TITLE PAGE

Protocol Title:	Open-Label Extension Study to Evaluate the Safety of Efgartigimod in Adult Patients With Primary Sjögren's Syndrome (pSS) who Complete Qualifying Efgartigimod pSS Studies
Protocol Number:	ARGX-113-2211
Version Number:	1
Compound:	Efgartigimod (ARGX-113)
Study Phase:	2
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Protocol Title:	Open-Label Extension Study to Evaluate the Safety of Efgartigimod in Adult Patients With Primary Sjögren's Syndrome (pSS) who Complete Qualifying Efgartigimod pSS Studies
Protocol Number:	ARGX-113-2211

Sponsor Signatory:

See appended signature page

PPD MD, PhD
Chief Medical Officer

Date

SIGNATURE OF THE INVESTIGATOR

Investigator's Acknowledgment

I have read the protocol for study ARGX-113-2211.

Title: Open-Label Extension Study to Evaluate the Safety of Efgartigimod in Adult Patients With Primary Sjögren's Syndrome (pSS) who Complete Qualifying Efgartigimod pSS Studies

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and will not be disclosed, except to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a participant in order to obtain their consent to participate.

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

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

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

Investigator Name _____
Institution _____
Address _____
(please handprint or type) _____

Signature _____

Date _____

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

List of Abbreviations

Abbreviation	Expansion
21 CFR	Title 21 of the Code of Federal Regulations
AChR-Ab	anti-acetylcholine receptor antibody
ACR	American College of Rheumatology
ADA	antidrug antibody(ies)
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
BL	Baseline
CIDP	chronic inflammatory demyelinating polyneuropathy
clinESSDAI	clinical EULAR Sjögren's syndrome disease activity index
CQ	chloroquine
CRESS	Composite of Relevant Endpoints for Sjögren's Syndrome
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DMARD	disease-modifying antirheumatic drug
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EDV	early discontinuation visit
efgartigimod IV	efgartigimod formulation for intravenous administration
EMA	European Medicines Agency
EMG	electromyography
ESSDAI	EULAR Sjögren's syndrome disease activity index
ESSPRI	EULAR Sjögren's Syndrome Patient-Reported Index
EULAR	European Alliance of Associations for Rheumatology
FcRn	neonatal crystallizable fragment receptor
FDA	Food and Drug Administration

Abbreviation	Expansion
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
gMG	generalized myasthenia gravis
HRCT	High-resolution computed tomography
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IFN	interferon
CCI	CCI
IgG	immunoglobulin G
CCI	CCI
IMP	investigational medicinal product
IRB	institutional review board
ITP	immune thrombocytopenia
IV	intravenous
IVIg	intravenous immunoglobulin
JAK	Janus kinase
MedDRA	Medical Dictionary for Regulatory Activities
MFI	Multidimensional Fatigue Inventory
NCI	National Cancer Institute
NCS	Nerve conduction studies
NSAID	non-steroidal anti-inflammatory drug
OLE	open-label extension
OSS	ocular staining score
PASS	patient acceptable symptom state
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PGA	patient global assessment
PI	principal investigator

Abbreviation	Expansion
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
pSS	primary Sjögren's syndrome
PT	preferred term
QW	once weekly
Q2W	every 2 weeks
RF	rheumatoid factor
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCIg	subcutaneous immunoglobulin
SF-36	36-Item Short Form Survey
SFV	safety follow-up visit
SGUS	salivary gland ultrasonography
SoA	schedule of activities
SOC	system organ class
SS-A	Sjögren's syndrome–related antigen A
SS-B	Sjögren's syndrome–related antigen B
STAR	Sjögren's Tool for Assessing Response
SUSAR	suspected unexpected serious adverse reaction
SWSF	stimulated whole salivary flow
TEAE	treatment-emergent adverse event
UWSF	unstimulated whole salivary flow
VAS	visual analog scale
WOCBP	women of childbearing potential

Definitions of Terms

Term	Definition
Nonresponder	Participant who does not have a reduction in ClinESSDAI score of ≥3 points and/or a change in score that alters their disease severity category
Responder	Participant who has a reduction in ClinESSDAI score of ≥3 points and/or a change in score that reclassifies their disease from moderate severity to mild severity
Therapeutic failure	Participant who are nonresponder at week 24. This participant will discontinue study treatment

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

Open-Label Extension Study to Evaluate the Safety of Efgartigimod in Adult Patients With Primary Sjögren's Syndrome (pSS) who Complete Qualifying Efgartigimod pSS Studies

Rationale: Efgartigimod contributes to successfully treat pSS and has the potential to improve disease manifestations by the reduction of IgG autoantibodies in pSS. This open-label extension study will evaluate the long-term safety of efgartigimod in participants with pSS who have completed the treatment period of the qualifying efgartigimod studies (including ARGX-113-2106).

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
• To evaluate the long-term safety of efgartigimod in patients with pSS	• Incidence and severity of AEs and AESIs, incidence SAEs, changes in laboratory test results, vital signs, and ECG results
Secondary	
• To evaluate effect and assess long-term data on durability of CRESS response	• Proportion of CRESS responders on ≥ 3 of 5 items at weeks 24 and 48. The 5 items are: – Systemic disease activity: clinESSDAI – Patient-reported symptoms: ESSPRI – Tear gland function: Schirmer's test and OSS – Salivary gland function: UWSF rate and SGUS – Serology: serum IgG and/or RF
• To evaluate the effect of efgartigimod on clinical efficacy parameters	• Proportion of participants with minimal clinically important improvement from baseline in ESSDAI: improvement of ≥ 3 points in ESSDAI score at weeks 24 and 48 • Proportion of participants with low disease activity: ESSDAI score of < 5 at weeks 24 and 48 • Proportion of participants with minimal clinically important improvement from baseline in clinESSDAI: improvement of ≥ 3 points in clinESSDAI score at weeks 24 and 48 • Proportion of participants with low disease activity: clinESSDAI score of < 5 at weeks 24 and 48

Objectives	Endpoints
	• Proportion of participants with minimal clinically important improvement from baseline in ESSPRI: decrease of 1 point or ≥ 15% at weeks 24 and 48 • Change from baseline in ESSDAI score at weeks 24 and 48 • Change from baseline in clinESSDAI score at weeks 24 and 48 • Change from baseline in ESSPRI score at weeks 24 and 48
• To evaluate the effect of efgartigimod on STAR	• Proportion of STAR responders (score of ≥5) at weeks 24 and 48 when compared to baseline
• To assess the PD effect of efgartigimod	• Values, changes from baseline, and percent reduction from baseline in total IgG levels in serum over the 48-week treatment period • Values, changes from baseline, and percent reduction from baseline in autoantibodies in serum over the 48-week treatment period: – Anti-Ro/SS A – Anti-La/SS B
• To assess the exposure to efgartigimod	• Efgartigimod serum concentrations over the 48-week treatment period
• To assess the immunogenicity of efgartigimod	• Incidence and prevalence of ADA against efgartigimod over the 48-week treatment period

ADA = antidrug antibody; AESI = adverse event of special interest; clinESSDAI = clinical EULAR Sjögren's syndrome disease activity index; CRESS = Composite of Relevant Endpoints for Sjögren's Syndrome; ECG = electrocardiogram; ESSDAI = EULAR Sjögren's syndrome disease activity index; ESSPRI = EULAR Sjögren's Syndrome Patient-Reported Index; IFN = interferon; IgG = immunoglobulin G; RF = rheumatoid factor; IV = intravenous; OSS = ocular staining score; PD = pharmacodynamic(s); PK = pharmacokinetic(s); pSS = primary Sjögren's syndrome; PT = preferred term; SAE = serious adverse event; SGUS = salivary gland ultrasonography; SOC = system organ class; STAR = Sjögren's Tool for Assessing Response; TEAE = treatment-emergent adverse event; UWSF = unstimulated whole salivary flow; VAS = visual analog scale.

No estimands have been defined for this study.

Overall Design:

ARGX-113-2211 is a long-term, single-arm, open-label, multicenter extension study of the pSS-qualifying efgartigimod studies designed to evaluate the long-term safety of efgartigimod in adult patients with pSS. Participants will be enrolled from both active and placebo arms of qualifying efgartigimod studies and receive efgartigimod 10 mg/kg over 48 weeks in the extension study without knowledge of their treatment assignment in the qualifying study. Eligible participants must have completed the treatment period of the qualifying study and must not have permanently discontinued the IMP in that study.

Brief Summary:

Participants will receive efgartigimod 10 mg/kg by IV infusion either Q2W or QW. The dosing regimen is based on whether the participant is a responder or nonresponder. Responder status will be determined by clinESSDAI assessments conducted on day 1, week 16, and week 24 and using the baseline of the qualifying study. Participants who are not responders at week 24 will be evaluated by PI for therapeutic failure. If a participant is a therapeutic failure, they will discontinue study treatment. If a participant is not a therapeutic failure, they will continue QW dosing regimen, and a clinESSDAI will be conducted at weeks 32, 36, 40, and 44 until confirming responder status and switching to Q2W dosing regimen. The PI will continue to evaluate the participant for therapeutic failure.

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

Number of Participants:

Up to approximately 30 subjects who have completed the efgartigimod pSS study (ARGX-113-2106) will be enrolled for in the OLE study (ARGX-113-2211).

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

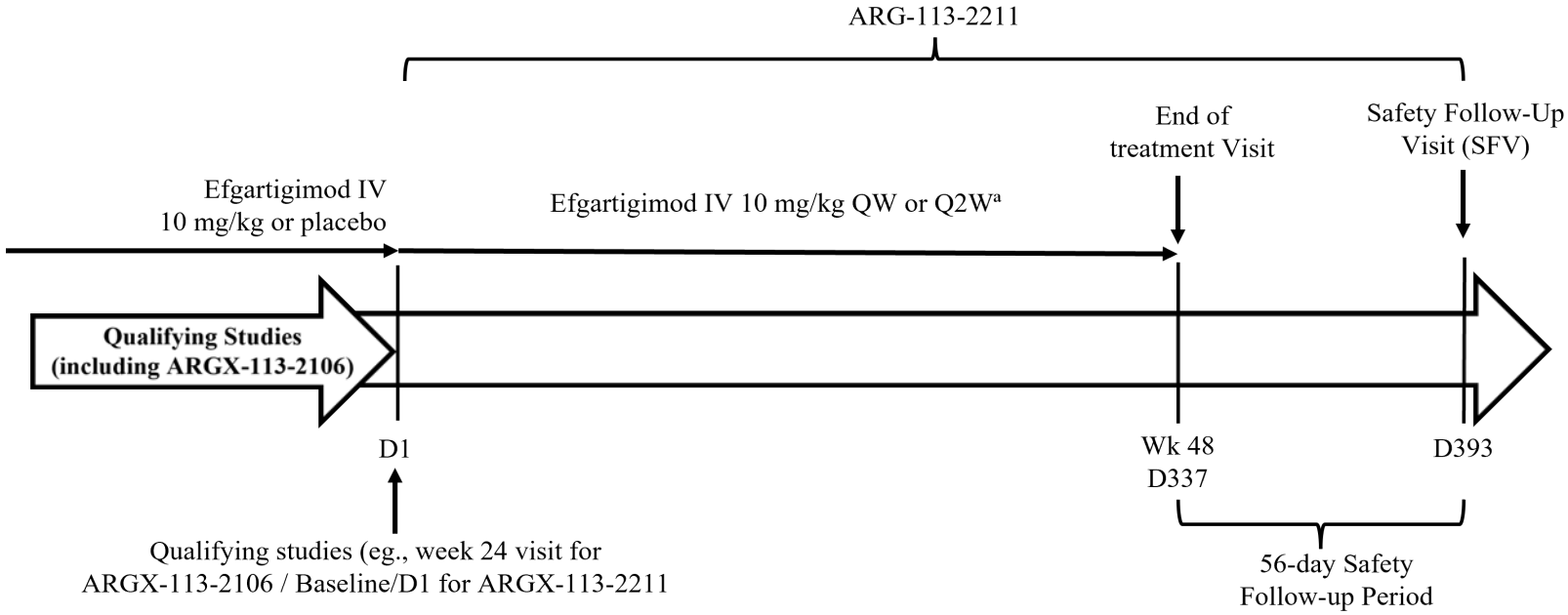
Study Arms and Duration:

Each participant will participate in the following study periods:

- Treatment period: 48-week treatment period in which participants will receive efgartigimod doses either QW or Q2W based on their responder status. Switch points (ie, time points when clinESSDAI is conducted to determine responder status) will occur on day 1, week 16, and week 24. A participant who is not a responder on week 24 and classified by the PI as a nontherapeutic failure will continue QW dosing regimen until confirming the responder status. The participant will begin Q2W dosing regimen upon confirmation of the responder status
- 56-day follow-up period starting after the final IMP administration

Data Monitoring/Other Committee: No

1.2. Schema



Abbreviations: D = day; IV = intravenous; QW = once weekly; Q2W = every 2 weeks; Wk = week.

[a] QW or Q2W dosing regimen depending on responder status. Responders (defined as participants with a decrease in clinESSDAI of ≥3 points from baseline of qualifying study or who have a change clinESSDAI score that reclassifies their disease from moderate severity to mild severity) will be switched from QW to Q2W dosing regimen. Nonresponders will remain on QW dosing regimen. Switch points (ie, timepoints where clinESSDAI are conducted to determine responder status) will occur on day 1, week 16, and week 24. If a participant is not a responder at week 24, they will be evaluated by the PI for therapeutic failure. If not considered a therapeutic failure, the participant will continue QW dosing regimen and will return at weeks 32, 36, 40 and 44 for a clinESSDAI assessment until confirming the responder status and switching to Q2W dosing regimen or PI considers the participant to be a therapeutic failure. For QW regimen, the final dose will be administrated at week 47. For Q2W regimen, the final dose will be administered at week 46.

1.3. Schedule of Activities

Table 1: Schedule of Activities

		Study week																	
	BL[a]	1	2	3	4	5-7	8	9-11	12	13-15	16	17-23	24	25-35	36	37-47	48	EDV[b]	SFV[c]
Study day (±2)	**1**	**8**	**15**	**22**	**29**	**36-50**	**57**	**64-78**	**85**	**92-120**	**127**	**134-162**	**169**	**176-246**	**253**	**260-330**	**337**		**393**
Note: All activities (safety and efficacy assessments, predose blood sampling) will be completed before administering the IMP infusion.																			
Visits that must be attended at the site are BL, W1 (for QW regimen), W2, W4, W8, W12, W16, W24, W36, W48, EDV, and SFV. Additionally, participants must attend visits at the site for their first 3 doses of efgartigimod in this OLE study. All other visits may be conducted by home health care service or telemedicine visit.																			
Informed consent	X																		
Eligibility check	X																		
Brief physical examination (symptom driven)	X[d]				X		X		X		X		X		X		X	X	X
Vital signs[e]	X				X		X		X		X		X		X		X	X	X
ECG	X				X		X		X		X		X		X		X	X	X
Glandular function																			
UWSF/SWSF	X										X		X		X		X	X	
Schirmer's test	X										X		X		X		X	X	

		Study week																
	BL[a]	1	2	3	4	5-7	8	9-11	12	13-15	16	17-23	24	25-35	36	37-47	48	EDV[b]	SFV[c]
Study day (±2)	**1**	**8**	**15**	**22**	**29**	**36-50**	**57**	**64-78**	**85**	**92-120**	**127**	**134-162**	**169**	**176-246**	**253**	**260-330**	**337**		**393**
OSS	X										X		X		X		X	X	
SGUS	X										X		X		X		X	X	
Safety laboratory assessments																			
Clinical laboratory tests (hematology and chemistry)	X				X		X		X		X		X		X		X	X	X
Urinalysis	X										X		X		X		X	X	X
Urine pregnancy testing	X																	X	X
Blood sampling																			
CCI																			
PK[h]	X[i]				X		X		X		X[i]		X		X		X		
Total IgG[f]	X				X		X		X		X		X		X		X		X
RF[f]	X				X						X		X		X		X		X
Anti-Ro/SS-A, anti-La/SS-B autoanti-bodies[f]	X				X		X		X		X		X		X		X		X

		Study week																	
	BL[a]	**1**	**2**	**3**	**4**	**5-7**	**8**	**9-11**	**12**	**13-15**	**16**	**17-23**	**24**	**25-35**	**36**	**37-47**	**48**	**EDV[b]**	**SFV[c]**
Study day (±2)	**1**	**8**	**15**	**22**	**29**	**36-50**	**57**	**64-78**	**85**	**92-120**	**127**	**134-162**	**169**	**176-246**	**253**	**260-330**	**337**		**393**
Immunogenicity[f]	X		X		X		X		X		X		X		X		X		X
Systemic disease activity																			
ESSDAI[j]	X										X		X		X		X		
clinESSDAI	X										X		X	W32[k]	X[k]	W40, W44[k]	X		
Patient-reported outcome questionnaires[l]																			
ESSPRI	X										X		X		X		X		
MFI	X										X		X		X		X		
PGA	X										X		X		X		X		
SF-36	X										X		X		X		X		
EQ-5D-5L	X										X		X		X		X		
PASS	X												X				X		
IMP infusion[m]	X[n]	X[o,p]																	
AE review	Continuous monitoring																		
Concomitant medications review	Continuous monitoring																		

		Study week																
	BL[a]	1	2	3	4	5-7	8	9-11	12	13-15	16	17-23	24	25-35	36	37-47	48	EDV[b]	SFV[c]
Study day (±2)	**1**	**8**	**15**	**22**	**29**	**36-50**	**57**	**64-78**	**85**	**92-120**	**127**	**134-162**	**169**	**176-246**	**253**	**260-330**	**337**		**393**

BL = baseline; clinESSDAI = clinical; ESSDAI; D = day; d/c = discontinuation; ECG = electrocardiogram; EDV = early discontinuation visit; ESSDAI = EULAR Sjögren's syndrome disease activity index; ESSPRI = EULAR Sjögren's Syndrome Patient-Reported Index; EULAR = European Alliance of Associations for Rheumatology; ICF = informed consent form; IgG = immunoglobulin G; IMP = investigational medicinal product; IV = intravenous; MFI = Multidimensional Fatigue Inventory; NA = not applicable; OSS = ocular staining score; PASS = patient acceptable symptom state; PCR = polymerase chain reaction; PD = pharmacodynamics; PGA = patient global assessment; PK = pharmacokinetics; RF = rheumatoid factor; SCR = screening; SFV = safety follow-up visit; SF-36 = 36-Item Short Form Survey; SGUS = salivary gland ultrasonography; SS-A = Sjögren's syndrome–related antigen A; SS-B = Sjögren's syndrome–related antigen B; SWSF = stimulated whole salivary flow; UWSF = unstimulated whole salivary flow; W = week.

[a] BL will coincide with the final visit of a previous qualifying study. Grayed-out assessments may be conducted as part of the previous qualifying pSS studies.
[b] The EDV will be performed within 7 days after last dose administration.
[c] Participants will attend a safety follow-up visit 56 ± 3 days after the final IMP administration.
[d] Weight mandatory at baseline.
[e] Vital signs will be measured before collecting any blood sample or administering IMP infusions.
[f] On IMP administration visits, blood samples must be collected predose (preferably within 2 hours before the infusion). On other visits, a blood sample may be collected at any time during the visit.
[redacted]
[h] On IMP administration visits, blood samples for PK analyses will be collected predose (preferably within 2 hours before IMP administration). On other visits, a blood sample may be collected at any time during the visit.
[i] A PK sample will also be collected within 30 minutes after the end of IMP infusion.
[j] The biological domain will remain blinded until the parent study is unblinded.
[k] ClinESSDAI will only be conducted at weeks 32, 36, 40, and 44 if the participant is a nonresponder at week 24 and not considered a therapeutic failure by the PI.
[l] The questionnaires should be performed before other study interventions and can be done one day in advance.

		Study week																	
	BL[a]	1	2	3	4	5-7	8	9-11	12	13-15	16	17-23	24	25-35	36	37-47	48	EDV[b]	SFV[c]
Study day (±2)	**1**	**8**	**15**	**22**	**29**	**36-50**	**57**	**64-78**	**85**	**92-120**	**127**	**134-162**	**169**	**176-246**	**253**	**260-330**	**337**		**393**

[m] The maximum total efgartigimod dose per efgartigimod IV infusion is 1200 mg for participants weighing ≥ 120 kg. The IMP weight-based dose will be recalculated if a participant's weight has changed (increased or decreased) by more than 10% from OLE baseline (ie, weight prior to IMP infusion on day 1 of the ARGX-113-2211 study).

[n] The IMP infusion on day 1 will occur following eligibility check, informed consent signature, and baseline assessments.

[o] Responders will reduce dosing frequency from QW to Q2W dosing regimen. Nonresponders will remain on QW dosing regimen. Switch points will occur at baseline, week 16, and week 24. The PI will evaluate a participant who is not a responder at week 24 for therapeutic failure. If the participant is not considered a therapeutic failure, QW dosing regimen will be continued, and the participant will return at weeks 32, 36, 40, and 44 for a clinESSDAI assessment up to confirming the responder status and switching to Q2W dosing regimen or if the PI considers the participant to be a therapeutic failure. For QW regimen, the final dose will be administrated at week 47. For Q2W regimen, the final dose will be administered at week 46.

[p] If a participant who has reduced dosing frequency to Q2W considers their condition worsening, an unscheduled visit will occur during which a clinESSDAI and blood sampling for PK and ADA will be conducted. The participant will revert to QW dosing regimen for the remainder of the treatment period if there has been an increase in clinESSDAI score of ≥ 3 points and/or a change in score that reclassifies their disease from mild severity (clinESSDAI < 5) to moderate severity (clinESSDAI ≥ 5).

2. INTRODUCTION

Participants will be enrolled from both active and placebo arms of qualifying efgartigimod studies in adult patients with pSS. The protocol will be amended to add additional studies at a later date.

In qualifying study ARGX-113-2106, the efficacy and safety of efgartigimod in adult patients with pSS was evaluated using a randomized, double-blinded, placebo-controlled study design. Participants were randomized to receive efgartigimod IV 10 mg/kg or matching placebo in a 2:1 ratio. The IMP (efgartigimod or matching placebo) was administered during the treatment period in approximately 1-hour IV infusion QW by site or a home nurse. The final dose was administered at week 23. At week 24, eligible participants from ARGX-113-2106 may roll over into the present single-arm OLE study: ARGX-113-2211.

2.1. Study Rationale

Efgartigimod is a first-in-class antibody fragment that binds to FcRn. This binding prevents FcRn from recycling IgG and leads to a reduction in circulating disease-causing autoantibodies. Efgartigimod is being clinically developed in autoimmune diseases mediated by pathogenic IgG autoantibodies after approval by the United States FDA, EMA, and Japan's PMDA for use in adult patients with AChR-Ab seropositive gMG.

Efgartigimod may be a viable treatment option for individuals diagnosed with pSS because it has been shown to reduce IgG levels, including IgG autoantibodies, that may underlie some of the autoimmune disease manifestations in these participants. Therefore, the reduction of autoantibodies may successfully reduce disease activity and symptoms in pSS participants.

This open-label extension study will evaluate the long-term safety of efgartigimod in participants with pSS who have completed the treatment period of the qualifying studies.

2.2. Background

Efgartigimod is a neonatal FcRn antagonist designed to treat autoimmune diseases mediated by IgG autoantibodies. pSS is a chronic, progressive autoimmune disease of unknown etiology, typically characterized by an autoimmune exocrinopathy. Along with symptoms of excessive dryness, manifestations include profound fatigue, chronic pain, extraglandular organ system involvement, and increased risk of lymphomas. A hallmark of pSS is B-cell hyperactivity, causing a vicious cycle of immune activation through cytokine production, antigen presentation, and autoantibody secretion, potentially causing tissue damage. Currently, no immunomodulatory treatment is available for pSS.

Efgartigimod, an FcRn antagonist that can rapidly reduce IgG, including pathogenic antibodies, contributes to successfully treat pSS and has the potential to improve disease manifestations by the reduction of IgG autoantibodies in pSS. This study aims to evaluate the long-term safety of efgartigimod in participants with pSS who have completed the treatment period of the qualifying studies.

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

2.3. Benefit/Risk Assessment

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

2.3.1. Risk Assessment

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

Potential clinically significant risk	Summary of data/rationale for risk	Mitigation strategy
Serious infection	Efgartigimod reduces IgG levels, potentially hindering immune response and increasing the risk of infection.	Exclude participants with clinically significant active infection not sufficiently resolved in the investigator's opinion (Section 5.2). Infections are considered adverse event of special interest (AESI; Section 8.4.6). Monitor for infections and temporarily interrupt IMP dosing as specified in Section 7.1.
Infusion/injection-related reactions	All therapeutic proteins can elicit immune responses, potentially resulting in hypersensitivity, or allergic reactions such as rash, urticaria, angioedema, serum sickness, and anaphylactoid, or anaphylactic reactions.	Monitor participants during administration and for 30 minutes thereafter for clinical signs and symptoms of infusion/injection-related reactions. Infusion/injection-related reactions are considered AEs of clinical interest (Section 8.4.7). If an infusion reaction occurs, interrupt the infusion and implement appropriate supportive measures. Once resolved, the infusion can be resumed, and at a slower rate if necessary.
Infusion/injection site reactions	Most AEs have been mild, transient injection site reactions, including erythema, pain, bruising, pruritus, burning, tenderness, edema, induration, irritation, paresthesia, numbness, and rash. Moderate injection site reactions occurring less frequently include burning, erythema, pain, and numbness. Mild to moderate headache is commonly reported.	Continuously monitor participants for injection site reactions. Infusion/injection site reactions are considered AEs of clinical interest (Section 8.4.7).

Potential clinically significant risk	Summary of data/rationale for risk	Mitigation strategy

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

2.3.2. Benefit Assessment

Efgartigimod has been investigated in nonclinical studies, phase 1 clinical pharmacology studies in healthy participants, and phase 2/3 clinical studies in participants with IgG-driven autoimmune diseases, including gMG, primary ITP, CIDP, and pemphigus.

In clinical studies, efgartigimod effectively reduces IgG antibody levels, including pathogenic autoantibodies. The efficacy of efgartigimod to improve clinical outcomes in gMG and reduce pathogenic autoantibodies was confirmed in a pivotal phase 3 study in participants with gMG (ARGX-113-1704). In addition, clinical benefit was observed in phase 2 studies in primary ITP (ARGX-113-1603) and pemphigus (ARGX-113-1701), in which pathogenic autoantibodies underlie the disease pathology (refer to current efgartigimod IB). Available clinical data support the clinical benefit of efgartigimod for reducing pathogenic IgG autoantibodies, which may mitigate autoimmune dysfunction and improve symptoms, as well as the ability to function, in participants with pSS.

2.3.3. Overall Benefit-Risk Conclusion

The potential risks associated with efgartigimod are justified by the anticipated benefits posssibly afforded to participants with pSS in this study and considering the measures implemented to minimize risks. The favorable balance between risks and anticipated efficacy/benefit supports the use of efgartigimod in the clinical development for pSS.

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

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 2: Study ARGX-113-2211 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the long-term safety of efgartigimod in patients with pSS	• Incidence and severity of AEs and AESIs, incidence SAEs, changes in laboratory test results, vital signs, and ECG results
Secondary	
• To evaluate effect and assess long-term data on durability of CRESS response	• Proportion of CRESS responders on ≥ 3 of 5 items at weeks 24 and 48 (refer to Section 8.2.1). The 5 items are: – Systemic disease activity: clinESSDAI – Patient-reported symptoms: ESSPRI – Tear gland function: Schirmer's test and OSS – Salivary gland function: UWSF rate and SGUS – Serology: serum IgG and/or RF
• To evaluate the effect of efgartigimod on clinical efficacy parameters	• Proportion of participants with minimal clinically important improvement from baseline in ESSDAI: improvement of ≥ 3 points in ESSDAI score at weeks 24 and 48 • Proportion of participants with low disease activity: ESSDAI score of < 5 at weeks 24 and 48 • Proportion of participants with minimal clinically important improvement from baseline in clinESSDAI: improvement of ≥ 3 points in clinESSDAI score at weeks 24 and 48 • Proportion of participants with low disease activity: clinESSDAI score of < 5 at weeks 24 and 48 • Proportion of participants with minimal clinically important improvement from baseline in ESSPRI: decrease of ≥ 1 point or ≥ 15% at weeks 24 and 48 • Change from baseline in ESSDAI score at weeks 24 and 48 • Change from baseline in clinESSDAI score at weeks 24 and 48 • Change from baseline in ESSPRI score at weeks 24 and 48
• To evaluate the effect of efgartigimod on STAR	• Proportion of STAR responders (score of ≥ 5) at weeks 24 and 48 when compared to baseline

Objectives	Endpoints
• To assess the PD effect of efgartigimod	• Values, changes from baseline, and percent reduction from baseline in total IgG levels in serum over the 48-week treatment period • Values, changes from baseline, and percent reduction from baseline in autoantibodies in serum over the 48-week treatment period: – Anti-Ro/SS A – Anti-La/SS B
• To assess the exposure to efgartigimod	• Efgartigimod serum concentrations over the 48-week treatment period
• To assess the immunogenicity of efgartigimod	• Incidence and prevalence of ADA against efgartigimod over the 48-week treatment period
Exploratory	
• To explore the effect of efgartigimod on additional clinical pSS measures	• Proportion of responders on 2 of 4 items of the adjusted CRESS (without serology item) at weeks 24 and 48 when compared to baseline • Change from baseline in activity of individual ESSDAI domains at weeks 24 and 48
• To explore the effect of efgartigimod on glandular measures	• Change from baseline in: o SWSF rate at weeks 24 and 48 o UWSF rate at weeks 24 and 48 o Hocevar score at weeks 24 and 48 o Schirmer's test at weeks 24 and 48 o OSS at weeks 24 and 48 • Response in salivary gland as defined in CRESS at weeks 24 and 48 when compared to baseline • Response in tear gland as defined in CRESS at weeks 24 and 48 when compared to baseline
• To explore the effect of efgartigimod on patient-reported outcomes	• Change from baseline in: o Total MFI score at weeks 24 and 48 o Physical component and mental component scores of SF-36 at weeks 24 and 48 o PGA at weeks 24 and 48 o Individual ESSPRI scores at weeks 24 and 48 o EQ-5D-5L utilities and VAS scores at weeks 24 and 48 • PASS at weeks 24 and 48 when compared to baseline

Objectives	Endpoints
• CCI [redacted]	• CCI [redacted] • Values, changes from baseline, and percent reduction from baseline in RF in serum over the 48-week treatment period

ADA = antidrug antibody; AESI = adverse event of special interest; clinESSDAI = clinical EULAR Sjögren's syndrome disease activity index; CRESS = Composite of Relevant Endpoints for Sjögren's Syndrome; ECG = electrocardiogram; ESSDAI = EULAR Sjögren's syndrome disease activity index; ESSPRI = EULAR Sjögren's Syndrome Patient-Reported Index; IFN = interferon; CCI [redacted]; IgG = immunoglobulin G; CCI [redacted] RF = rheumatoid factor; IV = intravenous; MFI = Multidimensional Fatigue Inventory; OSS = ocular staining score; PASS = patient acceptable symptom state; PD = pharmacodynamic(s); PK = pharmacokinetic(s); pSS = primary Sjögren's syndrome; PT = preferred term; SAE = serious adverse event; SGUS = salivary gland ultrasonography; SOC = system organ class; STAR = Sjögren's Tool for Assessing Response; SWSF = stimulated whole salivary flow; TEAE = treatment-emergent adverse event; UWSF = unstimulated whole salivary flow; VAS = visual analog scale.

No estimands have been defined for this study.

4. STUDY DESIGN

4.1. Overall Design

Study ARGX-113-2211 is a long-term, single-arm, open-label, multicenter extension of pSS-qualifying efgartigimod studies designed to evaluate the long-term safety of efgartigimod in adult patients with pSS. Participants will be enrolled from both active and placebo arms of qualifying efgartigimod studies and receive efgartigimod IV 10 mg/kg over 48 weeks in the extension study without knowledge of their treatment assigned in the qualifying study. To be eligible to enroll in this study, participants must have completed the treatment period of the qualifying study and must not have permanently discontinued the IMP in that study.

Participants will receive efgartigimod 10 mg/kg by IV infusion either Q2W or QW. The dosing regimen is based on whether the participant is a responder or nonresponder on day 1. Participants will be considered as responders if they have a reduction in clinESSDAI score of ≥ 3 points from baseline (ie, the final visit of a previous qualifying study) and/or a change in score that reclassifies their disease from moderate severity (clinESSDAI ≥ 5) to mild severity (clinESSDAI < 5). Participants will be considered as nonresponders if they do not have a reduction in clinESSDAI score of ≥ 3 points from baseline and/or did not reach a clinESSDAI < 5. ClinESSDAI assessments to determine responder status using the baseline will be conducted on day 1 and weeks 16 and 24. Responders will receive IV infusions Q2W. Nonresponders will receive an infusion QW until such time that they are considered to be responders. If a participant is not a responder at week 24, they will be evaluated by the PI for therapeutic failure:

- Therapeutic failure - the participant will discontinue study treatment
- Not a therapeutic failure - the participant will continue QW dosing regimen. ClinESSDAI will be conducted at weeks 32, 36, 40, and 44 until confirming responder status and switching to Q2W dosing regimen. The PI will continue to evaluate the participant for therapeutic failure

If the participant and/or investigator consider there to be a reduction in therapeutic effect once the patient has switched to Q2W, the participant will return for an unscheduled visit during which a clinESSDAI, a blood sampling for PK and ADA will be collected.

If there has been an increase in clinESSDAI score of ≥ 3 points and/or a change in score that reclassifies their disease from mild severity to moderate severity the participant will revert to QW dosing regimen and will remain on this dose regimen for the remainder of the treatment period.

IMP infusions must occur at the site for a minimum of 3 consecutive visits (for QW dosing regimen: baseline visit and the week 1 and 2 visits; for Q2W dosing regimen: baseline visit and the week 2 and 4 visits) before home infusions are allowed. If doses are missed at 1 or more of these visits, then dosing at subsequent visits will also be on-site. IMP administration at home will not commence until after 3 consecutive doses have been administered on-site.

Participants will return for a follow-up visit approximately 56 days after the final IMP administration.

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

A minimum of 10 study site visits over the 48-week treatment period and 56-day follow-up period are planned (baseline, weeks 1 [for QW regimen], 2, 4, 8, 12, 16, 24, 36, 48, and the SFV); all other visits (except for the first 3 consecutive visits) may be conducted by home health care service, or telemedicine visits.

The maximum length of time a participant can be in the study is approximately 56 weeks (48 weeks treatment plus 8 weeks of follow-up).

4.2. Scientific Rationale for Study Design

pSS is characterized by mononuclear inflammatory infiltrates and IgG plasma cells in salivary and lacrimal glands that lead to irreversible destruction of the glandular tissue and is accompanied by a sensation of dryness of mouth and eyes. B cells play a central role in the immunopathogenesis and exhibit signs of hyperactivity.[1]

In addition, autoantibodies can create immune complexes that maintain and amplify the production of IFN alpha. This combination results in a cycle of immune activation that leads to tissue damage. Currently, no immunomodulatory treatment is available for pSS. In this study, we aim to evaluate the effect of efgartigimod, an FcRn antagonist that can rapidly reduce IgG, including pathogenic antibodies. Efgartigimod contributes to successfully treat pSS and has the potential to improve disease manifestations by the reduction of IgG autoantibodies and immune complexes in pSS.

In the present OLE study (ARGX-113-2211), the long-term safety, efficacy, PD, and PK of efgartigimod will be evaluated in participants with pSS.

The study includes a 48-week treatment period in which patients will receive QW or Q2W doses of efgartigimod 10 mg/kg by IV infusion, ie, at the same dose per body weight, and mode of administration as in the preceding qualifying parent studies.

The treatment allocation (efgartigimod or placebo) from the qualifying studies will be kept blinded in current study.

The primary outcome measure is the ongoing safety of efgartigimod for approximately 1 year after completing the qualifying study. The endpoint aims to demonstrate that efgartigimod is a safe long-term treatment option for pSS. The safety endpoints selected for this study are those considered to be standard for any clinical trial evaluating the safety of an IMP.

The secondary endpoint is the effect of efgartigimod compared to placebo on CRESS (Section 8.2.1). The CRESS composite measures systemic disease activity, patient-reported symptoms, tear gland function, salivary gland function, and serology, developed to assess treatment efficacy in participants with pSS.

All other secondary efficacy endpoints complement the first secondary endpoint and provide additional information on efficacy (ESSDAI, clinESSDAI, ESSPRI, STAR [Section 8.2]), histology, PK, PD, and immunogenicity. The totality of data from all endpoints used in the study will be utilized to determine treatment response in this population.

4.3. Justification for Dose

Doses of efgartigimod 10 mg/kg either QW or Q2W will be administered. For responders a Q2W regimen has been selected to evaluate whether a less frequent dosing regimen can maintain clinical efficacy, while the QW regimen for nonresponders targets efgartigimod's to achieve a near maximal total IgG reduction (PD effect), thereby maximizing the chance of a clinical response on the efficacy outcomes in nonresponders.

As the hypothesis for treating pSS with efgartigimod is to reduce the pathogenic autoreactive IgG, the selected doses and dose regimen target a nearly maximal PD effect (ie, reduction of pathogenic IgGs). The chronic nature of pSS reflects the need for chronic treatment to maintain pathogenic IgG autoantibody suppression and symptom reduction.

The cumulative data from a phase 1 study in healthy adult subjects; phase 2 studies in participants with gMG, ITP, and pemphigus; phase 3 studies in gMG; and PK/PD modeling results demonstrate that a 10 mg/kg efgartigimod dose administered QW through IV infusion achieved 60% to 70% total IgG reduction, including the reduction of pathogenic autoantibodies. Maximal IgG reduction was associated with clinical efficacy observed in gMG, ITP, and pemphigus studies. Furthermore, this dose has been safe and well-tolerated in all study populations and has demonstrated similar PK and PD profiles across indications. Accordingly, the 10 mg/kg IV dose regimen (QW or Q2W) was selected for this study.

4.4. End-of-Study Definition

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

A participant will have completed the study if the SFV assessments have been completed.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

Participants can be included in the study only if all of the following criteria apply:

1. Is at least the legal age of consent for clinical trials when signing the ICF
2. Is capable of providing signed informed consent, as described in Section 10.1.3, and complying with protocol requirements
3. Agrees to use contraceptive measures consistent with local regulations and the following:
    a. WOCBP (defined in Section 10.4.1) must have a negative urine pregnancy test at baseline before receiving IMP (Section 10.4.2.1)
4. Has completed the qualifying efgartigimod pSS studies and agrees to continue study drug treatment without interruption in the extension study

5.2. Exclusion Criteria

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

1. Clinically significant disease (including newly diagnosed malignancy or cardiovascular disease) or intention to have surgery during the study; or any other medical condition that, in the investigator's opinion, would confound the results of the study or put the participant at undue risk
2. Pregnant or intention to become pregnant during the study
3. Any severe systemic pSS manifestation that may put the participant at undue risk based on the investigator's opinion

5.3. Lifestyle Considerations

Not applicable.

5.4. Screen Failures

Eligibility to roll over must be verified at the last visit of the preceding qualifying studies.

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

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

5.5. Criteria for Temporarily Delaying Enrollment

Not applicable.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

6.1. Investigational Medicinal Product Administered

Table 3: IMP Administered

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

AxMP = auxiliary medicinal product; IMP = investigational medicinal product; IV = intravenous; NIMP = noninvestigational medicinal product; Q2W = every 2 weeks; QW = once weekly

[a] QW or Q2W frequency dependent on responder status

6.2. Preparation, Handling, Storage, and Accountability

- The IMP will be supplied to the investigational site by the sponsors' designated IMP supply vendor.
- The pharmacy manual provides detailed instructions on the preparation, handling, storage, accountability, and disposition of unused IMP.
- The investigator or designee is responsible for the correct and safe storage of the IMP. All IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area following the labeled storage conditions, with access limited to the investigator and authorized site staff.
- The investigator or designee must confirm that appropriate temperature conditions have been maintained for all IMP received during transit. Any discrepancies are reported and resolved before using the IMP.

- Only participants enrolled in the study are permitted to receive IMP, and only authorized site staff or designee are allowed to supply IMP.
- Appropriate dilutions in a 0.9% saline solution in an infusion bag will be prepared before administration with an IV pump.
- IMP must be stored refrigerated (2°C to 8°C) and protected from direct sunlight in secondary packaging. Do not shake IMP or expose it to freezing temperatures.
- Participants will be observed for at least 30 minutes after the end of IMP infusion for routine safety monitoring.
- The pharmacy manual and home guide provide further guidance and information for the final disposition of unused IMP.
- Accountability of home-administered IMP will be documented as instructed in the home guide.

6.3. Assignment to IMP

All participants will receive efgartigimod 10 mg/kg by IV infusion either Q2W or QW based on whether the participant is a responder or nonresponder, respectively.

6.4. Blinding

ARGX-113-2211 is an open-label study. The treatment allocation (efgartigimod or placebo) from the double-blind qualifying studies will be kept blinded in the current study.

6.5. Study Compliance

IMP infusions must occur at the site for a minimum of 3 consecutive visits (for QW dosing regimen: baseline visit and the week 1 and 2 visits; for Q2W dosing regimen: baseline visit and the week 2 and 4 visits) before home infusions are allowed. If doses are missed at 1 or more of these visits, then dosing at subsequent visits will also be on-site. IMP administration at home will not commence until after 3 doses have been administered on-site.

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

6.6. Dose Modification

The maximum total efgartigimod dose per efgartigimod infusion is 1200 mg for participants weighing ≥ 120 kg. The IMP weight-based dose will be recalculated if a participant's weight has changed (increased or decreased) by more than 10% from OLE baseline (ie, weight prior to IMP infusion on day 1 of the ARGX-113-2211 study).

Modifications to the schedule of dosing are permitted as described in Section 4.1.

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

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

6.8. Treatment of Overdose

Any dose of efgartigimod greater than the intended QW or Q2W amount will be considered an overdose.

The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator or treating physician will:

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

6.9. Prior and Concomitant Therapy

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

- Reason for use
- Dates of administration, including start and end dates
- Dosage information (ie, dose and frequency)

The following medications or treatments are not permitted during the periods listed in Table 4.

Table 4: Prior and Concomitant Therapy

Medication	Period participant is receiving IMP	Follow-up period
Live or live-attenuated vaccines	Prohibited	Permitted from 28 days after the last IMP dose
SCIg	Prohibited	Permitted
IVIg	Prohibited	Permitted
Corticosteroid steroids:		
Intra-muscular or intravenous corticosteroids	Prohibited	Permitted
Oral corticosteroids	Stable dose up to 10 mg daily	Permitted

Medication	Period participant is receiving IMP	Follow-up period
Inhaled corticosteroids	Permitted	Permitted
Intra-articular steroids	Prohibited	Permitted
Topical steroids	Topical (non-ophthalmic) steroids are permitted Topical ophthalmic steroids are prohibited.	Permitted
DMARDs		
Conventional DMARDS / Antimalarials	Permitted HCQ, CQ, AZA, MTX, MMF, leflunomide or cyclosporin at stable dose	Permitted
Cyclophosphamide	Prohibited	Permitted
Biologic DMARDS	Prohibited	Permitted
Targeted synthetic DMARDs:		
JAK inhibitors	Prohibited	Permitted
IMPs:		
IMP in another clinical trial	Prohibited	Permitted
Nonbiologic IMP in another clinical trial	Prohibited	Prohibited
Biologic IMP in another clinical trial	Prohibited	Prohibited
Other:		
Chinese traditional medicine with known immunomodulatory action	Prohibited	Permitted
Anticholinergic agents	Permitted at stable dose	Permitted
Topical symptomatic medications for pSS	At visits with planned efficacy assessments, participants will be required to withhold ophthalmic lubricants, ophthalmic lubricating ointments, hydroxyl cellulose ophthalmic inserts, and saliva substitutes before efficacy assessments are completed.	Permitted
Pharmacological topical ophthalmic agents (eg, NSAIDs, cyclosporine)	Prohibited	Permitted

Medication	Period participant is receiving IMP	Follow-up period
Pilocarpine and/or any other pharmacological stimulant for salivary and lacrimal glands	Permitted at stable dose Not to be taken within 24 hours of clinical assessments	Permitted

AZA = azathioprine; CQ = chloroquine; DMARD = disease-modifying antirheumatic drug; EDV = early discontinuation visit; HCQ = hydroxychloroquine; IMP = investigational medicinal product; IVIg = intravenous immunoglobulin; JAK = Janus kinase; MMF = mycophenolate mofetil; MTX = methotrexate; NSAID = non-steroidal anti-inflammatory drug; pSS = primary Sjögren's syndrome; SCIg = subcutaneous immunoglobulin

7. DISCONTINUATION OF IMP AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

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

7.1. Discontinuation of IMP

7.1.1. Permanent Discontinuation

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

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

Participants who permanently discontinue IMP will complete the EDV.

The study sites will attempt to perform the EDV within 7 days after the participant's final IMP administration. The SFV will occur 56 ± 3 days after the participant's final IMP administration.

Additionally, the following circumstances will result in the permanent discontinuation of IMP:

- The participant becomes pregnant or intends to become pregnant (see Section 8.3.5)
- The investigator considers discontinuing IMP is in the participant's best interest (the sponsor will be informed)
- The participant develops an SAE or AE that contraindicates further administration of IMP in the investigator's opinion or an AE of CTCAE severity grade 4 that is considered related to IMP by the sponsor
- The participant develops a new or recurrent malignancy except for basal cell carcinoma of the skin, regardless of relationship to IMP
- The participant receives a prohibited medication or substance (Section 6.9)

7.1.2. Temporary Discontinuation

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

Reasons requiring temporary interruption may include an AE that meets the following criteria:

- Any SAE considered related to IMP by the sponsor
- Clinically significant active infection considered related to the IMP by the sponsor

7.2. Participant Discontinuation/Withdrawal from the Study

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

The primary reason for permanent study withdrawal will be recorded.

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

- Participant withdrawal of consent
- Sponsor request

If the participant also withdraws consent to participate in future research, the sponsor can retain and continue to use any data collected before such a withdrawal of consent.

- Samples collected from participants who have withdrawn from the study will be used for the study results but not for future research.

7.3. Lost to Follow-up

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

The following actions must be completed if a participant fails to complete a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to continue in the study
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (when 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 will be documented in the participant's medical record
  - Participants who continue to be unreachable will be considered to have withdrawn from the study

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Adherence to the study design requirements, including those specified in the SoA, is required for study conduct.

All baseline evaluations must be completed and reviewed to confirm that participants meet all eligibility criteria before first dose.

Operational considerations due to the COVID-19 pandemic are provided in Section 10.5.

8.1. Administrative and Baseline Procedures

The baseline visit for study ARGX-113-2211 will be conducted after the participant has completed the qualifying study. All baseline assessments will be performed before first administration of efgartigimod in ARGX-113-2211, if applicable. Assessments do not need to be repeated if they are performed as part of the last visit of the qualifying study.

8.1.1. Use and Storage of Biological Samples

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

As stated in Section 7.2, samples collected from participants who have withdrawn from the study will be used for the study results but not for future research.

8.2. Efficacy Assessments

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

Patient-reported outcome questionnaires should be administered before any other study assessment and may be completed up to 1 day before the visit. It is preferrable that the same physician assesses the clinical efficacy parameters at all visits.

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

8.2.1. CRESS

CRESS has been developed to assess treatment efficacy in participants with pSS. CRESS consists of the following items, with definitions of treatment response and lower disease:[2]

- Systemic disease activity: As measured with clinESSDAI (Section 8.2.3)
  - Response is defined as a score of < 5 points
- Patient-reported symptoms: As measured with ESSPRI (Section 8.2.5.1)
  - Response is defined as a decrease of ≥ 1 point or ≥ 15% from baseline

- Tear gland function: as measured with Schirmer's test (Section 8.2.6.3) and OSS (Section 8.2.6.4)
  - If Schirmer's test is ≤ 5 mm at baseline (abnormal), a response is defined as an increase of at least 5 mm from baseline OR
  - If OSS is ≥ 3 points at baseline (abnormal), a response is defined as a decrease of at least 2 points from baseline OR
  - If both OSS and Schirmer's scores are normal at baseline, a response is defined as no change that results in an abnormal OSS or Schirmer's score
- Salivary gland function: As measured with UWSF (Section 8.2.6.2) and SGUS
  - UWSF: At least 25% increase in score, or if score is 0 mL/min at baseline, any increase from baseline OR
  - SGUS: At least 25% decrease in total Hocevar[3] from baseline
- Serology: As measured with serum IgG and RF
  - RF: Decrease of at least 25% from baseline OR
  - IgG: Reduction of at least 10% from baseline

8.2.2. ESSDAI

The ESSDAI was designed to measure disease activity in patients with pSS.[5] The ESSDAI consists of 12 domains, 11 related to organ involvement (cutaneous, pulmonary, renal, articular, muscular, peripheral nervous system, central nervous system, hematological, glandular, constitutional, and lymphadenopathic) and 1 biological domain reflecting B-cell activity (Section 10.7.1). The activity levels of each domain (range: 0-3 points) are multiplied by their respective weights (range: 1-6 points) to obtain the total score.

ESSDAI-related laboratory tests include the following:

- Gammaglobulins
- Cryoglobulins
- C3, C4 and CH50

The gammaglobulin and cryoglobulin results will be blinded postbaseline.

8.2.3. ClinESSDAI

ClinESSDAI derives from the ESSDAI, and its score provides an accurate evaluation of disease activity independent of B-cell biomarkers.[6] The clinical domains in clinESSDAI have different weights than in ESSDAI (Table 5).

Table 5: Comparison of Domain Weights of Original ESSDAI and clinESSDAI

Domain (activity level)	ESSDAI	clinESSDAI
Constitutional (0-2)	3	4
Lymphadenopathy (0-3)	4	4
Glandular (0-2)	2	2
Articular (0-3)	2	3
Cutaneous (0-3)	3	3
Pulmonary (0-3)	5	6
Renal (0-3)	5	6
Muscular (0-3)	6	7
Peripheral nervous system (0-3)	5	5
Central nervous system (0-3)	5	5
Hematological (0-3)	2	2
Biological (0-2)	1	NA
Score total	0-123	0-135

Source: Seror et al[6]
clinESSDAI = clinical EULAR Sjögren's syndrome disease activity index; ESSDAI = EULAR Sjögren's syndrome disease activity index; EULAR = European Alliance of Associations for Rheumatology; NA = not applicable

The biological domain will remain blinded until the parent study is unblinded, therefore study sites are only expected to report clinESSDAI in the eCRF.

8.2.4. STAR

STAR has been developed to assess the efficacy of treatments for pSS.[7]

This composite measure contains 5 domains:

- Systemic activity: 3 points
  - clinESSDAI decrease of ≥ 3 points (Section 8.2.3)
- Patient-reported outcome: 3 points
  - ESSPRI decrease of at least 1 point or ≥ 15% (Section 8.2.5.1)
  - Symptoms of dryness, pain, and fatigue rated on 3 numeric rating scales
- Lacrimal gland function (assessed by Schirmer's test or OSS): 1 point
  - Schirmer's test (Section 8.2.6.3)
    - If abnormal score at baseline: increase of ≥ 5 mm from baseline
    - If normal score at baseline: no change to abnormal
  - OSS (Section 8.2.6.4)

- If abnormal score at baseline: decrease of ≥ 2 points from baseline
- If normal score at baseline: no change to abnormal

- Salivary gland function: 1 point
  - UWSF:
    - If score > 0 at baseline: increase of ≥ 25% from baseline
    - If score is 0 at baseline: any increase in UWSF from baseline

  OR

  - SGUS:
    - ≥ 25% decrease in total Hocevar score from baseline
- Biological (assessed by IgG or RF): 1 point
  - IgG: ≥ 10% reduction
  - RF: ≥ 25% decrease

8.2.5. Patient-Reported Outcomes

8.2.5.1. ESSPRI

ESSPRI is a questionnaire that has been developed to measure self-reported symptoms in participants with pSS.[8] CCI

8.2.5.2. MFI

CCI

8.2.5.3. PGA

PGA is a tool that measures a participant's global evaluation of their overall disease activity at the time of assessment.[10]

The participant rates their overall disease activity by drawing a vertical mark on a 10-cm VAS from the left end of the line (no evidence of disease activity) to the right end of the line (extremely active or severe disease activity).

8.2.5.4. SF-36

The SF-36 is a 36-item scale constructed to survey health-related quality of life on 8 domains:

CCI [redacted]

8.2.5.5. PASS

PASS is a patient-reported outcome measure that assesses the "value beyond which patients consider themselves well".[12] PASS measures participant well-being and overall feeling that symptoms are in remission, through a single question that is dependent on the indication.

PASS assesses the level of symptoms at which participants with rheumatic diseases consider themselves well. To record the PASS, the rheumatologist will ask the participant whether they consider their current state to be satisfactory, considering all of the consequences of their disease.

8.2.5.6. EQ-5D-5L

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

CCI [redacted]

8.2.6. Additional Efficacy Measures

8.2.6.1. SGUS

The SGUS grading system of Hocevar[13] rates 5 parameters: parenchymal echogenicity, homogeneity, presence of hypoechogenic areas, hypoechogenic reflections, and the clearness of salivary gland borders. The overall ultrasound score will be calculated by summation of the grades for the 5 subscores for all 4 major salivary glands (left and right parotid and submandibular glands). The overall ultrasound score can range from 0 to 48.

8.2.6.2. Salivary Flow Rate

SWSF and UWSF rates will be assessed in this study. Details of the collection will be further specified in the Investigator Site File.

8.2.6.3. Schirmer's Test

Schirmer's test is an assessment of tear gland function in which a strip of filter paper is applied under the eyelid to measure the quantity of tear production. A result of $\leq$ 5 mm indicates abnormal tear gland function.[14] Test is performed without anesthesia.

8.2.6.4. OSS

OSS will be used in this study to assess tear gland function in participants with pSS. OSS uses lissamine green dye to grade the conjunctiva, and fluorescent dye to grade the cornea. A score of $\geq$ 3 points indicates abnormal tear gland function.[15]

8.3. Safety Assessments

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

8.3.1. Physical Examinations

- Brief physical examination will include weight; assessments of gastrointestinal, pulmonary, cardiovascular, and respiratory systems; and general appearance. Additionally, physical examinations will be performed to assess ESSDAI, as appropriate

8.3.2. Vital Signs

- Body temperature, pulse rate, respiratory rate, and blood pressure will be recorded before blood collection for laboratory tests and IMP administration
- Blood pressure and pulse will be assessed with the participant rested and seated

8.3.3. Electrocardiograms

- Single 12-lead ECG(s) will be obtained using an ECG machine

8.3.4. Protocol-Required Laboratory Tests

- Blood and urine samples will be analyzed at a central laboratory for serum chemistry and hematology, urinalysis, and specialty laboratory parameters
- Refer to Appendix 2 (Section 10.2) for the list of protocol-required laboratory tests to be performed and the SoA (Section 1.3) for the timing
- The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition

8.3.5. Pregnancy Testing

- WOCBP will be tested for pregnancy. Urine tests for pregnancy will occur at the time points specified in the SoA (Section 1.3)
- Pregnancy testing in WOCBP will be conducted at the end of relevant systemic exposure (ie, at the SFV)
- Additional pregnancy testing could be performed, as deemed necessary by the investigator or required by local regulations, to establish the absence of pregnancy at any time during the study

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

The definitions of AEs and SAEs are provided in Appendix 3 (Section 10.3).

AEs will be reported by the participant (or, if appropriate, by the caregiver or surrogate).

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

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

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

All AEs will be collected from the signing of the ICF until the SFV, as specified in the SoA (Section 1.3).

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

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

8.4.2. Method of Detecting AEs and SAEs

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

8.4.3. Follow-up of AEs and SAEs

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

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of IMP under clinical investigation are met
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of IMP under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators
- An investigator who receives a safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and file it with the IB and notify the IRB/IEC, if appropriate, according to local requirements

- The sponsor or designee will be responsible for reporting SUSARs to the relevant regulatory authorities and IEC/IRB, as per applicable regulatory requirements. The sponsor or designee will also be responsible for forwarding SUSAR reports to all study investigators, who will be required to report these SUSARs to their respective IECs/IRBs per local regulatory requirements

8.4.5. Pregnancy

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

8.4.6. AESIs

An AESI is an event of scientific and medical concern specific to the sponsor's product or program. An AESI can be serious or nonserious, related or unrelated to the IMP or study procedures. These events will be reported according to the same timeframe as that for SAEs specified in Section 8.4.1 and Section 10.3.4.

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

For this study, infections will be AESIs as discussed in Section 8.4.6.1.

8.4.6.1. Infections

Efgartigimod treatment leads to reduced IgG levels. As low IgG levels can be associated with increased infection risks, events in the MedDRA SOC Infections and Infestations are considered AESIs in this study. These events will be reported according to the timeframe specified in Section 8.4.1 and Section 10.3.4, with the following information provided:

- Causal pathogen
- Location of infection

- Relationship to an underlying medical condition, medical history, and concomitant medications
- Reoccurrence of a previous infection
- Any confirmatory procedure, culture, or urgent medical intervention

8.4.7. AEs of Clinical Interest

8.4.7.1. Infusion/Injection-Related Reactions

All therapeutic proteins can elicit immune responses, potentially resulting in hypersensitivity or allergic reactions such as rash, urticaria, angioedema, serum sickness, and anaphylactoid or anaphylactic reactions. As with any SC or IV injection, injection- or infusion-related reactions can occur during or after administration.

The efgartigimod IB provides more information on infusion/injection-related reactions.

8.4.7.2. Injection Site Reaction

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

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

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

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

8.5. Pharmacokinetics

On IMP administration visits, blood samples for PK analysis will be collected predose (preferably within 2 hours before IMP administration) and post-dose (within 30 minutes after the end of IMP infusion) at baseline and week 16, as described in the SoA (Section 1.3). Samples collected after the end of infusion should be collected in the opposite arm from the arm used for IMP infusion. At visits where the IMP is not administered, blood samples may be collected at any time during that visit.

Efgartigimod serum concentrations will be determined using a validated method.

8.6. Pharmacodynamics

Baseline and postbaseline PD blood samples will be collected predose on IMP administration visits (preferably within 2 hours before IMP administration) as described in the SoA (Section 1.3). At visits where the IMP is not administered, blood samples may be collected at any time during that visit.

Total IgG concentrations will be quantified at a diagnostical laboratory. Results will not be reported to investigative sites or other study personnel to maintain the parent study blind.

Participants will also be tested for anti-Ro/SS-A and anti-La/SS-B autoantibodies at the time points specified in the SoA (Section 1.3), as a part of secondary PD measures. All results will be blinded.

8.7. Genetics

Not applicable.

8.8. Biomarkers

Blood will be collected, whereas serum will be aliquoted at the time points specified in the SoA (Section 1.3) to explore the relation between relevant biomarkers and clinical effects.

8.9. Immunogenicity Assessments

Blood samples will be collected at the time points indicated in the SoA (Section 1.3) to evaluate serum levels of ADAs against efgartigimod.

On IMP administration visits, the blood samples will be collected predose, preferable within 2 hours before the IMP administration. Date and time of sample collection will be recorded in the participant's eCRF. On other visits, blood samples may be collected at any time during the visit as specified in the SoA (Section 1.3).

Samples will be analyzed by the designated laboratory in a 3-tiered approach using validated immunogenicity assays.[16] Initially, samples will be screened for a positive assay response (tier 1). Screened positive samples will then be tested in a confirmation assay (tier 2). Finally, a titration of the ADA response will be performed on positive tier 2 samples to characterize the magnitude of the antibody response (tier 3).

8.10. Health Economics or Medical Resource Utilization and Health Economics

Not applicable.

9. STATISTICAL CONSIDERATIONS

The SAP will be finalized before database lock and includes a more technical and detailed description of the statistical analyses described in this section.

9.1. Statistical Hypothesis

No formal hypothesis will be tested in this phase 2 open-label extension study.

9.2. Analysis Sets

The following analysis sets are defined:

Analysis set	Description
Full analysis set (FAS)	All enrolled subjects in the OLE study.
Safety set	All FAS subjects who have been administered study treatment during the OLE.

9.3. Statistical Analyses

9.3.1. General Considerations

- Data collected will be listed with derived variables. Descriptive statistical methods will be used to analyze safety and efficacy data
- The results of this study will not be used inferentially
- No formal sample size calculation is presented
- Summaries will include the number of observations (n), mean, SE, 90% CI, median, minimum, and maximum for continuous measures
- Summaries will include sample size, frequencies, and percentages for categorical variables
- The baseline value will be the last assessment before the first administration of the study drug in OLE
- All study visits will be recalculated based on actual dates. The rules for calculating the analysis visits will be documented in the SAP
- Rules for imputing partial dates or missing dates will be provided in the SAP
- Exposure to IMP will be summarized
- TEAEs, AESIs, SAEs, and other safety parameters will be summarized
- AEs will be classified using the latest version of the MedDRA classification system
- AEs, AESIs, and SAEs will be listed corresponding to MedDRA SOC and PT

- Multiple occurrences of a single PT in a participant will be counted only once at the maximum severity/grade
- 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
- Population PK/PD analysis may be performed based on the PK and PD data and reported separately
- Laboratory parameters, physical examinations, vital sign measurements, ECG data and PK, PD, immunogenicity, and biomarker results will be summarized descriptively

9.3.2. Primary Endpoint Analysis

Primary endpoint of long-term safety will be assessed through AEs, AESI, incidence of SAEs, changes in laboratory test results, vital signs, and ECG. Please refer the Section 8.3 for more details. Full details of the secondary analyses will be included in the SAP.

9.3.3. Secondary Endpoint(s) Analysis

The key secondary endpoints of CRESS, ESSDAI, clinESSDAI, ESSPRI, and STAR responders will be assessed at week 24 and week 48.

The proportion along with an exact 90% CI of CRESS, ESSDAI, clinESSDAI, ESSPRI, and STAR responders will be presented at week 24 and week 48.

Secondary endpoints of change from OLE baseline in ESSDAI, clinESSDAI, and ESSPRI scores will be summarized descriptively at week 24 and week 48. Observed data will also be summarized at OLE baseline, week 24 and week 48.

Plots of mean changes from the OLE baseline will be presented along with their 90% confidence intervals at each scheduled timepoint for ESSDAI, clinESSDAI, and ESSPRI. Box and Whisker plots will also be presented for the change from OLE baseline for each scheduled timepoint.

9.3.4. Exploratory Endpoints Analysis

To explore the effect of efgartigimod on clinical pSS, glandular measures and patient-reported outcomes, serum and blood biomarkers the following analysis will be performed:

- The proportion along with an exact 90% CI of adjusted CRESS (without serology item) will be presented at week 24 and week 48
- Change from OLE baseline in activity of individual ESSDAI domains score, Hocevar score, Schirmer's test score, OSS score, MFI score, physical component and mental component scores of SF-36, PGA score, individual ESSPRI score, EQ-5D-5L utilities score, VAS score will be summarized descriptively at week 24 and week 48. Observed data will also be summarized at OLE baseline, week 24 and week 48

- Percentage change from OLE baseline scores of SWSF, UWSF will be summarized descriptively at week 24 and week 48. Observed data will also be summarized at OLE baseline, week 24 and week 48
- Observed data for response in salivary gland function and tear gland function (CRESS) and PASS score will be summarized descriptively at OLE baseline, week 24 and week 48
- CCI
- Counts and percentages of number of subjects who are on Q2W and QW dosing regimen will be presented at each scheduled visit
- Counts and percentage of the number of subjects with different clinESSDAI scores will be presented by each scheduled visit and the subgroups
- Time from first infusion to revert to QW dosing regimen will be analyzed using a Kaplan-Meier (KM) method. Summary statistics will include the upper and lower quartiles of duration (days) with 95% confidence interval, median duration (days), 95% confidence interval for median duration (days). KM probability of staying on Q2W dosing regimen will also be presented

All the primary, secondary and exploratory analysis will be based on the FAS.

9.4. Interim Analysis

An interim analysis may be conducted to support regulatory submissions if considered necessary by the sponsor.

9.5. Sample Size Determination

No formal sample size calculation has been planned for this phase 2 OLE study. Up to approximately 30 subjects who have completed the efgartigimod pSS studies will be enrolled for the OLE study.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

10.1.2. Financial Disclosure

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

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

10.1.3. Informed Consent Process

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

10.1.4. Recruitment Strategy

Not applicable.

10.1.5. Data Protection

- The sponsor will assign participants a unique identifier. Any participant records or datasets transferred to the sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred
- The participant must be informed that the sponsor, sponsor representatives, competent authorities, etc., can review source data containing identifiers and will use their personal study-related data per local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect

such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access

10.1.6. Committees Structure

Not applicable.

10.1.7. Dissemination of Clinical Trial Data

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

10.1.8. Data Quality Assurance

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

10.1.9. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available
- Definition of what constitutes source data, and its origin can be found in the monitoring plan
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF
- The sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements

10.1.10. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the first participant rolls over to ARGX-113-2211.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

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

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

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

- Total number of participants included earlier than expected

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

10.1.11. Publication Policy

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

10.2. Appendix 2: Clinical Laboratory Tests

- The tests listed in Table 6 will be performed as described in the Laboratory Manual
- Additional tests can be performed during the study as determined necessary by the investigator or required by local regulations
- Investigators must document their review of each laboratory test result

Table 6: Protocol-Required Laboratory Tests

Laboratory Test	Parameters		
Hematology	RBC count platelet count hemoglobin hematocrit	RBC indices: MCV MCH %reticulocytes	WBC count with differential: neutrophils eosinophils lymphocytes basophils monocytes
Serum chemistry	ALT AST GGT alkaline phosphatase albumin[a]	creatinine potassium BUN CRP glucose	sodium total protein[a] calcium bilirubin (total and direct)
Routine urinalysis	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase Microscopic examination (if blood or protein is abnormal)		
Pregnancy testing	Urine test at baseline and other time points (as needed for WOCBP potential, defined in Section 10.4.1)		

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CRP = C-reactive protein; GGT = gamma-glutamyl transferase; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; RBC = red blood cell; WBC = white blood cell

[a] This result will be blinded baseline and up to the week 4 (day 29) visit.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of IMP, whether or not considered related to the IMP • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of IMP

Events to be Collected as AEs
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease) • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition • New condition detected or diagnosed after IMP administration even though it could have been present before the start of the study • Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction • Signs, symptoms, or the clinical sequelae of a suspected overdose of either IMP or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses will be reported regardless of sequelae • Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE

Events <u>NOT</u> to be Collected as AEs
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

10.3.2. Definition of SAE

An SAE is Defined as Any Untoward Medical Occurrence That, at Any Dose:

Results in death

Is life threatening

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

Requires inpatient hospitalization or prolongation of existing hospitalization

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

Results in persistent or significant disability/incapacity

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

Is a congenital anomaly/birth defect

Other situations:

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

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

AE and SAE Recording

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

Assessment of Severity

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

All AEs observed will be graded using the NCI CTCAE (version 5.0) definitions.

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

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

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between IMP and each occurrence of each AE/SAE as **related** or **not related**. The investigator will use clinical judgment to determine whether there is reasonable possibility that the IMP caused the AE

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

Follow-up of AEs and SAEs

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

10.3.4. Reporting of SAEs and AESIs

SAE and AESI reporting

- All SAEs and AESIs will be recorded on the AE form of the eCRF. SAEs will also be recorded on the paper SAE report form
- The investigator or designated site staff will ensure all entered data are consistent
- An alert email for the SAE and AESI reports on the eCRF will automatically be sent by email to the sponsor or designee's safety mailbox via the EDC system

- The paper SAE report form will be faxed or emailed to the sponsor's designee (see the Serious Adverse Event Reporting details on page 2 of this protocol)

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Women of Childbearing Potential Definition

A female is considered a WOCBP unless she is either:

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

10.4.2. Contraception Guidance

10.4.2.1. Female Contraception for Women of Childbearing Potential

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

The following Clinical Trials Facilitation and Coordination Group[17] acceptable methods are permitted for efgartigimod studies:

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

10.4.2.2. Male Contraception

There are no contraception requirements for men in this study.

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

Participants will be tested for SARS-CoV-2 if they are symptomatic or if applicable law requires testing.

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

This appendix is intended for use only if unforeseen changes in the COVID-19 pandemic result in new restrictions at the site or new risks for participants or site staff from attending visits at the site.

Testing for COVID-19 is not required during the study unless required by local authorities. However, it is recommended that participants who develop COVID-19 symptoms while receiving IMP be tested, with results reported for the study.

Critical Parameters to Be Collected During the Study

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

10.6. Appendix 6: Home Study Visits

A home nurse can travel to the participant's home to conduct visits (or meet the participant at a convenient alternate location). For each home visit, the investigator or designee will confer with the participant via an audio or video interview to elicit AEs and concomitant medications and the participant's general well-being. The investigator or designee will also ensure the participant has completed all required efficacy assessments that can be done at home (eg, questionnaires). Any scheduled assessments will be conducted before the home nurse administers IMP.

10.7. Appendix 7: Efficacy Endpoint Data

10.7.1. ESSDAI

Table 7: ESSDAI: Domain and Item Definitions and Weights

Domain [Weight]	Activity level	Description
Constitutional [3] *Exclusion of fever of infectious origin and voluntary weight loss*	No = 0	Absence of the following symptoms
	Low = 1	Mild or intermittent fever (37.5 to 38.5°C)/night sweats and/or involuntary weight loss of 5 to 10% of body weight
	Moderate = 2	Severe fever (> 38.5°C)/night sweats and/or involuntary weight loss of > 10% of body weight
Lymphadenopathy [4] *Exclusion of infection*	No = 0	Absence of the following features
	Low = 1	Lymphadenopathy ≥ 1 cm in any nodal region or ≥ 2 cm in inguinal region
	Moderate = 2	Lymphadenopathy ≥ 2 cm in any nodal region or ≥ 3 cm in inguinal region, and/or splenomegaly (clinically palpable or assessed by imaging)
	High = 3	Current malignant B-cell proliferative disorder
Glandular [2] *Exclusion of stone or infection*	No = 0	Absence of glandular swelling
	Low = 1	Small glandular swelling with enlarged parotid (≤ 3 cm), or limited submandibular or lachrymal swelling
	Moderate = 2	Major glandular swelling with enlarged parotid (> 3 cm), or important submandibular or lachrymal swelling
Articular [2] *Exclusion of osteoarthritis*	No = 0	Absence of currently active articular involvement
	Low = 1	Arthralgias in hands, wrists, ankles, and feet, accompanied by morning stiffness (> 30 minutes)
	Moderate = 2	1 to 5 (of 28 total count) synovitis
	High = 3	≥ 6 (of 28 total count) synovitis
Cutaneous [3] *Rate as "No activity" stable long-lasting features related to damage*	No = 0	Absence of currently active cutaneous involvement
	Low = 1	Erythema multiforme
	Moderate = 2	Limited cutaneous vasculitis, including urticarial vasculitis, or purpura limited to feet and ankle, or subacute cutaneous lupus
	High = 3	Diffuse cutaneous vasculitis, including urticarial vasculitis, or diffuse purpura, or ulcers related to vasculitis

Table 7: ESSDAI: Domain and Item Definitions and Weights (Continued)

Domain [Weight]	Activity level	Description
Pulmonary [5] *Rate as "No activity" stable long-lasting features related to damage, or respiratory involvement not related to the disease (tobacco use etc)*	No = 0	Absence of currently active pulmonary involvement
	Low = 1	Persistent cough or bronchial involvement with no radiographic abnormalities on radiography; or radiological or HRCT evidence of interstitial lung disease with: no breathlessness and normal lung function test
	Moderate = 2	Moderately active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath on exercise (NHYA II) or abnormal lung function tests restricted to: 70% > DLCO ≥ 40% or 80% > FVC ≥ 60%
	High = 3	Highly active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath at rest (NHYA III, IV) or with abnormal lung function tests: 70% > DLCO ≥ 40% or 80% > FVC ≥ 60%
Renal [5] *Rate as "No activity" stable long-lasting features related to damage, and renal involvement not related to the disease. If biopsy has been performed, please rate activity based on histological features first*	No = 0	Absence of currently active renal involvement with proteinuria < 0.5 g/day, no hematuria, no leucocyturia, no acidosis, or long-lasting stable proteinuria due to damage
	Low = 1	Evidence of mild active renal involvement, limited to tubular acidosis without renal failure or glomerular involvement with proteinuria (between 0.5 and 1 g/day) and without hematuria or renal failure (GFR ≥ 60 mL/min)
	Moderate = 2	Moderately active renal involvement, such as tubular acidosis with renal failure (GFR < 60 mL/min) or glomerular involvement with proteinuria between 1 and 1.5 g/day and without hematuria or renal failure (GFR ≥ 60 mL/min) or histological evidence of extra-membranous glomerulonephritis or important interstitial lymphoid infiltrate
	High = 3	Highly active renal involvement, such as glomerular involvement with proteinuria > 1.5 g/day or hematuria or renal failure (GFR < 60 mL/min), or histological evidence of proliferative glomerulonephritis or cryoglobulinemia related renal involvement
Muscular [6] *Exclusion of weakness due to corticosteroids*	No = 0	Absence of currently active muscular involvement
	Low = 1	Mild active myositis shown by abnormal EMG or biopsy with no weakness and creatine kinase (N < CK ≤ 2N)

Table 7: ESSDAI: Domain and Item Definitions and Weights (Continued)

Domain [Weight]	Activity level	Description
	Moderate = 2	Moderately active myositis proven by abnormal EMG or biopsy with weakness (maximal deficit of 4/5), or elevated creatine kinase (2N < CK ≤ 4N)
	High = 3	Highly active myositis shown by abnormal EMG or biopsy with weakness (deficit ≤ 3/5) or elevated creatine kinase (> 4N)
PNS [5] *Rate as "No activity" stable long-lasting features related to damage or PNS involvement not related to the disease*	No = 0	Absence of currently active PNS involvement
	Low = 1	Mild active peripheral nervous system involvement, such as pure sensory axonal polyneuropathy shown by NCS or trigeminal (V) neuralgia
	Moderate = 2	Moderately active PNS involvement shown by NCS, such as axonal sensory-motor neuropathy with maximal motor deficit of 4/5, pure sensory neuropathy with presence of cryoglobulinemic vasculitis, ganglionopathy with symptoms restricted to mild/moderate ataxia, CIDP with mild functional impairment (maximal motor deficit of 4/5or mild ataxia), or cranial nerve involvement of peripheral origin (except trigeminal [V] neuralgia)
	High = 3	Highly active PNS involvement shown by NCS, such as axonal sensory-motor neuropathy with motor deficit ≤ 3/5, peripheral nerve involvement due to vasculitis (mononeuritis multiplex, etc), severe ataxia due to ganglionopathy, CIDP with severe functional impairment: motor deficit ≤ 3/5 or severe ataxia
CNS [5] *Rate as "No activity" stable long-lasting features related to damage or CNS involvement not related to the disease*	No = 0	Absence of currently active CNS involvement
	Low = 1	Moderately active CNS features, such as cranial nerve involvement of central origin, optic neuritis, or multiple sclerosis–like syndrome with symptoms restricted to pure sensory impairment or proven cognitive impairment
	High = 3	Highly active CNS features, such as cerebral vasculitis with cerebrovascular accident or transient ischemic attack, seizures, transverse myelitis, lymphocytic meningitis, multiple sclerosis–like syndrome with motor deficit

Table 7: ESSDAI: Domain and Item Definitions and Weights (Continued)

Domain [Weight]	Activity level	Description
Hematological [2] *For anemia, neutropenia, and thrombopenia, only autoimmune cytopenia must be considered* *Exclusion of vitamin or iron deficiency, drug-induced cytopenia*	No = 0	Absence of autoimmune cytopenia
	Low = 1	Cytopenia of autoimmune origin with neutropenia ($1000 < \text{neutrophils} < 1500/mm^3$), and/or anemia ($10 < \text{hemoglobin} < 12$ g/dL), and/or thrombocytopenia ($100\,000 < \text{platelets} < 150\,000/mm^3$); or lymphopenia ($500 < \text{lymphocytes} < 1000/mm^3$)
	Moderate = 2	Cytopenia of autoimmune origin with neutropenia ($500 \leq \text{neutrophils} \leq 1000/mm^3$), and/or anemia ($8 \leq \text{hemoglobin} \leq 10$ g/dL), and/or thrombocytopenia ($50\,000 \leq \text{platelets} \leq 100\,000/mm^3$); or lymphopenia ($\leq 500/mm^3$)
	High = 3	Cytopenia of autoimmune origin with neutropenia ($\text{neutrophils} < 500/mm^3$) and/or anemia (hemoglobin < 8 g/dL) and/or thrombocytopenia ($\text{platelets} < 50\,000/mm^3$)
Biological [1]	No = 0	Absence of any of the following biological features
	Low = 1	Clonal component and/or hypocomplementemia (low C4 or C3 or CH50) and/or hypergammaglobulinemia or high IgG level between 16 and 20 g/L
	Moderate = 2	Presence of cryoglobulinemia and/or hypergammaglobulinemia or high IgG level > 20 g/L, and/or recent onset hypogammaglobulinemia or recent decrease of IgG level (< 5 g/L)

Source: Seror et a, 2011[8]
C3 = Complement component 3; C4 = Complement component 4; CH50 = Total hemolytic complement; CIDP = chronic inflammatory demyelinating polyneuropathy; CK = creatine kinase; CNS = central nervous system; DLCO = diffusing capacity of the lungs for carbon monoxide; EMG = electromyogram; ESSDAI = EULAR Sjögren's syndrome disease activity index; FVC = forced vital capacity; GFR = glomerular filtration rate; HRCT = high-resolution computed tomography; IgG = immunoglobulin G; N = normal; NCS = nerve conduction studies; NHYA = New York Heart Association (classification); PNS = peripheral nervous system

10.8. Appendix 8: ACR-EULAR Classification Criteria

The ACR-EULAR classification of pSS applies to any individual who meets the following inclusion and exclusion criteria and has a score of ≥ 4 when summing the weights from the items presented in Table 8.

Inclusion Criteria

Inclusion criteria apply to any patient with ≥ 1 symptom of ocular or oral dryness, defined as a positive response to ≥ 1 of the following questions:

1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
2. Do you have a recurrent sensation of sand or gravel in the eyes?
3. Do you use tear substitutes more than 3 times a day?
4. Have you had a daily feeling of dry mouth for more than 3 months?
5. Do you frequently drink liquids to aid in swallowing dry food?

OR suspicion of pSS from the ESSDAI questionnaire (with ≥ 1 positive domain item)

Exclusion Criteria

Prior diagnosis of any of the following conditions would exclude diagnosis of pSS and participation in pSS studies or therapeutic studies because of overlapping clinical features or interference with criteria tests:

- AIDS
- Active hepatitis C infection (with positive PCR)
- Sarcoidosis
- Amyloidosis
- Graft-versus-host disease
- History of head and neck radiation treatment
- IgG4-related disease

Table 8: ACR-EULAR Classification Criteria for Primary Sjögren's Syndrome

Item	Weight/Score
Labial salivary gland with focal lymphocytic sialadenitis and focus score of ≥ 1[a]	3
Anti-Ro/SS-A positive	3
OSS of ≥ 5[18] (or van Bijsterfeld score of ≥ 4[19]) on at least 1 eye	1
Schirmer's test of ≤ 5 mm/5 minutes on at least 1 eye[b]	1
UWSF rate of ≤ 0.1 mL/min[20,b]	1

Source: Shiboski et al[21]
ACR = American College of Rheumatology; EULAR = European Alliance of Associations for Rheumatology; OSS = ocular staining score; SS-A = Sjögren's syndrome–related antigen A; UWSF = unstimulated whole salivary flow

[a] A pathologist with expertise in the diagnosis of focal lymphocytic sialadenitis and focus score count (based on number of foci per 4 mm^2) should perform the histopathologic examination following a protocol by Daniels et al[22].
[b] Patients who are normally taking anticholinergic drugs should be evaluated for objective signs of salivary hypofunction and ocular dryness after a sufficient interval off these medications so that these components can be a valid measure of oral and ocular dryness.

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