color.
  - Grade 2: covering 10 to 30% BSA; OR associated with striae or adnexal structure loss.
  - Grade 3: covering >30% BSA; OR associated with ulceration.
- Erosions/tears/ulcerations
  - Grade 1: combined area of ulcers <1 cm; nonblanchable erythema of intact skin associated with warmth or erythema.
  - Grade 2: combined area of ulcers 1-2 cm; partial thickness skin loss involving skin or subcutaneous fat.
  - Grade 3: combined area of ulcers >2 cm; full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to the fascia.

Severity of neuropsychiatric glucocorticoid toxicity:

- Manifestations to be considered
  - Insomnia
  - Mania
  - Cognitive impairment
  - Depression

Table 14: Severity Categorization of Neuropsychiatric Manifestations by Grade

Minor/mild	Moderate	Severe (specific domain)
Insomnia – (grade 1)	Insomnia – (grade 2)	
Mania (grade 1)	Mania (grade 2)	Mania (grade 3)
Cognitive impairment (grade 1)	Cognitive impairment (grade 2)	Cognitive impairment (grade 3)
Depression (grade 1)	Depression (grade 2)	Depression (grade 3)

Definitions of severity within the neuropsychiatric domain:

- Insomnia: dissatisfaction with sleep quality and difficulty initiating or maintaining sleep or early morning awakening
  - Grade 1: mild difficulty falling asleep, staying asleep or waking up early.

  - Grade 2: Moderate difficulty falling asleep, staying asleep or waking up early (typically associated with some degree of functional impairment).

- Mania

  - Grade 1: mild manic symptoms (eg, elevated mood, rapid thoughts, rapid speech, decreased need for sleep). Grade 1 mania is typically associated with a slightly or occasionally elevated or irritable mood, often accompanied by one of the following symptoms: mild or occasional inflated self-esteem, decreased need for sleep, increased talkativeness, feeling that thoughts are faster than usual, distractibility, increased activity or agitation, and impulsive actions.

  - Grade 2: moderate manic symptoms (eg, relationship and work difficulties; poor hygiene). Grade 2 mania is typically associated with a slightly or occasionally elevated (or irritable) mood, often accompanied by 2 to 3 of the following symptoms: mild or occasional inflated self-esteem, decreased need for sleep, increased talkativeness, feeling that thoughts are faster than usual, distractibility, increased activity or agitation, and impulsive actions.

  - Grade 3: severe manic symptoms (eg, hypomania; major sexual or financial indiscretions); hospitalization not indicated; new onset. Grade 3 mania is typically associated with a slightly or occasionally elevated (or irritable) mood, often accompanied by 4 or more of the following symptoms: mild or occasional inflated self-esteem, decreased need for sleep, increased talkativeness, feeling that thoughts are faster than usual, distractibility, increased activity or agitation, and impulsive actions.

- Cognitive impairment

  - Grade 1: mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated. Grade 1 cognitive dysfunction is noted by the patient but is not apparent to the examiner.

  - Grade 2: moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part time basis indicated. Grade 3: severe cognitive disability; significant impairment of work/school/life performance. This may correspond to a glucocorticoid-induced delirium.

- Depression

  - Grade 1: mild depressive symptoms. Grade 1 depression is often associated with mild, occasional symptoms of up to 2 of the following: loss of interest, low energy, guilt, poor concentration, insomnia, restlessness, or change in appetite.

  - Grade 2: moderate depressive symptoms; limiting instrumental activities of daily living. Grade 2 depression is often associated with frequent or moderate feelings of

being down or depressed and/or up to 4 of the following: loss of interest, low energy, guilt, poor concentration, insomnia, restlessness, or change in appetite.

- Grade 3: severe depressive symptoms; limiting self-care ADL; hospitalization not indicated. Grade 3 depression is often associated with a constant feeling of being down or depressed and/or 5 or more symptoms of loss of interest, low energy, guilt, poor concentration, insomnia, restlessness, change in appetite, or suicidal thoughts.

Infection Definitions

- No or no significant infection: no grade 3, grade 4, or grade 5 infection, and no minor Candida infection and no localized zoster (see grade 2 specific infection) as defined below. Grade 1 infections and grade 2 infections other than the specific infections are recorded on this form as no infection or no significant infection. Grade 2 specific infection/Minor Candida or localized zoster: oral or vaginal candidiasis or zoster infections without post-herpetic neuralgia or eye involvement (Both of these infections correspond to grade 2 CTCAE infections). Grade 3 infection: any infection requiring intravenous antibiotic, antifungal, or antiviral intervention or hospitalization indicated OR radiologic or operative intervention indicated OR herpes zoster complicated by post-herpetic neuralgia or eye involvement

- Grade 4 infection: life-threatening consequences (eg, septic shock, hypotension, acidosis, necrosis); urgent intervention indicated

- Grade 5: death from infection

Definitions for the Specific List

- Hypertensive emergency: the blood pressure has reached levels that are damaging organs

  - Hypertensive emergencies generally occur at blood pressure levels exceeding 180 mm Hg systolic OR 120 mm Hg diastolic, but can occur at even lower levels in patients whose blood pressure has not been elevated.

  - Complications can include stroke, loss of consciousness, memory loss, myocardial infarction, hypertensive retinopathy or nephropathy, aortic dissection, angina, and pulmonary edema.

- Posterior reversible leukoencephalopathy syndrome (PRES): a clinical radiological entity. Clinical features may include headaches, altered mental status, seizures, and visual loss depending on the affected neuroanatomy

  - Characteristic magnetic resonance imaging (MRI) findings include vasogenic edema involving the white matter that predominantly affects the posterior occipital and parietal lobes of the brain, although other brain regions may also be affected. Confirmation by MRI is required as is exclusion of the other potential causes (including hypertensive emergency).

- Severe glucocorticoid myopathy: Grade 3 or worse myopathic weakness or respiratory myopathic weakness attributable to glucocorticoid myopathy

- Central serous retinopathy: a fluid detachment of macula layers from their supporting tissue

  – Requires formal ophthalmology examination, typically accompanied by optical coherence tomography and/or fluorescein angiography for diagnostic confirmation.

- Diabetic nephropathy: Macroalbuminuria; ie, a urinary albumin excretion > 300 mg in a 24-hour collection or a urinary protein: creatinine ratio > 300mg/g

- Diabetic neuropathy: any of 4 types of peripheral neuropathy occurring in the setting of diabetes mellitus as follows:

  – A distal sensory polyneuropathy

  – Autonomic neuropathy (hypoglycemia unawareness, bladder or bowel problems, erectile dysfunction, and other autonomic nervous system issues)

  – Diabetic amyotrophy (muscle infarction)

  – Mononeuritis (eg, foot drop attributed to diabetic neuropathy or a diabetic sixth cranial nerve palsy)

- Diabetic retinopathy: any form of retinopathy associated with diabetes mellitus, including both non-proliferative and proliferative forms of diabetic retinopathy as well as diabetic macular edema

  – These complications must be confirmed by an ophthalmologist

- Severe skin toxicity: any of the 3 following manifestations

  – Grade 4 acneiform lesions: papules or pustules covering an percent of the BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated or life-threatening consequences.

  – Grade 3 striae: covering >30% BSA or associated with ulceration.

  – Grade 3 ulcers: combined area of ulcers >2cm or full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia.

- Symptomatic adrenal insufficiency: symptoms resulting from failure of the adrenal cortex to produce sufficient cortisol and, in some cases, aldosterone

- Psychosis: hallucinations, delusions, or disorganized thought processes (occurring in the absence of mania, delirium, or depression)

- Steroid-induced violence: glucocorticoid-induced violence toward self or others

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