Clinical Trial Protocol

Protocol Title:	A Randomized, Double-Blinded, Placebo-Controlled Trial to Investigate the Efficacy, Safety, and Tolerability of Efgartigimod PH20 SC in Adult Patients With Pemphigus (Vulgaris or Foliaceus) (ADDRESS)
Protocol Number:	ARGX-113-1904
Version Number:	5.0 (Amendment 4)
Compound:	Efgartigimod (ARGX-113)
Investigational Medicinal Product:	Efgartigimod PH20 SC (efgartigimod coformulated with recombinant human hyaluronidase PH20 [rHuPH20] for subcutaneous [SC] administration) / Placebo (placebo with rHuPH20 for SC administration)
Trial Phase:	3
Sponsor Name:	argenx BV
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Regulatory Agency Identifier Number(s)

IND: [redacted]

EudraCT: 2020-002915-23

Date and Version: 09 Dec 2022, Version 5.0

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Confidentiality Statement

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

The aim of the ARGX-113-1904 trial 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 pemphigus patients.

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 reported during argenx BV clinical trials.

During the COVID-19 pandemic, it may not be possible to perform all assessments as planned for this trial (see Schedule of Activities [SoA] in Section 1.3).

In order to provide participants with pemphigus the opportunity to continue the trial during the COVID-19 pandemic, an appendix with possible adaptations to the ARGX-113-1904 trial 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 the possibility of efgartigimod administration in the participant's home. This appendix is included in Section 10.14 (Appendix 14) of this protocol.

SIGNATURE OF SPONSOR

Protocol Title: A Randomized, Double-Blinded, Placebo-Controlled Trial to Investigate the Efficacy, Safety, and Tolerability of Efgartigimod PH20 SC in Adult Patients With Pemphigus (Vulgaris or Foliaceus) (ADDRESS)

Protocol Number: ARGX-113-1904

Acronym: ADDRESS

Sponsor Representative:

See appended signature page

_____ _____

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

Date

SIGNATURE OF PRINCIPAL INVESTIGATOR

PROTOCOL TITLE: A Randomized, Double-Blinded, Placebo-Controlled Trial to Investigate the Efficacy, Safety, and Tolerability of Efgartigimod PH20 SC in Adult Patients With Pemphigus (Vulgaris or Foliaceus) (ADDRESS)

PROTOCOL NO: ARGX-113-1904

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 designee or designated CRO.

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

Signature of Principal Investigator: _____ Date: _____

Printed Name: _____

Principal Investigator Title: _____

Name/Address of Site: _____

_____

_____

Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Protocol v5.0 (Amendment 4)	09 Dec 2022
Protocol v4.0 (Amendment 3)	09 Jun 2022
Protocol v3.0 (Amendment 2)	18 May 2021
Protocol v2.0 (Amendment 1)	10 Feb 2021
Protocol v1.0	22 Jul 2020

Amendment 4 (09 Dec 2022)

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

Overall Rationale for the Amendment

The overall rationale for this protocol amendment is to clarify the assessments performed during an unscheduled visit.

The relevant changes implemented in the Germany and China country-specific protocols, v4.1-Germany and v4.1-China are included also in this protocol amendment. Country-specific requirements are described in the applicable sections of the protocol and/or in Section 10.16.

The main changes from protocol version 4.0 to protocol version 5.0 are summarized in the following table. A strikethrough indicates text that was removed, and bold font indicates text that was added. Minor editorial changes, including the correction of typographical errors and formatting inconsistencies, are not summarized.

Summary of Changes Between Protocol Version 4.0 and Protocol Version 5.0

Section and name	Description of change	Brief rationale
Section 1.1. Synopsis	The following text was revised: "Approximately 213 participants with PV or PF will be randomized as follows: • Approximately 183 participants with PV will be randomized in a 2:1 ratio to receive efgartigimod PH20 SC or placebo, respectively. The target number of Japanese participants with PV is 9 **(included in the 183 participants globally)**. Among the Japanese participants with PV, the randomization ratio will also be 2:1 to receive efgartigimod PH20 SC or placebo, respectively. • Up to approximately 30 participants with PF may be randomized in a 2:1 ratio to receive efgartigimod PH20 SC or placebo, respectively. The target range for the number of Japanese participants with PF is 1 to 3 (included in the ~~24~~ **30** participants globally). Among the Japanese participants with PF, the randomization ratio will also be 2:1 to receive efgartigimod PH20 SC or placebo, respectively."	Revised for accuracy and clarity
Section 8. Trial Assessments and Procedures Other sections impacted by this change: Section 1.3. Schedule of activities Section 10.14. Table 10: Modified schedule of activities during COVID-19 pandemic Section 10.16.1.1. Table 16: Schedule of Activities for Trial ARGX-113-1904 - China Section 10.16.1.4. Table 19: Modified Schedule of Activities During COVID-19 Pandemic - China	The assessments to be performed during an unscheduled visit in case of new lesions, flare, AEs, or other safety reasons have been clarified.	Modified to provide a clear overview of assessments to be performed during unscheduled visits

Summary of Changes Between Protocol Version 4.0 and Protocol Version 5.0

Section and name	Description of change	Brief rationale
Section 1.3. Schedule of activities Other sections impacted by this change: Section 10.14. Table 10: Modified schedule of activities during COVID-19 pandemic Section 10.16.1.1. Table 16: Schedule of Activities for Trial ARGX-113-1904 - China Section 10.16.1.4. Table 19: Modified Schedule of Activities During COVID-19 Pandemic - China	In footnote p, the timing of pregnancy tests was further specified: "A urine pregnancy test will be ~~performed~~ **conducted and analyzed** locally ~~and~~ **during on-site visits** at least once every 4 weeks **(before and after CR) and at the time of CR**."	Revised for accuracy
Section 5.1. Inclusion Criteria	Inclusion criterion 5A.i was revised: "Male participants must agree to use an acceptable method of contraception (as described in Appendix 5, Section 10.5.2.2) ~~and not donate sperm~~ from signing the ICF until the ~~end~~**last dose** of ~~the~~ ~~study~~**IMP**."	Adjusted to align with the current guidance for efgartigimod on sperm donation
Section 8. Trial Assessments and Procedures	Because the sponsor can review the eligibility of participants but the decision to randomize a participant is up to the investigator, the following sentence has been updated: "At screening, all eligibility assessments should be performed after obtaining informed consent. All screening evaluations must be completed and reviewed~~, and confirmed by the sponsor's designated CRO and medical monitor~~ before enrollment to confirm that potential participants meet all eligibility criteria. ~~Pseudonymized source documents confirming the diagnosis (histology, DIF, and IIF or ELISA) may be sent for this eligibility confirmation.~~ The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable."	Correction

Summary of Changes Between Protocol Version 4.0 and Protocol Version 5.0

Section and name	Description of change	Brief rationale
Section 10.2. Table 7: Protocol-Required Laboratory Assessments Other sections impacted by this change: Section 6.3. Measures to Minimize Bias: Randomization and Blinding Section 10.16.1.3. Table 17: Protocol-Required Laboratory Assessments – China	Study sites will no longer be provided with the albumin and total protein results in real time. The investigator will receive an alert if a participant's results are outside of the normal range. In addition, it has been clarified that PK, PD, immunogenicity, albumin, total protein, and exploratory research data (where applicable) will also remain blinded until database lock. The following footnote has therefore been added in Table 7 and Table 17: "**PK, PD, immunogenicity, albumin, and total protein data will not be reported to the site. A system will be implemented that will alert the investigator of out-of-range albumin and total protein values, to allow for appropriate safety follow-up."**	Caution regarding data integrity in double-blinded efgartigimod studies
Section 10.6. Administrative Structure	The legal entity of the laboratory used for the analysis of PK and ADA changed from LGC to DDS.	Administrative update
Throughout	Clarifications have been added to specify the aspects of the protocol that are globally applicable and those that are distinct for China.	Clarification

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1.1. Synopsis

Protocol Title:

A Randomized, Double-Blinded, Placebo-Controlled Trial to Investigate the Efficacy, Safety, and Tolerability of Efgartigimod PH20 SC in Adult Patients With Pemphigus (Vulgaris or Foliaceus) (ADDRESS)

Short Title:

Not applicable.

Indication:

Pemphigus

Trial Sites/Countries:

This is a global, multicenter trial

Target Population:

Adult patients with moderate to severe pemphigus vulgaris (PV) or pemphigus foliaceus (PF)

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

Efgartigimod PH20 SC will be administered by subcutaneous (SC) injection on day 1 and day 8 at a dose of [redacted] mg, followed by weekly SC administrations of 1000 mg until complete remission on minimal therapy (CRmin).

Comparator, Dose, and Mode of Administration:

Participants will also be administered placebo with the same regimen.

Rationale:

In the previous trial ARGX-113-1701, a phase 2, open-label, proof-of-concept trial in mild-to-moderate PV and PF, efgartigimod was found to rapidly decrease the serum levels of pathogenic anti-desmoglein (Dsg)-1 antibodies for PV and PF and anti-Dsg-3 antibodies for PV. Decreases in these autoantibodies were associated with clinical improvement and reduction in disease activity and progression, as shown by results on the Pemphigus Disease Area Index (PDAI) scoring system. Efgartigimod was found to have a fast onset of action in that disease control (DC), defined as the absence of new lesions and the start of healing of established lesions, was achieved in 24 out of 31 participants (77.4%) within 4 weeks. Weekly or biweekly efgartigimod administration with an add-on therapy of stable low doses of oral prednisone (0.25–0.5 mg/kg/day) resulted in complete clinical remission (CR), defined as the absence of new lesions and complete healing of established lesions, in a majority of these participants in 2 to 13 weeks.

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; 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 an adjunctive treatment to a short course of prednisone, rituximab 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 intravenous (IV) rituximab frequently results in infusion-related reactions (IRRs) and adverse events (AEs), which may be of late onset. 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.[1]

Consequently, 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 (CR at tapered prednisone dose), and a favorable safety profile.

This trial 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, the administration of which will lead to early disease remission at minimal prednisone dose. The efficacy, safety, patient outcome measures, tolerability, immunogenicity, pharmacokinetics (PK), and pharmacodynamics (PD) of efgartigimod PH20 SC will be evaluated in participants with PV or PF.

Objectives and Endpoints

The objectives and endpoints are applicable globally, except for IgG subtypes and exploratory objectives/endpoints, which are not assessed in China.

Objectives	Endpoints
Primary	
• To demonstrate the efficacy of efgartigimod PH20 SC compared to placebo in the treatment of participants with PV	• Proportion of PV participants who achieve CRmin within 30 weeks
Secondary	
• To demonstrate the efficacy of efgartigimod PH20 SC in the treatment of participants with PV or PF	<u>Key Secondary Endpoints</u> • Proportion of PV and PF participants who achieve CRmin within 30 weeks • Cumulative prednisone dose over the trial in PV participants • Time to CR in PV participants • Time to DC in PV participants <u>Other Secondary Endpoints</u> • Proportion of PF participants who achieve CRmin within 30 weeks • Cumulative prednisone dose over the trial in PV and PF participants • Time to CR in PV and PF participants • Time to DC in PV and PF participants • Rate of treatment failure

Objectives	Endpoints
	• Rate of flare • PDAI at each visit
• To assess the safety of 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 signs, physical examination, electrocardiogram (ECG), and clinical laboratory safety evaluations
• 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) Scale • Autoimmune Bullous Disease Quality of Life (ABQOL) score
• To evaluate the 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
• To evaluate the immunogenicity of efgartigimod PH20 SC in participants with PV or PF	• Incidence and prevalence of anti-drug antibodies (ADAs) against efgartigimod and antibodies against recombinant human hyaluronidase (rHuPH20)
• To evaluate the competency of participants or caregivers to self-administer efgartigimod PH20 SC	• Number and percentage of participants or caregivers completing the self-administration training • Number and percentage of participants or caregivers determined by the site staff to be sufficiently competent to self-administer efgartigimod PH20 SC • Number and percentage of participants or caregivers that self-administer efgartigimod PH20 SC under site staff supervision
Exploratory	
• To evaluate the disease-specific genetic background and effects of efgartigimod PH20	• Anti-Dsg-1 and -3 autoantibody subtypes and autoantibody reactivity to Dsg domains and other antigens

Objectives	Endpoints
SC on the serological and immunological profiles of participants with PV or PF	• Lymphocyte dynamic changes • Serum cytokines profiles • DNA and RNA genetic profiles
• To evaluate the effects of efgartigimod PH20 SC on markers of pemphigus pathology in skin of participants with PV or PF	• Markers of pemphigus pathology in lesional and non-lesional skin

Overall Design

This is a prospective, multicenter, randomized, double-blinded, placebo-controlled trial to investigate the efficacy, safety, patient outcome measures, tolerability, immunogenicity, PK, and PD of efgartigimod PH20 SC in adult participants aged from 18 years with PV or PF. Enrolled participants are either those who are newly diagnosed or experiencing flare as follows:

- Moderate to severe (PDAI activity score ≥15) newly diagnosed and naïve to treatment.
- Moderate to severe (PDAI activity score ≥15) newly diagnosed while receiving a first course of oral prednisone (or equivalent). According to clinical judgment, the participant has shown no significant improvement of PV or PF signs for at least 2 weeks before baseline and is considered fit to start prednisone treatment at 0.5 mg/kg daily (qd) at baseline.
- Moderate to severe (PDAI activity score ≥15), experiencing flare, and off prednisone therapy ± a conventional immunosuppressant (eg, azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil) or dapsone. Note: conventional immunosuppressants and dapsone must be discontinued before baseline.
- Moderate to severe (PDAI activity score ≥15), experiencing flare, while receiving a tapered dose of oral prednisone (or equivalent), provided that prednisone (or equivalent) has been given at stable dose ± a conventional immunosuppressant (eg, azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil) or dapsone and participants are fit to start prednisone treatment at 0.5 mg/kg qd at baseline. Note: conventional immunosuppressants and dapsone must be discontinued before baseline.

The trial comprises a screening period of up to 3 weeks, a treatment period of up to 30 weeks, and an 8-week follow-up period for participants who do not enroll into the open-label extension (OLE) trial ARGX-113-1905.

After confirmation of eligibility, participants will be randomized in a 2:1 ratio to receive efgartigimod PH20 SC or placebo, as follows:

- Efgartigimod PH20 SC will be administered by SC injection on day 1 and day 8 at a dose of [redacted] mg, followed by weekly administrations of 1000 mg until CRmin is observed. Efgartigimod PH20 SC will be administered at on-site visits until CR, with a minimum of 6 weekly on-site visits (W1 to W6). After achieving CR, efgartigimod PH20 SC will be administered at on-site visits or at home by a nurse until CRmin is achieved.

- Placebo (vehicle with 2000 U/mL of rHuPH20) SC will be administered using the same regimen.

All participants or their caregivers will be invited to receive training for future self-administration of efgartigimod PH20 SC in the OLE trial ARGX-113-1905. The caregiver is a person of legal age that the participant proposes to perform the administrations. If the participants or caregivers have successfully completed self-administration training to the satisfaction of authorized staff, then the participants or caregivers may self-administer the next injections at the site under supervision of authorized staff.

CR is defined as the absence of new lesions and complete healing of established lesions (except for post-inflammatory hyperpigmentation or erythema from resolving lesions). CRmin is 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). Randomization will be stratified by disease status (experiencing flare and newly diagnosed), disease severity (PDAI activity score <30 and PDAI activity score ≥30), and body weight (<77.5 kg and ≥77.5 kg) at baseline. Participants with severe PV or PF (PDAI activity score ≥45) will comprise a maximum of 30% of the overall trial population.

All participants, regardless of treatment assignment, will concomitantly receive oral prednisone (or equivalent such as prednisolone) at a starting dose of 0.5 mg/kg qd. Except for oral prednisone (or equivalent), no other systemic therapies (eg, immunosuppressants, intravenous immunoglobulin [IVIg]), immunoadsorption, anti-CD20 biologics) will be permitted during the trial.

Participants will visit the clinic weekly until CR and for a minimum of 6 on-site visits, V1(BL)/W1 to W6, to receive investigational medicinal product (IMP) and to be evaluated for disease activity and disease outcome. After CR, IMP will be administered weekly at on-site or home visits by a nurse until CRmin. At any post-baseline 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 (refer to Table 3) 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 post-baseline visit before DC
- Insufficient clinical change: absence of DC after 3 to 4 weeks of the participant being treated at the starting baseline prednisone (or equivalent) 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, 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.

For participants achieving DC with a daily prednisone dose of 0.5 mg/kg, prednisone will be maintained at 0.5 mg/kg qd until CR and 2 weeks thereafter, or until end of consolidation (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) 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), the prednisone dose will be maintained until 2 weeks after achieving DC, then tapering will be performed according to the following stepwise procedure: dose reductions by 0.25 mg/kg qd (according to Table 3) every 2 weeks until the starting dose is reached (ie, 0.5 mg/kg qd). Then the starting dose (0.5 mg/kg qd) 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 at least 4 weeks. Further tapering will be performed thereafter, as long as CR or EoC are sustained. The rules for tapering are shown in Table 3. 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 until CRmin has been achieved. Prednisone can then be further tapered upon clinical judgment by the investigator.

In case of flare in the period between DC and CRmin, the prednisone dose will be increased. A flare is defined by 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. 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 prednisone dose that is 2 dose levels above the dose at which the flare between DC and CRmin therapy is observed and that is at least 0.3 mg/kg/day (eg, according to Table 3) will be considered treatment failures. At visits when at least 1 new lesion is observed or established lesions remain extensive without being defined as a flare, the prednisone dose will be maintained or may be increased, according to clinical judgment. If the lesion resolves, then tapering of the prednisone dose will be pursued as planned.

Participants who experience treatment failure, or flare after achieving CRmin, will be allowed to roll over into the OLE trial ARGX-113-1905 earlier than W31. Participants who do not roll over into the OLE trial ARGX-113-1905 will complete the treatment-free follow-up period. Participants experiencing an SAE related to prednisone may also benefit from an early roll over to the OLE trial ARGX-113-1905, according to clinical judgment.

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

Disclosure Statement: ARGX-113-1904 is a double-blinded, randomized, parallel-group trial to evaluate efficacy of fixed doses of efgartigimod PH20 SC compared to placebo.

Number of Participants:

- Approximately 213 participants with PV or PF will be randomized as follows:Approximately 183 participants with PV will be randomized in a 2:1 ratio to receive efgartigimod PH20 SC or placebo, respectively. The target number of Japanese participants with PV is 9 (included in the 183 participants globally). Among

the Japanese participants with PV, the randomization ratio will also be 2:1 to receive efgartigimod PH20 SC or placebo, respectively.

- Up to approximately 30 participants with PF may be randomized in a 2:1 ratio to receive efgartigimod PH20 SC or placebo, respectively. The target range for the number of Japanese participants with PF is 1 to 3 (included in the 30 participants globally). Among the Japanese participants with PF, the randomization ratio will also be 2:1 to receive efgartigimod PH20 SC or placebo, respectively.

For Japanese participants enrolled in sites in Japan only: A Japanese participant is defined as a participant whose parents and 4 grandparents are Japanese, and who has Japanese nationality, was born in Japan, has not lived outside of Japan for a total of >10 years, and currently lives in Japan.

Intervention Groups and Duration:

The maximum possible total trial duration for each participant is up to 41 weeks:

- Screening period: up to 3 weeks
- Treatment period: up to 30 weeks from baseline
- Follow-up period: up to 8 weeks after the last dose of IMP for participants who do not enroll in the OLE trial

Data Safety Monitoring Board: Yes

See Section 10.1.5.1.

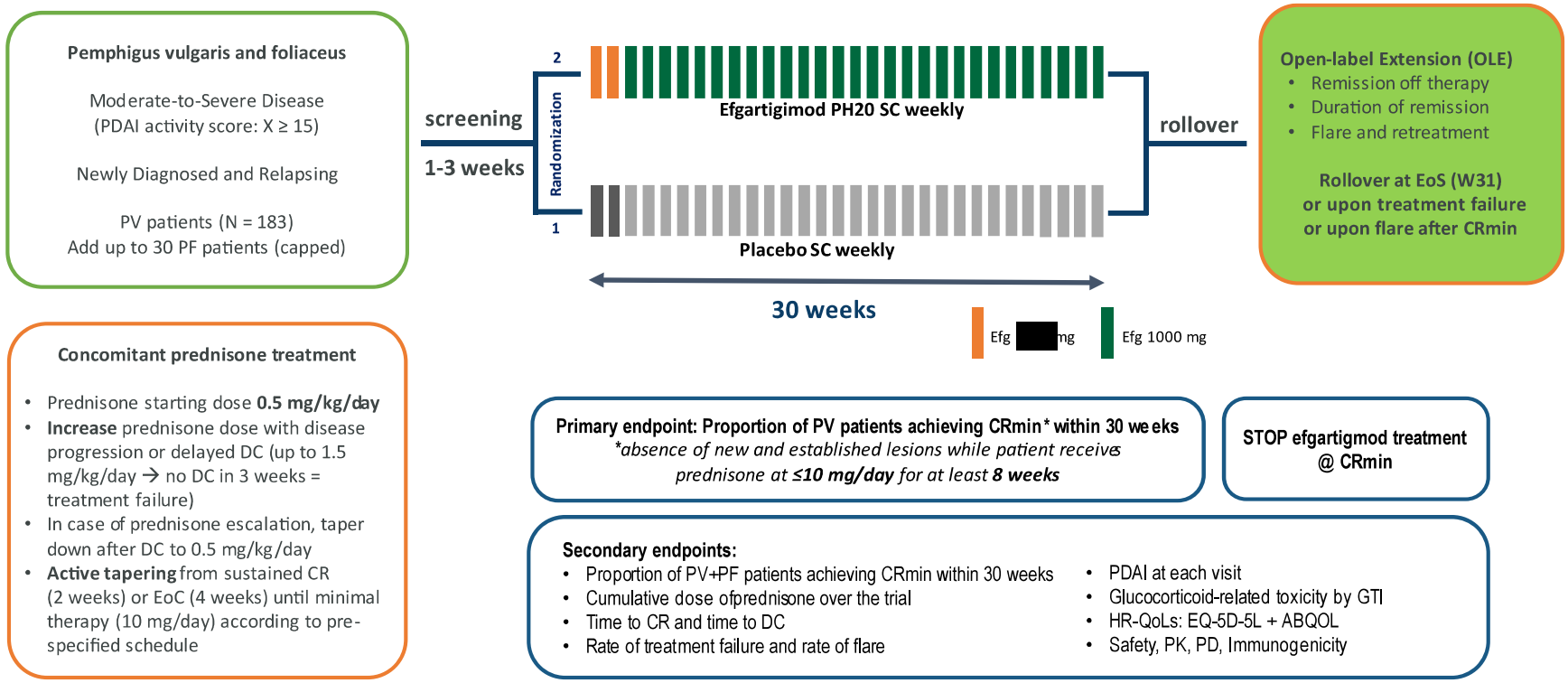
Definitions of Clinical Terms:

- **Complete clinical remission (CR):** the absence of new lesions and complete healing of established lesions (except for post-inflammatory 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: In this trial, when 10 mg/day is reached, this dose level must be maintained for 8 weeks until CRmin has been achieved)
- **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 post-baseline 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:** 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 a flare will be recorded as new transient or new persistent lesions. Transient new lesions are defined as new lesions that heal within 1 week. Persistent new lesions are defined as new lesions that last more than 1 week.
- **Treatment failure:** absence of DC with oral prednisone 1.5 mg/kg/day for a minimum of 3 weeks, or flare between DC and CRmin that is not controlled by a prednisone dose that is 2 dose levels above the dose at which the flare is observed and that is at least 0.3 mg/kg qd (refer to Table 3), or the occurrence of an SAE considered related to prednisone by the investigator.

1.2. Schema

Figure 1: Schema Detailing IMP Treatment and Assessments for Trial ARGX-113-1904



ABQOL=Autoimmune Bullous Disease Quality of Life; CR=complete clinical remission; CRmin=complete remission on minimal therapy; DC=disease control; Efg=efgartigimod PH20 SC; EoC=end of consolidation; EoS=end of study; EQ-5D-5L=EuroQol 5-dimension 5-level; GTI=Glucocorticoid Toxicity Index; OLE=open-label extension; PD=pharmacodynamics; PDAI=Pemphigus Disease Area Index; PF=pemphigus foliaceus; PK=pharmacokinetics; PV=pemphigus vulgaris; SC=subcutaneous.

1.3. Schedule of Activities

The schedule of activities is applicable globally, except for China. The China-specific Schedule of Activities is provided in Section 10.16.1.1.

Table 1: Schedule of Activities for Trial ARGX-113-1904

Trial Period	**Screening**	**Treatment**						**EoS/ ED[a]**	**UNS[b]**	**Follow-up**	
		V1 (BL)	**V2**	**Observational visits**	**IMP admin only visit**	**Observational visits**					
Visit Number				**Weekly on-site visits until CR[c]**	**Weekly home or on-site visits until CRmin[d]**	**On-site visits every 4 weeks until CRmin**	**On-site visits every 4 weeks after CRmin until W31**	**W31**		**Follow-up W34**	**Follow-up W38[e]**
Trial Day/Week	**D-21 to D-1**	**D1 (W1)**	**D8 (W2)**	**D15 (W3) until CR**	**CR until CRmin**	**CR until CRmin**	**CRmin until W31**	**W31**		**EoS/ED +3W**	**EoS/ED +7W**
Visit Window		**±0 days**	**±2 days[f]**	**V1 + 7× ±2 days[f]**				**±2 days[f]**		**±3 days[f]**	
Assessment/ Procedure											
Informed consent[g]	X										
Inclusion/exclusion criteria	X	X									
DIF/histopathology[h]	X										
Concomitant therapies/procedures	X	Continuous monitoring									
Karnofsky performance score	X										
Demography	X										
Height and weight[i]	X			X[i]		X[i]	X[i]	X			

Trial Period	**Screening**	**Treatment**						**EoS/ ED[a]**	**UNS[b]**	**Follow-up**	
		V1 (BL)	**V2**	**Observational visits**	**IMP admin only visit**	**Observational visits**					
Visit Number				**Weekly on-site visits until CR[c]**	**Weekly home or on-site visits until CRmin[d]**	**On-site visits every 4 weeks until CRmin**	**On-site visits every 4 weeks after CRmin until W31**	**W31**		**Follow-up W34**	**Follow-up W38[e]**
Trial Day/Week	**D-21 to D-1**	**D1 (W1)**	**D8 (W2)**	**D15 (W3) until CR**	**CR until CRmin**	**CR until CRmin**	**CRmin until W31**	**W31**		**EoS/ED +3W**	**EoS/ED +7W**
Visit Window		**±0 days**	**±2 days[f]**	**V1 + 7× ±2 days[f]**				**±2 days[f]**		**±3 days[f]**	
Physical examination and vital signs[j,k]	X	X	X	X		X	X	X	X	X	X
ECG[j]	X			X[l]		X[l]		X			
Medical and surgical history	X										
Randomization[m]		X									
Urinalysis[j,n,o]	X	X	X	X		X	X	X	X[b]	X	X
Urine pregnancy test[j,p]		X		X[p]		X	X	X	X[b]	X	X
Blood sampling:											
Active viral infection test[q]	X										
Serum pregnancy test[r]	X										
Clinical chemistry & hematology[j,o,s]	X	X	X	X		X	X	X	X[b]	X	X

Trial Period	**Screening**	**Treatment**						**EoS/ ED[a]**	**UNS[b]**	**Follow-up**	
		V1 (BL)	**V2**	**Observational visits**	**IMP admin only visit**	**Observational visits**					
Visit Number				**Weekly on-site visits until CR[c]**	**Weekly home or on-site visits until CRmin[d]**	**On-site visits every 4 weeks until CRmin**	**On-site visits every 4 weeks after CRmin until W31**	**W31**		**Follow-up W34**	**Follow-up W38[e]**
Trial Day/Week	**D-21 to D-1**	**D1 (W1)**	**D8 (W2)**	**D15 (W3) until CR**	**CR until CRmin**	**CR until CRmin**	**CRmin until W31**	**W31**		**EoS/ED +3W**	**EoS/ED +7W**
Visit Window		**±0 days**	**±2 days[f]**	**V1 + 7× ±2 days[f]**				**±2 days[f]**		**±3 days[f]**	
Anti-Dsg-1 and anti-Dsg-3 antibodies[j,o]	X	X	X	X		X	X	X	X[b]	X	X
PK[j,o,t]		X	X[t]	X		X	X	X	X[b,t]	X	X
Total IgG and IgG subtypes[j,o,u]	X	X	X	X		X	X	X	X[b]	X	X
Vaccination antibodies[j,o,v]	X	X	X	X		X	X	X	X[b]	X	X
Anti-drug antibodies[j,w]		X		X (every 2 weeks)		X	X	X		X	X
IgG autoantibody subtypes/specificity and cytokines[j,x]		X		X[x]		X	X	X	X[b]	X	X
B- and T-cell populations[j]		X		X[y]				X			
RNA transcriptional profile[j]		X		X[y]				X			

Trial Period	**Screening**	**Treatment**						**EoS/ ED[a]**	**UNS[b]**	**Follow-up**	
		V1 (BL)	**V2**	**Observational visits**	**IMP admin only visit**	**Observational visits**					
Visit Number				**Weekly on-site visits until CR[c]**	**Weekly home or on-site visits until CRmin[d]**	**On-site visits every 4 weeks until CRmin**	**On-site visits every 4 weeks after CRmin until W31**	**W31**		**Follow-up W34**	**Follow-up W38[e]**
Trial Day/Week	**D-21 to D-1**	**D1 (W1)**	**D8 (W2)**	**D15 (W3) until CR**	**CR until CRmin**	**CR until CRmin**	**CRmin until W31**	**W31**		**EoS/ED +3W**	**EoS/ED +7W**
Visit Window		**±0 days**	**±2 days[f]**	**V1 + 7× ±2 days[f]**				**±2 days[f]**		**±3 days[f]**	
HLA/non-HLA genotyping[j]		X		X[z]							
Substudies:											
Skin biopsies (at selected sites)[j,aa]		X		X[aa]				X[aa]			
Photography (at selected sites)[j,bb]		X	X[bb]	X[bb]					X[b,bb]		
QoL Assessments:											
EQ-5D-5L[j,cc]		X		X[dd]		X[dd]	X[dd]	X			
ABQOL[j,cc]		X		X[dd]		X[dd]	X[dd]	X			
GTI[j]		X		X[ee]		X[ee]	X[ee]	X			
IMP self-administration training[ff]				X		X					
IMP administration[gg]		X ([redacted] mg)	X ([redacted] mg)	X	X	X			X[b]		
PDAI[j]	X	X	X	X		X	X	X	X	X	X

Trial Period	Screening	Treatment						EoS/ ED[a]	UNS[b]	Follow-up	
		V1 (BL)	V2	Observational visits	IMP admin only visit	Observational visits					
Visit Number				Weekly on-site visits until CR[c]	Weekly home or on-site visits until CRmin[d]	On-site visits every 4 weeks until CRmin	On-site visits every 4 weeks after CRmin until W31	W31		Follow-up W34	Follow-up W38[e]
Trial Day/Week	D-21 to D-1	D1 (W1)	D8 (W2)	D15 (W3) until CR	CR until CRmin	CR until CRmin	CRmin until W31	W31		EoS/ED +3W	EoS/ED +7W
Visit Window		±0 days	±2 days[f]	V1 + 7× ±2 days[f]				±2 days[f]		±3 days[f]	
Disease assessment[hh]			X	X		X	X	X	X	X	X
Prednisone taper[ii]				X	X	X	X	X	X	X	X
AE monitoring	Continuous monitoring										

ABQOL=Autoimmune Bullous Disease Quality of Life; admin=administration; BL=baseline; BMI=body mass index; CR=complete clinical remission; CRmin=CR on minimal therapy; D=day; DC=disease control; DIF=direct immunofluorescence; Dsg=desmoglein; ECG=electrocardiogram; ED=early discontinuation; EoC=end of consolidation; EoS=end of study; FSH=follicle-stimulating hormone; GTI=Glucocorticoid Toxicity Index; HLA=human leukocyte antigen; IgG=immunoglobulin G; ICF=informed consent form; IMP=investigational medicinal product; OLE=open-label extension; PDAI=Pemphigus Disease Area Index; PK=pharmacokinetics; RBC=red blood cells; UNS=unscheduled visit; WBC=white blood cells; W=week; V=visit

[a] All participants will complete EoS/ED, which will be the end of the trial for participants who enroll in the OLE trial ARGX-113-1905. Participants who do not enroll in the OLE trial ARGX 113 1905 will complete the follow-up visits at W34 and W38.

[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. See Section Section 8 for more information. Participants with new lesions or flare after achieving CR should return to weekly on-site visits until CR is achieved again.

[c] A minimum of 6 on-site visits, V1(BL)/W1 to W6, are required before switching to home administrations, even if CR is achieved earlier than W6. The W7 visit is the first eligible "IMP administration only" visit (refer to column "Weekly home or on-site visits until CRmin"), at home or on-site, if CR is achieved between W1 and W6.

[d] Home visits are allowed once participants achieve CR, but not before W7. The investigator should call the participant every 2 weeks until CRmin is achieved to confirm the participant is still in CR. On-site visits may continue at the investigator's discretion.

[e] W38 (follow-up visit 2) is the end of the trial for participants who do not enroll in the OLE trial ARGX-113-1905. The W38 follow-up visit will only be required for those participants who were still receiving IMP at least once from W27 onward. For participants who ended treatment prior to W27, W34 will be the end of the trial.

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

[g] No trial-related assessments can be initiated before the participant has provided a signed ICF.
[h] Only required if not available from medical history.
[i] Height and weight will be measured (and BMI will be calculated accordingly) at screening, at week W15 (or the next on-site visit if W15 does not coincide with an on-site visit), and EoS/ED. Weight will also be measured if there has been an obvious change since the last measurement.
[j] At visits in which IMP is administered, the assessment or procedure should be completed before dosing.
[k] A complete physical examination will be completed at each on-site visit. Vital sign measurements include systolic and diastolic blood pressure, heart rate, and body temperature. Supine blood pressure and heart rate will be measured using standard equipment after at least 10 minutes rest.
[l] ECG to be taken at W12. If the W12 visit does not coincide with an on-site visit, then the assessment should be performed at the next on-site visit. ECG (heart rate, PR, QT, and QRS interval) will be read centrally. QTcF and QTcB will be calculated.
[m] Randomization will take place on day 1 after all eligibility checks are confirmed (eg, PDAI) and before other baseline assessments are run, and prior to dosing.
[n] 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 test results are abnormal).
[o] Samples will be taken every week from V1(BL)/W1 to W9 and then every 4 weeks and at the visit where CR is observed. Once CR is achieved, samples will be taken every 4 weeks at on-site visits until EoS/ED. For participants achieving CR between V1(BL)/W1 and W6, samples will be taken weekly from W1 to W6 and then every 4 weeks at on-site visits until EoS/ED.
[p] A urine pregnancy test will be conducted and analyzed locally during on-site visits at least once every 4 weeks (before and after CR) and at the time of CR.
[q] Viral testing for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc), hepatitis B virus (HBV) DNA, hepatitis C virus (HCV) antibodies, HCV messenger RNA (mRNA), and human immunodeficiency virus (HIV) antibodies.
[r] At screening, a serum pregnancy test must be performed in women of childbearing potential or FSH test to confirm postmenopausal status.
[s] Clinical blood laboratory tests will include hematology and blood chemistry at all visits and international normalized ratio (INR) or activated partial thromboplastin time (aPTT) at screening only. The hematology profile includes hemoglobin, hematocrit, mean corpuscular volume (MCV), RBC count, platelet count, WBC count with differential. The blood chemistry profile includes sodium, potassium, calcium, hemoglobin A1c (HbA1c), creatinine, creatinine clearance, blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, gamma-glutamyl transferase (GGT), C-reactive protein (CRP), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol, triglycerides, uric acid, total protein, and albumin.
[t] For PK assessment, blood samples will be taken predose (within 2 hours before the start of IMP administration at visits where IMP is administered). An additional PK sample will be taken on D3 and on D11 (±1 day) until samples from 24 participants are obtained. At unscheduled visits blood samples for PK will only be taken if IMP is administered.
[u] At screening, total IgG will be measured as part of inclusion and exclusion criteria. The pharmacodynamic (PD) biomarkers total IgG and its subtypes (IgG1, IgG2, IgG3, and IgG4) will be measured centrally from a blood sample taken predose.
[v] An extra sample(s) will be taken for additional research (including vaccination antibodies and other additional research). The actual testing of vaccination antibodies depends on (a) whether a vaccination was given to the participant; (b) whether a test is available for the vaccination given to the participant; and (c) whether the sample requirements (serum, volume, frozen sample, storage duration) match the serum samples taken and reserved for this. Timepoints for analysis will be decided upon occurrence of vaccination during the study.
[w] Anti-drug antibodies to efgartigimod (in serum samples) and antibodies against rHuPH20 (in plasma samples) will be tested predose every 2 weeks from V1(BL)/W1 to W9 and then every 4 weeks at on-site visits and at the visit where CR is observed. Once CR is achieved, samples will be taken every 4 weeks at on-site visits until EoS/ED. For participants achieving CR between V1(BL)/W1 and W6, samples will be taken predose at V1(BL)/W1, W3, W5, the visit

where CR is observed, W10, and then every 4 weeks at on-site visits until EoS/ED. Neutralizing antibodies (Nab) will be tested for all confirmed positive ADA samples.

[x] Blood sampling for IgG autoantibody subtypes and specificity will be taken every 4 weeks (V1[BL]/W1, W5, W9, etc) and at the visit where CR is observed. Once CR is achieved, samples will be taken every 4 weeks at on-site visits until EoS/ED. For participants achieving CR between V1(BL)/W1 and W6, samples will be taken at V1(BL)/W1, W5, the visit where CR is observed, W10, and then every 4 weeks at on-site visits until EoS/ED. Serum aliquots from all time points will be used for IgG subtype and specificity analyses. For cytokines and complementary specificity analyses, aliquots from baseline, after 4 weeks (W5), W13 (or the visit at which CR is observed if before W13), and EoS/ED will be used.

[y] Samples for B- and T-cell populations and RNA transcriptional profiles will be performed at baseline, after 4 weeks (W5) and at W13 (or the visit at which CR is observed if before W13) and at EoS/ED.

[z] HLA/non-HLA genotyping will be performed at baseline and D15.

[aa] Two 4 mm skin biopsies, 1 peri-lesional and 1 non-lesional, will be collected solely based on voluntary participation at baseline and after healing of 80% of blisters (EoC) or at EoS/ED (in case EoC has not been achieved) for scientific purposes.

[bb] 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 timepoints.

[cc] Questionnaires are to be completed prior to any other activity.

[dd] Assessments will be performed at baseline, after 4 weeks (W5), W15, and EoS/ED visits. If the W15 visit does not coincide with an on-site visit, then the assessment should be performed at the next on-site visit.

[ee] The GTI assessment will be performed only at baseline, W15 and EoS/ED. If W15 does not coincide with an on-site visit, then the assessment should be performed at the next on-site visit.

[ff] Participants will be trained to self-administer IMP (foreseen in the OLE trial; not in the ARGX-113-1904 trial) during the first 4 visits as of V3 when IMP is administered; thereafter, training for self-administration is optional (only if needed).

[gg] IMP will be administered until CRmin. To ensure proper safety monitoring, participants should remain at the site for at least 1 hour after the first administration and for 15 minutes after subsequent administrations. Participants will be released according to their clinical status. For Germany-specific monitoring instructions, refer to Section 10.16.2.1. Participants who experience treatment failure, or flare after achieving CRmin, will be allowed to roll over into the OLE trial ARGX-113-1905 earlier than W31. Participants who do not roll over into trial ARGX-113-1905 will complete the treatment-free follow-up period.

[hh] Disease assessment parameters include disease control (DC), end of consolidation (EoC), complete clinical remission (CR), complete remission on minimal therapy (CRmin), complete remission off therapy (CRoff), flare, and treatment failure. Participants who have achieved CR and have new lesions should come to the clinic for a UNS for disease assessment.

[ii] 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

The proposed trial is a prospective, multicenter, randomized, double-blinded, placebo-controlled trial to investigate the efficacy, safety, tolerability, immunogenicity, pharmacokinetics (PK), and pharmacodynamics (PD) of efgartigimod PH20 SC in adult participants aged from 18 years with moderate to severe pemphigus vulgaris (PV) or pemphigus foliaceus (PF). This trial 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, the administration of which will lead to early disease remission at minimal prednisone dose.

In order to allow for a convenient subcutaneous (SC) administration with efgartigimod to achieve the targeted exposure and PD effect, efgartigimod will be coformulated with recombinant human hyaluronidase PH20 (rHuPH20). This compound is being used in coformulations with approved therapeutic antibodies to facilitate SC administration with volumes >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.

China- and Germany-specific modifications to the protocol are outlined in Section 10.16 .

2.1. Trial Rationale

The mainstays of therapy in PV are systemic corticosteroids and rituximab. Corticosteroids also 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, 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 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 intravenous (IV) rituximab frequently results in infusion-related reactions (IRRs) and adverse events (AEs), which may be of late onset. The late onset of action of rituximab is well-documented in the literature: in a meta-analysis reviewing 30 studies, it was shown that rituximab did not result in an early achievement of disease control (DC) (mean time from first infusion: 6–7 weeks[1]) or CRmin (mean of 6–7 months on minimal prednisone therapy, 9 months off-therapy[1,2]). Furthermore, rituximab therapy carries the risk of inducing serious adverse events (SAEs, eg, 33% of infections[3]). Late onset neutropenia and hypogammaglobulinemia and the risk for patients to develop potentially fatal infections (eg, *Pneumocystis carinii*, multifocal leukoencephalopathy, septicemia) require a long-term monitoring of the clinical and immunological status of the patients under rituximab.[4]

Other therapies for PV are now classified as corticosteroid-sparing agents.[5] They include immunosuppressants (azathioprine, mycophenolate mofetil, cyclophosphamide), intravenous

immunoglobulin (IVIg) and immunoadsorption. Among immunosuppressants, azathioprine and mycophenolate mofetil are preferentially used as first-line corticosteroid-sparing agents, whereas cyclophosphamide is more considered as a second-line adjuvant treatment.[5] Because immunosuppressants have a delayed onset of action, they have no significant effect on DC,[6] and their use as monotherapy is only conceivable in mild and stable cases when a delay in achieving DC can be tolerated. The most documented effects of immunosuppressants are a decrease in the occurrence of flares, by about 30% compared to prednisone alone,[7] and a saving effect on the consumption of prednisone. There is evidence that azathioprine has a greater corticosteroid-sparing effect.[8]

Like corticosteroids and rituximab, the side effects of immunosuppressants are of clinical concern. They all may result in infections related to their broad immunosuppressive action. Azathioprine can cause potentially life-threatening bone marrow suppression, hepatitis, and is associated with increased risk of lymphoma. Assessment of methyltransferase activity of each individual before beginning azathioprine treatment is recommended, in order to prevent overdosage of the drug. The most frequent side effects of mycophenolate mofetil are gastrointestinal disturbance and hematologic disorders (lymphocytopenia). It is contraindicated in pregnant women and patients with renal insufficiency. Cyclophosphamide has an unfavorable safety profile and, for this reason, must be used as a second-line therapeutic option when immunosuppressants are indicated. Its main side effects include hemorrhagic cystitis, hematologic abnormalities, cancer, and infertility.

Neonatal crystallized fragment receptor (FcRn) inhibition is the mode of action shared by IVIg and efgartigimod. IVIg is today the only therapy other than corticosteroids that has demonstrated to improve DC (4–8 weeks), indicating the short onset of action of the drug.[9] It has been shown to also have a corticosteroid saving effect. Its use as a monotherapy has been reported in a few case series.[10] Interestingly, IVIg has been tested in combination with rituximab (sequential administration of 3 weekly infusions of rituximab and then IVIg at week 4; 6 cycles in 6 months[11]). Nine out of 11 patients reached complete remission as early as 8 to 11 weeks.

Overall, IVIg is relatively safe to use. Its main side effects are hypertension, coagulation disorders, aseptic meningitis and renal insufficiency. However, it is an expensive blood-derived product that must be used at high dosage (2 g/kg monthly) to achieve its immunomodulatory effects. Furthermore, it is not approved for the treatment of PV and other autoimmune bullous dermatoses (AIBD). Consequently, the availability of IVIg remains limited, especially in countries that have implemented a strict control of its use.

Immunoadsorption is a procedural treatment that consists of selectively removing the circulating immunoglobulin G (IgG) and pathogenic antibodies by extracorporeal adsorption from serum with protein A. Plasmapheresis is a less common alternative, involving plasma exchange using albumin and fresh frozen plasma. These treatments are only available in a few specialized centers, and thus are indicated in cases resistant or intolerant to other adjuvant therapies. When immunoadsorption is used, it is typically combined with immunosuppressants to prevent a rebound phenomenon, with a post-procedural rise in autoantibodies and transient lesion flare.[12] Otherwise, immunoadsorption treatment results in early DC in a majority of PV patients, ie, 4 to 8 weeks.[13] Its combination with rituximab has also been tried with success.[14] Some procedure-related side effects have been described, including infections at the central catheter site that appear to be more frequent in the PV population than in the autoimmune non-PV population.[15]

Non-mainstay adjuvant therapies of PV include methotrexate and ciclosporin as immunosuppressants, dapsone, and tetracyclines associated or not with niacinamide. Dapsone at high doses frequently induces side effects (hemolysis, hepatitis). Local therapies such as potent topical corticosteroids and topical antibiotics are often helpful to amend the mucosal and superinfected cutaneous lesions, respectively.

Patients with PF typically follow the same type of management and monitoring of the clinical outcome measures as PV patients, although rituximab has not been labeled in the condition. Dapsone as initial treatment has been reported in mild cases, with a satisfactory outcome.[16]

There is a need in pemphigus patients for a safer drug with a rapid onset of action and a favorable safety profile that would achieve early DC, be corticosteroid sparing, and achieve and maintain CR, with or without a low dose of corticosteroids.

This trial 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, the administration of which will lead to early disease remission at minimal prednisone dose. The efficacy, safety, patient outcome measures, tolerability, immunogenicity, PK, and PD of efgartigimod PH20 SC will be evaluated in patients with PV or PF.

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.[17,18] 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.[19] 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 per million in Finland to around 1.5 per million in France, 4 to 5 per million in Italy and up to 8 per million in Greece and even 16 per million in Israel.[20] 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 a 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.[21] 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 supra-basal 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.[22]

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.[23] 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.[5]

Because Dsg-1 is expressed in the superficial portion of the epidermis, PF patients 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 patient reaches rapidly minimal corticosteroid dose (prednisone ≤10 mg/day) or even no concomitant treatment (off prednisone therapy).

The therapeutic management of patients 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, patients must be managed by referral centers, where they can be monitored carefully by experienced dermatologists. In many patients, 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 patients, consensual definitions of the most important clinical endpoints among national and international experts,[24] as well as regular guidelines for the diagnosis and treatment of these diseases are available.[2,10,25,26] 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.[27,28] 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 patient's daily life.[29]

According to the most recent international guideline,[22] 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.[30-32] Oral prednisone is the most commonly used corticosteroid. The starting oral prednisone dose is high, ranging from 1–2 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 3–4 weeks at the latest, the prednisone dose must be increased. In patients with very active disease, an IV bolus of corticosteroids (eg, methylprednisolone) may be preferred, especially at treatment initiation.

Tapering of oral prednisone is initiated as soon as DC is achieved or up to the end of 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 PV patients with prednisone could achieve a first complete remission on minimal dose after 12 months.[33] Flare occurred frequently, ie, in 45% of the cases within 6 months. Finally, the common course of PV is 1 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.[34] Meanwhile, the risk of corticosteroid-related side effects increased with treatment duration (osteoporosis, diabetes, hypertension, Cushing syndrome, cataract, glaucoma, infections, etc).[35] Accordingly, most PV patients 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 was primarily used in refractory PV patients, 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 (1–2 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[25]). 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 (0.5-1 mg/kg per day according to disease severity[2]). 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 issue of the respective Investigator's Brochures (IBs).

2.3.1. Risk Assessment

In clinical studies to date, efgartigimod has been well-tolerated in healthy adult subjects and patients 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 reported non-related 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 (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 haematoma* 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 subjects 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 subjects 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 healthy subjects or patients 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 electrocardiogram (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 rats and rabbits 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 rats 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 SC 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 coadministered 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 co-mixed with 2000 U/mL rHuPH20 was well-tolerated by all subjects. No deaths, 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%) subjects 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*) that was reported as moderate in severity. Dose-related effects were observed. All subjects recovered from their TEAEs by the end of the study, except for 1 subject who experienced 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 subjects (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 subjects with 1 or more abnormalities at the injection site appeared to increase with increasing SC doses of efgartigimod co-mixed with rHuPH20.

2.3.2. Benefit Assessment

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

In the phase 2 trial ARGX-113-1701 in participants with pemphigus, the efficacy of efgartigimod was supported by PD effects (effects on IgG, 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 were able to achieve DC with or without

concomitant prednisone, whereas CR was achieved in combination with low prednisone dose. Flare was prevented when efgartigimod was given at weekly intervals, before and after DC or CR.

In December 2021, the FDA approved efgartigimod for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody seropositive. In the phase 2 trial (ARGX-113-1602) of participants with gMG, 4 weekly IV infusions of 10 mg/kg efgartigimod led to statistically significant improvements in clinical scales and were well-tolerated.[36] Additionally, in a randomized, double-blinded, placebo-controlled, phase 3 trial in participants with gMG (ARGX-113-1704), the primary endpoint of the percentage of acetylcholine receptor–antibody (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 was met. 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 the phase 2 trial (ARGX-113-1603) in participants with ITP, efgartigimod resulted in a rapid and marked reduction of IgG antibodies (maximum mean reduction of 65%) and of all IgG subtypes.[37] 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 is under investigation in an ongoing phase 2 trial (ARGX-113-1802) in participants with chronic inflammatory demyelinating polyneuropathy (CIDP) using efgartigimod PH20 SC, which uses the same formulation used in the current trial in pemphigus participants.

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 pemphigus.

3. OBJECTIVES AND ENDPOINTS

The objectives and endpoints are applicable globally, except for IgG subtypes and exploratory objectives/endpoints which are not assessed in China.

Objectives	Endpoints
Primary	
• To demonstrate the efficacy of efgartigimod PH20 SC compared to placebo in the treatment of participants with PV	• Proportion of PV participants who achieve CRmin within 30 weeks
Secondary	
• To demonstrate the efficacy of efgartigimod PH20 SC in the treatment of participants with PV or PF	<u>Key Secondary Endpoints</u> • Proportion of PV and PF participants who achieve CRmin within 30 weeks • Cumulative prednisone dose over the trial in PV participants • Time to CR in PV participants • Time to DC in PV participants <u>Other Secondary Endpoints</u> • Proportion of PF participants who achieve CRmin within 30 weeks • Cumulative prednisone dose over the trial in PV and PF participants • Time to CR in PV and PF participants • Time to DC in PV and PF participants • Rate of treatment failure • Rate of flare • PDAI at each visit
• To assess the safety of efgartigimod PH20 SC in participants with PV or PF	• Incidence and severity of TEAEs, adverse events of special interest (AESIs), and SAEs by system organ class (SOC) and preferred term (PT) • Vital signs, physical examination, ECG, and clinical laboratory safety evaluations
• 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) Scale • ABQOL score
• To evaluate the 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
• To evaluate the immunogenicity of efgartigimod PH20 SC in participants with PV or PF	• Incidence and prevalence of anti-drug antibodies (ADAs) against efgartigimod and antibodies against recombinant human hyaluronidase (rHuPH20)
• To evaluate the competency of participants or caregivers to self-administer efgartigimod PH20 SC	• Number and percentage of participants or caregivers completing the self-administration training • Number and percentage of participants or caregivers determined by the site staff to be sufficiently competent to self-administer efgartigimod PH20 SC • Number and percentage of participants or caregivers that self-administer efgartigimod PH20 SC under site staff supervision
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 • Serum cytokines profiles • DNA and RNA genetic profiles
• To evaluate the effects of efgartigimod PH20 SC on markers of pemphigus pathology in skin of participants with PV or PF	• Markers of pemphigus pathology in lesional and non-lesional skin

4. TRIAL DESIGN

4.1. Overall Design

This is a prospective, multicenter, randomized, double-blinded, placebo-controlled trial to investigate the efficacy, safety, patient outcome measures, tolerability, immunogenicity, PK, and PD of efgartigimod PH20 SC in adult participants aged from 18 years with PV or PF. See Section 1.2 for a diagram of the trial design. Enrolled participants are those who are either newly diagnosed or experiencing flare as follows:

- Moderate to severe (PDAI activity score ≥15) newly diagnosed and naïve to treatment.
- Moderate to severe (PDAI activity score ≥15) newly diagnosed while receiving a first course of oral prednisone (or equivalent). According to clinical judgment, the participant has shown no significant improvement of PV or PF signs for at least 2 weeks before baseline and is considered fit to start prednisone treatment at 0.5 mg/kg daily (qd) at baseline.
- Moderate to severe (PDAI activity score ≥15), experiencing flare, and off prednisone therapy ± a conventional immunosuppressant (eg, azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil) or dapsone. Note: conventional immunosuppressants and dapsone must be discontinued before baseline.
- Moderate to severe (PDAI activity score ≥15), experiencing flare, while receiving a tapered dose of oral prednisone (or equivalent), provided that prednisone (or equivalent) has been given at stable dose ± a conventional immunosuppressant (eg, azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil) or dapsone and participants are fit to start prednisone treatment at 0.5 mg/kg qd at baseline. Note: conventional immunosuppressants and dapsone must be discontinued before baseline.

The trial comprises a screening period of up to 3 weeks, a treatment period of up to 30 weeks, and an 8-week follow-up period for participants who do not enroll into the OLE trial ARGX-113-1905.

After confirmation of eligibility, participants will be randomized in a 2:1 ratio to receive efgartigimod PH20 SC or placebo, as follows:

- Efgartigimod PH20 SC will be administered by SC injection on day 1 and day 8 at a dose of [redacted] mg, followed by weekly SC administrations of 1000 mg until CRmin is observed. Efgartigimod PH20 SC will be administered at on-site visits until CR. After achieving CR, efgartigimod PH20 SC will be administered at on-site visits or at home by a nurse until CRmin is achieved.
- Placebo (vehicle with 2000 U/mL of rHuPH20) SC will be administered using the same regimen.

All participants or their caregivers will be invited to receive training for future self-administration of IMP in the OLE trial ARGX-113-1905. The caregiver is a person of legal age that the participant proposes to perform the administrations. If the participants or caregivers have successfully completed self-administration training to the satisfaction of authorized staff, then the participants or caregivers may self-administer the next injections at the site under supervision of authorized staff.

CR is defined as the absence of new lesions and complete healing of established lesions (except for post-inflammatory hyperpigmentation or erythema from resolving lesions). CR on minimal therapy (CRmin) is 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). In non-Japanese participants, randomization will be stratified by disease status (experiencing flare and newly diagnosed), disease severity (PDAI activity score <30 and PDAI activity score ≥30), and body weight (<77.5 kg and ≥77.5 kg) at baseline. Participants with severe PV or PF (PDAI activity score ≥45) will comprise a maximum of 30% of the overall trial population.

All participants, regardless of treatment assignment, will concomitantly receive oral prednisone (or equivalent such as prednisolone) at 0.5 mg/kg qd starting dose. Except for oral prednisone (or equivalent), no other systemic therapies (eg, immunosuppressants, IVIg, immunoadsorption, anti-CD20 biologics) will be permitted during the trial.

Participants will visit the clinic weekly until CR and for a minimum of 6 weeks to receive IMP and be evaluated for disease activity and disease outcome. After CR, IMP will be administered weekly at on-site or at home visits by a nurse until CRmin. At any post-baseline 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 (refer to Table 3) 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 post-baseline visit before DC.
- Insufficient clinical change: absence of DC after 3 to 4 weeks of the participant being treated at the starting baseline prednisone (or equivalent) 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 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, 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.

For participants achieving DC with a daily prednisone dose of 0.5 mg/kg, prednisone will be maintained at 0.5 mg/kg qd until CR and 2 weeks thereafter, or until 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) 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), the prednisone dose will be maintained until 2 weeks after achieving DC, then tapering will be performed according to the following stepwise procedure: dose reductions by 0.25 mg/kg qd (according to Table 3) every 2 weeks until the starting dose is reached (ie, 0.5 mg/kg qd). Then the starting dose (0.5 mg/kg qd) 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 at least 4 weeks. Further tapering will be performed thereafter, as long as CR or EoC are sustained. The rules for tapering are shown in Table 3. 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 until CRmin has been achieved. Prednisone can then be further tapered upon clinical judgment by the investigator.

In case of flare in the period between DC and CRmin, the prednisone dose will be increased. A flare is defined by 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. 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 prednisone dose that is 2 dose levels above the dose at which the flare between DC and CRmin is observed and that is at least 0.3 mg/kg/day (eg, according to Table 3) will be considered treatment failures. At visits when at least 1 new lesion is observed or established lesions remain extensive without being defined as a flare, 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.

Participants who experience treatment failure, or flare after achieving CRmin, will be allowed to roll over into the OLE trial ARGX-113-1905 earlier than W31. Participants who do not roll over into the OLE trial ARGX-113-1905 will complete the treatment-free follow-up period. Participants experiencing an SAE related to prednisone may also benefit from an early roll over to the OLE trial, according to clinical judgment.

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

4.2. Scientific Rationale for Trial Design

Concomitant therapy of oral prednisone at a starting dose level of 0.5 mg/kg per day: The active treatment (efgartigimod PH20 SC) will be used in association with oral prednisone (or prednisolone as prednisone equivalent) at the starting dose of 0.5 mg/kg per day, because results of the phase 2 study ARGX-113-1701 showed that CR was achieved best in combination with prednisone at doses ranging from 0.25 to 0.5 mg/kg per day. Taking into account that the proposed trial plans to include participants of higher disease severity (moderate to severe, instead of mild-to-moderate in phase 2), a concomitant prednisone dose of 0.5 mg/kg per day has been chosen as a starting dose, with an active stepwise tapering schedule initiated when CR is achieved (Section 6.8.1).

Prednisone dose escalation for achieving DC: Disease activity varies among pemphigus participants. In addition, oral prednisone doses as part of standard of care ranges from 1.0–1.5 mg/kg per day. Rapid dose adjustment by incremental doses of prednisone is therefore allowed to achieve DC (Section 6.8.1). This approach is taken to allow for timely DC and therefore avoiding participants with uncontrolled disease symptoms dropping out of the trial early.

Dose escalation guidance is based on disease progression or insufficient clinical change before DC happens or flare. Whereas flare is well-defined by guidelines (appearance of 3 or more new lesions a month that do not heal within 1 week, or extension of established lesions), disease progression and insufficient clinical change are not defined by consensus. Accordingly, the trial protocol specifies that the assessment of these conditions will be based on clinical judgment. In order to facilitate some common judgments between investigators, recommendations for assessment of disease progression and insufficient clinical change are:

- For disease progression, an increase in the active PDAI activity score of at least 5 compared to baseline or the preceding visit, as observed at any post-baseline visit before DC
- For insufficient clinical change, the absence of DC for 3 to 4 weeks after baseline or after a new incremented dose of prednisone.

Treatment failure: Prednisone dose escalation in the trial will happen in a stepwise approach (from 0.5 to 0.75, 1, 1.25 and 1.5 mg/kg per day), investigators being able to increase the dose by 1 or more steps according to the severity of the disease progression. The prednisone dose of 1.5 mg/kg per day for 3 weeks without DC defines treatment failure, in accordance with the guidelines.[24] In such circumstances, participants will be considered as nonresponders and will be invited to roll over prematurely into the OLE (trial ARGX-113-1905). Additionally, flare between DC and CRmin that is not controlled by a prednisone dose that is 2 dose levels above the dose at which the flare is observed and that is of at least 0.3 mg/kg qd (refer to Table 3) or the occurrence of an SAE considered related to prednisone by the investigator will be defined as treatment failure.

Prednisone tapering: Two weeks after DC is achieved after an escalated prednisone dose above 0.5 mg/kg qd, prednisone tapering will begin (Section 6.8.1). Prednisone tapering is a procedure that is applied by all practitioners, in order to minimize the side effects of corticosteroids while preventing a flare of the disease. In this trial:

- Two-week intervals between tapering are defined with a step down of 0.25 mg/kg from 1.5 to 0.5 mg/kg per day (eg, from 1.5 to 1.25 mg/kg per day, then to 1 mg/kg and 0.75 mg/kg per day; refer to Table 3). The dosage of prednisone at which CR is achieved (which cannot be lower than the starting dose 0.5 mg/kg per day) will be maintained for 2 weeks after CR for observing a sustained CR, or prednisone tapering may be initiated or continued in case of sustained EoC (defined by the time at which no new lesions have developed for a minimum of 2 weeks and approximately 80% of lesions have healed) for at least 4 weeks.
- When CR is observed on daily prednisone of no lower than 0.5 mg/kg for 2 weeks, or when sustained EoC is observed, tapering may be initiated (see Section 6.8.1). 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 until CRmin has been achieved.

- When CRmin is achieved, prednisone can be tapered further upon clinical judgment, with the recommendation of a prednisone decrease by 2.5 mg/day every 4 weeks.

When transient lesions appear, prednisone tapering will be temporarily delayed, or prednisone may be increased according to clinical judgment. Dose escalation will be performed when flare occurs. Taken together, the trial aims to be as close as possible to the real-world clinical practice regarding the prednisone regimen policy, while it allows studying the potential of prednisone sparing when associated with efgartigimod PH20 SC treatment.

Definitions of clinical outcomes: Consensual definitions of the most important clinical outcomes have been established through international guidelines[24], and are now accepted by the vast majority of clinicians taking care of participants with PV and PF. They include in particular DC (no new lesions and established lesions beginning to heal), which corresponds to the beginning of the healing, and CR (no new lesions and established lesions completely healed), which is the end of the healing. The international guidelines recommend assessing CR in the light of the concomitant therapy status by corticosteroids, eg, achievement of CR associated with a minimal dose (minimal therapy, prednisone ≤10 mg/day for 2 months) as this is more clinically meaningful than CR itself. Rollover to the OLE trial will occur at W31 or earlier in case of treatment failure or flare after CRmin.

Flare is defined in international guidelines as 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. 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 new lesions that heal within 1 week. Persistent new lesions are defined as new lesions that last more than 1 week. As nonspecific lesions frequently occur in participants with pemphigus, it will be the duty of the investigators to confirm the nature of new pemphigus lesions through a physical examination during the visits. A historical report of new lesions by participants will not be evidence of a diagnosis of transient lesions or flare of pemphigus unless deemed indicative of pemphigus by the investigator.

Proportion of participants who achieve CRmin within 30 weeks as primary endpoint and treatment duration of 30 weeks: A trial duration of 30 weeks was selected based on results from the phase 2 trial ARGX-113-1701 in participants with pemphigus for encompassing the observation of the primary endpoint of CRmin in the majority of participants belonging to the active group. The time point at which CRmin is anticipated to be achieved for most participants varies between 24 and 30 weeks in participants under active treatment and depends on the body weight of the participants. Accounting for this variation between participants, all participants having achieved CRmin within the 30 weeks of the trial will be considered in the primary endpoint as responsive to treatment.

Tailored regimen of efgartigimod PH20 SC and rollover to the OLE: The trial comprises a screening period of up to 3 weeks, a treatment period until CRmin of up to 30 weeks, and an 8-week follow-up period for participants who do not enroll into the OLE trial ARGX-113-1905. A tailored efgartigimod PH20 SC regimen is proposed due to its rapid effect and the variability of disease activity between participants. Participants will be administered the efgartigimod PH20

SC with concomitant low dose prednisone regimen subcutaneously until CRmin is achieved. Then, efgartigimod PH20 SC administration will be stopped, whereas the concomitant treatment by prednisone will be pursued with the option for further tapering to achieve CR off therapy (CRoff).

4.3. Justification for Dose

SC administration is highly preferred over an IV formulation for pemphigus patients in view of the expected need for prolonged weekly administration. Therefore, efgartigimod with rHuPH20 will be administered SC each week for a maximum of 30 weeks in this trial. To achieve a fast PD effect and clinical response a dose of [redacted] mg will be administered in the first 2 weeks, 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.[5]

Trial ARGX-113-1701 showed that IV administration of efgartigimod resulted in a rapid DC with or without associated prednisone, as well as CR 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 to reduce the time to a clinically relevant improvement. Subsequently, a lower weekly dose is expected to maintain improvement in this patient 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 of the phase 1 trial in healthy subjects, the phase 2 studies in 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 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 participants with pemphigus.

PK and PD data from trial 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 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% 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 efgartigimod PH20 SC 1000 mg doses is comparable to that of efgartigimod IV 10 mg/kg.

Based on the chronic dosing data from nonclinical studies, it is anticipated that this chronic dosing regimen in pemphigus is safe. A chronic dosing regimen of weekly IV infusions of 10 mg/kg efgartigimod, or a SC equivalent as proposed for pemphigus, is anticipated to be safe as indicated by a 6-month study in cynomolgus monkey. In this study, animals were dosed with weekly efgartigimod infusions of up to 100 mg/kg. The no-observed-adverse-effect level (NOAEL) was set at the highest administered dose of 100 mg/kg. Both the C_{max} and exposure data at the NOAEL observed in the nonclinical toxicity studies have been considered to provide sufficient exposure multiples to support the proposed dosing regimen for this trial. Furthermore, a bridging toxicity study of efgartigimod co-administered with rHuPH20 has been performed. In this 12-week bridging SC repeat-dose study, cynomolgus monkeys were treated with efgartigimod SC ± rHuPH20. As efgartigimod SC was well-tolerated, without toxicologically relevant systemic adverse findings up to the highest dose tested, a NOAEL above 100 mg/kg ±2000 U/mL rHuPH20 (the highest tested dose) was established. No efgartigimod-related toxicity via SC injection was noted for behavior, external appearance, condition of feces, body weight, or food and water consumption, and there were no overt signs of toxicity or mortality or any influence on the myeloid:erythroid ratio in bone marrow.

In view of the severity of the disease, a fast onset of action is desirable. Therefore, the dose regimen for the phase 3 trial starts with a dose that achieves close to maximal IgG reduction within 2 weeks, after which the PD effect is maintained with a lower weekly dose.

PK/PD modeling indicated that 2 weekly doses of [redacted] mg efgartigimod PH20 SC result within 2 weeks in total IgG reduction close to maximal IgG reduction comparable to maximal IgG reductions achieved at steady state with 1000 mg efgartigimod PH20 SC.

A maintenance dose of 1000 mg efgartigimod has been selected for this trial to be administered as weekly SC administrations coformulated with rHuPH20 until CRmin.

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 end of study (EoS)/early discontinuation (ED) visit and any follow-up visits, if applicable, depending on whether the participant rolls over to ARGX-113-1905 or continues the treatment-free follow-up period in ARGX-113-1904.

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 meet any of the exclusion criteria will not be eligible to receive any trial 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/sponsor's designee 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 is male or female, and aged from 18 years at the time of signing the informed consent form (ICF).
3. The participant has a clinical diagnosis of PV (mucosal, cutaneous, mucocutaneous) or PF that has been confirmed by cutaneous histology, positive DIF, and positive IIF and/or ELISA.
4. The participant meets 1 of the following profiles:
    i. Newly diagnosed disease with PDAI activity score ≥15 (see Section 10.8) at baseline and naïve to treatment.
    ii. Newly diagnosed disease with PDAI activity score ≥15 while receiving a first course of oral prednisone (or equivalent). According to clinical judgment, the participant has shown no significant improvement of PV or PF signs for at least 2 weeks before baseline and is considered fit to start prednisone treatment at 0.5 mg/kg qd at baseline.
    iii. Experiencing flare with PDAI activity score ≥15, a maximum of 4 years since disease onset, and off prednisone therapy ± a conventional immunosuppressant (eg, azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil) or dapsone. Note: conventional immunosuppressants and dapsone must be discontinued before baseline.
    iiii. Experiencing flare with PDAI activity score ≥15, a maximum of 4 years since disease onset, and receiving a tapered dose of oral prednisone (or equivalent), provided that prednisone has been given at stable dose ± a conventional immunosuppressant (eg, azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil) or dapsone for at least 2 weeks and participants are fit to start prednisone treatment at 0.5 mg/kg

qd at baseline. Note: conventional immunosuppressants and dapsone must be discontinued before baseline.

5A. Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating clinical trials and:

i. Male participants:

– Male participants must agree to use acceptable method of contraception (as described in Appendix 5, Section 10.5.2.2) from signing the ICF until the last dose of IMP.

ii. Female participants:

– Women of childbearing potential (defined in Appendix 5, Section 10.5.1) must:

- have a negative serum pregnancy test at screening and 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 Appendix 5, Section 10.5.2.2), which should be maintained at minimum until after the last dose of IMP.

6. For Japanese participants enrolled in sites in Japan only: A Japanese participant is defined as a participant whose parents and 4 grandparents are Japanese, and who has Japanese nationality, was born in Japan, has not lived outside of Japan for a total of >10 years, and currently lives in Japan.

5.2. Exclusion Criteria

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

1. Participant has a confirmed diagnosis of paraneoplastic pemphigus, drug-induced pemphigus, pemphigus vegetans, pemphigus erythematosus, or any other non-PV/non-PF autoimmune blistering disease.
2. Participants with mild disease severity as defined by PDAI activity score <15 at baseline.
3. Participants who show a significant improvement of PV or PF in the period from screening to baseline according to clinical judgment (eg, the participant has achieved DC or a substantial reduction in PDAI activity score during screening period).
4. The participant has been administered therapy(ies) other than oral prednisone, conventional immunosuppressants (eg, azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil) or dapsone within 2 months before the baseline visit and that can affect clinical disease activity. For example, excluded medications are intravenous methylprednisolone, sulfasalazine, tetracyclines, nicotinamide at doses above the recommended daily allowance (RDA)/dietary reference intake (DRI), plasmapheresis/ plasma exchange, immunoadsorption, and IVIg. Note: conventional immunosuppressants and dapsone must be discontinued before baseline. Nicotinamide doses at or below RDA/DRI from oral supplements is allowed.
5. Use of any monoclonal antibody (including rituximab or another anti-CD20 biologic) within 6 months before the baseline visit.

6. Known hypersensitivity to any of the components of the administered treatments.
7. The participant has a known contraindication to oral prednisone.
8. The participant has a history of refractory disease, as defined by a failure to respond to first-line and second-line therapies.
9. Participants who have a history of malignancy unless deemed cured by adequate treatment with no evidence of recurrence for ≥3 years before first IMP administration. Participants with any of the following cancers can be included at any time, provided they are adequately treated prior to their participation in the study:
    i. Basal cell or squamous cell skin cancer
    ii. Carcinoma in situ of the cervix
    iii. Carcinoma in situ of the breast
    iiii. Incidental histological finding of prostate cancer (TNM stage T1a or T1b)
10. 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.
11. Pregnant and lactating women and those intending to become pregnant during the trial.
12. Current or history (ie, within 12 months of screening) of alcohol, drug, or medication abuse.
13. Any other known autoimmune disease that, in the opinion of the investigator, would interfere with an accurate assessment of clinical symptoms of PV or PF or put the participant at undue risk.
14. The participant has a Karnofsky performance score <60% (see Section 10.9).
15. Vaccination with live/attenuated viral vaccines within 28 days prior to randomization (see Section 8.3.7).
16. The participant has clinically significant uncontrolled active or chronic bacterial, viral, or fungal infection.
17. Positive serum test at screening for an active viral infection with any of the following conditions (refer to Section 10.2.1):
    i. Hepatitis B Virus (HBV) that is indicative of an acute or chronic infection, unless associated with a negative HBV DNA test. (https://www.cdc.gov/hepatitis/HBV/PDFs/SerologicChartv8.pdf; refer to Table 8).
    ii. Hepatitis C Virus (HCV) based on HCV antibody assay (unless associated with a negative HCV mRNA test; refer to Section 10.2.1.2).
    iii. HIV based on test results that are associated with an AIDS-defining condition or a CD4 count ≤200 cells/mm^3 (refer to Table 9).
18. The participant has total IgG <6 g/L at screening.

19. The participant has previously participated in a trial with efgartigimod and has received at least 1 administration of IMP.
20. Use of an investigational drug within 3 months or 5 half-lives of the drug (whichever is longer) prior to first IMP administration.
21. For Chinese participants enrolled in China only: Use of complementary therapies, including traditional Chinese medications, herbs, or procedures (eg, acupuncture) within 4 weeks prior to randomization, that can potentially interfere with the efficacy assessments and the safety of the participant, as assessed by the investigator.

5.3. Lifestyle Considerations

No lifestyle restrictions are required.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to trial intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Participants may be rescreened (ie, redoing the full assessments), per the SoA (Section 1.3) or retested once (ie, redoing 1 assessment) after the sponsor's written approval.

Examples of conditions under which retesting may be considered include the following:

- Participants who have clinical laboratory test values meeting 1 or more exclusion criteria that are not in line with the medical history and clinical evaluation of the participant, may be retested to confirm the value of the tests, if still allowed within the screening period. If not feasible, the participant should be rescreened.

Participants may be rescreened once under the following conditions:

- Participants who required treatment for an acute illness that resolved (eg, a urinary tract infection) or had stabilization of a chronic medical problem (eg, uncontrolled hypertension).
- Participants who are not on a stable dose of a concomitant medication prior to randomization as per inclusion and exclusion criteria may be rescreened once the stable dose criterion is met.

The decision to rescreen participants may be optional based on clinical state of the participant and the decision to rescreen will solely be made per the sponsor's discretion on a case-by-case basis. For the purpose of rescreening, a new ICF should be completed.

5.5. Criteria for Temporarily Delaying Randomization

Refer to Section 5.4.

6. TRIAL INTERVENTION

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

6.1. Trial Intervention(s) Administered

A list of trial interventions is presented in Table 2. 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 (thighs and the arms) may be chosen. The placebo solution for injection will contain the same excipients as the efgartigimod PH20 SC solution for injection but without the active ingredient efgartigimod. Masked vials will be provided to preserve the study blind (see Section 6.2.1). Refer to the Pharmacy Manual and preparation guide for further details. Additionally, participants will receive oral prednisone (or equivalent such as prednisolone) as concomitant therapy (see Section 6.8.1).

Table 2: Trial Interventions

Intervention	Efgartigimod PH20 SC	Placebo	Prednisone (or Equivalent)
Type	Biologic	Other: placebo	Non-IMP
Dose formulation	Efgartigimod 165 mg/mL or 180 mg/mL + 2000 U/mLrHuPH20 solution for SC injection to be dosed at a fixed dose of 1000 mg per injection	Vehicle + 2000 U/mL rHuPH20 for SC administration	Prednisone/prednisolone tablets for oral administration
Unit dose strength(s)	165 mg/mL or 180 mg/mL	Placebo	Prednisone 5 mg, 10 mg, 20 mg, 50 mg Prednisolone 5 mg
Dosage level(s)	[redacted] mg administered in separate sites on day 1 and day 8 followed by weekly 1000 mg administrations until CRmin	[redacted] SC administrations in separate sites on day 1 and day 8 followed by weekly single administrations until CRmin	Refer to Section 6.8.1
Route of administration	Abdominal SC injection(s); preferred site[a]	Abdominal SC injection(s); preferred site[a]	Oral administration
Use	Investigational drug	Placebo for investigational drug	Non-IMP or concomitant therapy
IMP	IMP	IMP	Non-IMP
Sourcing	Provided by the sponsor to the trial site	Provided by the sponsor to the trial site	Provided by the sponsor to the trial site, or sourced locally

Intervention	Efgartigimod PH20 SC	Placebo	Prednisone (or Equivalent)
Packaging and Labeling	The IMP will be provided in glass vials. Each glass vial will be labeled as required per country requirement	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 requirements, or as magistral preparation upon prescription by the investigator

CRmin=complete remission on minimal therapy; IMP=investigational medicinal product; SC=subcutaneous(ly)
[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 (165 mg/mL and 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 a higher concentration of efgartigimod (180 mg/mL) reduces the dosing volume for each SC injection.

Placebo will be vehicle (with 2000 U/mL of rHuPH20) provided in a vial as a ready to use SC formulation. For both efgartigimod PH20 SC formulations (with efgartigimod at a concentration of 165 mg/mL or 180 mg/mL), a corresponding placebo is available containing placebo drug product at the same volume and in the same vial as the active drug product.

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Preparation

Refer to the Pharmacy Manual for information about IMP preparation, including the volume of efgartigimod PH20 SC or placebo to be administered.

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

Placebo will be provided as a sterile, colorless, clear solution for injection in glass vials with the same formulation as the efgartigimod PH20 SC solution for injection, but without the active ingredient efgartigimod. Vials for both IMP and placebo will be covered with a blinding shell.

The trained and authorized staff will use an amber colored syringe for preparation and administration of IMP. The administration will be performed by the site staff who prepared the syringe.

Efgartigimod PH20 SC and placebo will be manufactured in accordance with Good Manufacturing Practice regulations.

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 the IMP.

Only participants enrolled in the trial may receive IMP. IMP administration must be performed by authorized and trained site staff or by an adequately trained and supervised participant or caregiver.

6.2.3. Storage

Efgartigimod PH20 SC and placebo 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. The IMP supply vendor will also provide the investigator with the certificate of analysis, certificate of conformity, and European Union qualified person release documents (if applicable).

The IMP 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 the IMP assigned to the clinical site, in a locked, secure storage facility with access limited to those individuals authorized to dispense the IMP and maintained within the appropriate temperature ranges.

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

For home administrations, the participant is responsible for the correct storage of the IMP at home. Participants will receive a guide on transport, storage and temperature monitoring of the IMP.

6.2.4. Accountability

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

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

6.3. Measures to Minimize Bias: Randomization and Blinding

Once the participant has provided informed consent, the site will enroll the participant and a screening number will be allocated through the interactive response technology (IRT).

The results of all screening procedures have to be available prior to baseline (day 1) to determine the eligibility for entering the trial. Randomization should be performed as soon as the participants meet the appropriate criteria to begin treatment.

Participants will be randomized in a 2:1 ratio to receive efgartigimod PH20 SC or placebo.

As this is a randomized, double-blinded trial, access to the IMP treatment assigned will be limited. No trial team members from the investigating staff, the sponsor (except the sponsor's clinical trial supplies team), and the sponsor's designated CRO/sponsor's designee (except the specialty laboratories responsible for PK, PD, and immunogenicity [ie, ADA] analysis), will have access to the information related to IMP treatment assigned until after database lock.

The following data will remain blinded until database lock:

- PK
- PD
- Immunogenicity
- Albumin and total protein
- Exploratory research

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

6.3.1. Emergency Unblinding

The process of breaking the blind will be handled through the IRT.

Participant safety is of utmost importance. If a safety issue is deemed a medical emergency by an investigator and timing is critical, then the investigator is permitted to use the IRT directly to unblind an IMP assignment code in order to ensure the medical emergency is properly managed and participant safety is maintained. If the issue is not deemed an emergency and timing permits, then the investigator is encouraged to first discuss the need to break a blind with the medical monitor at the sponsor's designated CRO/sponsor's designee or the sponsor's medical expert in order to preserve the integrity of study data.

If the blind is broken by the investigator, then it may be broken only for the participant concerned, and the IMP treatment assignment should not be revealed to the trial team members from the sponsor, nor from the sponsor's designated CRO/sponsor's designee, pharmacy personnel, or other site staff.

Once unblinded, the participant should be discontinued from the trial. When the participant is withdrawn from the trial, the participant will be followed for 8 weeks for ongoing safety monitoring.

Pertinent information regarding the circumstances of unblinding of a participant's IMP treatment code must be documented in the participant's source documents and electronic case report form (eCRF) without breaking the blind.

The sponsor and monitor at the sponsor's designated CRO/sponsor's designee must be notified immediately if a participant and/or investigator is unblinded during the course of the trial.

6.4. Trial Intervention Compliance

The participants are dosed by qualified approved personnel. They will receive IMP 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 on-site under supervision from the authorized staff. The date and time of each dose administered at the site will be recorded in the source documents and recorded in 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 IMP administration, and any deviations from the intended regimen must be recorded in the eCRF.

A sponsor's designated 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 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.

Errors that are identified will be communicated to the site personnel to ensure that the errors are not repeated. The sponsor's designated monitor's report will include details of any missed doses, medication errors (see Section 6.7), treatment or scheduling errors, and the associated explanations. It will be evaluated if these dosing 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 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.

If a dose of IMP is missed or cannot be administered within the window of ±2 days of the planned administration day, this should be communicated to the medical monitor. The next dose should be planned as scheduled in the SoA (refer to Section 1.3).

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 prior to review and documented approval of an amendment from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) and regulatory authority as 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.

6.5. Dose Modification

Not applicable.

6.6. Continued Access to Study Intervention After the End of the Trial

Efgartigimod PH20 SC or placebo SC will be administered subcutaneously until CRmin. Participants at the EoS visit or ED visit in trial ARGX-113-1904 will be given the option to enroll into the OLE trial ARGX-113-1905 after confirmation of eligibility, while retaining the blinding of trial ARGX-113-1904. For each participant, the date of the baseline visit in the OLE trial ARGX-113-1905 will be the same as the date of the EoS visit in trial ARGX-113-1904. There is no need to schedule an additional visit for a roll over visit. At baseline of the OLE study, participants will be treated according to their clinical status at entry of the OLE trial ARGX-113-1905, as defined in the trial protocol.

Week 34 (follow-up visit 1) or week 38 (follow-up visit 2) is the EoS for participants who do not enroll in the OLE trial ARGX-113-1905. The week 38 follow-up visit will only be required for those participants who were still receiving IMP at least 1 visit between week 26 and EoS/ED. For participants who ended treatment prior to week 26, week 34 will be the EoS visit.

If a participant withdraws/discontinues early and does not roll over to the OLE trial (ARGX-113-1905), usual treatment will be administered, if required, in accordance with the trial site's standard of care and generally accepted medical practice depending on the participant's individual needs. Depending on the clinical status of the participant and the clinical judgment from the investigator, completion of the treatment-free follow-up period may be performed.

6.7. 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 assigned to that participant per the trial 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 in 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.

6.8. Concomitant Therapy

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

6.8.1. Concomitant Pemphigus Therapy

All participants, regardless of treatment assignment, will concomitantly receive oral prednisone (or equivalent such as prednisolone) at 0.5 mg/kg qd as a starting dose. Except for oral prednisone (or equivalent), no other systemic therapies (eg, immunosuppressants, IVIg, immunoadsorption, anti-CD20 biologics) will be permitted during the trial.

At any post-baseline 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 (refer to Table 3) 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 post-baseline visit before DC.

- Insufficient clinical change: absence of DC after 3 to 4 weeks of the participant being treated at the starting baseline prednisone (or equivalent) 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.

For participants achieving DC with a daily prednisone dose of 0.5 mg/kg, prednisone will be maintained at 0.5 mg/kg qd until CR and 2 weeks thereafter, or until 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) 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), the prednisone dose will be maintained until 2 weeks after achieving DC, then tapering will be performed according to the following stepwise procedure: dose reductions by 0.25 mg/kg qd (according to Table 3) every 2 weeks until the starting dose is reached (ie, 0.5 mg/kg qd). Then the starting dose (0.5 mg/kg qd) 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 at least 4 weeks. Further tapering will be performed thereafter, as long as CR or EoC are sustained. The rules for tapering are shown in Table 3. 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 until CRmin has been achieved. Prednisone can then be further tapered upon clinical judgment by the investigator.

In case of flare in the period between DC and CRmin, the prednisone dose will be increased. A flare is defined by 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. 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 prednisone dose that is 2 dose levels above the dose at which the flare between DC and CRmin is observed and that is at least 0.3 mg/kg/day (according to Table 3) will be considered treatment failures. At visits when at least 1 new lesion is observed or established lesions remain extensive without being defined as a flare, 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.

The investigator should not implement any deviation from the concomitant oral prednisone (or equivalent) regimen, except for immediate safety concerns of the participants. After taking

appropriate action to ensure the safety of the participants, such concerns should be documented and communicated to the CRO's medical monitor and the sponsor.

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 supportive 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 3: 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	125 mg	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	
Below 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.

6.8.2. 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 RDA/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 from baseline
- Other investigational drug
- For Chinese participants enrolled in China only: Complementary therapies, including traditional Chinese medicines, herbs, or procedures (eg, acupuncture) that can potentially interfere with the efficacy assessments and the safety of the participant, as assessed by the investigator

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 trial intervention. If study intervention is permanently discontinued, the participant will enter the treatment-free follow-up period or be invited to roll over into the OLE trial ARGX-113-1905. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed (refer to Section 1.3).

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 ED visit (equivalent to EoS visit) should be conducted, as shown in the SoA (refer to 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 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 EoS 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 ED from the trial include:

- It is in the participant's best interest – discussion with the medical monitor of the CRO/sponsor's designee and the sponsor's medical director is encouraged prior to 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 became 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
- Unblinding occurred
- 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 he or she 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, he/she 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 (refer to 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 he/she has 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.

Screening

At screening, all eligibility assessments should be performed after obtaining informed consent. All screening evaluations must be completed and reviewed before enrollment to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

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

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 ICF 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 screens in the eCRF.

Immediate safety concerns should be discussed first with the CRO's medical monitor/sponsor's designee 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.

A minimum of 6 on-site visits, V1(BL)/W1 to W6, is required before switching to home administrations, even if CR is achieved earlier than W6. Home visits are allowed once participants achieve CR, but not before the W7 visit. The investigator should call the participant at least every 2 weeks until CRmin is achieved to confirm the participant is still in CR. On-site visits may continue at the investigator's discretion.

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 (see Section 8.4), and the recording of concomitant therapy and procedures (see Section 8.3.5).

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

End of Study (EoS)/Early Discontinuation (ED)

All participants will complete W31/ED, which will be EoS for participants who enroll in the OLE trial ARGX-113-1905.

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-only visit. At this visit, assessments need to be performed as follows:

- Assessments as specified in Table 4 below:

  Note: In case of new lesions or flare, the assessments indicated with footnote "b" in Table 4 should be performed only once at the visit where the new lesions or the flare is confirmed. These should not be repeated at subsequent visits (even if more new lesions develop at these subsequent visits or the flare is sustained) unless the subsequent visits coincide with planned observational or IMP-only visits and the assessments are to be performed during those visits per the SoA .

- Assessments specified for the planned observational or IMP-only visit per the SoA (Section 1.3), 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 in participants who had achieved CRmin, participants will be allowed to roll over into the OLE trial ARGX-113-1905 earlier than week 31.

Table 4: Assessments to be Performed During an Unscheduled Visit

Assessment[a]	**UNS – any reason other than new lesion(s) or flare**	**UNS – new lesion(s)**	**UNS – flare**
Physical examination & vital signs	X	X[b]	X[b]
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

Assessment[a]	UNS − any reason other than new lesion(s) or flare	UNS – new lesion(s)	UNS – flare
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[b]
Vaccination antibodies[c]			X[b]
Total IgG (no IgG subtypes)	X		
IgG autoantibody subtypes and cytokines[c]			X[b]
Photography[c] (substudy conducted at selected sites)	At the discretion of the investigator	At the discretion of the investigator	At the discretion of the investigator
IMP administration	Only if the UNS coincides with a planned IMP-only visit	Only if the UNS coincides with a planned IMP-only visit	Only if the UNS coincides with a planned IMP-only visit
Prednisone taper	X	X	X
AE monitoring	X	X	X
Concomitant therapies	X	X	X

IgG=immunoglobulin gamma; IMP=investigational medicinal product; PDAI=Pemphigus Disease Area Index; UNS=unscheduled visit

[a] These assessments can coincide with a planned observational or IMP-only visit.

[b] These assessments should be performed once (only during the visit where the new lesion(s) or flare is confirmed. They should not be repeated at subsequent visits (even if more new lesions develop at these subsequent visits or the flare is sustained) unless the subsequent visits coincide with planned observational or IMP-only visits and the assessment is to be performed during those visits per the SoA.

[c] These assessments will not be performed in China.

Treatment-free Follow-up Period

Participants who reach week 31, discontinue early, or participants under treatment failure, and who do not roll over to the OLE trial, will enter the treatment-free follow-up period. 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 as 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 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 at least every 2 weeks until CRmin is achieved to confirm the participant is still in CR.

The clinical activity of pemphigus will be assessed using the PDAI (see Section 10.8), which has been developed by the International Pemphigus Committee.[24,27] 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 (refer to Section 1.3).

8.3.1. Physical Examinations

Physical examinations will be performed at the time points indicated in the SoA (refer to 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.

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

8.3.2. Height and Weight

Height and weight will be measured at screening, and body mass index (BMI) will be calculated accordingly. Weight will be measured again at week 15 (or the first on-site visit thereafter if week 15 does not coincide with an on-site visit), and EoS/ED. Weight will also be measured if there has been an obvious change since the last measurement. For the assessment of height and 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 (refer to 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.

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

8.3.4. Electrocardiography

Electrocardiography (ECG) will be performed at the time points indicated in the SoA (refer to 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.

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

8.3.5. Medical and Surgical History

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

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

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

All available vaccination history will be recorded as part of the participant's prior medication for vaccinations received in the past, or concomitant medication for vaccinations received during the trial as described in the SoA (Section 1.3). Any vaccination information the participant, his/her caregiver, or his/her legally authorized representative can remember should be recorded in the eCRF (with the brand name of the vaccine and date of vaccination, if possible).

For vaccines where multiple doses or boosters are received, only the last 1 must be recorded in the eCRF (with the brand name of the vaccine and the date of vaccine administration entered, if known).

8.3.6. Clinical Safety Laboratory Assessments

This section is applicable globally, except for China. For China-specific instructions, refer to Section 10.16.1.2.

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

Participants may be rescreened (ie, redoing the full assessments as per SoA in Section 1.3) or retested once (ie, repeating 1 test, see Section 5.4) if still within the screening period.

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 910 mL for the entire duration of the trial.

For all female participants of childbearing potential, a serum pregnancy test will be performed centrally at screening (on the samples taken for clinical laboratory tests), and a urine pregnancy test will be conducted and analyzed locally at the site visits specified in the SoA (Section 1.3). A follicle-stimulating hormone (FSH) test will be run to confirm postmenopausal status and exclude that a woman is of childbearing potential; see Section 10.5.

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, then it may be documented accordingly without being reported as an AE.

The details of sampling, handling, storage, and transportation of the samples will be described in the Laboratory Manual.

Refer to Section 10.6 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 event must be recorded in the eCRF.

8.3.6.1. Vaccination Antibodies Testing

Vaccination antibodies testing will not be performed in China.

Sites participating in the vaccination antibody testing will collect all available vaccination history from participants. Serum samples collected at screening and further visits according the SoA (Section 1.3) may be used to analyze vaccination antibodies and any response to vaccines received during the trial. Data from testing of vaccination antibodies will be described in a separate report.

8.3.6.2. Storage of Blood and Tissue Samples After the Trial

This section is applicable globally, except for China. For China-specific instructions, refer to Section 10.16.1.2.1.

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 and tissue 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

Pemphigus patients are prone to develop infections. They include infections 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. For these reasons, the following actions are excluded for trial entry (refer to Section 5.2):

- the administration of live/attenuated vaccines (eg, measles, mumps, rubella, rotavirus, smallpox, chickenpox, yellow fever) within the 4-week period prior to baseline visit (exclusion criterion 15) or during the trial.
- participants with an active or uncontrolled bacterial, viral, or fungal infection at screening (exclusion criterion 16).
- Participants that tested positive for an active viral infection at screening with HBV type B or type C, and HIV (exclusion criterion 17).
- participants with hypogammaglobulinemia, ie, total IgG <6 g/L (exclusion criterion 18).

The following measures prior to 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) in participants susceptible to enter the trial, at least 4 weeks before baseline visit.
- To vaccinate participants that are especially prone to or with an history of respiratory infections against *Pneumococcus* or *Streptococcus pneumoniae*.
- To vaccinate pemphigus 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 before baseline visit.
- 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/sponsor's designee and, subsequently, the sponsor's medical monitor, before the participant enters the trial.

All available vaccination history and any vaccination received during the study should be recorded in the eCRF with the brand name of the vaccine and the date of vaccine administration.

8.3.8. Suicidal Ideation and Behavior Risk Monitoring

Not applicable.

8.3.9. Additional Safety Assessment

As an additional assessment of the impact of glucocorticoid morbidity, the 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.[38] 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.[39] In this new version, the weights derived in the initial GTI validation study are used to generate 2 scores from the composite GTI, ie, the CWS and the 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 Composite GTI (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). The C-GTI 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 10.15 (Appendix 15).

8.4. Adverse Events and Serious Adverse Events

Definitions of AE and SAE are provided in Section 10.4 as well as guidelines for assessing causality and relationship to IMP.

AEs may 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 (see Section 7).

An unexpected AE is any adverse drug event that 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 the ICF until the last follow-up visit (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 10.4. 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 conclusion of the 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, trial participation, or corticosteroid (non-IMP) use, 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 10.4.

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. 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 until End-of-Treatment, the last follow-up visit, until the participant is lost to follow-up, or until the participant withdraws consent (as defined in Section 7.3) must be followed until resolution. 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. See Section 10.5.

For SAEs, AESIs (see Section 8.4.8), non-serious 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 10.4.

8.4.4. Reporting of AEs and SAEs

All AEs that occur during the trial, from signing of the ICF until End-of-Treatment or the last follow-up visit, are to be recorded on the appropriate AE pages (either "serious" or "non-serious") 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 in the eCRF.

Any SAE, including death due to any cause, which occurs during this trial after the signing 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 8.4.3 and Section 10.4.

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/sponsor's designee.

8.4.5. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of 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, IRB/ 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, as 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, as per their local regulatory requirements.

8.4.6. Pregnancy

If a pregnancy is reported, then the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the pregnancy of a female participant or female partner of male participant (after obtaining the necessary signed ICF from the female partner; see Section 10.5).

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

Not applicable.

8.4.8. Adverse Events of Special Interest

An AESI (serious or non-serious, 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 in 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 (see Section 8.3.7).

The characteristics of infections in the phase 2 trial ARGX-113-1701 with efgartigimod in pemphigus patients are summarized in Table 5. A total of 32 TEAEs related to infections were reported in 21 (61.8%) patients; 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 5: Trial 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
Subjects 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**
Rhinitis	0	2 (13.3) 3	2 (5.9) 3
Urinary tract infection	1 (5.3) 2	2 (13.3) 2	3 (8.8) 4
Bronchitis	2 (10.5) 2	0	2 (5.9) 2
Gastroenteritis	1 (5.3) 1	1 (6.7) 1	2 (5.9) 2
Nasopharyngitis	0	4 (26.7) 4	4 (11.8) 4
Upper respiratory tract infection	0	1 (6.7) 1	1 (2.9) 1
Oral herpes	1 (5.3) 1	0	1 (2.9) 1
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
Impetigo	1 (5.3) 1	1 (6.7) 1	2 (5.9) 2
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

Source: ARGX-113-1701 CTR Table 14.3.1.2 all available data; Listing 16.2.7.1
e=number of events; IV=intravenous(ly); n=number of subjects; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; TEAE=Treatment-emergent adverse events,
Notes: Percentages are based on the number of patients in the safety analysis set. Adverse event terms are coded by SOC and PT 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

IRRs are defined as AEs within the standardized Medical Dictionary for Regulatory Activities (MedDRA) queries 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 co-mixed with rHuPH20 in single-dose SC administrations was well-tolerated in healthy subjects 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).

An additional PK sample will be taken on day 3 and on day 11 (±1 day) until samples from 24 participants are obtained.

Concentrations of efgartigimod will be determined using a validated assay.

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.

8.6. Pharmacodynamics

This section is applicable globally, except for China, where IgG subtypes will not be determined.

At screening, total IgG will be measured as part of inclusion and exclusion criteria, but they will not be part of PD evaluation parameters at this time point.

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.

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. Skin Biopsies

A substudy to evaluate markers of pemphigus pathology in skin biopsies will be conducted at selected sites. Not all countries participating in the study, including China, will include sites that perform the substudy.

At participating sites, two 4-mm skin biopsies, 1 peri-lesional and 1 non-lesional, will be collected solely based on voluntary participation and giving informed consent, at 2 time points: at baseline and after healing of 80% of blisters (EoC) or at End-of-Treatment if 80% of healing is not achieved, to scientifically address the disease dynamics in response to experimental therapy with efgartigimod plus corticosteroids or corticosteroids only.

Collected biopsy samples will be immediately fixed in 10% neutral buffered formalin, at room temperature, and after 24 hours transferred in ethanol for shipment to a central laboratory for processing and analysis.

The following markers are planned to be measured in these samples:

- Total IgG and subtypes IgG1, IgG2, IgG3, and IgG4
- Inflammatory cytokines: IL-1, IL-2, IL-4, IL-6, TNF-α, and IFN-γ
- Cellular infiltrates: CD45+ leukocytes, CD3+ T cells, CD4+ T helper cells, CD8+ cytotoxic T cells, CD20+ B cells, CD138+ plasma cells, neutrophils
- Desmoglein and FcRn expression level

Skin biopsies for this exploratory substudy will be collected as indicated in the SoA (Section 1.3). To maintain the study blind, samples will be recoded before analysis.

8.8. Imaging

For illustrative purposes, pictures of different anatomical regions may be taken at selected sites at the discretion of the investigator. The imaging substudy will be performed at selected sites and will not be performed in China.

As a guidance for participating sites, time points of baseline, DC, CR and flare are indicated. Pictures may also be taken at intermediate timepoints.

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

8.9. Exploratory Research

The subsections below are applicable globally, except for China, where no exploratory research will be conducted.

8.9.1. 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.[40] 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.[40-42]

Efgartigimod, an FcRn inhibitor that gives a targeted reduction of IgG antibodies of all subtypes[43] has been evaluated in the treatment of participants with MG,[36] ITP,[37] and pemphigus (trial 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 -3 whole extracellular domains) with clinical observations.

Blood samples for this exploratory research will be collected as indicated in the SoA (Section 1.3). To maintain the study blind, samples will be recoded before analysis.

8.9.2. Immunological Profiling

Immunological profiling 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. Specific analysis will include evaluation of:

- Anti-non-Dsg specific autoantibodies
- Pro-inflammatory cytokines
- T- and B-cell populations

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

8.9.3. Genetics

The genetics study aims to understand how specific human leukocyte antigen (HLA) and non-HLA genes affect dynamic changes in T- and B-cell receptor repertoires and changes in RNA transcriptional profiles of genes linked to disease activity. Participation is optional and participants who do not wish to partake in the genetic research may still join in the trial.

A blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study (Section 8.9.2).

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. A signed ICF will be required to obtain a replacement sample unless it was included in the original consent.

Blood samples for RNA extraction will be collected at baseline, after 4 weeks (W5), W13 (or the visit at which CR is observed if before W13), and at EoS/ED.

See Section 10.7 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the Laboratory Manual.

8.10. Immunogenicity Assessments

Blood samples to assess immunogenicity of efgartigimod and rHuPH20 will be collected as indicated in the SoA (Section 1.3). Sampling will be done predose on IMP administration visits.

All samples will be analyzed first in a validated screening assay, followed by an assessment of specificity of the measured ADA response in screening positive samples in a confirmation assay. Finally, in samples scoring positive in both screening and confirmatory assays, a titration of the ADA response will be performed. Neutralizing antibodies (Nab) will be tested for all confirmed positive ADA samples.

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.

8.11. Medical Resource Utilization and Health Economics

See Section 8.12.

8.12. Quality of Life and Patient-Reported Outcomes

The participant will complete the patient-reported outcome (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 (see Section 10.10). 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 patient's daily life (see Section 10.11).[29]

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.

A detailed and comprehensive Statistical Analysis Plan (SAP) will be written and signed-off prior to 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.

9.1. Statistical Methods

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

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

9.2. Statistical Hypotheses

The statistical hypothesis is derived from the primary trial objective as stated in Section 3.

- Null hypothesis: There is no difference between efgartigimod PH20 SC and placebo in the proportion of participants with PV having achieved CRmin within 30 weeks.
- Alternative hypothesis: There is a difference between efgartigimod PH20 SC and placebo in the proportion of participants with PV having achieved CRmin within 30 weeks.

9.3. Sample Size Determination

The sample size calculation is based on the following assumptions:

- Endpoint: proportion of PV participants having achieved CRmin within 30 weeks
- Percentages for sample size calculation
  - Efgartigimod: 40% to 50%
  - Placebo: 1% to 20%
- Power: 90%
- Significance level: 5% (two-sided)

The sample size calculation was performed using PASS 2019 software (NCSS Statistical Software, Kaysville, Utah). The assumption is made that the responses from each group follow a binomial distribution.

Table 6 presents the number of participants needed in the placebo group; with a randomization ratio of 2:1 the efgartigimod group should have twice the number of participants.

Table 6: Sample Size Calculation

		Efgartigimod		
		40%	**45%**	**50%**
Placebo	**1%**	16	14	12
	5%	22	19	16
	10%	34	27	22
	15%	52	39	30
	20%	87	59	42

Assuming a clinically relevant difference of 30% and an expectation to achieve CRmin in 50% of PV participants, a total of 126 participants randomized to either the efgartigimod arm or the placebo arm in a 2:1 ratio (84 participants in the efgartigimod arm and 42 participants in the placebo arm) will yield more than 90% power in a 2-sided test at the 5% significance level. The target number of Japanese participants with PV is 9.

A representative number of participants with PF (up to approximately 24 participants or 16% of the total target population) may participate in the trial, although they are not included in the sample size calculation. The target range for the number of Japanese participants with PF is 1 to 3 (included in the 24 participants globally). Thus, a total of 150 participants can be randomized in an allocation ratio of 2:1.

As a result of regulatory interactions, this amendment includes an additional analysis: absence of new or established lesions while a participant is off IMP and is receiving minimal therapy for at least 2 months (8 weeks).

For this additional analysis, the assumed response rates are 34% and 11% for efgartigimod and placebo, respectively. With 183 participants with PV, this will result in 95% power in a 2-sided test at the 5% significance level, assuming that the geopolitical situation in Ukraine and impacted areas might result in a 5% power loss.

In addition, the representative number of participants with PF may increase (up to approximately 30 participants or 14% of the total target population) to compensate for participants whose data are at risk due to the geopolitical situation.

9.4. Populations for Analyses

The following populations are defined:

Population	Description
Modified intent-to-treat (mITT)	All randomized participants (PV and PF participants) who received at least 1 dose or part of a dose of IMP. Two subsets are identified: PV participants and PV+PF participants. Participants will be analyzed according to their randomized treatment.
Per protocol (PP)	All participants in the mITT population for whom no major protocol deviations were reported

Population	Description
Safety (SAF)	All randomized participants (PV and PF participants) who received at least 1 dose or part of a dose of IMP. Participants will be analyzed according to the treatment actually received.
Pharmacokinetic	All participants in the SAF population for whom at least 1 serum PK concentration is available
Pharmacodynamic	All participants in the SAF population for whom at least 1 serum PD concentration is available

9.5. Statistical Analyses

The SAP will be finalized prior to 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 key secondary endpoints.

9.5.1. General Considerations

The primary efficacy analysis will be performed on the mITT population subset of PV participants. All efficacy key secondary and other secondary analyses will be performed on the PV+PF participants population, unless otherwise specified. The safety analyses will also be performed on the SAF population (PV+PF participants).

The baseline value will be the last assessment prior to the first administration of efgartigimod PH20 SC treatment.

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. Patient Disposition

Patient disposition will be summarized in a table. It will include the number of participants screened, enrolled or randomized, 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 overall and by treatment group, for the overall trial period, by treatment period and, by follow-up period.

9.5.3. Analysis Sets and Protocol Deviations

The number of participants for each analysis set, as described in Section 9.4, will be presented in a table and listing.

Major protocol deviations, by treatment group and trial stage, 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 (see Section 9.1) and listed.

9.5.5. Safety Analyses

Exposure to IMP and cumulative prednisone statistics will be summarized by treatment group, separately.

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. Adverse events 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.

9.5.6. Primary Endpoint

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] E9 (R1) provides further information on estimands and sensitivity analyses in clinical trials; ICH E9 (R1) came into effect on 30 Jul 2020 and follows below.

Definition of the Estimand for the Primary Endpoint

- Population: adult participants with moderate to severe PV newly diagnosed or experiencing flare, on add-on therapy of low doses of oral prednisone, and that are further defined by the inclusion (Section 5.1) and exclusion (Section 5.2) criteria.
- Variable: proportion of PV participants who achieve CRmin within 30 weeks
- Main intercurrent events (ICEs):
  1. Intercurrent medications before CRmin
     a. Immunosuppressants or dapsone at therapeutic doses for at least 4 weeks
     b. IVIg at immunomodulating dose (≥1 g/kg/month)
     c. Immunoadsorption or plasma exchange
     d. Rituximab or other anti-CD20 biologics
     e. IV corticosteroids >200 mg cumulatively within 2 weeks
  2. Discontinuation of IMP before CRmin due to lack of efficacy
- Population-level summary: the strata-adjusted difference in the proportion of responders (95% CI) between efgartigimod PH20 SC in combination with add-on therapy of low doses of oral prednisone and placebo in combination with add-on therapy of low doses of oral prednisone.

Handling of Main ICEs

A composite strategy approach will be taken to address both main ICEs. This implies that participants that take intercurrent medications before CRmin as specified previously, as well as participants that discontinue IMP before CRmin due to lack of efficacy, will be considered nonresponders for the primary endpoint analysis.

Estimation of Treatment Effect and Statistical Inference

The proportion of participants with PV having achieved CRmin within 30 weeks will be tested by means of a stratified Cochran-Mantel-Haenszel (CMH) test using the mITT population. The model will be stratified by disease status, disease severity, and body weight at randomization. The strata-adjusted difference of proportions will be presented with its 95% CI and 2-sided p-value. In addition, the odds ratio and its 95% CI will be provided.

Handling of Missing Data

Missing data for reason of 1 of the main ICEs will be handled as described above.

If, for the primary endpoint, CR assessment is missing, the participant will be considered a nonresponder. Further details on other imputation techniques for missing CR values will be provided in the SAP.

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

Supplementary Analyses

To facilitate interpretation of the estimated treatment effect in the primary analysis, supplementary analyses will be conducted on the supportive estimands where the main ICEs are handled differently (eg, by using the hypothetical or treatment policy strategy instead of a composite strategy). Moreover, a supplementary landmark analysis will be performed at week 30 using the same CMH test. Details will be provided in the SAP.

The proportion of participants with PV who have achieved CRmin and sustain CR while not receiving IMP and while receiving minimal prednisone therapy of ≤10 mg/day for 2 months (8 weeks) will be analyzed within the scope of the integrated summary of efficacy with combined data from trial ARGX-113-1904 and the open-label follow-on trial ARGX-113-1905.

9.5.7. Key Secondary Endpoints Subject to Alpha Control

The first key secondary endpoint, defined by the proportion of PV+PF participants that have achieved CRmin within 30 weeks, will be tested using a stratified CMH test with stratification variables similar as for the primary endpoint, using the mITT population. As this first key secondary endpoint is similar to the primary endpoint, the same approach for handling the main ICEs, as suggested for the primary analysis, will be applied.

The second key secondary endpoint, cumulative prednisone dose over the trial duration, will be analyzed in the form of a normalized cumulative prednisone dose (NCPD), normalizing by weight and by number of days in study and will be denoted as NCPD. The NCPD endpoint will be analyzed using the mITT population in PV participants. The following formula will be adopted to calculate NCPD for each participant.

$$\text{NCPD} = \frac{Cumulative\ Prednisone\ Dose\ during\ the\ treament\ period\ of\ the\ patient}{(Weight\ of\ the\ patient\ at\ baseline)\ \text{x}\ (number\ of\ days\ treated)}$$

For the NCPD endpoint, the analysis of variance (ANOVA) model will be used to compare both treatment groups. The model will include treatment and the stratification variables will be considered as factors.

For the third and fourth key secondary endpoint, respectively time to CR and time to DC, both treatment groups will be compared using the Fleming-Harrington weighted log-rank statistic FH (1,0).[44] This analysis will be performed using the mITT population (PV participants). For both endpoints, survival curves will be estimated using the Kaplan-Meier time to event method.

Details on how to deal with the main ICEs for the second, third, and fourth key secondary endpoints will be provided in the SAP.

The primary endpoint will be tested at a 5% 2-sided alpha level and will act as a gatekeeper for testing the secondary endpoints. Subject to meeting significance for the primary endpoint, secondary endpoints will be tested at the 5% 2-sided significance level in a strict **hierarchical order** as follows:

1. Comparison of the proportion of PV+PF participants having achieved CRmin within 30 weeks between efgartigimod PH20 SC and placebo
2. Comparison of the NCPD in PV participants between efgartigimod PH20 SC and placebo
3. Comparison of time to CR in PV participants between efgartigimod PH20 SC and placebo
4. Comparison of time to DC in PV participants between efgartigimod PH20 SC and placebo

Supplementary analyses for the key secondary endpoints will be conducted. Subgroup analyses for the primary and/or key secondary endpoints may also be conducted. Details will be provided in the SAP.

9.5.8. Other Secondary Endpoints

The time to event and cumulative prednisone dose endpoints that are part of the other secondary efficacy endpoints will be analyzed in the mITT population (PV+PF participants) in line with the methodologies outlined above for the key secondary efficacy endpoints.

The remaining binary endpoints will be analyzed in the mITT population using the same methodology as for the primary endpoint (stratified CMH test).

The magnitude of the effect of efgartigimod PH20 SC compared to placebo in the PF subpopulation will be evaluated using the posterior distribution of the treatment effect (difference between efgartigimod PH20 SC and placebo) obtained in a Bayesian analysis. This Bayesian analysis will incorporate historical data for the placebo in an informative maximum a posteriori probability estimate prior with robustness modifier.[45] Details of this analysis will be included in the SAP.

Analysis of the continuous endpoints GTI-CWS and GTI-AIS (as components of the C-GTI) at week 15 and the EoS/ED visit will be analyzed in the mITT using the ANOVA model to compare both treatment groups (see Section 9.5.7). The complementary GTI-SL will be analyzed descriptively. More details on additional analyses (eg, correlation between GTI-CWS and GTI-AIS and cumulative or average daily prednisone dose) will be specified in the SAP.

Summary statistics and/or summary plots will be presented for all other endpoints, including PK, PD, immunogenicity, QoL, and self-administration training. More details for the analysis of the endpoints will be described in the SAP.

9.5.9. Other Endpoints

Results from the exploratory research will be described in a separate report.

9.6. Interim Analyses

Not applicable.

9.7. Data Safety Monitoring Board (DSMB)

Refer to Section 10.1.5.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

This trial 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, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the 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 prior to 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 trial 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 trial at the site and adherence to requirements of 21 Code of Federal Regulations (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 trial as outlined in the clinical trial agreement.

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

The sponsor maintains an insurance coverage for this trial in accordance with the laws and regulations of the countries in which the trial is performed. Liability and insurance provisions for

this trial 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

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

Any participant who provides informed consent will be 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 trial, 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 trial 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 trial, that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or trial center.

The ICF will be used to explain the potential risks and benefits of trial 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 trial 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 prior to any trial-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 ICF prior to the performance of any protocol procedures and prior to the administration of IMP.

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

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

Participants may be rescreened (ie, redoing the full assessments as per SoA, Section 1.3) or retested once (ie, redoing 1 test) if still within the screening period. See Section 5.4.

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 that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal trial-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 at baseline and at subsequent visits to document response and progression. Participants will be requested to provide consent for any use that will be made of the image and for sharing anonymized pictures with the sponsor.

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

10.1.5. 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 trial management. They will be supplemented by an independent statistician. The objective of the DSMB will be to review all unblinded safety data (including the overall number of participants treated up to that point, rates, and participant-level details) 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 trial by either the sponsor or the DSMB. The DSMB will advise the sponsor regarding continuation, modification, or termination of the trial 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 Trial Data

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

The investigator is responsible for maintaining source documents. These will be made available for verification by the sponsor's designated monitor at each monitoring visit. The investigator must submit an eCRF for each participant, regardless of duration of participation or administration of IMP (ie, an eCRF has to be submitted for screen failures as well). All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the trial 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 trial will be recorded on 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 CRF.

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

The investigator must permit trial-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 trial including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (eg, CROs/sponsor's designee).

Trial monitors will perform ongoing source data verification to confirm that data entered into the CRF 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 trial is being conducted in accordance with the currently approved protocol and any other trial 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 trial documents (records and documents pertaining to the conduct of this trial 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 trial site should plan on retaining such documents for approximately 25 years after trial completion. The trial 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 trial is being conducted. Participant identification codes (ie, participant names and corresponding trial 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 prior to changing the location or status of any essential clinical trial documents. The investigator must contact the sponsor prior to disposing of any trial 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

Trial processes, trial sites (including, but not limited to site visits, central laboratories, vendors), the trial database, and trial documentation may be subject to quality assurance audit during the course of the trial 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 trial.

10.1.7.3. Quality Control

Quality control will be applied to each stage of trial-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 monitors of safety parameters and adherence to selection criteria
- Eligibility review by sponsor's designated CRO and medical monitors/sponsor's designee
- Data management quality control checks
- Continuous data acquisition and cleaning
- Quality control check of the clinical trial report (CTR)
- 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 trial-related documents including medical history and concomitant medication documentation to the authorized sponsor's representatives and regulatory authorities.

10.1.8. Source Documents

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

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

The definition of what constitutes source data can be found in the source data agreement, defined per site and agreed upon between the CRO/sponsor's designee and the investigator.

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

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF 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 outside of China. In China, the sponsor has engaged a designee. The sponsor's designated monitors will work in accordance with their applicable SOPs.

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

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

The investigator and the head of the medical institution (where applicable) agree to allow the sponsor's designated 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 monitor will perform an eCRF review, source document verification (wherever allowed as per local regulations), and source document review.

The source documentation agreement form describes the source data for the different data in the eCRF. This document should be completed and signed by the sponsor's designated 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 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's designee/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/sponsor's designee.

Case report forms are provided for each participant in electronic format (ie, eCRF). Data will be transcribed by the study site staff from the source documents onto the eCRF, as 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/sponsor's designee. Appropriate training and security measures will be completed by the investigator and all designated site staff prior to the study being initiated, and any data being entered into the system for any study participant at the site.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Only if requested as 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. Prior to 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/sponsor's designee will provide the details of the review process in a data management plan and a monitoring plan. Any change, including the issuing of queries, will be fully audit-trailed by the electronic data capture 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 in the eCRF before it can be merged with the eCRF data into the clinical database. The CRO/sponsor's designee will provide a data management plan detailing this reconciliation.

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

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

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

10.1.11. Study and Site Start and Closure

The study start date is the date 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, any CRO(s) used in the study, and the sponsor's designee of 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 monitor and other contact personnel at the sponsor and the sponsor's designee are listed in the investigator study file provided to each site.

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

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

The CTR 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 prior to 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 is applicable globally, except for China. An overview of the protocol-required laboratory assessments performed in China is provided in Section 10.16.1.3, Table 17.

Table 7: Protocol-Required Laboratory Assessments

Hematology	Hemoglobin, hematocrit, MCV, RBC count, platelet count, WBC count with differential
Clinical chemistry	Sodium, potassium, calcium, HbA1c, creatinine, creatinine clearance, BUN, ALT, AST, total bilirubin, GGT, LDL-C, CRP, ALP, LDH, HDL-C, total cholesterol, triglycerides, uric acid, total protein[a], and albumin[a]
Coagulation	INR or aPTT
Urinalysis	Specific gravity, pH, protein, glucose, ketones, blood, bilirubin, urobilinogen, nitrite, leukocyte esterase, and microscopic examination (if blood or protein test results are abnormal)
Serology	HIV antibodies (1 and 2), HBsAg, anti-HBs; anti-HBc, HBV DNA, HCV antibodies, HCV mRNA
Other	Serum ß-HCG, FSH test
Pharmacokinetics[a]	Serum levels of efgartigimod
Pharmacodynamic markers[a]	Serum levels of total IgG and IgG subtypes (IgG1, IgG2, IgG3, and IgG4) and anti-Dsg-1 and anti-Dsg-3 autoantibodies
Immunogenicity[a]	Serum levels of ADA to efgartigimod and plasma levels of antibodies against rHuPH20
Local evaluations	Urine pregnancy test

ß-HCG= ß subunit of human chorionic gonadotrophin; ADA= antidrug antibodies; ALP= alkaline phosphatase; ALT= alanine aminotransferase; anti-Dsg-1=anti-desmoglein-1; anti-Dsg-3=anti-desmoglein-3; anti-HBs=antibodies to the surface antigens of the hepatitis B virus; anti-HBc= antibodies to the surface core antigens of the hepatitis B virus; aPTT= activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CRP=C-reactive protein; DNA= deoxyribonucleic acid; FSH=follicle-stimulating hormone GGT=gamma-glutamyl transferase; HbA1c= hemoglobin A1c; HBV=hepatitis B virus; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HDL-C=high-density lipoprotein cholesterol; HIV= human immunodeficiency viruses; IgG=immunoglobulin G; INR=international normalized ratio; LDH= lactate dehydrogenase; LDL-C=low-density lipoprotein cholesterol MCV=mean corpuscular volume; mRNA= messenger RNA; RBC= red blood cell; rHuPH20=recombinant human hyaluronidase; RNA=ribonucleic acid; WBC=white blood cell

[a] PK, PD, immunogenicity, albumin, and total protein data will not be reported to the site. A system will be implemented that will alert the investigator of out-of-range albumin and total protein values, to allow for appropriate safety follow-up.

10.2.1. Other Screening Tests

10.2.1.1. Hepatitis B Virus

Patients with an active acute or chronic hepatitis B viral (HBV) infection at screening cannot be enrolled in the trial.

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

Table 8: Interpretation of Hepatitis B Serological Test Results

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

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

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

10.2.1.2. Hepatitis C Virus

Patients with an active acute or chronic hepatitis C viral infection at screening cannot be enrolled in the trial. Patients with positive serology for hepatitis C virus antibody should not be enrolled unless associated with a negative HCV mRNA test.

10.2.1.3. Human Immunodeficiency Virus

Patients who are HIV positive and do not have an AIDS-defining condition or a CD4 count >200 cells/mm^3 at screening can be enrolled in the trial (see Table 9). Patients who are HIV positive and have an AIDS-defining condition or a CD4 count ≤200 cells/mm^3 at screening cannot be enrolled in the trial. The following are considered AIDS-defining conditions:

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

Table 9: Interpretation of HIV Test Results in Combination With the Patient's Clinical Condition and CD4 Count

HIV Test Result	Clinical Condition or CD4 Count	Interpretation
Positive	AIDS-defining condition is present or CD4 count ≤200 cells/mm^3	The patient cannot be enrolled in the trial because test results and clinical condition or CD4 count confirm the diagnosis of AIDS.

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

10.3. Appendix 3: Washout Requirements Prior to First IMP Administration

Drug/Intervention/Event	Prohibited Period (from Last Dose of Agent)
Any monoclonal antibody (including rituximab or another anti-CD20 biologic)	6 months
Intravenous methylprednisolone, sulfasalazine, tetracyclines, nicotinamide[a], plasmapheresis/plasma exchange, immunoadsorption, and IVIg	2 months
Live/attenuated viral vaccines	28 days
Any investigational drug	3 months or 5 half-lives of the drug (whichever is longer)
Conventional immunosuppressants (eg, azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil) or dapsone	Allowed until baseline
For Chinese participants enrolled in China only: Complementary therapies, including traditional Chinese medicines, herbs, or procedures (eg, acupuncture) that can potentially interfere with the efficacy assessments and the safety of the participant, as assessed by the investigator	4 weeks

DRI=dietary reference intake; IVIg=immunoglobulins given intravenously; RDA=recommended daily allowance

[a] Only nicotinamide above the RDA/DRI must fulfill the washout requirements. Nicotinamide doses at or below the RDA/DRI are allowed and do not required washout.

10.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1. 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.

Definition of Unsolicited and Solicited AE
• 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 non-serious 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 pre-existing 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 pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.4.2. Definition of SAE

A 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 pre-existing condition that did not worsen from baseline will 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

A 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.

10.4.3. Recording and Follow-up of AEs and/or SAEs

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) Common Terminology Criteria for Adverse Events (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 semi-colon 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; 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 patient'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 always make an assessment of causality for every event before the initial transmission of the SAE data.

Assessment of Causality
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 CIOMS. Unrelated and Unlikely Related will be merged into "Unrelated" and Related, Possibly Related, and Probably Related 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.

10.4.4. 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/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 Serious Adverse Event Reporting on page 2 of this protocol).

10.5. Appendix 5: Contraceptive and Barrier Guidance and Collection of Pregnancy Information

10.5.1. Definitions:

10.5.1.1. 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 (ie, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).

10.5.2. Contraception Guidance:

10.5.2.1. Female Contraception for Women of Childbearing Potential

Women of childbearing potential 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:

1. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
    a. Oral
    b. Intravaginal
    c. Transdermal
2. Progestogen-only hormonal contraception associated with inhibition of ovulation
    a. Oral
    b. Injectable
    c. Implantable
3. Intrauterine device (IUD)
4. Intrauterine hormone-releasing system (IUS)
5. Bilateral tubal occlusion
6. Vasectomized partner
7. Sexual abstinence

Acceptable methods of contraception are:

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

10.5.2.2. Male Contraception:

An acceptable method of contraception is a condom.

10.5.3. Collection of Pregnancy Information

Male Participants With Partners Who Become Pregnant

- Male participants will be instructed through 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 (see 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.

Female Participants Who Become Pregnant

- A serum pregnancy test will be performed at screening. 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 treatment.
  - The participant should have the ED assessments and enter the follow-up period.
  - All assessments for ED (see Section 7) 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 (see 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.

10.6. Appendix 6: Administrative Structure

The vendors listed below are applicable globally, except for China, where only SGS Life Sciences and Clario are used.

Central Laboratories
Cerba Research NV Industriepark Zwijnaarde 3 B-9052 Gent Belgium
Analysis of Pharmacokinetics (PK) and Antidrug Antibodies (ADA)
DDS (formerly known as LGC) Newmarket Road Fordham Cambridgeshire CB7 5WWW United Kingdom
Total IgG and IgG Subtypes
PPD Central Lab PPD Laboratories – US 2 Tesseneer Drive Highland Heights, KY 41076 USA
Antibodies and Neutralizing Antibodies Against rHuPH20
Labcorp Bioanalytical Services LLC 8211 SciCor Drive, Suite B Indianapolis, IN 46214 USA
Long-term Storage of Samples
Azenta Life Sciences BioStorage Technologies GmbH Im Leuschnerpark 1B 64347 Griesheim Germany
Central ECG Reading
Clario 1818 Market Street, Suite 2600 Philadelphia, PA 19103 USA
Trial Monitoring/Medical Monitoring
Pharmaceutical Product Development (PPD) Global Ltd 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 and Peripheral Blood Mononuclear Cell (PBMC) Processing – India only
IQVIA RDS (India) Private Limited 301-A-2, Leela Business Park M.V. Road, Andheri (East) Mumbai- 400059 India

10.7. Appendix 7: Genetics

The instructions outlined in this section are applicable globally, except for China, where no genetic research will be conducted.

Use/Analysis of DNA

Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact intervention absorption, distribution, metabolism, and excretion; mechanism of action of the intervention; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to efgartigimod or pemphigus and related diseases. They may also be used to develop tests/assays including diagnostic tests related to efgartigimod and pemphigus. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to efgartigimod PH20 SC or study interventions of this class to understand study disease or related conditions.

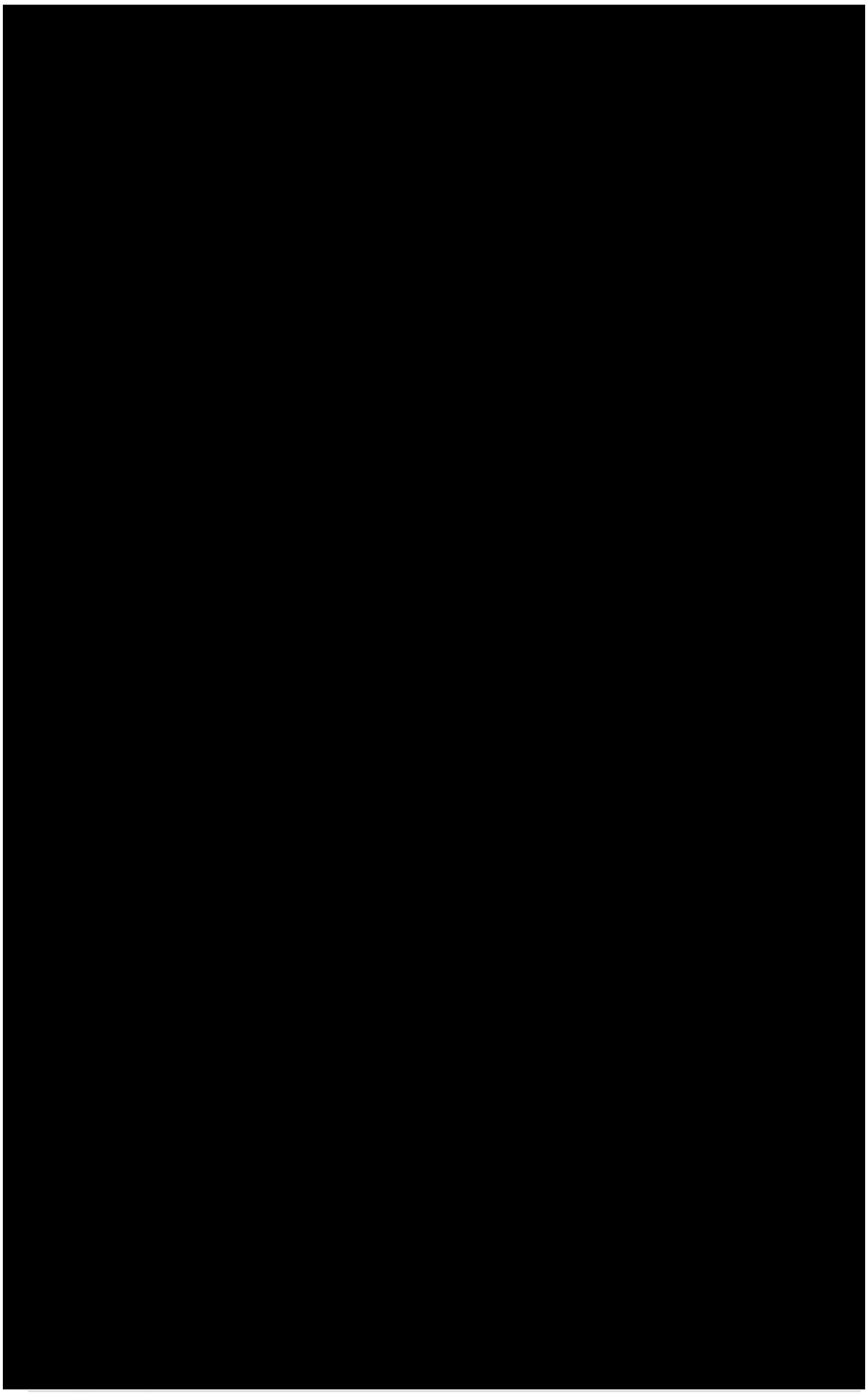
The results of genetic analyses may be reported in the clinical study report or in a separate study summary.

The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on efgartigimod continues but no longer than 15 years or other period as per local requirements.

10.8. Appendix 8: Pemphigus Disease Area Index (PDAI) Scoring System

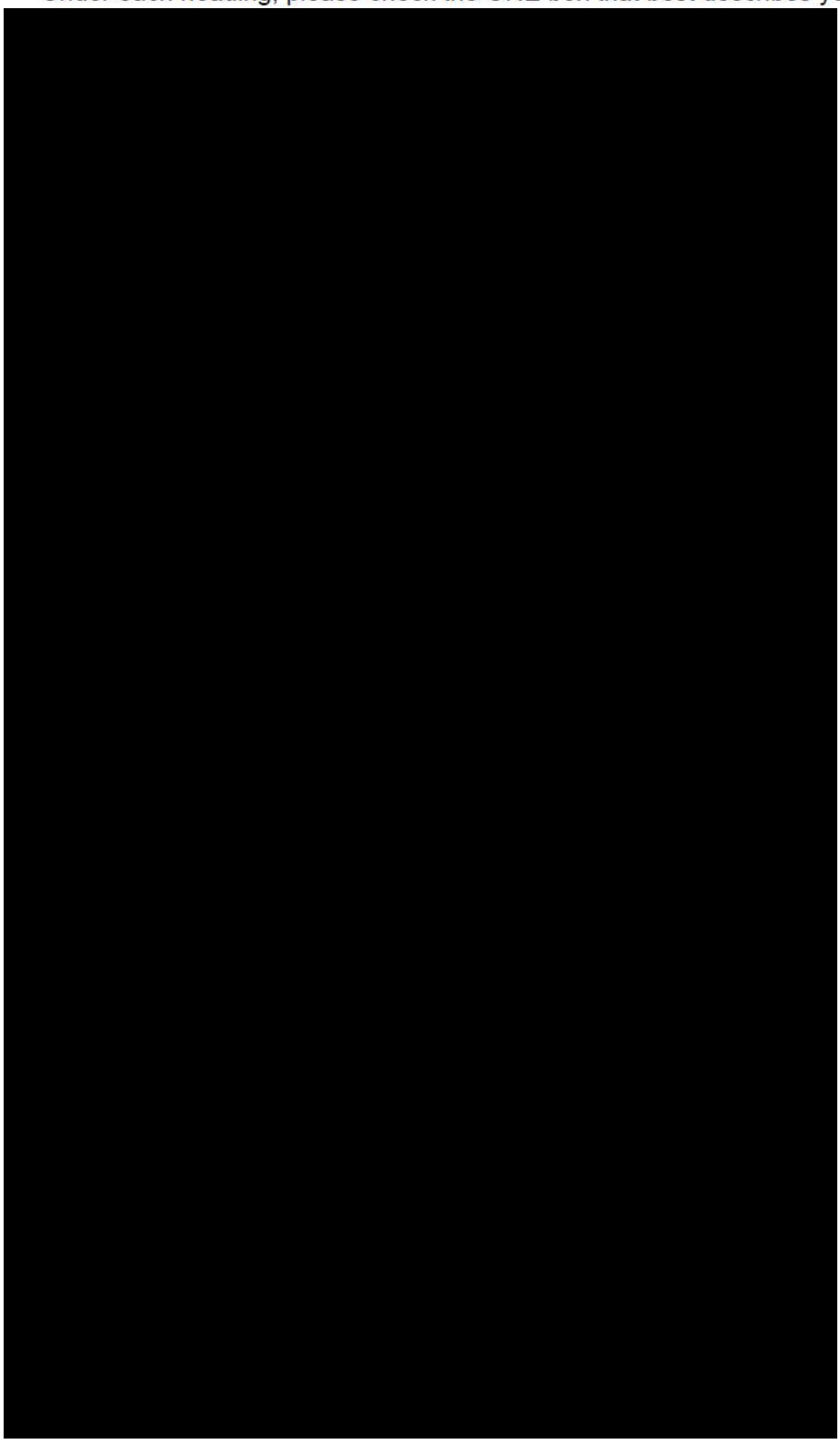
Pemphigus Disease Area Index (PDAI)



10.9. Appendix 9: Karnofsky Performance Score

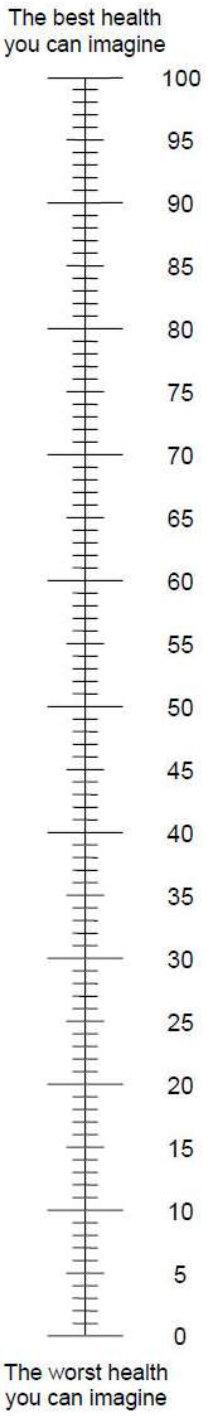
10.10. Appendix 10: EQ-5D-5L Instrument

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

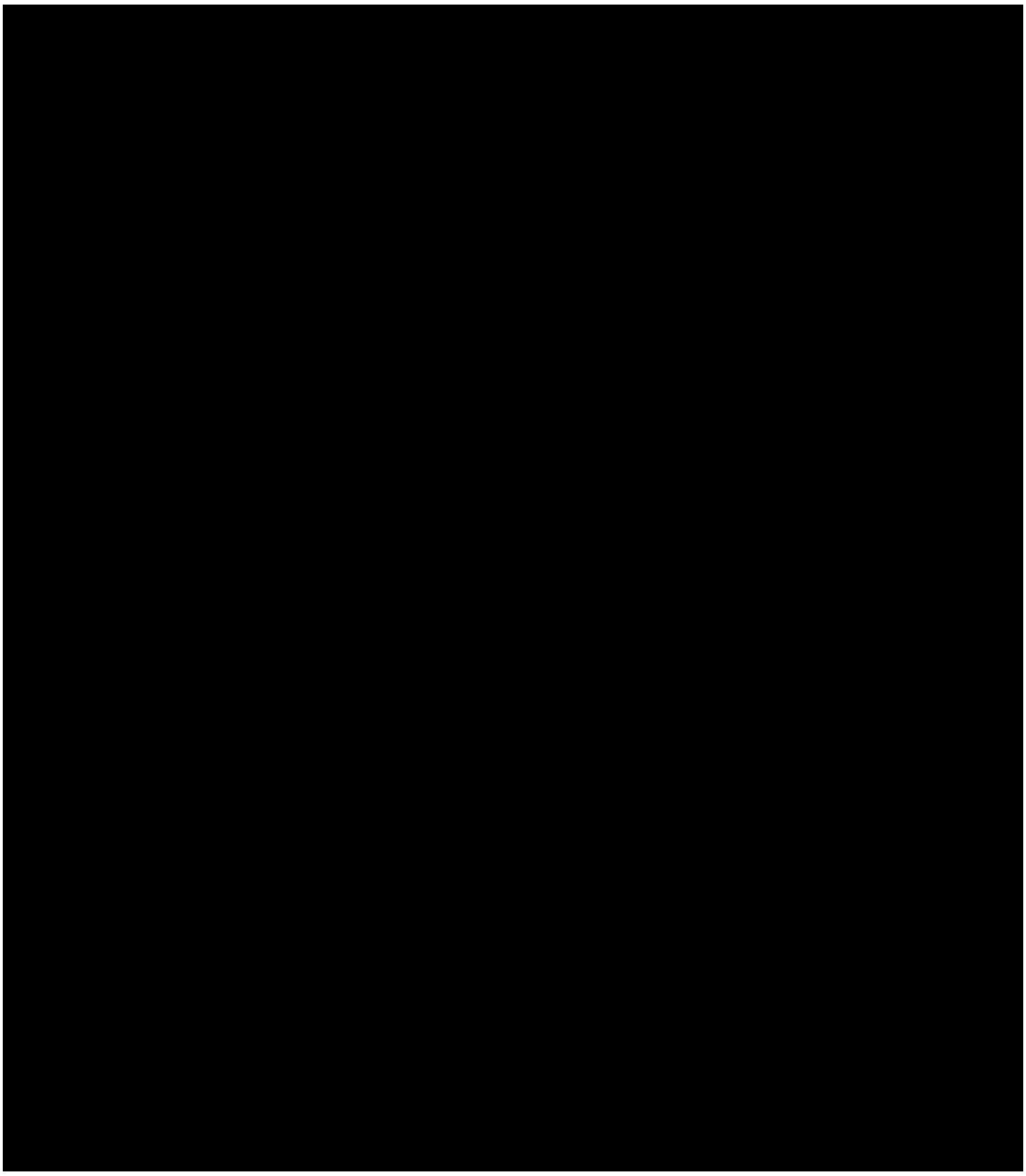


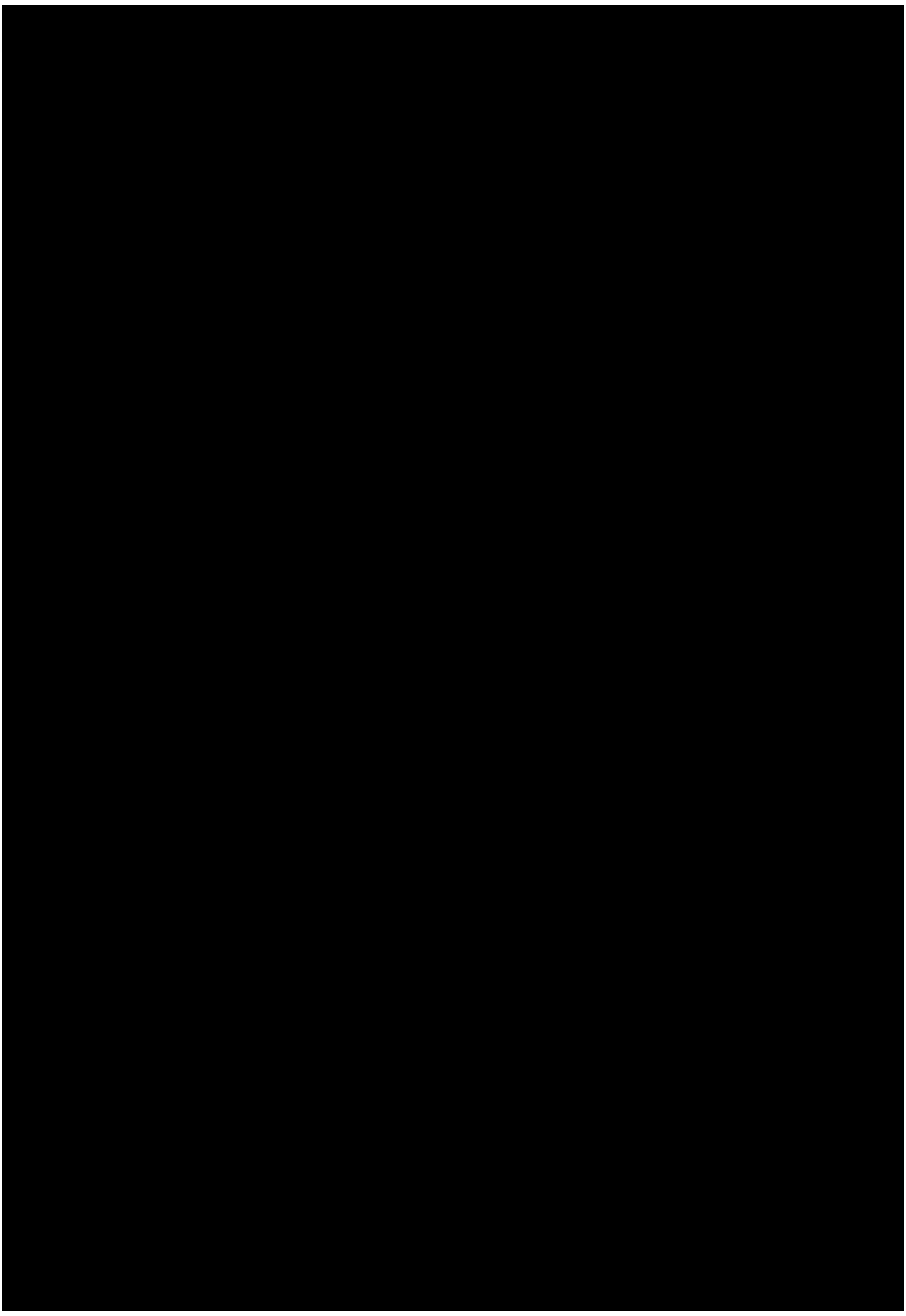
[redacted]

YOUR HEALTH TODAY = [ ]



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





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

Thank you for taking the time to complete this questionnaire

10.12. Appendix 12: Definition of Terms

Blinding:

A procedure in which 1 or more parties to the trial are kept unaware of the treatment assignment in order to reduce the risk of biased trial outcomes. The level of blinding is maintained throughout the conduct of the trial, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of an AE or SAE. In a double-blinded trial, the participant, the investigator, site staff, and sponsor staff who are involved in the treatment or clinical evaluation of the participants and the review or analysis of data are all unaware of the treatment assignment.

Complete clinical remission (CR):

The absence of new lesions and complete healing of established lesions (except for post-inflammatory 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: In this trial, when 10 mg/day is reached, this dose level must be maintained for 8 weeks until CRmin has been achieved.)

Council for International Organizations of Medical Sciences (CIOMS):

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 ADRs/suspected unexpected serious adverse reaction (SUSARs) in clinical trials.

Contract Research Organization (CRO):

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 it 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 post-baseline 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:

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 subjects 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 subjects.

Informed consent/ Informed Consent Form (ICF):

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 3–4 weeks of the participant being treated at the starting baseline dose or after 3–4 weeks of any new incremented dose of prednisone.

International Council for Harmonisation (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.

Japanese participant:

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

Protocol amendment:

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

Randomization:

Process of random attribution of treatment to subjects 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 new lesions that heal within 1 week. Persistent new lesions are defined as 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:

Absence of DC with oral prednisone 1.5 mg/kg/day for a minimum of 3 weeks, or flare between DC and CRmin that is not controlled by a prednisone dose that is 2 dose levels above the dose at which the flare is observed and that is of at least 0.3 mg/kg qd (according to Table 3), or the occurrence of an SAE considered related to prednisone by the investigator.

10.13. Appendix 13: Abbreviations

ABQOL	Autoimmune Bullous Disease Quality of Life
ABSIS	Autoimmune Bullous Skin Disorder Intensity Score
AChR-Ab	acetylcholine receptor–antibody
ADA	anti-drug antibodies
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AIBD	autoimmune bullous dermatoses
AIDS	acquired immunodeficiency syndrome
AIS	aggregate improvement score
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
anti-HBc	total hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
BMI	body mass index
BP	bullous pemphigoid
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 Sciences
CMH	Cochran-Mantel-Haenszel
CONSORT	Consolidated Standards of Reporting Trials
CPK	creatine phosphokinase
CR	complete clinical remission
CRmin	complete remission on minimal therapy
CRF	case report form
CRO	contract research organization
CRoff	complete remission off therapy
CRP	C-reactive protein

CTCAE	common terminology criteria for adverse events
CTR	clinical trial report
CWS	cumulative worsening score
DC	disease control
DIF	direct immunofluorescence
DNA	deoxyribonucleic acid
DRI	dietary reference intake
Dsg	desmoglein
DSMB	data safety monitoring board
ECG	electrocardiogram
ED	early discontinuation
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
ENT	ear-nose-throat
EoC	end of consolidation
EoS	end of study
EQ-5D-5L	EuroQol 5-Dimension 5-Level Scale
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
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL-C	high-density lipoprotein cholesterol
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
IB	Investigator’s Brochure
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG	immunoglobulin G
IIF	indirect immunofluorescence
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IRB	Institutional Review Board
IRR	infusion-related reaction
IRT	interactive response technology
ITP	immune thrombocytopenia
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVIg	immunoglobulins given intravenously
LDH	lactate dehydrogenase
LDL-C	low-density lipoprotein cholesterol
MedDRA	Medical Dictionary for Regulatory Activities
MG	myasthenia gravis
MG-ADL	Myasthenia Gravis Activities of Daily Living
mITT	modified intent-to-treat
mRNA	messenger RNA
NCI	National Cancer Institute
NCPD	normalized cumulative prednisone dose
Nab	neutralizing antibody
NOAEL	no-observed-adverse-effect level
OLE	open-label extension
PD	pharmacodynamic
PDAI	Pemphigus Disease Area Index
PF	pemphigus foliaceus
PK	pharmacokinetics
PP	per protocol
PPE	personal protective equipment
PT	preferred term
PV	pemphigus vulgaris
qd	daily

QoL	quality of life
rHuPH20	recombinant human hyaluronidase PH20
RDA	recommended daily allowance
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SoA	schedule of activities
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
US	United States
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

10.14. Appendix 14: Possible Adaptations of Trial Protocol During COVID-19 Pandemic

Introduction

The aim of the ARGX-113-1904 trial is to investigate a new 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 pemphigus patients.

The sponsor (argenx BV) has performed a critical assessment of the use of efgartigimod during the COVID-19 pandemic. Based on the risk-benefit assessment, the clinical trial ARGX-113-1904 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 (see the SoA in 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 the participant's safety and the participant's data collection.

For participants with no suspected signs of COVID-19 or have tested negative:

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.

Data collection:

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-113-1904 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 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 in 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 during trial participation, the following applies.

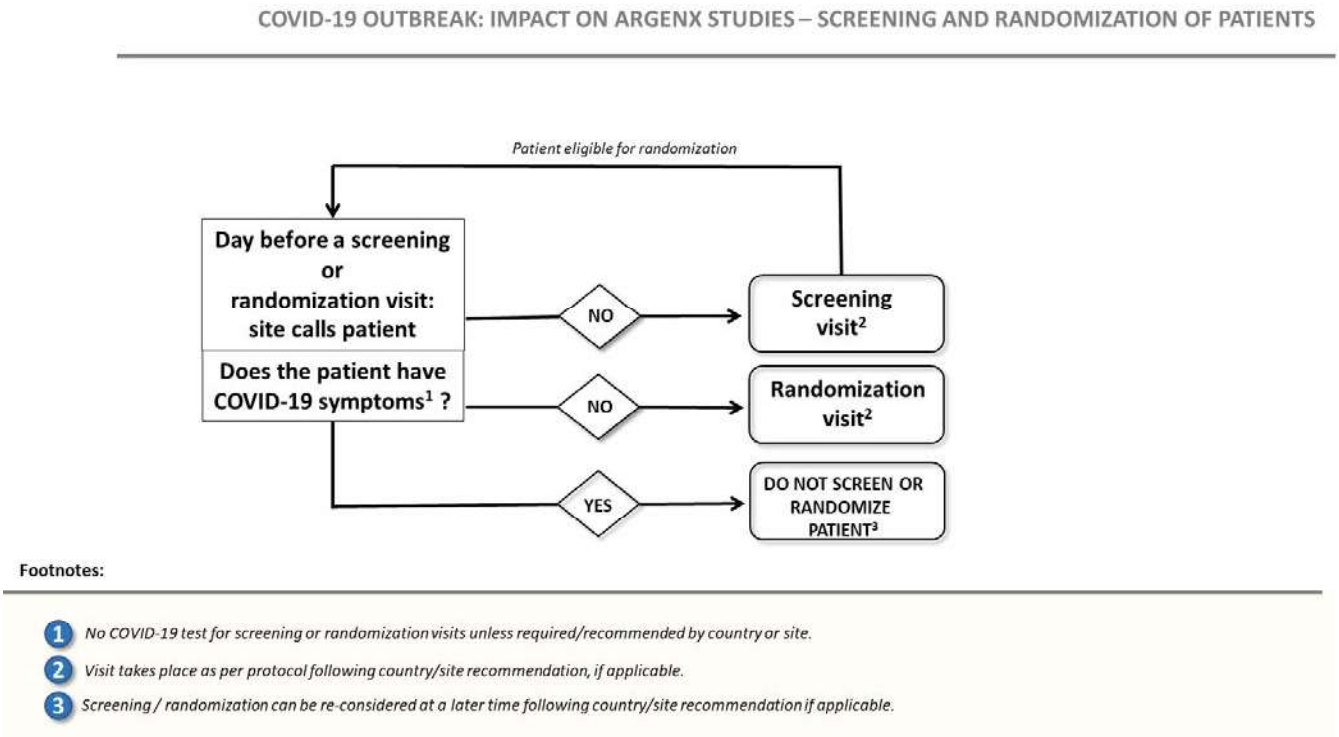
The instructions to manage an infection that are in the main protocol are also applicable in case of an infection with COVID-19 (ie, it will be considered an AESI similar to all infections). Treatment should be interrupted until the participant is considered recovered from COVID-19 (according to the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

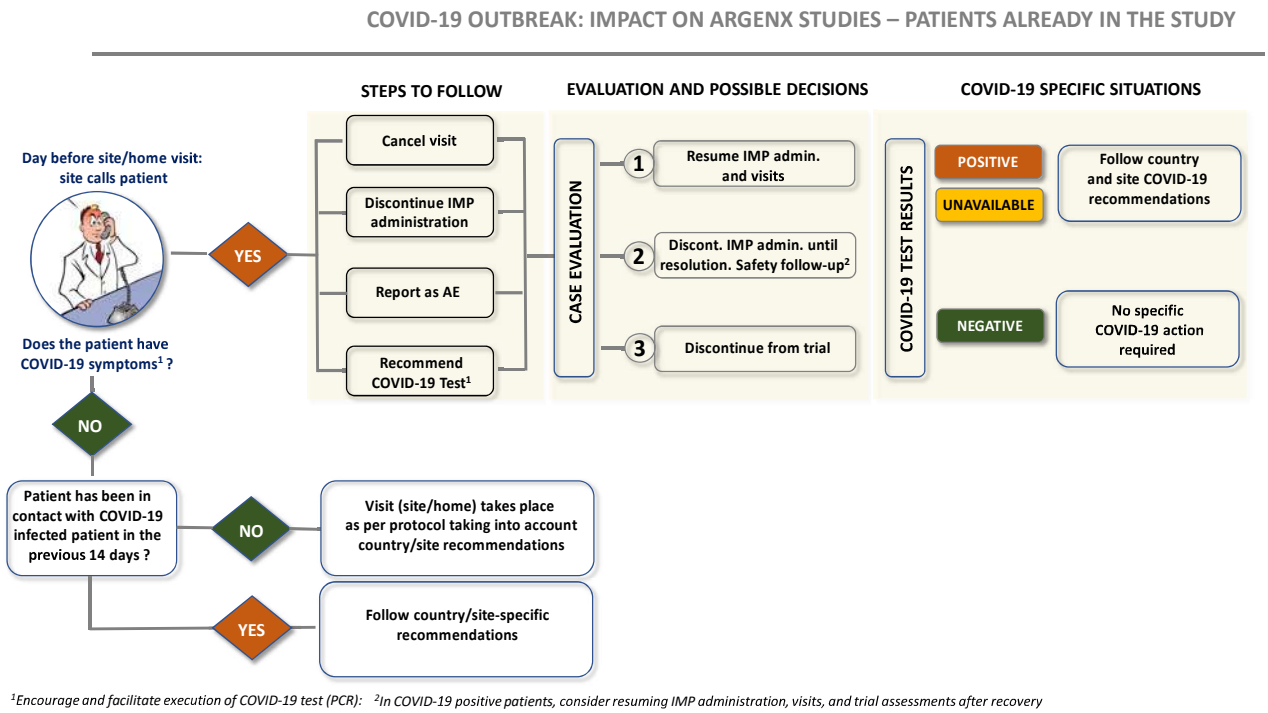
During the pandemic, the trial site staff should contact participants prior to each visit to inquire about COVID-19 symptoms and exposure using the flow charts below and make a decision on proceeding or postponing the visit according to the following flow charts.

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, the participant can continue the trial and receive trial medication, provided that the participant has not received/is not receiving prohibited medication (see Section 6.8.2).

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 that must be collected during the trial are summarized in the following table:

Eligibility • ICF • Demographics • Disease and medical history • Physical examination and study assessments • Other parameters to confirm eligibility	**Efficacy** • Disease assessment (DC, CR, EoC, 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 SoA in Table 10.

- 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 (screening, baseline, and EoS/ED) and other visits can be at home ("home" as described in this Appendix could also be a visit at an alternative convenient location).

- Screening Visit

The screening visit of the trial needs to be performed at the trial site. If it is not possible to go to the trial site due to the COVID-19 situation, the participant cannot start screening and has to wait until the situation changes and the participant is able to go to the trial site. Note that

transportation to the trial site can be facilitated if the situation due to the COVID-19 pandemic allows this.

- Baseline Visit

The baseline visit has to be performed at the trial site. If it is not possible to go to the trial 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.

- Other Trial Visits

During the COVID-19 pandemic, study visits after the screening and baseline visits 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 AE, concomitant medications, and general wellbeing of the participant. The investigator will also perform efficacy assessments using an audio or video interview with the participant. 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 following scheme. 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 may be administered through self- or caregiver administration, provided that the participant or caregiver has completed the training and has been deemed competent. IMP administration by the patient or caregiver can be supported by a video connection. Such an exception will require concurrent sponsor and investigator approval on a case-by-case basis.

- EoS/ED

The EoS/ED 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.

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) • Adverse events • Concomitant medication (including prednisone dosage)	Investigator	Audio or video interview
• Vital signs • IMP administration • Blood sampling (weekly until week 6, then every 4 weeks until EoS/ED) • Urine collection	Home nurse	In person at participant's home[a]

a. Note that 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 (IgG subtypes are not determined in China), and ADA weekly until week 6 and then every 4 weeks until EoS/ED. Additionally, urine samples will be collected for urinalysis and urine pregnancy testing.

- Electrocardiogram (ECG)

At screening (which is performed at the site), ECGs are required. 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 can be administered at home by trained and authorized personnel (eg, home nurse).

Trial Endpoint

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

Table 10: Modified Schedule of Activities During COVID-19 Pandemic

A China-specific version of the modified schedule of activities during COVID-19 pandemic is provided in Section 10.16.1.4.

In the SoA of the ARGX-113-1904 trial (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	**Screening**	**Treatment**						**EoS/ ED[a]**	**UNS[b]**	**Follow-up**	
		V1 (BL)	**V2**	**Observational visits**	**IMP admin only visit**	**Observational visits**					
Visit Number				**Weekly on-site visits until CR[c]**	**Weekly home or on-site visits until CRmin[d]**	**On-site visits every 4 weeks until CRmin**	**On-site visits every 4 weeks after CRmin until W31**	**W31**		**Follow-up W34**	**Follow-up W38[e]**
Trial Day/Week	**D-21 to D-1**	**D1 (W1)**	**D8 (W2)**	**D15 (W3) until CR**	**CR until CRmin**	**CR until CRmin**	**CRmin until W31**	**W31**		**EoS/ED +3W**	**EoS/ED +7W**
Visit Window		**±0 days**	**±2 days[f]**	**V1 + 7× ±2 days[f]**				**±2 days[f]**		**±3 days[f]**	
Assessment/ Procedure											
Informed consent[g]	**X**										
Inclusion/exclusion criteria	**X**	**X**									
DIF/histopathology[h]	**X**										
Concomitant therapies/procedures	**X**	Continuous monitoring									
Karnofsky performance score	**X**										
Demography	**X**										

Trial Period	**Screening**	**Treatment**						**EoS/ ED[a]**	**UNS[b]**	**Follow-up**	
		V1 (BL)	**V2**	**Observational visits**	**IMP admin only visit**	**Observational visits**					
Visit Number				**Weekly on-site visits until CR[c]**	**Weekly home or on-site visits until CRmin[d]**	**On-site visits every 4 weeks until CRmin**	**On-site visits every 4 weeks after CRmin until W31**	**W31**		**Follow-up W34**	**Follow-up W38[e]**
Trial Day/Week	**D-21 to D-1**	**D1 (W1)**	**D8 (W2)**	**D15 (W3) until CR**	**CR until CRmin**	**CR until CRmin**	**CRmin until W31**	**W31**		**EoS/ED +3W**	**EoS/ED +7W**
Visit Window		**±0 days**	**±2 days[f]**	**V1 + 7× ±2 days[f]**				**±2 days[f]**		**±3 days[f]**	
Height and weight[i]	X			X[i]		X[i]	X[i]	X			
Physical examination and vital signs[j,k]	X	X	X	X		X	X	X	X	X	X
ECG[j]	X			X[l]		X[l]		X			
Medical and surgical history	X										
Randomization[m]		X									
Urinalysis[j,n,o]	X	X	X	X		X	X	X	X[b]	X	X
Urine pregnancy test[j,p]		X		X[p]		X	X	X	X[b]	X	X
Blood sampling:											
Active viral infection test[q]	X										
Serum pregnancy test[r]	X										

Trial Period	**Screening**	**Treatment**						**EoS/ ED[a]**	**UNS[b]**	**Follow-up**	
		V1 (BL)	**V2**	**Observational visits**	**IMP admin only visit**	**Observational visits**					
Visit Number				**Weekly on-site visits until CR[c]**	**Weekly home or on-site visits until CRmin[d]**	**On-site visits every 4 weeks until CRmin**	**On-site visits every 4 weeks after CRmin until W31**	**W31**		**Follow-up W34**	**Follow-up W38[e]**
Trial Day/Week	**D-21 to D-1**	**D1 (W1)**	**D8 (W2)**	**D15 (W3) until CR**	**CR until CRmin**	**CR until CRmin**	**CRmin until W31**	**W31**		**EoS/ED +3W**	**EoS/ED +7W**
Visit Window		**±0 days**	**±2 days[f]**	**V1 + 7× ±2 days[f]**				**±2 days[f]**		**±3 days[f]**	
Clinical chemistry & hematology[j,o,s]	**X**	**X**	X	X		X	X	**X**	X[b]	X	X
Anti-Dsg-1 and anti-Dsg-3 antibodies[j,o]	**X**	**X**	X	X		X	X	**X**	X[b]	X	X
PK[j,o,t]		**X**	X[t]	X		X	X	**X**	X[b,t]	X	X
Total IgG and IgG subtypes[j,o,u]	**X**	**X**	X	X		X	X	**X**	X[b]	X	X
Vaccination antibodies[j,o,v]	**X**	**X**	X	X		X	X	**X**	X[b]	X	X
Anti-drug antibodies[j,w]		**X**		X (every 2 weeks)		X	X	**X**		X	X
IgG autoantibody subtypes/specificity and cytokines[j,x]		X		X[x]		X	X	X	X[b]	X	X
B- and T-cell populations[j]		X		X[y]				X			

Trial Period	**Screening**	**Treatment**						**EoS/ ED[a]**	**UNS[b]**	**Follow-up**	
		V1 (BL)	**V2**	**Observational visits**	**IMP admin only visit**	**Observational visits**					
Visit Number				**Weekly on-site visits until CR[c]**	**Weekly home or on-site visits until CRmin[d]**	**On-site visits every 4 weeks until CRmin**	**On-site visits every 4 weeks after CRmin until W31**	**W31**		**Follow-up W34**	**Follow-up W38[e]**
Trial Day/Week	**D-21 to D-1**	**D1 (W1)**	**D8 (W2)**	**D15 (W3) until CR**	**CR until CRmin**	**CR until CRmin**	**CRmin until W31**	**W31**		**EoS/ED +3W**	**EoS/ED +7W**
Visit Window		**±0 days**	**±2 days[f]**	**V1 + 7× ±2 days[f]**				**±2 days[f]**		**±3 days[f]**	
RNA transcriptional profile[j]		X		X[y]				X			
HLA/non-HLA genotyping[j]		X		X[z]							
Substudies:											
Skin biopsies (at selected sites)[j,aa]		X		X[aa]				X[aa]			
Photography (at selected sites)[j,bb]		X	X[bb]	X[bb]					X[b,bb]		
QoL Assessments:											
EQ-5D-5L[j,cc]		**X**		X[dd]		X[dd]	X[dd]	**X**			
ABQOL[j,cc]		**X**		X[dd]		X[dd]	X[dd]	**X**			
GTI[j]		**X**		X[ee]		X[ee]	X[ee]	**X**			
IMP self-administration training[ff]				X		X					

Trial Period	Screening	Treatment						EoS/ ED[a]	UNS[b]	Follow-up	
		V1 (BL)	V2	Observational visits	IMP admin only visit	Observational visits					
Visit Number				Weekly on-site visits until CR[c]	Weekly home or on-site visits until CRmin[d]	On-site visits every 4 weeks until CRmin	On-site visits every 4 weeks after CRmin until W31	W31		Follow-up W34	Follow-up W38[e]
Trial Day/Week	D-21 to D-1	D1 (W1)	D8 (W2)	D15 (W3) until CR	CR until CRmin	CR until CRmin	CRmin until W31	W31		EoS/ED +3W	EoS/ED +7W
Visit Window		±0 days	±2 days[f]	V1 + 7× ±2 days[f]				±2 days[f]		±3 days[f]	
IMP administration[gg]		X [redacted]	X [redacted]	X	X	X			X[b]		
PDAI[j]	X	X	X	X		X	X	X	X	X	X
Disease assessment[hh]			X	X		X	X	X	X	X	X
Prednisone taper[ii]				X	X	X	X	X	X	X	X
AE monitoring	Continuous monitoring										

ABQOL=Autoimmune Bullous Disease Quality of Life; BL=baseline; BMI=body mass index; CR=complete clinical remission; CRmin=CR on minimal therapy; D=day; DC=disease control; DIF=direct immunofluorescence; Dsg=desmoglein; ECG=electrocardiogram; ED=early discontinuation; EoC=end of consolidation; EoS=end of study; EQ-5D-5L=EuroQol 5-dimension 5-level; FSH=follicle-stimulating hormone; GTI=Glucocorticoid Toxicity Index; HLA=human leukocyte antigen; IgG=immunoglobulin G; IMP=investigational medicinal product; OLE=open-label extension; PDAI=Pemphigus Disease Area Index; PK=pharmacokinetics; RBC=red blood cells; WBC=white blood cells; W=week; V=visit

[a] All participants will complete EoS/ED, which will be the end of the trial for participants who enroll in the OLE trial ARGX-113-1905. Participants who do not enroll in the OLE trial ARGX 113 1905 will complete the follow-up visits at W34 and W38.

[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. See Section 8 for more information. Participants with new lesions or flare after achieving CR should return to weekly on-site visits until CR is achieved again.

[c] A minimum of 6 on-site visits, V1(BL)/W1 to W6, are required before switching to home administrations, even if CR is achieved earlier than W6. The W7 visit is the first eligible "IMP administration only" visit (refer to column "Weekly home or on-site visits until CRmin"), at home or on-site, if CR is achieved between W1 and W6.

[d] Home visits are allowed once participants achieve CR, but not before W7. The investigator should call the participant every 2 weeks until CRmin is achieved to confirm the participant is still in CR. On-site visits may continue at the investigator's discretion.

[e] W38 (follow-up visit 2) is the end of the trial for participants who do not enroll in the OLE trial ARGX-113-1905. The W38 follow-up visit will only be required for those participants who were still receiving IMP at least once from W27 onward. For participants who ended treatment prior to W27, W34 will be the end of the trial.

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

[g] No trial-related assessments can be initiated before the participant has provided as signed ICF.

[h] Only required if not available from medical history.

[i] Height and weight will be measured (and BMI will be calculated accordingly) at screening, at week W15 (or the next on-site visit if W15 does not coincide with an on-site visit), and EoS/ED. Weight will also be measured if there has been an obvious change since the last measurement.

[j] At visits in which IMP is administered, the assessment or procedure should be completed before dosing.

[k] A complete physical examination will be completed at each on-site visit. Vital sign measurements include systolic and diastolic blood pressure, heart rate, and body temperature. Supine blood pressure and heart rate will be measured using standard equipment after at least 10 minutes rest.

[l] ECG to be taken at W12. If the W12 visit does not coincide with an on-site visit, then the assessment should be performed at the next on-site visit. ECG (heart rate, PR, QT, and QRS interval) will be read centrally. QTcF and QTcB will be calculated.

[m] Randomization will take place on day 1 after all eligibility checks are confirmed (eg, PDAI) and before other baseline assessments are run, and prior to dosing.

[n] 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 test results are abnormal).

[o] Samples will be taken every week from V1(BL)/W1 to W9 and then every 4 weeks and at the visit where CR is observed. Once CR is achieved, samples will be taken every 4 weeks at on-site visits until EoS/ED. For participants achieving CR between V1(BL)/W1 and W6, samples will be taken weekly from W1 to W6 and then every 4 weeks at on-site visits until EoS/ED.

[p] A urine pregnancy test will be conducted and analyzed locally during on-site visits at least once every 4 weeks (before and after CR) and at the time of CR.

[q] Viral testing for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc), hepatitis B virus (HBV) DNA, hepatitis C virus (HCV) antibodies, HCV messenger RNA (mRNA), and human immunodeficiency virus (HIV) antibodies.

[r] At screening, a serum pregnancy test must be performed in women of childbearing potential or FSH test to confirm postmenopausal status.

[s] Clinical blood laboratory tests will include hematology and blood chemistry at all visits and international normalized ratio (INR) or activated partial thromboplastin time (aPTT) at screening only. The hematology profile includes hemoglobin, hematocrit, mean corpuscular volume (MCV), RBC count, platelet count, WBC count with differential. The blood chemistry profile includes sodium, potassium, calcium, hemoglobin A1c (HbA1c), creatinine, creatinine clearance, blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, gamma-glutamyl transferase (GGT), C-reactive protein (CRP), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol, triglycerides, uric acid, total protein, and albumin.

[t] For PK assessment, blood samples will be taken predose (within 2 hours before the start of IMP administration at visits where IMP is administered). An additional PK sample will be taken on D3 and on D11 (±1 day) until samples from 24 participants are obtained. At unscheduled visits blood samples for PK will only be taken if IMP is administered.

[u] At screening, total IgG will be measured as part of inclusion and exclusion criteria. The pharmacodynamic (PD) biomarkers total IgG and its subtypes (IgG1, IgG2, IgG3, and IgG4) will be measured centrally from a blood sample taken predose.

[v] An extra sample(s) will be taken for additional research (including vaccination antibodies and other additional research). The actual testing of vaccination antibodies depends on (a) whether a vaccination was given to the participant; (b) whether a test is available for the vaccination given to the participant; and (c)

whether the sample requirements (serum, volume, frozen sample, storage duration) match the serum samples taken and reserved for this. Timepoints for analysis will be decided upon occurrence of vaccination during the study.

[w] Anti-drug antibodies to efgartigimod (in serum samples) and antibodies against rHuPH20 (in plasma samples) will be tested predose every 2 weeks from V1(BL)/W1 to W9 and then every 4 weeks at on-site visits and at the visit where CR is observed. Once CR is achieved, samples will be taken every 4 weeks at on-site visits until EoS/ED. For participants achieving CR between V1(BL)/W1 and W6, samples will be taken predose at V1(BL)/W1, W3, W5, the visit where CR is observed, W10, and then every 4 weeks at on-site visits until EoS/ED. Neutralizing antibodies (NAb) will be tested for all confirmed positive ADA samples.

[x] Blood sampling for IgG autoantibody subtypes and specificity will be taken every 4 weeks (V1[BL]/W1, W5, W9, etc) and at the visit where CR is observed. Once CR is achieved, samples will be taken every 4 weeks at on-site visits until EoS/ED. For participants achieving CR between V1(BL)/W1 and W6, samples will be taken at V1(BL)/W1, W5, the visit where CR is observed, W10, and then every 4 weeks at on-site visits until EoS/ED. Serum aliquots from all time points will be used for IgG subtype and specificity analyses. For cytokines and complementary specificity analyses, aliquots from baseline, after 4 weeks (W5), W13 (or the visit at which CR is observed if before W13), and EoS/ED will be used.

[y] Samples for B- and T-cell populations and RNA transcriptional profiles will be performed at baseline, after 4 weeks (W5) and at W13 (or the visit at which CR is observed if before W13) and at EoS/ED.

[z] HLA/non-HLA genotyping will only be performed at baseline and D15.

[aa] Two 4 mm skin biopsies, 1 peri-lesional and 1 non-lesional, will be collected solely based on voluntary participation at baseline and after healing of 80% of blisters (EoC) or at EoS/ED (in case EoC has not been achieved) for scientific purposes.

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

[cc] Questionnaires are to be completed prior to any other activity.

[dd] Assessments will be performed at baseline, after 4 weeks (W5), W15, and EoS/ED visits. If the W15 visit does not coincide with an on-site visit, then the assessment should be performed at the next on-site visit.

[ee] The GTI assessment will be performed only at baseline, W15 and EoS/ED. If W15 does not coincide with an on-site visit, then the assessment should be performed at the next on-site visit.

[ff] Participants will be trained to self-administer IMP (foreseen in the OLE trial; not in the ARGX-113-1904 trial) during the first 4 visits as of V3 when IMP is administered; thereafter, training for self-administration is optional (only if needed).

[gg] IMP will be administered until CRmin. To ensure proper safety monitoring, participants should remain at the site for at least 1 hour after the first administration and for 15 minutes after subsequent administrations. Participants will be released according to their clinical status. For Germany-specific monitoring instructions, refer to Section 10.16.2.1. Participants who experience treatment failure, or flare after achieving CRmin, will be allowed to roll over into the OLE trial ARGX-113-1905 earlier than W31. Participants who do not roll over into trial ARGX-113-1905 will complete the treatment-free follow-up period.

[hh] Disease assessment parameters include disease control (DC), end of consolidation (EoC), complete clinical remission (CR), complete remission on minimal therapy (CRmin), complete remission off therapy (CRoff), flare, and treatment failure. Participants who have achieved CR and have new lesions should come to the clinic for a UNS for disease assessment.

[ii] 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).

10.15. Appendix 15: Glucocorticoid Toxicity Index (GTI)

Table 11: Approach to Calculating the Baseline GTI 2.0 Score: Toxicities Assigned Weighted Scores From C-GTI to Establish a Baseline GTI Score

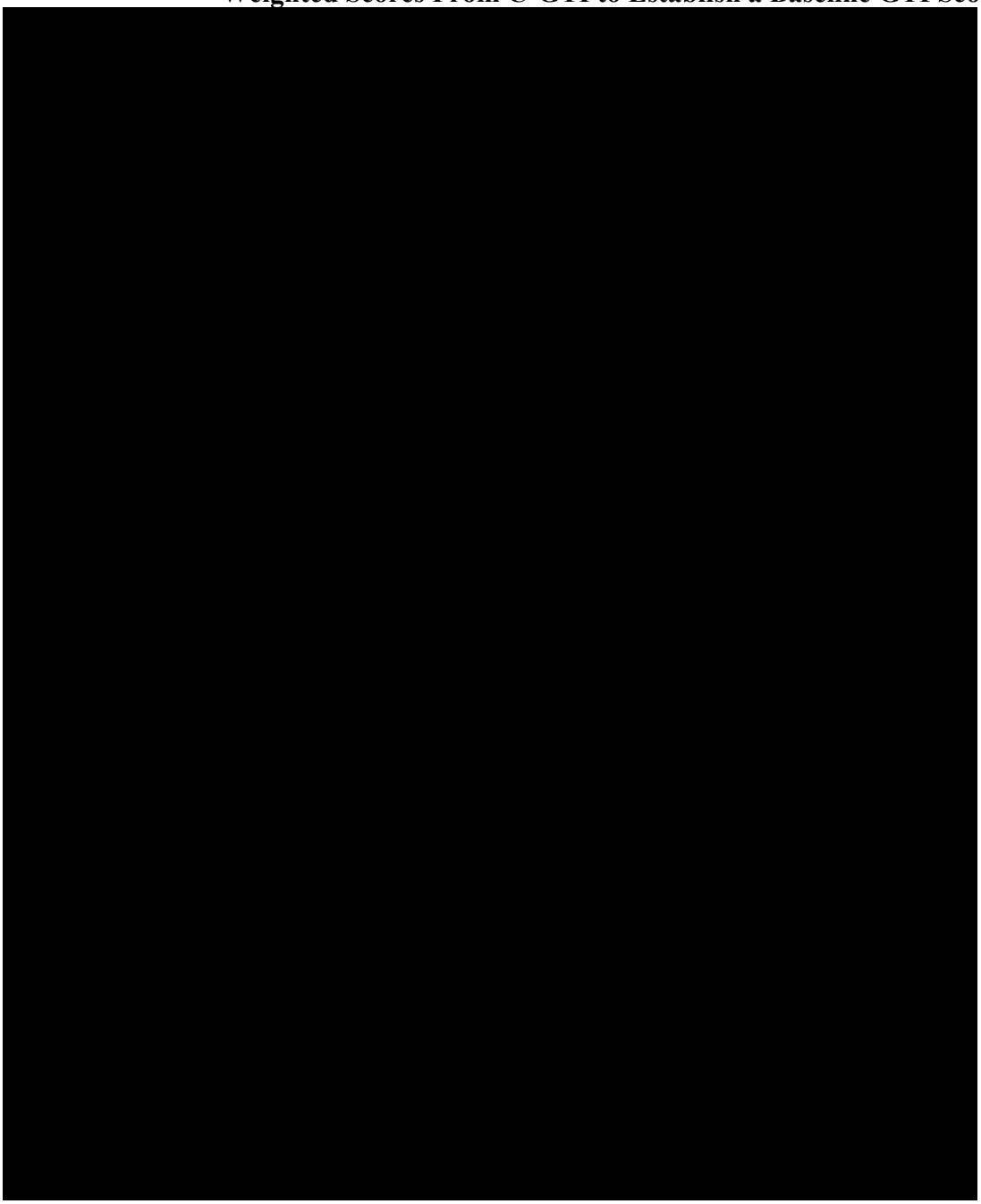


Table 12: Approach to Calculating the Changes in GTI 2.0 Score: Weighted Scores Assigned to Improvements or Worsenings in the C-GTI

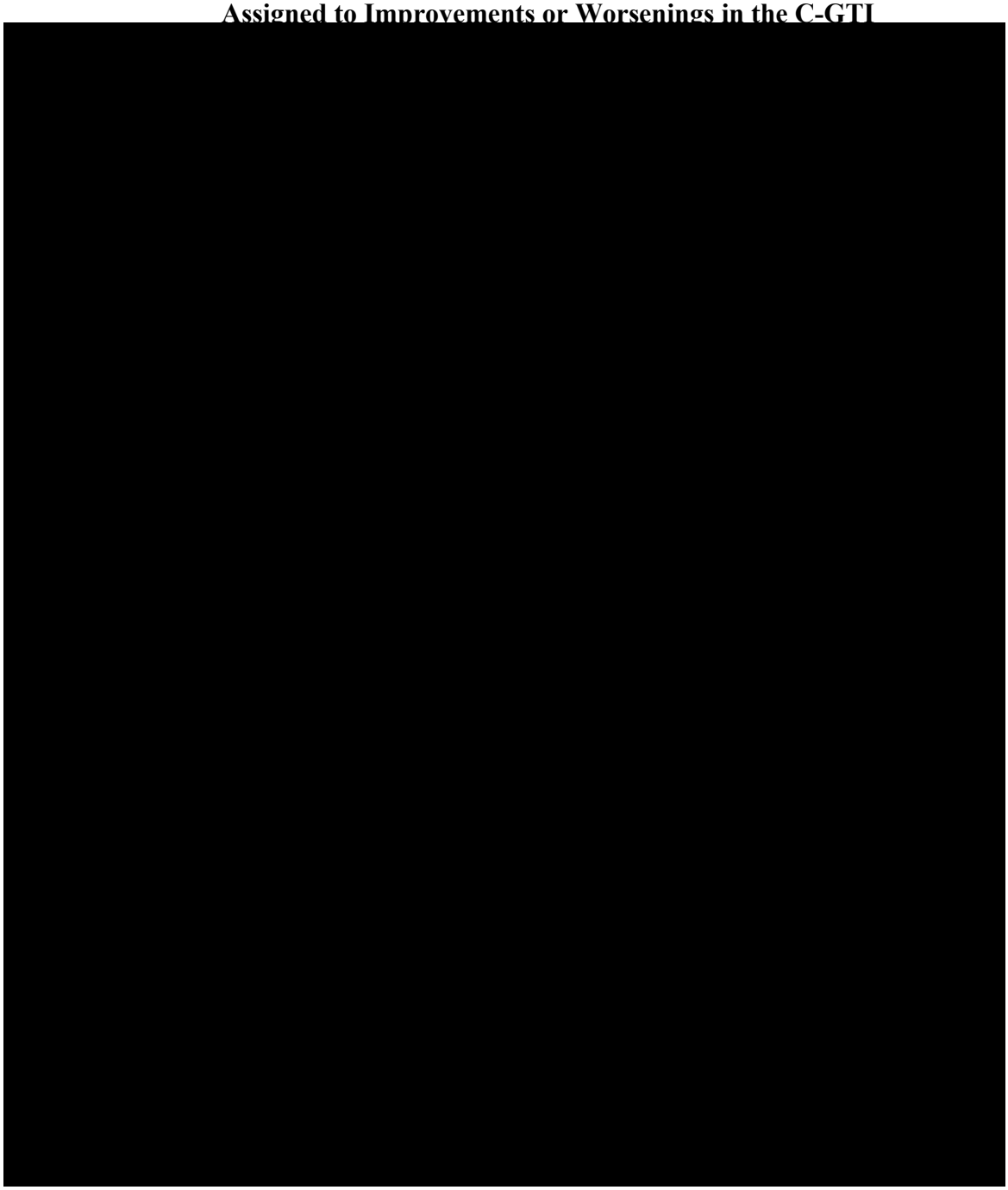
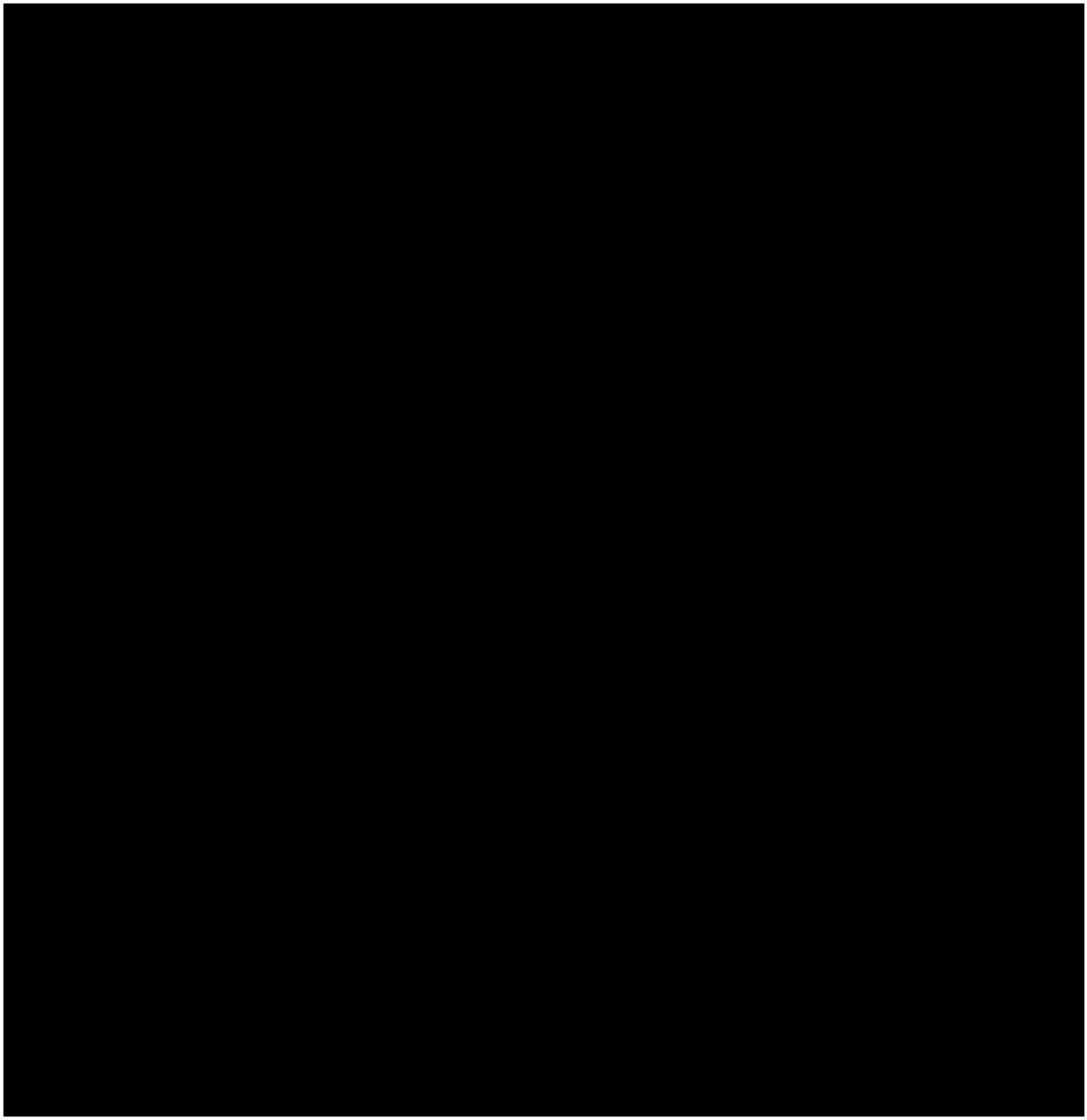


Table 13: GTI 2.0 Specific List: 11 Domains (9 of Which Are Shared by the C-GTI) and 23 Unique Items



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 14: 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)

Minor/Mild	Moderate	Severe (Specific Domain)
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% body surface area (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 15: 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 1 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 a 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

10.16. Appendix 16: Country-Specific Requirements

10.16.1. China

10.16.1.1. Section 1.3. Schedule of Activities - China

Table 16: Schedule of Activities for Trial ARGX-113-1904 – China

Trial Period	**Screening**	**Treatment**						**EoS/ ED[a]**	**UNS[b]**	**Follow-up**	
		V1(BL)	**V2**	**Observational visits**	**IMP admin only visit**	**Observational visits**					
Visit Number				**Weekly on-site visits until CR[c]**	**Weekly home or on-site visits until CRmin[d]**	**On-site visits every 4 weeks until CRmin**	**On-site visits every 4 weeks after CRmin until W31**	**W31**		**Follow-up W34**	**Follow-up W38[e]**
Trial Day/Week	**D-21 to D-1**	**D1 (W1)**	**D8 (W2)**	**D15 (W3) until CR**	**CR until CRmin**	**CR until CRmin**	**CRmin until W31**	**W31**		**EoS/ED +3W**	**EoS/ED +7W**
Visit Window		**±0 days**	**±2 days[f]**	**V1 + 7× ±2 days[f]**				**±2 days[f]**		**±3 days[f]**	
Assessment/ Procedure											
Informed consent[g]	X										
Inclusion/exclusion criteria	X	X									
DIF/histopathology[h]	X										
Concomitant therapies/procedures	X	Continuous monitoring									
Karnofsky performance score	X										
Demography	X										
Height and weight[i]	X			X[i]		X[i]	X[i]	X			

Trial Period	**Screening**	**Treatment**						**EoS/ ED[a]**	**UNS[b]**	**Follow-up**	
		V1(BL)	**V2**	**Observational visits**	**IMP admin only visit**	**Observational visits**					
Visit Number				**Weekly on-site visits until CR[c]**	**Weekly home or on-site visits until CRmin[d]**	**On-site visits every 4 weeks until CRmin**	**On-site visits every 4 weeks after CRmin until W31**	**W31**		**Follow-up W34**	**Follow-up W38[e]**
Trial Day/Week	**D-21 to D-1**	**D1 (W1)**	**D8 (W2)**	**D15 (W3) until CR**	**CR until CRmin**	**CR until CRmin**	**CRmin until W31**	**W31**		**EoS/ED +3W**	**EoS/ED +7W**
Visit Window		**±0 days**	**±2 days[f]**	**V1 + 7× ±2 days[f]**				**±2 days[f]**		**±3 days[f]**	
Physical examination and vital signs[j,k]	X	X	X	X		X	X	X	X	X	X
ECG[j]	X			X[l]		X[l]		X			
Medical and surgical history	X										
Randomization[m]		X									
Urinalysis[j,n,o]	X	X	X	X		X	X	X	X[b]	X	X
Urine pregnancy test[j,p]		X		X[p]		X	X	X	X[b]	X	X
Blood sampling:											
Active viral infection test[q]	X										
Serum pregnancy test[r]	X										
Clinical chemistry & hematology[j,o,s]	X	X	X	X		X	X	X	X[b]	X	X

Trial Period	**Screening**	**Treatment**						**EoS/ ED[a]**	**UNS[b]**	**Follow-up**	
		V1(BL)	**V2**	**Observational visits**	**IMP admin only visit**	**Observational visits**					
Visit Number				**Weekly on-site visits until CR[c]**	**Weekly home or on-site visits until CRmin[d]**	**On-site visits every 4 weeks until CRmin**	**On-site visits every 4 weeks after CRmin until W31**	**W31**		**Follow-up W34**	**Follow-up W38[e]**
Trial Day/Week	**D-21 to D-1**	**D1 (W1)**	**D8 (W2)**	**D15 (W3) until CR**	**CR until CRmin**	**CR until CRmin**	**CRmin until W31**	**W31**		**EoS/ED +3W**	**EoS/ED +7W**
Visit Window		**±0 days**	**±2 days[f]**	**V1 + 7× ±2 days[f]**				**±2 days[f]**		**±3 days[f]**	
Tuberculosis QuantiFERON/IGRA or equivalent test[j,t]		X									
Anti-Dsg-1 and anti-Dsg-3 antibodies[j,o]	X	X	X	X		X	X	X	X[b]	X	X
PK[j,o,u]		X	X[u]	X		X	X	X	X[b,u]	X	X
Total IgG[j,o,v]	X	X	X	X		X	X	X	X[b]	X	X
Immunogenicity[j,w]		X		X (every 2 weeks)		X	X	X		X	X
QoL Assessments:											
EQ-5D-5L[j,x]		X		X[y]		X[y]	X[y]	X			
ABQOL[j,x]		X		X[y]		X[y]	X[y]	X			
GTI[j]		X		X[z]		X[z]	X[z]	X			
IMP self-administration training[aa]				X		X					

Trial Period	Screening	Treatment						EoS/ ED[a]	UNS[b]	Follow-up	
		V1(BL)	V2	Observational visits	IMP admin only visit	Observational visits					
Visit Number				Weekly on-site visits until CR[c]	Weekly home or on-site visits until CRmin[d]	On-site visits every 4 weeks until CRmin	On-site visits every 4 weeks after CRmin until W31	W31		Follow-up W34	Follow-up W38[e]
Trial Day/Week	D-21 to D-1	D1 (W1)	D8 (W2)	D15 (W3) until CR	CR until CRmin	CR until CRmin	CRmin until W31	W31		EoS/ED +3W	EoS/ED +7W
Visit Window		±0 days	±2 days[f]	V1 + 7× ±2 days[f]				±2 days[f]		±3 days[f]	
IMP administration[bb]		X [redacted]	X [redacted]	X	X	X			X[b]		
PDAI[j]	X	X	X	X		X	X	X	X	X	X
Disease assessment[cc]			X	X		X	X	X	X	X	X
Prednisone taper[dd]				X	X	X	X	X	X	X	X
AE monitoring	Continuous monitoring										

ABQOL=Autoimmune Bullous Disease Quality of Life; admin=administration; BL=baseline; BMI=body mass index; CR=complete clinical remission; CRmin=CR on minimal therapy; D=day; DC=disease control; DIF=direct immunofluorescence; Dsg=desmoglein; ECG=electrocardiogram; ED=early discontinuation; EoC=end of consolidation; EoS=end of study; FSH=follicle-stimulating hormone; GTI=Glucocorticoid Toxicity Index; HLA=human leukocyte antigen; IgG=immunoglobulin G; ICF=informed consent form; IMP=investigational medicinal product; OLE=open-label extension; PDAI=Pemphigus Disease Area Index; PK=pharmacokinetics; RBC=red blood cells; UNS=unscheduled visit; WBC=white blood cells; W=week; V=visit

[a] All participants will complete EoS/ED, which will be the end of the trial for participants who enroll in the OLE trial ARGX-113-1905. Participants who do not enroll in the OLE trial ARGX 113 1905 will complete the follow-up visits at W34 and W38.

[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. See Section 8 for more information. Participants with new lesions or flare after achieving CR should return to weekly on-site visits until CR is achieved again.

[c] A minimum of 6 on-site visits, V1(BL)/W1 to W6, are required before switching to home administrations, even if CR is achieved earlier than W6. The W7 visit is the first eligible "IMP administration only" visit (refer to column "Weekly home or on-site visits until CRmin"), at home or on-site, if CR is achieved between W1 and W6.

[d] Home visits are allowed once participants achieve CR, but not before W7. The investigator should call the participant every 2 weeks until CRmin is achieved to confirm the participant is still in CR. On-site visits may continue at the investigator's discretion.

[e] W38 (follow-up visit 2) is the end of the trial for participants who do not enroll in the OLE trial ARGX-113-1905. The W38 follow-up visit will only be required for those participants who were still receiving IMP at least once from W27 onward. For participants who ended treatment prior to W27, W34 will be the end of the trial.

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

[g] No trial-related assessments can be initiated before the participant has provided a signed ICF.

[h] Only required if not available from medical history.

[i] Height and weight will be measured (and BMI will be calculated accordingly) at screening, at week W15 (or the next on-site visit if W15 does not coincide with an on-site visit), and EoS/ED. Weight will also be measured if there has been an obvious change since the last measurement.

[j] At visits in which IMP is administered, the assessment or procedure should be completed before dosing.

[k] A complete physical examination will be completed at each on-site visit. Vital sign measurements include systolic and diastolic blood pressure, heart rate, and body temperature. Supine blood pressure and heart rate will be measured using standard equipment after at least 10 minutes rest.

[l] ECG to be taken at W12. If the W12 visit does not coincide with an on-site visit, then the assessment should be performed at the next on-site visit. ECG (heart rate, PR, QT, and QRS interval) will be read centrally. QTcF and QTcB will be calculated.

[m] Randomization will take place on day 1 after all eligibility checks are confirmed (eg, PDAI) and before other baseline assessments are run, and prior to dosing.

[n] Urinalysis will include specific gravity, pH, protein, glucose, ketones, blood, bilirubin, urobilinogen, nitrite, leukocyte esterase, and microscopic examination (if blood or protein test results are abnormal).

[o] Samples will be taken every week from V1(BL)/W1 to W9 and then every 4 weeks and at the visit where CR is observed. Once CR is achieved, samples will be taken every 4 weeks at on-site visits until EoS/ED. For participants achieving CR between V1(BL)/W1 and W6, samples will be taken weekly from W1 to W6 and then every 4 weeks at on-site visits until EoS/ED.

[p] A urine pregnancy test will be conducted and analyzed locally during on-site visits at least once every 4 weeks (before and after CR) and at the time of CR.

[q] Viral testing for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc), hepatitis B virus (HBV) DNA, hepatitis C virus (HCV) antibodies, HCV messenger RNA (mRNA), and human immunodeficiency virus (HIV) antibodies.

[r] At screening, a serum pregnancy test must be performed in women of childbearing potential or FSH test to confirm postmenopausal status.

[s] Clinical blood laboratory tests will include hematology and blood chemistry at all visits and international normalized ratio (INR) or activated partial thromboplastin time (aPTT) at screening only. The hematology profile includes hemoglobin, hematocrit, mean corpuscular volume (MCV), RBC count, platelet count, WBC count with differential. The blood chemistry profile includes sodium, potassium, calcium, hemoglobin A1c (HbA1c), creatinine, creatinine clearance, blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, gamma-glutamyl transferase (GGT), C-reactive protein (CRP), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol, triglycerides, uric acid, total protein, and albumin.

[t] At the discretion of investigator, additional testing may be performed to rule out active tuberculosis infection, including but not limited to chest computed tomography (CT) or X-ray.

[u] For PK assessment, blood samples will be taken predose (within 2 hours before the start of IMP administration at visits where IMP is administered). An additional PK sample will be taken on D3 and on D11 (±1 day) until samples from 24 participants are obtained. At unscheduled visits blood samples for PK will only be taken if IMP is administered.

[v] At screening, total IgG will be measured as part of inclusion and exclusion criteria. The pharmacodynamic (PD) biomarker total IgG will be measured centrally from a blood sample taken predose.

[w] Anti-drug antibodies to efgartigimod (in serum samples) and antibodies against rHuPH20 (in plasma samples) will be tested predose every 2 weeks from V1(BL)/W1 to W9 and then every 4 weeks at on-site visits and at the visit where CR is observed. Once CR is achieved, samples will be taken every 4 weeks at

on-site visits until EoS/ED. For participants achieving CR between V1(BL)/W1 and W6, samples will be taken predose at V1(BL)/W1, W3, W5, the visit where CR is observed, W10, and then every 4 weeks at on-site visits until EoS/ED. Neutralizing antibodies (Nab) will be tested for all confirmed positive ADA samples.

[x] Questionnaires are to be completed prior to any other activity.

[y] Assessments will be performed at baseline, after 4 weeks (W5), W15, and EoS/ED visits. If the W15 visit does not coincide with an on-site visit, then the assessment should be performed at the next on-site visit.

[z] The GTI assessment will be performed only at baseline, W15 and EoS/ED. If W15 does not coincide with an on-site visit, then the assessment should be performed at the next on-site visit.

[aa] Participants will be trained to self-administer IMP (foreseen in the OLE trial; not in the ARGX-113-1904 trial) during the first 4 visits as of V3 when IMP is administered; thereafter, training for self-administration is optional (only if needed).

[bb] IMP will be administered until CRmin. Participants should remain at the site for at least 1 hour after the first administration and 15 minutes after subsequent administrations for safety monitoring. Participants will be released according to their clinical status. Participants who experience treatment failure, or flare after achieving CR on minimal therapy, will be allowed to roll over into the OLE trial ARGX-113-1905 earlier than W31. Participants who do not roll over into trial ARGX-113-1905 will complete the treatment-free follow-up period.

[cc] Disease assessment parameters include disease control (DC), end of consolidation (EoC), complete clinical remission (CR), complete remission on minimal therapy (CRmin), complete remission off therapy (CRoff), flare, and treatment failure. Participants who have achieved CR and have new lesions should come to the clinic for a UNS for disease assessment.

[dd] 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).

10.16.1.2. Section 8.3.6. Clinical Safety Laboratory Assessments – China

Blood and urine samples for determination of clinical chemistry, hematology, coagulation, urinalysis, serology (ie, viral testing), and tuberculosis QuantiFERON/IGRA test and other tests that have been approved in China with similar validity versus QuantiFERON (eg, T-SPOT) will be collected and analyzed as indicated in the SoA (refer to Section 10.16) and Section 10.16.1.3. In China, a certified laboratory will be used for clinical safety laboratory assessment. The urine sample for the pregnancy test will be analyzed locally.

Participants may be rescreened (ie, redoing the full assessments as per SoA in Section 10.16) or retested once (ie, repeating 1 test, see Section 5.4) if still within the screening period.

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.

For all female participants of childbearing potential, a serum pregnancy test will be performed at screening (on the samples taken for clinical laboratory tests), and a urine pregnancy test will be conducted and analyzed locally at the site at the visits specified in the SoA (Section 10.16). A follicle-stimulating hormone (FSH) test will be run to confirm postmenopausal status and exclude that a woman is of childbearing potential; see Section 10.5.

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, then it may be documented accordingly without being reported as an AE.

The details of sampling, handling, storage, and transportation of the samples will be described in the Laboratory Manual.

All laboratory tests with values considered clinically significantly abnormal during participation in the 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 10.16.1.3, must be conducted in accordance with the Laboratory Manual and the SoA (Section 10.16).
- If laboratory values from non-protocol specified laboratory assessments (except for total IgG; refer to Section 8.6) 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 event must be recorded in the eCRF.

10.16.1.2.1. Section 8.3.6.2. Storage of Blood Samples in the Trial - China

Upon approval from the Human Genetic Resources (HGR) in China and in compliance with local regulations, blood samples collected from Chinese participants may be used to validate methods to support the efgartigimod program.

The storage duration and destruction of blood samples collected from Chinese participants will comply with HGR Administration of China (HGRAC) requirements and other relevant regulations.

10.16.1.3. Section 10.2. Appendix 2: Laboratory Tests – Table 7 - China

Table 17: Protocol-Required Laboratory Assessments - China

Hematology	Hemoglobin, hematocrit, MCV, RBC, platelet count, WBC with differential
Clinical chemistry	Sodium, potassium, calcium, HbA1c, creatinine, creatinine clearance, BUN, ALT, AST, total bilirubin, GGT, LDL-C, CRP, ALP, LDH, HDL-C, total cholesterol, triglycerides, uric acid, total protein[a], and albumin[a]
Coagulation	INR or aPTT
Urinalysis	Specific gravity, pH, protein, glucose, ketones, blood, bilirubin, urobilinogen, nitrite, leukocyte esterase, and microscopic examination (if blood or protein test results are abnormal)
Serology	HIV antibodies (1 and 2), HBsAg, anti-HBs and anti-HBc, HBV DNA, HCV antibodies, HCV mRNA
Other	Serum human ß-HCG, FSH test, tuberculosis QuantiFERON/IGRA test (and other tests that have been approved in China with similar validity versus QuantiFERON, eg, T-SPOT), urine pregnancy test
Pharmacokinetics[a]	Serum levels of efgartigimod
Pharmacodynamic markers[a]	Serum levels of total IgG and anti-Dsg-1 and anti-Dsg-3 autoantibodies
Immunogenicity[a]	Serum levels of ADA to efgartigimod and plasma levels of antibodies against rHuPH20

ß-HCG= ß subunit of human chorionic gonadotrophin; ADA= antidrug antibodies; ALP= alkaline phosphatase; ALT= alanine aminotransferase; anti-Dsg-1=anti-desmoglein-1; anti-Dsg-3=anti-desmoglein-3; anti-HBs=antibodies to the surface antigens of the hepatitis B virus; anti-HBc= antibodies to the surface core antigens of the hepatitis B virus; aPTT= activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CRP=C-reactive protein; DNA= deoxyribonucleic acid; FSH=follicle-stimulating hormone GGT=gamma-glutamyl transferase; HbA1c= hemoglobin A1c; HBV=hepatitis B virus; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HDL-C=high-density lipoprotein cholesterol; HIV= human immunodeficiency viruses; IgG=immunoglobulin G; INR=international normalized ratio; LDH= lactate dehydrogenase; LDL-C=low-density lipoprotein cholesterol MCV=mean corpuscular volume; mRNA= messenger RNA; RBC= red blood cell; rHuPH20=recombinant human hyaluronidase; RNA=ribonucleic acid; WBC=white blood cell

[a] PK, PD, immunogenicity, albumin, and total protein data will not be reported to the site. A system will be implemented that will alert the investigator of out-of-range albumin and total protein values, to allow for appropriate safety follow-up.

10.16.1.4. Section 10.14. Possible Adaptations of Trial Protocol During COVID-19 Pandemic - Table 10 - China

Table 18: Modified Schedule of Activities During COVID-19 Pandemic - China

In the SoA of the ARGX-113-1904 trial (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	**Screening**	**Treatment**						**EoS/ ED[a]**	**UNS[b]**	**Follow-up**	
		V1(BL)	**V2**	**Observational visits**	**IMP admin only visit**	**Observational visits**					
Visit Number				**Weekly on-site visits until CR[c]**	**Weekly home or on-site visits until CRmin[d]**	**On-site visits every 4 weeks until CRmin**	**On-site visits every 4 weeks after CRmin until W31**	**W31**		**Follow-up W34**	**Follow-up W38[e]**
Trial Day/Week	**D-21 to D-1**	**D1 (W1)**	**D8 (W2)**	**D15 (W3) until CR**	**CR until CRmin**	**CR until CRmin**	**CRmin until W31**	**W31**		**EoS/ED +3W**	**EoS/ED +7W**
Visit Window		**±0 days**	**±2 days[f]**	**V1 + 7× ±2 days[f]**				**±2 days[f]**		**±3 days[f]**	
Assessment/ Procedure											
Informed consent[g]	**X**										
Inclusion/exclusion criteria	**X**	**X**									
DIF/histopathology[h]	**X**										
Concomitant therapies/procedures	**X**	**Continuous monitoring**									
Karnofsky performance score	**X**										
Demography	**X**										
Height and weight[i]	**X**			X[i]		X[i]	X[i]	**X**			

Trial Period	**Screening**	**Treatment**						**EoS/ ED**[a]	**UNS**[b]	**Follow-up**	
		V1(BL)	**V2**	**Observational visits**	**IMP admin only visit**	**Observational visits**					
Visit Number				**Weekly on-site visits until CR**[c]	**Weekly home or on-site visits until CRmin**[d]	**On-site visits every 4 weeks until CRmin**	**On-site visits every 4 weeks after CRmin until W31**	**W31**		**Follow-up W34**	**Follow-up W38**[e]
Trial Day/Week	**D-21 to D-1**	**D1 (W1)**	**D8 (W2)**	**D15 (W3) until CR**	**CR until CRmin**	**CR until CRmin**	**CRmin until W31**	**W31**		**EoS/ED +3W**	**EoS/ED +7W**
Visit Window		**±0 days**	**±2 days**[f]	**V1 + 7× ±2 days**[f]				**±2 days**[f]		**±3 days**[f]	
Physical examination and vital signs[j,k]	X	X	X	X		X	X	X	X	X	X
ECG[j]	X			X[l]		X[l]		X			
Medical and surgical history	X										
Randomization[m]		X									
Urinalysis[j,n,o]	X	X	X	X		X	X	X	X[b]	X	X
Urine pregnancy test[j,p]		X		X[p]		X	X	X	X[b]	X	X
Blood sampling:											
Active viral infection test[q]	X										
Serum pregnancy test[r]	X										
Clinical chemistry & hematology[j,o,s]	X	X	X	X		X	X	X	X[b]	X	X

Trial Period	**Screening**	**Treatment**						**EoS/ ED[a]**	**UNS[b]**	**Follow-up**	
		V1(BL)	**V2**	**Observational visits**	**IMP admin only visit**	**Observational visits**					
Visit Number				**Weekly on-site visits until CR[c]**	**Weekly home or on-site visits until CRmin[d]**	**On-site visits every 4 weeks until CRmin**	**On-site visits every 4 weeks after CRmin until W31**	**W31**		**Follow-up W34**	**Follow-up W38[e]**
Trial Day/Week	**D-21 to D-1**	**D1 (W1)**	**D8 (W2)**	**D15 (W3) until CR**	**CR until CRmin**	**CR until CRmin**	**CRmin until W31**	**W31**		**EoS/ED +3W**	**EoS/ED +7W**
Visit Window		**±0 days**	**±2 days[f]**	**V1 + 7× ±2 days[f]**				**±2 days[f]**		**±3 days[f]**	
Tuberculosis QuantiFERON/IGRA or equivalent test[j,t]		X									
Anti-Dsg-1 and anti-Dsg-3 antibodies[j,o]	X	X	X	X		X	X	X	X[b]	X	X
PK[j,o,u]		X	X[u]	X		X	X	X	X[b,u]	X	X
Total IgG[j,o,v]	X	X	X	X		X	X	X	X[b]	X	X
Immunogenicity[j,w]		X		X (every 2 weeks)		X	X	X		X	X
QoL Assessments:											
EQ-5D-5L[j,x]		X		X[y]		X[y]	X[y]	X			
ABQOL[j,x]		X		X[y]		X[y]	X[y]	X			
GTI[j]		X		X[z]		X[z]	X[z]	X			
IMP self-administration training[aa]				X		X					

Trial Period	Screening	Treatment						EoS/ ED[a]	UNS[b]	Follow-up	
		V1(BL)	V2	Observational visits	IMP admin only visit	Observational visits					
Visit Number				Weekly on-site visits until CR[c]	Weekly home or on-site visits until CRmin[d]	On-site visits every 4 weeks until CRmin	On-site visits every 4 weeks after CRmin until W31	W31		Follow-up W34	Follow-up W38[e]
Trial Day/Week	D-21 to D-1	D1 (W1)	D8 (W2)	D15 (W3) until CR	CR until CRmin	CR until CRmin	CRmin until W31	W31		EoS/ED +3W	EoS/ED +7W
Visit Window		±0 days	±2 days[f]	V1 + 7× ±2 days[f]				±2 days[f]		±3 days[f]	
IMP administration[bb]		X [redacted]	X [redacted]	X	X	X			X[b]		
PDAI[j]	X	X	X	X		X	X	X	X	X	X
Disease assessment[cc]			X	X		X	X	X	X	X	X
Prednisone taper[dd]				X	X	X	X	X	X	X	X
AE monitoring	Continuous monitoring										

ABQOL=Autoimmune Bullous Disease Quality of Life; admin=administration; BL=baseline; BMI=body mass index; CR=complete clinical remission; CRmin=CR on minimal therapy; D=day; DC=disease control; DIF=direct immunofluorescence; Dsg=desmoglein; ECG=electrocardiogram; ED=early discontinuation; EoC=end of consolidation; EoS=end of study; EQ-5D-5L=EuroQol 5-dimension 5-level; FSH=follicle-stimulating hormone; GTI=Glucocorticoid Toxicity Index; HLA=human leukocyte antigen; IgG=immunoglobulin G; ICF=informed consent form; IMP=investigational medicinal product; OLE=open-label extension; PDAI=Pemphigus Disease Area Index; PK=pharmacokinetics; RBC=red blood cells; UNS=unscheduled visit; WBC=white blood cells; W=week; V=visit

[a] All participants will complete EoS/ED, which will be the end of the trial for participants who enroll in the OLE trial ARGX-113-1905. Participants who do not enroll in the OLE trial ARGX 113 1905 will complete the follow-up visits at W34 and W38.

[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 should be performed. See Section 8 for more information. Participants with new lesions or flare after achieving CR should return to weekly on-site visits until CR is achieved again.

[c] A minimum of 6 on-site visits, V1(BL)/W1 to W6, are required before switching to home administrations, even if CR is achieved earlier than W6. The W7 visit is the first eligible "IMP administration only" visit (refer to column "Weekly home or on-site visits until CRmin"), at home or on-site, if CR is achieved between W1 and W6.

[d] Home visits are allowed once participants achieve CR, but not before W7. The investigator should call the participant every 2 weeks until CRmin is achieved to confirm the participant is still in CR. On-site visits may continue at the investigator's discretion.

[e] W38 (follow-up visit 2) is the end of the trial for participants who do not enroll in the OLE trial ARGX-113-1905. The W38 follow-up visit will only be required for those participants who were still receiving IMP at least once from W27 onward. For participants who ended treatment prior to W27, W34 will be the end of the trial.

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

[g] No trial-related assessments can be initiated before the participant has provided a signed ICF.

[h] Only required if not available from medical history.

[i] Height and weight will be measured (and BMI will be calculated accordingly) at screening, at week W15 (or the next on-site visit if W15 does not coincide with an on-site visit), and EoS/ED. Weight will also be measured if there has been an obvious change since the last measurement.

[j] At visits in which IMP is administered, the assessment or procedure should be completed before dosing.

[k] A complete physical examination will be completed at each on-site visit. Vital sign measurements include systolic and diastolic blood pressure, heart rate, and body temperature. Supine blood pressure and heart rate will be measured using standard equipment after at least 10 minutes rest.

[l] ECG to be taken at W12. If the W12 visit does not coincide with an on-site visit, then the assessment should be performed at the next on-site visit. ECG (heart rate, PR, QT, and QRS interval) will be read centrally. QTcF and QTcB will be calculated.

[m] Randomization will take place on day 1 after all eligibility checks are confirmed (eg, PDAI) and before other baseline assessments are run, and prior to dosing.

[n] Urinalysis will include specific gravity, pH, protein, glucose, ketones, blood, bilirubin, urobilinogen, nitrite, leukocyte esterase, and microscopic examination (if blood or protein test results are abnormal).

[o] Samples will be taken every week from V1(BL)/W1 to W9 and then every 4 weeks and at the visit where CR is observed. Once CR is achieved, samples will be taken every 4 weeks at on-site visits until EoS/ED. For participants achieving CR between V1(BL)/W1 and W6, samples will be taken weekly from W1 to W6 and then every 4 weeks at on-site visits until EoS/ED.

[p] A urine pregnancy test will be conducted and analyzed locally during on-site visits at least once every 4 weeks (before and after CR) and at the time of CR.

[q] Viral testing for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc), hepatitis B virus (HBV) DNA, hepatitis C virus (HCV) antibodies, HCV messenger RNA (mRNA), and human immunodeficiency virus (HIV) antibodies.

[r] At screening, a serum pregnancy test must be performed in women of childbearing potential or FSH test to confirm postmenopausal status.

[s] Clinical blood laboratory tests will include hematology and blood chemistry at all visits and international normalized ratio (INR) or activated partial thromboplastin time (aPTT) at screening only. The hematology profile includes hemoglobin, hematocrit, mean corpuscular volume (MCV), RBC count, platelet count, WBC count with differential. The blood chemistry profile includes sodium, potassium, calcium, hemoglobin A1c (HbA1c), creatinine, creatinine clearance, blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, gamma-glutamyl transferase (GGT), C-reactive protein (CRP), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol, triglycerides, uric acid, total protein, and albumin.

[t] At the discretion of investigator, additional testing may be performed to rule out active tuberculosis infection, including but not limited to chest computed tomography (CT) or X-ray.

[u] For PK assessment, blood samples will be taken predose (within 2 hours before the start of IMP administration at visits where IMP is administered). An additional PK sample will be taken on D3 and on D11 (±1 day) until samples from 24 participants are obtained. At unscheduled visits blood samples for PK will only be taken if IMP is administered.

[v] At screening, total IgG will be measured as part of inclusion and exclusion criteria. The pharmacodynamic (PD) biomarker total IgG will be measured centrally from a blood sample taken predose.

[w] Anti-drug antibodies to efgartigimod (in serum samples) and antibodies against rHuPH20 (in plasma samples) will be tested predose every 2 weeks from V1(BL)/W1 to W9 and then every 4 weeks at on-site visits and at the visit where CR is observed. Once CR is achieved, samples will be taken every 4 weeks at on-site visits until EoS/ED. For participants achieving CR between V1(BL)/W1 and W6, samples will be taken predose at V1(BL)/W1, W3, W5, the visit where CR is observed, W10, and then every 4 weeks at on-site visits until EoS/ED. Neutralizing antibodies (Nab) will be tested for all confirmed positive ADA samples.

[x] Questionnaires are to be completed prior to any other activity.

[y] Assessments will be performed at baseline, after 4 weeks (W5), W15, and EoS/ED visits. If the W15 visit does not coincide with an on-site visit, then the assessment should be performed at the next on-site visit.

[z] The GTI assessment will be performed only at baseline, W15 and EoS/ED. If W15 does not coincide with an on-site visit, then the assessment should be performed at the next on-site visit.

[aa] Participants will be trained to self-administer IMP (foreseen in the OLE trial; not in the ARGX-113-1904 trial) during the first 4 visits as of V3 when IMP is administered; thereafter, training for self-administration is optional (only if needed).

[bb] IMP will be administered until CRmin. Participants who do not roll over into trial ARGX-113-1905 will complete the treatment-free follow-up period. Participants should remain at the site for at least 1 hour after the first administration and 15 minutes for subsequent administrations for safety monitoring. Participants will be released according to their clinical status. Participants who experience treatment failure, or flare after achieving CR on minimal therapy, will be allowed to roll over into the OLE trial ARGX-113-1905 earlier than W31.

[cc] Disease assessment parameters include disease control (DC), end of consolidation (EoC), complete clinical remission (CR), complete remission on minimal therapy (CRmin), complete remission off therapy (CRoff), flare, and treatment failure. Participants who have achieved CR and have new lesions should come to the clinic for a UNS for disease assessment.

[dd] 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).

10.16.2. Germany

10.16.2.1. Section 1.3: Schedule of Activities – Post-Administration Safety Monitoring – Germany

To ensure proper safety monitoring, participants should remain at the site for at least 1 hour after the first administration. In Germany, participants should remain at the site for at least 30 minutes after the 5 subsequent administrations and for 15 minutes after all administrations thereafter. Participants will be released according to their clinical status.

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