CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2, Randomized, Placebo-Controlled, Parallel-Group, Double-Blinded, Proof-of-Concept Study to Evaluate the Safety and Efficacy of Intravenous Efgartigimod in Adult Participants With Primary Sjögren's Syndrome
Protocol Number:	ARGX-113-2106
Version Number:	2.0 (Amendment 1)
Compound:	Efgartigimod (ARGX-113)
Study Phase:	2
Sponsor Name:	argenx BV
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Regulatory Agency Identifier Number(s):	EUDRACT: 2021-005911-30
Approval Date:	05 Dec 2022

Sponsor's Medical Contact:	[redacted], MD Global Clinical Trial Physician argenx BV 33 Arch St Boston, MA United States Email: [redacted]
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SIGNATURE OF SPONSOR

Protocol Title:	A Phase 2, Randomized, Placebo-Controlled, Parallel-Group Double-Blinded, Proof-of-Concept Study to Evaluate the Safety and Efficacy of Intravenous Efgartigimod in Adult Participants With Primary Sjögren's Syndrome
Protocol Number:	ARGX-113-2106

Sponsor Signatory:

See appended signature page

[redacted], MD, PhD
Chief Medical Officer

Date

SIGNATURE OF THE INVESTIGATOR

Investigator's Acknowledgment

I have read the protocol for study ARGX-113-2106.

Title: A Phase 2, Randomized, Placebo-Controlled, Parallel-Group, Double-Blinded, Proof-of-Concept Study to Evaluate the Safety and Efficacy of Intravenous Efgartigimod in Adult Participants With Primary Sjögren's Syndrome

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

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

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

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

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

Investigator Name _____
Institution _____
Address _____
(please hand print or type) _____

Signature _____

Date _____

SUMMARY OF CHANGES

Protocol Amendment Summary of Changes Table

Global protocol document history	Date

v2.0 amendment 1	05 Dec 2022
Original Protocol v1.0	18 Aug 2022

Amendment 1 (05 Dec 2022)

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

Overall Rationale for the Amendment:

The primary rationale for this amendment is to permit the use of historic biopsy where taken within 12 months of enrollment to prevent participants from needing to undergo unnecessary procedures, and to update the permitted/excluded concomitant medications to allow participants to receive required therapy. Other clarifications and corrections have been made and are summarized below.

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

Section # and Name	Description of Change	Brief Rationale
Cover page	Sponsor's Medical Contact details updated from [redacted], MD to [redacted], MD.	To reflect change in personnel for this study role.
Section 1.1, Synopsis	Changed text stating 60-day follow-up period to 56-day (±3 days) follow-up period.	Minor error in original protocol wording required update.
Section 1.3, Schedule of Activities	Removed PK sampling requirement from Safety Follow-up Visit.	Not required as part of safety analyses. No IMP is expected to be detectable in the blood at the point of Safety Follow-Up Visit.
	Removed parotid biopsy sampling at IMP discontinuation visit.	Included in error in original protocol; parotid biopsy sampling to occur at week 24 or at the EDV, whichever is earlier.
	Clarified that participants at sites performing parotid biopsy may be enrolled based on a historical biopsy from within 12 months prior to screening, where participant has not received immunomodulatory treatment for pSS from 6 months prior to biopsy through to screening.	To prevent participants from needing to undergo unnecessary procedures.
	Added footnote for parotid biopsy EDV sampling timepoint stating that this should only occur when this visit occurs after week 16.	Changes in biopsy results are not expected to be visible prior to week 16.
Section 1.1, Synopsis	Minor updates made to description of pSS.	Wording updates made for accuracy and clarity.

Section # and Name	Description of Change	Brief Rationale
Section 2.2, Background		
Section 4.2, Scientific Rationale for Study Design	Addition of statement: "The totality of data from all endpoints used in the study will be utilized to determine treatment response in this population."	Added to clarify why various secondary endpoints were used for pSS.
Section 5.1, Inclusion Criteria	Updated inclusion criterion 4 to state "at screening".	All criteria based on status at screening instead of based on historical findings.
Section 5.2, Exclusion Criteria	Updated exclusion criterion 15 from "IVIg, SCIg, or PLEX < 12 weeks before screening" to "IVIg, SCIg, or PLEX ≤ 12 weeks before screening".	Changed to ≤ 12 weeks for consistency with other exclusion criteria.
	Clarified that exclusion criteria 18 requires anticholinergic agents to be at a stable dose 4 weeks prior to screening or during screening.	Requirement to be at a stable dose 4 weeks prior to screening was not included in original protocol in error.
	Modified exclusion criteria around prior and concomitant medications.	Prior and concomitant medications permitted during study have been modified to ensure participants have access to required therapies during study; prior and concomitant medication exclusion criteria have been updated to align with this.
Section 6.5, Study Compliance	Addition of requirement "Documentation will include both start and end time of infusion."	Sentence added to ensure start and end times are captured.
Section 6.6, Dose Modification	Replacement of text "weight has changed by more than ±10% during the insert time frame" with "weight has changed (increased or decreased) by more than 10% from baseline".	Minor error in original protocol wording required update.
Section 6.8, Treatment of Overdose	Modified text on treatment of overdose to remove requirement to immediately report and to clarify that overdose must be recorded in the eCRF.	Previous text was not clear regarding where the overdose should be captured or who it was to be reported to.
Section 6.9, Prior and Concomitant Therapy	Medication requirements added for the period prior to study treatment, and the follow-up period after study treatment.	Detail on prior therapies and therapies during follow-up period previously not detailed in this section.
	Addition of requirement: "Any treatment used for pSS in the last 6 months prior to screening should also be recorded."	Added to allow verification via eCRF that the patient has not taken any prohibited medications in the 6 months prior to screening

Section # and Name	Description of Change	Brief Rationale
Section 7.1.1, Permanent Discontinuation	Added in IMP discontinuation visit for participants who permanently discontinue IMP. Clarified that if the discontinued participant is unable or unwilling to attend further study visits, the study site will perform an EDV and the SFV.	IMP discontinuation visit previously not included in this section, in error. Updated to correct this and improve readability.
Section 7.1.1, Permanent Discontinuation Section 8.5, Pharmacokinetics	Added that blood samples for participants remaining in the study following IMP discontinuation will be collected for PK analyses as per the SoA for up to 3 weeks post IMP discontinuation.	IMP is expected to still be detectable in blood following permanent discontinuation.
Section 1.3, Schedule of Activities Section 8.2.3, ESSDAI	Added information on ESSDAI-related laboratory tests (gammaglobulins, cryoglobulins, C3, Cs4 and CH50).	Tests included in original protocol, but not detailed that this was part of the ESSDAI efficacy assessments.
Section 8.2, Efficacy Assessments Section 8.2.7.2, Salivary Flow Rate	Replaced “study manual” with “Investigator Site File”.	Study does not include use of a formal study manual; information will instead be included in Investigator Site File.
Section 8.2.7.1, SGUS	Added names of the 4 major salivary glands (left and right parotid and submandibular glands).	Added to clarify the glands used in calculation of the overall ultrasound score.
Section 8.3.2, Vital Signs	Changed “oral temperature” to “body temperature”.	Updated as non-oral methods of body temperature measurement are also considered acceptable.
Section 8.5, Pharmacokinetics	Updated to state that on visits without IMP administration, a single blood sample will be collected as described in the SoA.	Clarified for consistency with SoA.
	Added that “Samples collected after the end of infusion should be collected in the opposite arm from the arm used for IMP infusion.”	Clarification of required process.
Section 1.3, Schedule of Activities Section 8.5, Pharmacokinetics Section 8.6, Pharmacodynamics Section 8.8, [redacted] Section 8.9 Immunogenicity Assessments	Updated blood sampling requirements to state that on visits without IMP administration, samples may be collected at any time during the visit.	No restrictions are considered required around blood sample timings on these visits.

Section # and Name	Description of Change	Brief Rationale
Section 9.3.2, Primary Endpoint Analysis	Text amended to focus on effect estimates. Removed p-value from CRESS responder analysis text.	Sample size calculations were based upon the confidence interval for the proportion of CRESS responders in the efgartigimod treatment group.
Section 1.1, Synopsis Section 9.5, Sample Size Determination	Text updated from "approximately 30 participants will be enrolled" to state that participants will be randomized to achieve approximately 15 randomized participants with an IgG value at screening > 16.0 g/L and 15 participants without > 16.0 g/L.	Over 30 participants may be required to be enrolled to achieve approximately 15 randomized participants in each IgG subgroup. Approximately [redacted]% of participants are expected to have IgG > 16.0 g/L.

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LIST OF TABLES

LIST OF FIGURES

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
[redacted]	[redacted]
C3	complement component 3
C4	complement component 4
CIDP	chronic inflammatory demyelinating polyneuropathy
clinESSDAI	clinical EULAR Sjögren's syndrome disease activity index
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
eGFR	estimated glomerular filtration rate
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
GCP	Good Clinical Practice
gMG	generalized myasthenia gravis

Abbreviation	Expansion
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
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
[redacted]	[redacted]
[redacted]	[redacted]
IgG	immunoglobulin G
[redacted]	[redacted]
IMP	investigational medicinal product
IRB	institutional review board
IRT	interactive response technology
ITP	immune thrombocytopenia
IV	intravenous
IVIg	intravenous immunoglobulin
JAK	Janus kinase
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
NCI	National Cancer Institute
NSAID	non-steroidal anti-inflammatory drug
OLE	open-label extension
OSS	ocular staining score
[redacted]	[redacted]
[redacted]	[redacted]
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
[redacted]	[redacted]
PK	pharmacokinetic(s)
PLEX	plasma exchange

Abbreviation	Expansion
PMDA	Pharmaceuticals and Medical Devices Agency
pSS	primary Sjögren's syndrome
PT	preferred term
[redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SCIg	subcutaneous immunoglobulin
[redacted]	[redacted]
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
[redacted]	[redacted]
WOCBP	women of childbearing potential

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A phase 2, randomized, placebo-controlled, parallel-group, double-blinded, proof-of-concept study to evaluate the safety and efficacy of intravenous efgartigimod in adult participants with primary Sjögren's syndrome

Rationale:

pSS is a chronic, progressive autoimmune disease of unknown etiology, typically characterized by an autoimmune exocrinopathy. Currently, no immunomodulatory treatment is available for pSS. The purpose of this study is to evaluate the effect of efgartigimod, a human FcRn antagonist that can rapidly reduce IgG levels, including pathogenic antibodies. Efgartigimod has the potential to successfully treat pSS and improve disease manifestations by the reduction of IgG autoantibodies.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
• To evaluate the effect of efgartigimod IV compared to placebo on CRESS	• Proportion of CRESS responders on ≥ 3 of 5 items at week 24 (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)
Secondary	
• To evaluate the effect of efgartigimod IV compared to placebo on the histology of the parotid gland (selected sites only)	• Change in the relative counts of lymphocytic infiltrate (stained for CD45) at week 24 • Change in B/B+T cell ratio at week 24
• To evaluate the safety of efgartigimod IV compared to placebo in participants with pSS	• Incidence and severity of TEAEs, AESIs, and SAEs by SOC and PT • Changes in vital sign measurements, ECG results, and clinical laboratory safety evaluations
• To evaluate the effect of efgartigimod IV compared to placebo on clinical efficacy parameters	• Proportion of participants with minimal clinically important improvement in ESSDAI: improvement of ≥ 3 points in ESSDAI score at week 24 • Proportion of participants with low disease activity: ESSDAI score of < 5 at week 24

Objectives	Endpoints
	• Proportion of participants with minimal clinically important improvement in clinESSDAI: improvement of ≥ 3 points in clinESSDAI score at week 24 • Proportion of participants with low disease activity: clinESSDAI score of < 5 at week 24 • Proportion of participants with minimal clinically important improvement in ESSPRI: decrease of 1 point or ≥ 15% at week 24 • Change in ESSDAI score at week 24 • Change in clinESSDAI score at week 24 • Change in ESSPRI score at week 24
• To evaluate the effect of efgartigimod IV compared to placebo on STAR	• Proportion of participants with STAR score of ≥ 5 at week 24
• To evaluate the PK of efgartigimod IV	• Efgartigimod serum concentration-time profile
• To evaluate the PD of efgartigimod IV	• Values, changes from baseline, and percent reduction from baseline in total IgG levels in serum • Values, changes from baseline, and percent reduction from baseline in autoantibodies in serum: – Anti-Ro/SS-A – Anti-La/SS-B
• To evaluate the immunogenicity of efgartigimod IV	• Incidence and prevalence of ADA against efgartigimod in serum
Exploratory	
• [redacted]	• [redacted] • [redacted]
• [redacted]	• [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted]
• [redacted]	• [redacted] • [redacted]

Objectives	Endpoints
	• [redacted] • [redacted] • [redacted] • [redacted] • [redacted]
• [redacted]	• [redacted]
• [redacted]	• [redacted] • [redacted] • [redacted] • [redacted] • [redacted]
• [redacted]	• [redacted] • [redacted]
• [redacted]	• [redacted]

Note: Estimands are not defined for this phase 2 study.

Overall Design Synopsis:

This is a randomized, placebo-controlled, parallel-group, double-blinded, multicenter, proof-of-concept phase 2 study in pSS. Participants will be randomized to receive efgartigimod or placebo for 24 weeks. At the end of the randomized treatment period, eligible participants may roll over to an OLE study or remain in this study through the end of the 56-day (± 3 days) follow-up period.

Brief Summary:

The purpose of this study is to assess the efficacy and safety of FcRn blocking therapy with efgartigimod in participants with pSS. Efgartigimod has the potential to successfully treat pSS and improve disease manifestations by the reduction of IgG autoantibodies in pSS. After a

4-week screening period, participants will receive IMP weekly for 24 weeks, followed by entry into an OLE study or a 56-day (± 3 days) follow-up period.

Health Measurement/Outcome: The purpose of this study is to assess the efficacy and safety of FcRn blocking therapy with efgartigimod in participants with pSS.

Study Intervention and Intervention Form: The study intervention will be efgartigimod IV 10 mg/kg or placebo IV.

Condition/Disease: pSS

Study Duration:

- Approximately 36 weeks for participants not enrolling in the OLE study
- Approximately 28 weeks for participants enrolling in the OLE study

Treatment Duration: 24 weeks

Visit Frequency: weekly (site and home)

Number of Participants:

Participants will be randomized in a 2:1 ratio (efgartigimod:placebo) to achieve approximately 15 randomized participants with an IgG value at screening > 16.0 g/L and 15 randomized participants without an IgG value at screening > 16.0 g/L.

Eligibility of participants will be assessed during a 4-week screening period. After the screening period, eligible participants will be randomized in a 2:1 ratio between efgartigimod and placebo arms, respectively.

Note: Enrolled means the participant or their legally acceptable representative agrees to participate in the clinical study after completing the informed consent process.

Study Arms and Duration:

For participants not enrolling in the OLE study, the study duration is approximately 36 weeks, spanning the following study periods:

- Screening: ≤ 4 weeks
- Treatment: 24 weeks
- Follow-up: 56 days

For participants rolling over to the OLE study, the study duration is approximately 28 weeks, spanning the following study periods:

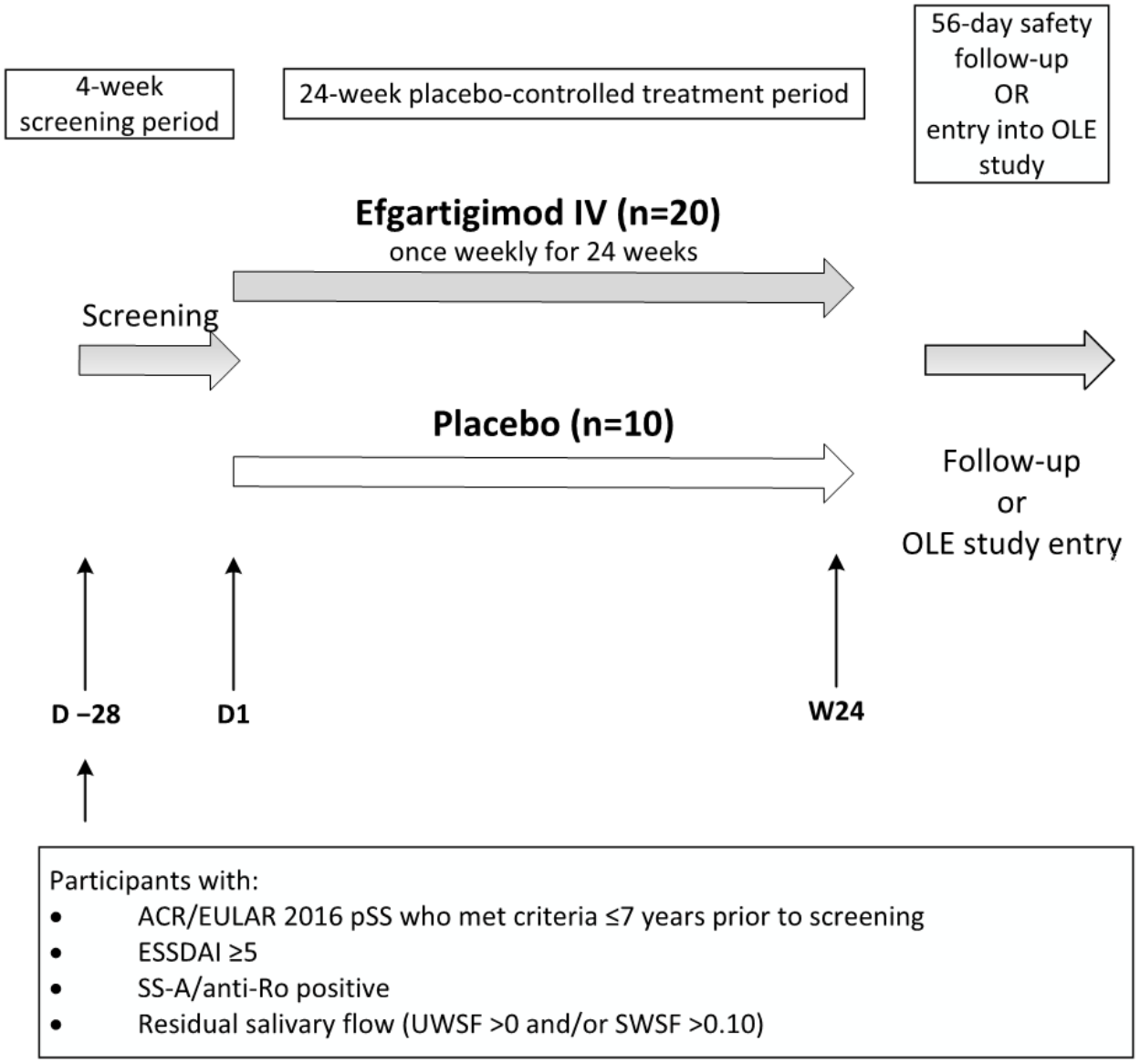
- Screening: ≤ 4 weeks
- Treatment: 24 weeks

All participants will receive efgartigimod IV 10 mg/kg or placebo once weekly for 24 weeks during the treatment period.

Data Monitoring/Other Committee: No

1.2. Schema

Figure 1: ARGX-113-2106 Study Overview



ACR=American College of Rheumatology; D=day; ESSDAI=EULAR Sjögren's syndrome disease activity index; EULAR=European Alliance of Associations for Rheumatology; IV=intravenous; n=number of participants; OLE=open-label extension; pSS=Sjögren's syndrome; SS-A=anti-Sjögren's syndrome–related antigen A; SWSF=stimulated whole salivary flow (rate); UWSF=unstimulated whole salivary flow (rate); W=week

1.3. Schedule of Activities

	SCR	Study week																									SFV[a] (56 d after final dose)	Applicable protocol section(s)
Study week			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	IMP d/c visit[b]	EDV[c] (≤ 7 d after final dose)		
±Days		BL	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	+2	±3	
Visits[d,e]	−28 to −2	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	NA	NA	NA	
Informed consent	X																													10.1.3
Inclusion and exclusion criteria	X	X																												5
Medical/ surgical history[f]	X																													8.3
Demography[g]	X																													
Physical examination[h]	X	X																												8.3.1
Brief physical examination (symptom driven)[i]			X	X		X				X				X				X				X				X	X	X	X	8.3.1
Vital signs[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	8.3.2
ECG	X	X																X								X	X	X	X	8.3.3
Randomization		X																												6.3
Glandular function																														
UWSF/SWSF	X	X																X								X	X	X		8.2.7.2
Schirmer’s test		X																X								X	X	X		8.2.7.3

Study week	SCR	Study week																									EDV[c] (≤ 7 d after final dose)	SFV[a] (56 d after final dose)	Applicable protocol section(s)
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	IMP d/c visit[b]			
±Days		**BL**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**		**+2**	**±3**	
Visits[d,e]	**−28 to −2**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**NA**	**NA**	**NA**	
OSS		X																X								X	X	X		8.2.7.4
SGUS		X																X								X	X	X		8.2.7.1
Histology																														
Parotid biopsy (selected sites only)[k]		X																								X		X[l]		8.2.2
Safety laboratory assessments (Table 6)																														
Clinical laboratory tests (hematology and chemistry)	X	X				X				X				X				X				X				X	X	X	X	8.3.4
Serology HIV/hepatitis	X																													8.3.4
Urinalysis	X	X																X								X	X	X	X	8.3
Pregnancy testing[m]	X	X				X				X				X				X				X				X	X	X	X	8.3.5
PCR COVID-19 test[n]	X																													10.2.1.1

	SCR	Study week																											Applicable protocol section(s)
Study week			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**IMP d/c visit[b]**	**EDV[c] (≤ 7 d after final dose)**	**SFV[a] (56 d after final dose)**	
±Days		**BL**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**±1**	**+2**	**±3**	
Visits[d,e]	**−28 to −2**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**NA**	**NA**	**NA**	
Blood samples																														
[redacted]	[redacted]																													8.8
PK[r]		X	X	X		X				X				X				X				X				X	X	X		8.5
Total IgG[o]	X	X	X	X		X				X				X				X				X				X	X	X	X	8.6
[redacted]	[redacted]																													8.8
Anti-Ro/SS-A, anti-La/SS-B autoanti-bodies[o]	X	X	X	X		X				X				X				X				X				X	X	X	X	5.1, 8.6
Immuno-genicity[o]	X	X		X		X				X				X				X				X				X	X	X	X	8.9
[redacted]																														
[redacted]	[redacted]																													8.8
Systemic disease activity																														
ESSDAI[t]	X	X																X								X	X	X		8.2.3
clinESSDAI		X																X								X	X	X		8.2.4
Patient-reported outcome questionnaires[v]																														
ESSPRI		X																X								X	X	X		8.2.6.1

Study week	SCR	Study week																								EDV[c] (≤ 7 d after final dose)	SFV[a] (56 d after final dose)	Applicable protocol section(s)
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	IMP d/c visit[b]		
±Days		BL	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	+2	±3	
Visits[d,e]	−28 to −2	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	NA	NA	NA	
[redacted]	[redacted]																													8.2.6.2
[redacted]	[redacted]																													8.2.6.3
[redacted]	[redacted]																													8.2.6.4
[redacted]	[redacted]																													8.2.6.6
[redacted]	[redacted]																													8.2.6.5
IMP administration[v]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					6
Concomitant therapies[w]		Continuous monitoring																												6.9
AEs[w]		Continuous monitoring																												8.4

BL=baseline; C3=Complement component 3; C4=Complement component 4; CH50=Total hemolytic complement; 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; [redacted]; NA=not applicable; OSS=ocular staining score; [redacted]; PCR=polymerase chain reaction; PD=pharmacodynamics; [redacted]; PK=pharmacokinetics; [redacted]; SCR=screening; SFV=safety follow-up visit; [redacted]; 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] For participants who discontinue IMP but remain in the study attending on-site visits, safety follow-up assessments will occur on the previously scheduled visit closest to 56 days (±3 days) from the final IMP dose.

[b] The IMP discontinuation visit will be performed at the next scheduled visit after permanent IMP discontinuation and applies for participants who discontinue IMP but remain in the study. Participants who permanently discontinue IMP will perform the IMP discontinuation visit and then be asked to proceed with their regularly scheduled visits (Section 7.1.1).

[c] The EDV applies for participants who discontinue the study.

[d] Visits 4, 6-8, 10-12, 14-16, 18-20, and 22-24 may be performed in the participant's home by a home nurse.
[e] Safety, efficacy, and predose sampling activities will be performed before administering IMP.
[f] Medical/surgical history includes all significant findings, surgeries, and preexisting conditions (including allergies, if any) present at screening including start and end date, if known.
[g] Demographic characteristics comprise age, birth year, sex, race, and ethnicity (per local regulations). Race and ethnicity data will be source verified only if permitted by local laws.
[h] Physical examination will include height and weight. Height will be measured at the baseline visit only.
[i] The brief physical examination is symptom driven and will be performed as necessary to assess the ESSDAI. It will also include weight.
[j] Vital signs (Section 8.3.2) will all be measured before collecting any blood sample or administering IMP infusions.
[k] [redacted]. Participants at sites performing parotid biopsy may be enrolled based on a historical biopsy obtained in the 12 months prior to baseline visit. Historical biopsy may only be used for participant enrollment when participant has not received immunomodulatory treatment for pSS (such as steroids, immunosuppressants, antimalarials, or biologics) from 6 months prior to biopsy through to screening.
[l] Participant should have a biopsy at EDV only when this visit occurs after week 16.
[m] Pregnancy testing will use a highly sensitive serum test at screening, and a urine test at all subsequent visits before IMP administration. Local regulations will be followed if they require more stringent or frequent testing.
[n] COVID-19 testing will occur within 72 hours of baseline. Participants will be tested for SARS-CoV-2 if they are symptomatic or if applicable law requires testing. COVID-19 testing may be performed at a central or local laboratory.
[o] On IMP administration visits, blood samples must be collected predose (preferably within 2 hours before the infusion). On other visits, the blood sample may be collected any time during the visit.
[p] Blood samples will be collected for [redacted]
[q] [redacted]
[r] On IMP administration visits, blood samples for PK analyses will be collected predose (preferably within 2 hours before IMP administration) and postdose (within 30 minutes after the end of infusion). On other visits, a single blood sample may be collected any time during the visit. Blood samples for participants remaining in the study following IMP discontinuation will be collected for PK analysis for up to 3 weeks post IMP discontinuation.
[s] [redacted]
[t] ESSDAI-related laboratory tests include gammaglobulins, cryoglobulins, C3, C4 and CH50. The biological domain will be blinded postbaseline and sites will score only the clinical domains of the ESSDAI.
[u] Patient-reported outcome questionnaires will be administered before any other study visit procedure where safe, and before discussions with staff about disease/treatment.
[v] The IMP will be administered as an approximately 1-hour IV infusion. Participants will be monitored for safety for ≥ 30 minutes after the end of IMP administration.
[w] AEs and use of concomitant therapies will be continuously monitored from the time the ICF is signed until the last study-related activity.

2. INTRODUCTION

The purpose of this study is to assess the efficacy and safety of human FcRn blocking therapy with efgartigimod compared to placebo, in participants with pSS.

2.1. Study Rationale

For many decades, the clinical needs for pSS have been left unresolved because of the rareness of the disease and the complexity of the underlying pathogenic mechanisms. It has become clear that B-cell activation and development of autoantibodies play an important role in pSS.

Efgartigimod is a first-in-class antibody fragment that binds to the 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 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.

2.2. Background

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.

This study aims to evaluate the effect of efgartigimod, an FcRn antagonist that can rapidly reduce IgG, including pathogenic antibodies. Efgartigimod has the potential to successfully treat pSS and improve disease manifestations by the reduction of IgG autoantibodies in pSS.

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 IV 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 infection risk.	Exclude participants with clinically significant uncontrolled infections (Section 5.2). Monitor for infections, considered an adverse event of special interest (AESI; Section 8.4.6), and temporarily interrupt IMP dosing as specified in Section 7.1.
Infusion-related reactions (IRR)	All therapeutic proteins have the potential to 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 IV infusion, the potential exists for IRR, which may occur during or within 48 hours after infusion. Pretreatment to prevent an IRR is not required. IMP will be administered by a healthcare professional.

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). Clinical benefit was also 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 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 1: Study ARGX-113-2106 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of efgartigimod IV compared to placebo on CRESS	• Proportion of CRESS responders on ≥ 3 of 5 items at week 24 (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)
Secondary	
• To evaluate the effect of efgartigimod IV compared to placebo on the histology of the parotid gland (selected sites only)	• Change in the relative counts of lymphocytic infiltrate (stained for CD45) at week 24 • Change in B/B+T cell ratio at week 24
• To evaluate the safety of efgartigimod IV compared to placebo in participants with pSS	• Incidence and severity of TEAEs, AESIs, and SAEs by SOC and PT • Changes in vital sign measurements, ECG results, and clinical laboratory safety evaluations
• To evaluate the effect of efgartigimod IV compared to placebo on clinical efficacy parameters	• Proportion of participants with minimal clinically important improvement in ESSDAI: improvement of ≥ 3 points in ESSDAI score at week 24 • Proportion of participants with low disease activity: ESSDAI score of < 5 at week 24 • Proportion of participants with minimal clinically important improvement in clinESSDAI: improvement of ≥ 3 points in clinESSDAI score at week 24 • Proportion of participants with low disease activity: clinESSDAI score of < 5 at week 24 • Proportion of participants with minimal clinically important improvement in ESSPRI: decrease of 1 point or ≥ 15% at week 24 • Change in ESSDAI score at week 24 • Change in clinESSDAI score at week 24 • Change in ESSPRI score at week 24
• To evaluate the effect of efgartigimod IV compared to placebo on STAR	• Proportion of participants with STAR score of ≥ 5 at week 24

Objectives	Endpoints
• To evaluate the PK of efgartigimod IV	• Efgartigimod serum concentration-time profile
• To evaluate the PD of efgartigimod IV	• Values, changes from baseline, and percent reduction from baseline in total IgG levels in serum • Values, changes from baseline, and percent reduction from baseline in autoantibodies in serum: – Anti-Ro/ SS-A – Anti-La/ SS-B
• To evaluate the immunogenicity of efgartigimod IV	• Incidence and prevalence of ADA against efgartigimod in serum
Exploratory	
• [redacted]	• [redacted]
• [redacted]	• [redacted]
• [redacted]	• [redacted]
• [redacted]	• [redacted]

Objectives	Endpoints
• [redacted]	• [redacted] • [redacted] • [redacted] • [redacted] • [redacted]
• [redacted]	• [redacted] • [redacted]
• [redacted]	• [redacted]

Note: Estimands are not defined for this phase 2 study.

ADA=antidrug antibody; AESI=adverse event of special interest; [redacted]; 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; [redacted] IgG=immunoglobulin G; [redacted]; IV=intravenous; [redacted]; OSS=ocular staining score; [redacted]; 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; SS-A=Sjögren's syndrome-related antigen A; SS-B=Sjögren's syndrome–related antigen B; STAR=Sjögren's Tool for Assessing Response; SWSF=stimulated whole salivary flow; TEAE=treatment-emergent adverse event; UWSF=unstimulated whole salivary flow; [redacted]

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blinded, placebo-controlled, phase 2, multicenter study.

For participants not enrolling in the OLE study, the study duration is approximately 36 weeks, spanning the following study periods:

- Screening: ≤ 4 weeks
- Treatment: 24 weeks
- Follow-up: 56 days

For participants enrolling in the OLE study, the study duration is approximately 28 weeks, spanning the following study periods:

- Screening: ≤ 4 weeks
- Treatment: 24 weeks

The study population includes adult participants with pSS, per ACR/EULAR 2016 classification criteria, with at least a moderate level of systemic disease activity (ESSDAI ≥ 5).

Participants will be randomized to receive efgartigimod IV 10 mg/kg or placebo in a 2:1 ratio, respectively.

All participants will receive efgartigimod IV 10 mg/kg or placebo once weekly for 24 weeks during the treatment period.

IMP will be administered as an approximately 1-hour IV infusion by site staff or a home nurse. The final dose will be administered at week 23.

At week 24, eligible participants may roll over to the single-arm OLE study.

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 has the potential to successfully treat pSS and improve disease manifestations by the reduction of IgG autoantibodies and immune complexes in pSS.

This study aims to investigate the efficacy and safety of efgartigimod compared to placebo in participants with pSS. The study design is randomized, double-blinded, and placebo-controlled to evaluate the effect of efgartigimod administered as an IV infusion compared to placebo. The study consists of a treatment period when all participants will receive weekly IV infusions for

24 weeks. The comparison to placebo is justified because there are no standardized approved therapies for pSS.

The primary endpoint is the effect of efgartigimod IV 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. CRESS has been selected as the primary efficacy endpoint because a composite is presumed to be more appropriate in demonstrating drug efficacy compared to an endpoint that reports on a single aspect of this heterogeneous disease.[2] In randomized controlled studies that previously showed negative primary endpoint results using ESSDAI, post hoc analysis of the study data using CRESS resulted in higher response rates in participants treated with efgartigimod, compared to those given placebo. Use of CRESS also resulted in decreased placebo response rates compared with the use of the ESSDAI minimal clinically important improvement, which is essential to demonstrating treatment efficacy.[2]

The secondary endpoints complement the primary endpoint and provide additional information on efficacy (ESSDAI, clinESSDAI, ESSPRI, STAR [Section 8.2]), histology, safety, 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

Weekly doses of efgartigimod IV 10 mg/kg will be administered to attain a maximal total IgG reduction (PD effect), thereby ensuring maximal clinical response on the efficacy outcomes.

Because the hypothesis for treating pSS with efgartigimod is to reduce the pathogenic autoreactive IgG, the selected dose and frequency target a nearly maximal PD effect (ie, reduction of pathogenic IgGs). Considering the chronic nature of pSS, the dosing regimen of weekly IV administration 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 participants; phase 2 studies in participants with gMG, ITP, and pemphigus; phase 3 studies in participants with gMG and ITP; and PK/PD modeling results showed that weekly infusions of efgartigimod IV 10 mg/kg demonstrated an approximately 70% reduction in IgG, including 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 weekly IV dose regimen 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 treatment period (or follow-up period, if applicable) has been completed.

- Participants rolling over to the OLE study will have completed this study at week 24

- Participants not rolling over to the OLE study will have completed this study after the SFV or EDV. If a participant continued in the study after discontinuing IMP, this will be week 24 or at the SFV (if permanent IMP discontinuation is < 56 days from week 24).

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 are eligible to 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 informed consent form
2. Is capable of providing signed informed consent, as described in Section 10.1.3, and complying with protocol requirements
3. Agrees to use contraceptive measures consistent with local regulations and the following:
   a. Male participants: refer to Section 10.4.2.2
   b. WOCBP (defined in Section 10.4.1) must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline before receiving IMP. Contraceptive requirements are provided in Section 10.4.
4. Meets the following criteria at screening:
   a. ACR/EULAR 2016 pSS who met criteria ≤ 7 years before screening
   b. ESSDAI ≥ 5
   c. Anti-Ro/SS-A positive
   d. Residual salivary flow (UWSF rate > 0 and/or SWSF rate > 0.10)

5.2. Exclusion Criteria

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

1. Known autoimmune disease or any medical condition that, in the investigator's judgment, would interfere with an accurate assessment of clinical symptoms of pSS or puts the participant at undue risk
2. History of malignancy unless considered cured by adequate treatment with no evidence of recurrence for ≥ 3 years before the first administration of IMP. Adequately treated participants with the following cancers may be included at any time:
   a. Basal cell or squamous cell skin cancer
   b. Carcinoma in situ of the cervix
   c. Carcinoma in situ of the breast
   d. Incidental histological finding of prostate cancer (TNM stage T1a or T1b)
3. Clinically significant uncontrolled active acute or chronic bacterial, viral, or fungal infection
4. Positive serum test at screening for an active infection with any of the following:
   a. HBV that is indicative of an acute or chronic infection, unless associated with a negative HBsAg or negative HBV DNA test
   b. HCV based on HCV antibody assay unless a negative RNA test is available

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

5. Clinically significant disease, recent major surgery (within 3 months of screening), 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
6. Current participation in another interventional clinical study
7. Known hypersensitivity to IMP or 1 of its excipients
8. History (within 12 months of screening) of current alcohol, drug, or medication abuse as assessed by the investigator
9. Pregnant or lactating state or intention to become pregnant during the study
10. Previously participation in an efgartigimod clinical study and treatment with ≥ 1 dose of IMP
11. Total IgG of < 4 g/L at screening
12. Secondary Sjögren's syndrome overlap syndromes where another confirmed autoimmune rheumatic or systemic inflammatory condition (eg, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, inflammatory bowel disease) is the primary diagnosis
13. Positive SARS-CoV-2 PCR test at screening
14. Any severe systemic pSS manifestation that may put the participant at undue risk based on the investigator's opinion

Note: Medications cited in exclusion criteria 15-22 are also prohibited during the screening period.

15. IVIg, SCIg, or PLEX ≤ 12 weeks before screening
16. Live or live-attenuated vaccine ≤ 4 weeks before screening
17. Pilocarpine and/or any other pharmacological stimulant for salivary and lacrimal glands that is not at a stable dose in the 4 weeks prior to screening or is started≤ 4 weeks from screening
18. Anticholinergic agents which are not at a stable dose [redacted] weeks prior to screening or during screening
19. Corticosteroids:
    a. Intramuscular or IV corticosteroids ≤ [redacted] weeks from screening
    b. Oral corticosteroids if above 10 mg, or if not at a stable dose ≤ [redacted] weeks from screening
    c. [redacted] ≤ [redacted] weeks from screening
    d. Use of [redacted] is prohibited

20. DMARDs:
    a. Cyclophosphamide ≤ 24 weeks from screening
    b. [redacted] ≤[redacted] weeks from screening.
    c. Antimalarials and conventional DMARDs: [redacted] are allowed only if started >[redacted] weeks before screening and at a stable dose ≥[redacted] weeks from screening. Combination therapies are not allowed.
    d. Biologic DMARDs: ≤[redacted] weeks from screening. Rituximab and other CD20 depleting monoclonal antibodies are not allowed ≤[redacted] weeks from screening.
21. IMP in another clinical study:
    a. Prohibited ≤ 12 weeks or 5 half-lives (whichever is longer), or for CD20 depleting monoclonal antibodies, ≤ 24 weeks or 5 half-lives (whichever is longer)
    b. Nonbiologic IMP: Prohibited ≤ 12 weeks or 5 half-lives (whichever is longer)
    c. Biologic IMP: Prohibited ≤ 24 weeks or 5 half-lives (whichever is longer) before screening
22. Chinese traditional medicine with known immunomodulatory action
23. Pharmacological topical ophthalmic agents (eg, non-steroidal anti-inflammatory drugs [NSAIDs], [redacted])

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

No restrictions apply.

5.3.2. Caffeine, Alcohol, and Tobacco

No restrictions apply except for those described in the exclusion criteria (Section 5.2, exclusion criterion 8).

5.3.3. Activity

No restrictions apply.

5.4. Screen Failures

A screen failure occurs when a participant consenting to participate in the clinical study is not assigned to IMP. A minimal set of screen failure information (demography, screen failure details, eligibility criteria, SAE reports) is required to ensure transparent reporting of screen failure participants and respond to regulatory authority queries.

- Retesting: Participants with exclusionary clinical laboratory results, ECGs, vital sign measurements, etc that are inconsistent with their medical history or clinical evaluation can be retested within the remaining screening period to confirm the test value(s).
- Rescreening: Participants who do not initially meet this study's eligibility criteria may be rescreened once. For example, if the participant does not meet eligibility

criteria because of an acute illness ongoing during screening (considering the illness itself does not violate inclusion/exclusion criteria), they may be rescreened once the illness is resolved or the medical issue stabilized. Rescreened participants will be reconsented and assigned a new participant number for each rescreening event.

5.5. Criteria for Temporarily Delaying Enrollment

Not applicable.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

All IMP is manufactured according to Good Manufacturing Practice regulations.

6.1. Study Intervention(s) Administered

Table 2: Study Intervention(s) Administered

Intervention label	**Efgartigimod IV**	**Placebo**
Intervention name	Efgartigimod IV concentrate for solution	Placebo solution for IV infusion
Intervention description	Sterile, colorless, clear concentrate solution for efgartigimod 20 mg/mL infusion	Sterile, colorless, clear concentrate solution for infusion, with the same excipients, but without the active ingredient (efgartigimod)
Type	Biologic	Placebo
Dose formulation	Infusion	Infusion
Unit dose strength(s)	20 mg/mL	Not applicable
Dosage level(s)	10 mg/kg once weekly for 24 weeks	Placebo once weekly for 24 weeks
Route of administration	IV infusion	IV infusion
Use	Experimental	Placebo comparator
IMP and NIMP/AxMP	IMP	IMP
Sourcing	Centrally by the sponsor	Centrally by the sponsor
Packaging and labeling	IMP will be provided in glass vials. Each vial will be labeled per country requirements.	IMP will be provided in glass vials. Each vial will be labeled per country requirements.
Former name	ARGX-113	Not applicable

AxMP=auxiliary medicinal product; IMP=investigational medicinal product; IV=intravenous; NIMP=noninvestigational medicinal product

Table 3: Study Arm(s)

Arm title	**IMP**	**Placebo**
Arm type	Experimental	Placebo
Arm description	Efgartigimod IV 10 mg/kg once weekly for 24 weeks	Placebo IV once weekly for 24 weeks
Associated intervention labels	Efgartigimod IV	Placebo

IMP=investigational medicinal product; IV=intravenous

6.2. Preparation, Handling, Storage, and Accountability

The IMP will be supplied to the investigational site by the sponsor's designated IMP supply vendor.

The pharmacy manual provides detailed instructions on the preparation, handling, storage, accountability, and disposition of unused IMP.

The investigator or designee is responsible for the correct and safe storage of 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 may receive IMP, and only authorized site staff or designee may 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. It should not be shaken or exposed to freezing temperatures.

Participants will be monitored for safety for ≥ 30 minutes after the end of IMP administration.

6.3. Assignment to Study Intervention

All participants will be randomized to IMP using IRT in a 2:1 ratio of efgartigimod or placebo, respectively.

Upon confirmation of eligibility at baseline, the participant will be randomized through IRT and stratified by IgG value at screening (> 16.0 g/L or ≤ 16 g/L).

6.4. Blinding

This is a double-blinded study. The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator is solely responsible for determining if unblinding of the IMP assignment is necessary. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator may contact the sponsor to discuss the situation before unblinding a participant's IMP unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded in the source documents.

6.5. Study Compliance

Participants will receive IMP under medical supervision at the site. The date and time of each dose administered will be recorded in the source documents. Documentation will include both start and end time of infusion.

At home visits (Section 1.3), IMP will be administered by a health care professional (nurse). The date and time of each dose administered will be recorded in the source documents.

Deviation(s) from the prescribed dosage regimen will be recorded.

Any participant who misses a scheduled dose (±2 days) will wait to receive the next scheduled dose (refer to Section 1.3).

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 baseline.

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

At the end of the study, argenx will comply with all local laws and regulations to ensure participants have continued access to IMP considered medically essential.

At week 24 (visit 25) eligible participants will have the option to enroll in the OLE study, where all participants will be treated with efgartigimod IV.

Participants will be ineligible for OLE study enrollment if either of the following criteria apply:

- Permanently discontinued from IMP (regardless of whether the participant completed the study)
- Discontinued from the study

Participants who complete the week 24 (visit 25) visit while temporarily interrupted from IMP (refer to Section 7.1.1) may enroll in the OLE study at the discretion of the investigator. These participants will enter the OLE study but will not be dosed with efgartigimod IV until they meet the relevant conditions specified by the protocol for the OLE study.

6.8. Treatment of Overdose

Any dose of efgartigimod > 10% of the intended weekly 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 should:

- Evaluate the participant to determine, in consultation with the medical monitor, if possible, whether IMP should 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, the quantity of the excess dose, and the duration of the overdose in the eCRF.

6.9. Prior and Concomitant Therapy

Participants should stay on a stable regimen of medications throughout the study. Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs,

vitamins, and/or herbal supplements [including Chinese traditional medicine]) or other specific categories of interest that the participant is receiving at the time of screening, or receives during the study must be recorded. Any treatment used for pSS in the 6 months prior to screening should also be recorded.

Recording should 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	Prior to study treatment period	Period participant is receiving IMP (Section 5.2)	Follow-up period
Live or live-attenuated vaccines	Prohibited ≤ 4 weeks before screening	Prohibited	Permitted from 28 days after the last IMP dose
SCIg	Prohibited ≤ 12 weeks before screening	Prohibited	Permitted
IVIg	Prohibited ≤ 12 weeks before screening	Prohibited	Permitted
Corticosteroid steroids:			
Intra-muscular or intravenous corticosteroids	Prohibited ≤ 4 weeks before screening	Prohibited	Permitted
Oral corticosteroids	Permitted at stable dose up to 10 mg at least 4 weeks before screening	Dose up to 10 mg	Permitted
Inhaled corticosteroids	Permitted	Permitted	Permitted
Intra-articular steroids	Prohibited ≤ 4 weeks before screening	Prohibited	Permitted
Topical steroids	Topical (non-ophthalmic) steroids are permitted Topical ophthalmic steroids are prohibited.	Topical (non-ophthalmic) steroids are permitted Topical ophthalmic steroids are prohibited.	Permitted
DMARDs			
Conventional DMARDS / antimalarials	[redacted]	[redacted]	Permitted

Medication	Prior to study treatment period	Period participant is receiving IMP (Section 5.2)	Follow-up period
Cyclophosphamide	Prohibited ≤ 24 weeks from screening	Prohibited	Permitted
Biologic DMARDS	Prohibited ≤ 12 weeks of screening Rituximab and other CD20 depleting mAbs: prohibited ≤ 24 weeks of screening	Prohibited	Permitted
Targeted synthetic DMARDs:			
[redacted]	Prohibited ≤ [redacted] weeks from screening	Prohibited	Permitted
IMPs:			
IMP in another clinical study	Prohibited ≤ 12 weeks or 5 half-lives (whichever is longer) CD20 depleting mAbs: prohibited ≤ 24 weeks or 5 half-lives (whichever is longer)	Prohibited	Permitted
Nonbiologic IMP in another clinical study	Prohibited ≤ 12 weeks or 5 half-lives (whichever is longer)	Prohibited	Permitted
Biologic IMP in another clinical study	Prohibited ≤ 24 weeks or 5 half-lives (whichever is longer) before screening	Prohibited	Permitted
Other:			
Chinese traditional medicine with known immunomodulatory action	Prohibited	Prohibited	Permitted
Anticholinergic agents	Permitted at stable dose 4 weeks prior to screening or during screening	Permitted at stable dose	Permitted

Medication	Prior to study treatment period	Period participant is receiving IMP (Section 5.2)	Follow-up period
Topical symptomatic medications for pSS	Permitted	Baseline, week 16, week 24, and EDV/IMP discontinuation visits, 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	Prohibited	Permitted
Pilocarpine and/or any other pharmacological stimulant for salivary and lacrimal glands	Permitted at stable dose in the [redacted] weeks prior to screening	Permitted at stable dose [redacted]	Permitted

[redacted]; DMARD=disease-modifying antirheumatic drug; EDV= early discontinuation visit; [redacted] IMP=investigational medicinal product; IVIg= intravenous immunoglobulin; [redacted]; [redacted] 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 IMP discontinuation visit and will be encouraged to remain in the study and attend any previously scheduled visits. Blood samples for participants remaining in the study following IMP discontinuation will be collected for PK analyses as per the SoA (Section 1.3) for up to 3 weeks post IMP discontinuation.

If the participant is unable or unwilling to attend study visits for any reason, the study site will perform an EDV and the SFV. The study sites will attempt to perform the EDV within the 7 (+2) 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 (refer to 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 receives a prohibited medication or substance (refer to Section 6.9).

Participants permanently discontinuing IMP will be ineligible for roll over to the OLE study.

7.1.2. Temporary Discontinuation

Temporary discontinuation occurs when the participant discontinues receiving IMP before the end of the study but may resume 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

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

The reason for permanent withdrawal from the study will be recorded.

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

- The participant withdraws consent
- At the request of the sponsor

If the participant also withdraws consent to disclose future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. Participants withdrawing from the study may request the destruction of collected, untested samples.

Participants withdrawn from the study will be ineligible to roll over into the OLE study.

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 should 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 screening evaluations must be completed and reviewed to confirm that participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants screened and confirm eligibility or record reasons for screening failure, as applicable.

Operational considerations because of the COVID-19 pandemic are provided in Section 10.5.

8.1. Administrative Procedures

All significant findings, surgeries, and preexisting conditions (including allergies, if any) present at screening will be reported. Complete information will be collected on medical and surgical history, and concomitant medical conditions, specifying those ongoing at screening.

8.1.1. Use and Storage of Biological Samples

Biological samples collected at the screening visit may be used to validate methods to measure efgartigimod, antibodies, and biomarkers. Participants must consent to their samples being used in this manner before such measurements are made.

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

As stated in Section 7.2, participants withdrawing from the study may request the destruction of collected, untested samples.

8.2. Efficacy Assessments

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

Patient-reported outcome questionnaires are recommended to be administered before any other study assessment and may be completed ≤ 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

The primary efficacy endpoint is the proportion of responders on ≥ 3 of 5 items at week 24 using 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 activity[2]:

- Systemic disease activity: as measured with clinESSDAI (Section 8.2.4)
  - Response is defined as a score of < 5 points.
- Patient-reported symptoms: as measured with ESSPRI (Section 8.2.6.1)
  - Response is defined as a decrease of ≥ 1 point or ≥ 15% from baseline.
- Tear gland function: as measured with Schirmer's test (Section 8.2.7.3) and OSS (Section 8.2.7.4)
  - 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 8.2.7.1) 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 score[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. Parotid Gland Histology

A secondary efficacy measure is the relative amount of lymphocytic infiltrate that can be assessed with CD45 immunohistochemical staining of the parotid gland. Increased lymphocytic infiltrate positive for CD45 has been observed in parotid gland biopsies of participants with pSS.[4] Additionally, the ratio of B/B+T cells will be assessed as a secondary outcome measure.

[redacted]:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
  - [redacted]

[redacted]

8.2.3. 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 post-baseline.

8.2.4. 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, 2016[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

8.2.5. STAR

STAR has been developed to assess the efficacy of treatments for pSS.[7] A secondary efficacy endpoint for this study will be the proportion of responders (STAR score of ≥ 5) at week 24.

This composite measure contains 5 domains:

- Systemic activity: 3 points
  - clinESSDAI decrease of ≥ 3 points (Section 8.2.4)
- Patient-reported outcome: 3 points
  - ESSPRI decrease of at least 1 point or ≥ 15% (Section 8.2.6.1)
  - 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 8.2.7.3)
    - If abnormal score at baseline: increase of ≥ 5 mm from baseline
    - If normal score at baseline: no change to abnormal
  - OSS (Section 8.2.7.4)
    - 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

8.2.6. Patient-Reported Outcomes

8.2.6.1. ESSPRI

ESSPRI is a questionnaire that has been developed to measure self-reported symptoms in participants with pSS.[8] The ESSPRI has 3 items that measure dryness, fatigue, and pain over a recall period of "the last 2 weeks." Each item includes a numeric rating scale ranging from 0 "No symptoms (dryness, fatigue or pain)" to 10 "Maximal imaginable (dryness, fatigue or pain)." The total global score ranges from 0 to 10 and the ESSPRI is calculated by averaging the numeric scores for pain, fatigue, and dryness, with higher scores indicating more symptoms. It has been shown to correlate well with PGA and has been validated in participants with pSS.[8]

8.2.6.2. [redacted]

[redacted]

8.2.6.3. [redacted]

[redacted]

8.2.6.4. [redacted]

[redacted]

8.2.6.5. [redacted]

[redacted]

8.2.6.6. [redacted]

[redacted]

- [redacted]
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- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

8.2.7. Additional Efficacy Measures

8.2.7.1. SGUS

The SGUS grading system of Hocevar et al[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.

8.2.7.2. 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.

8.2.7.3. 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 ≤ 5 mm indicates abnormal tear gland function.[14]

8.2.7.4. 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 ≥ 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 infusion unless otherwise stated.

At screening, clinically significant abnormalities in any safety assessment will be reported as medical history. New abnormal or worsened preexisting conditions observed after screening that the investigator considers clinically significant will be reported as an AE.

8.3.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the musculoskeletal, gastrointestinal, pulmonary, cardiovascular, respiratory, and neurological systems, and general appearance, skin, and lymph nodes. Additionally, physical examinations will be performed to assess ESSDAI, as appropriate. Height and weight will also be measured without shoes, attired in light clothing, and recorded using validated instruments.

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.

Blood pressure and pulse will be assessed with the participant rested and seated.

8.3.3. Electrocardiograms

Single 12-lead ECGs 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, serology (eg, viral marker testing), 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 by serum at screening. Urine tests for pregnancy will occur at the time points specified in the SoA (Section 1.3).

Pregnancy testing in WOCBP will be conducted at the end of relevant systemic exposure (ie, at the SFV).

Additional pregnancy testing may be performed as 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 will this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The investigator will submit any updated SAE data to the sponsor within 24 hours of being available.

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

8.4.2. Method of Detecting AEs and SAEs

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

8.4.3. Follow-up of AEs and SAEs

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

8.4.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of IMP under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of IMP under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

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

The sponsor or designee will be responsible for reporting SUSARs to the relevant regulatory authorities and IEC/IRB, 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. Adverse Events of Special Interest

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 timeframe specified in Section 8.4.1 and Section 10.3.4.

Efgartigimod treatment leads to reduced IgG levels. As low IgG levels are 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

Participants for whom an AESI has been reported may be temporarily interrupted from IMP treatment, as specified in Section 7.1.1.

8.5. Pharmacokinetics

On IMP administration visits, blood samples for PK analyses will be collected predose (preferably within 2 hours before IMP administration) and postdose (within 30 minutes after the end of infusion) as described in the SoA (Section 1.3). Date and time of sample collection will be recorded in the participant's eCRF. On other visits, a single blood sample may be collected any time during the visit as described in the SoA. Samples collected after the end of infusion should be collected in the opposite arm from the arm used for IMP infusion.

Blood samples for participants remaining in the study following IMP discontinuation will be collected as per the SoA for up to 3 weeks post IMP discontinuation. Efgartigimod serum concentrations will be determined using a validated method.

8.6. Pharmacodynamics

Baseline and postbaseline PD blood samples will be collected at time points specified in the SoA (Section 1.3). On IMP administration visits, PD blood samples will be collected predose, preferably within 2 hours before IMP administration. Date and time of sample collection will be recorded in the participant's eCRF. On other visits, blood samples may be collected any time during the visit as specified in the SoA (Section 1.3). Total IgG levels will be determined using a validated method.

IgG will be assessed at screening as part of the eligibility criteria (Section 5.1) and secondary efficacy measures. Total IgG concentrations will be quantified at a central laboratory, and postbaseline results will not be reported to investigative sites or other study personnel to maintain 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 inclusion criteria requirements (Section 5.1) and secondary efficacy measures. Postbaseline results will be blinded.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. [redacted]

[redacted]

- [redacted]

[redacted]

- [redacted]

[redacted]

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 antidrug antibodies (ADAs) against efgartigimod.

On IMP administration visits, the blood samples will be collected predose, preferably within 2 hours before IMP administration. Date and time of sample collection will be recorded in the participant's eCRF. On other visits, blood samples may be collected any time during the visit as specified in the SoA (Section 1.3). Samples will be analyzed by the designated laboratory in a tiered approach using validated immunogenicity assays.[16]

Immunogenicity blood samples that are collected at the screening visit will be used for methodology validation and/or for future research purposes (Section 8.1.1).

8.10. Health Economics or Medical Resource Utilization and Health Economics

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

9. STATISTICAL CONSIDERATIONS

A SAP will be finalized before database lock and include a more technical and detailed description of the statistical analyses to be completed. Any change to the data analysis methods described below will be described in the SAP. Any subsequent changes to the planned analysis methodology, and their justifications, will be described in the CSR. Additional exploratory analyses of the data will be conducted as appropriate and will be reported separately.

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

9.1. Statistical Hypothesis

The primary objective is to provide initial evidence of efficacy in this indication across a number of clinical endpoints. Accordingly, the focus of this study is on effect estimation with no formal statistical hypothesis.

9.2. Analysis Sets

The following analysis sets are defined:

Analysis set	Description
Full analysis set	All randomized participants who receive IMP. Participants will be assigned in the efficacy analyses according to the IMP they received.
Safety analysis set	All participants exposed to IMP. Participants will be assigned in the efficacy analyses according to the IMP they received.

The full analysis set will be used to analyze endpoints related to the efficacy objectives, and the safety analysis set will be used to analyze the endpoints and assessments related to safety.

9.3. Statistical Analyses

9.3.1. General Considerations

In general, data collected will be listed together with appropriate derived variables. Descriptive statistical methods will be used to analyze safety and efficacy data. Where appropriate, this may include summaries and graphical displays by time point.

Summaries will be provided by treatment assignment and overall. Summaries will include the number of observations (n), mean, SE, 95% CI, median, quartiles, minimum, and maximum for continuous measures and categorical measures sample size, frequencies, and percentages. P-values for comparing treatment groups may be provided, but these should be interpreted as supportive summary statistics.

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

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.

9.3.2. Primary Endpoint Analysis

The primary endpoint is response on ≥ 3 of 5 items of CRESS at week 24. The 5 items are systemic disease activity (clinESSDAI), patient-reported symptoms (ESSPRI), tear gland function (Schirmer's test, OSS), salivary gland function (UWSF, SGUS), and serology (serum IgG and RF).

A 95% Wilson Score CI for the proportion of CRESS responders will be presented for both treatment groups. This will be provided for all full analysis set participants and by IgG stratum at screening (> 16.0 g/L or ≤ 16 g/L) for the efgartigimod treatment group.

Additionally, the CRESS response will be analyzed between efgartigimod and placebo using the full analysis set by means of a Cochran-Mantel-Haenszel test, stratified by IgG value at screening (> 16.0 g/L or ≤ 16 g/L). The common odds ratio will be provided, along with the 95% CI.

In the event of missing values for the primary endpoint, only those participants who have a week 24 value will be included in the primary analysis. A sensitivity analysis, treating those participants with missing week 24 data as nonresponders, will be included.

9.3.3. Secondary Endpoint Analyses

The proportion of responders at week 24 in the clinESSDAI and ESSPRI components of the CRESS will be analyzed using the same approach as the overall CRESS response. The ESSDAI and STAR responder endpoints will be analyzed similarly.

Descriptive summaries by time point of the CRESS components, the ESSDAI and STAR scores, their changes, and percent changes from baseline will be provided, as appropriate. Estimates of the differences in response between treatment groups will be provided based on an analysis of covariance (ANCOVA), or suitable alternative, approach.

The histological parameters, relative counts of lymphocytic infiltrate (stained for CD45), and B/B+T cell ratio will be summarized descriptively as raw counts and their changes from baseline.

Full details of the secondary analyses will be included in the SAP.

9.3.4. Exploratory Endpoint Analyses

Summary statistics will be provided for the continuous exploratory endpoints, with frequency tables generated for all categorical endpoints. Full details of the analyses will be included in the SAP.

9.3.5. Safety Analyses

Exposure to IMP will be summarized by treatment group, using the safety analysis set.

AEs will be classified using the latest version of the MedDRA classification system. Any AEs with missing severity or relationship to IMP will be classified as severe and treatment related, respectively.

Incidence and maximal severity of TEAEs, AESIs, and SAEs will be summarized descriptively. Multiple occurrences of a single PT in a participant will be counted only once at the maximum grade. Summaries by IMP relatedness will also be provided. Any AEs leading to death or IMP discontinuation will also be summarized.

Laboratory parameters, vital signs, and ECG data will also be analyzed descriptively.

Full details of the safety summaries will be provided in the appropriate SAP.

9.3.6. Other Analyses

Additional analyses of the week 16 efficacy results may be provided.

PK, PD, immunogenicity, and biomarker results will be analyzed descriptively.

Population PK/PD analysis may be performed based on the PK and PD data and reported separately.

9.4. Interim Analysis

An unblinded interim analysis may be conducted midcourse at the sponsor/designee's discretion. Results will be made available to senior sponsor/designee staff only while maintaining the blind for the sites and sponsor clinical team members.

9.5. Sample Size Determination

Participants will be randomized in a 2:1 ratio (efgartigimod:placebo) to achieve approximately 15 randomized participants with an IgG value at screening > 16.0 g/L and 15 participants without an IgG value at screening > 16.0 g/L.

Assuming 50% of the 20 randomized efgartigimod participants are CRESS responders, the 95% 1-sided confidence limit lower bound for the proportion of responders is approximately 33% (Wilson score interval). Placebo response rates ranging from 24% to 32% have been reported.[2] Therefore the target sample size should provide sufficient precision of the efgartigimod treatment effect at week 24 for planning future studies.

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 ICF.

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, 21 CFR 50, 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 affect participant participation.

A copy of the ICF(s) must be provided to the participant (or their legally authorized representative).

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 may review source data containing identifiers and will use their personal study-related data per local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the ICF.

The contract between sponsor and study sites specifies responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.6. Committees Structure

Not applicable.

10.1.7. Dissemination of Clinical Study Data

The sponsor will register and disclose the 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 the 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 on 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 may be subject to quality assurance audits during the study by the sponsor or sponsor's designee on behalf of the sponsor. In addition, inspections may 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 may be transferred to another location or party without written notification to the sponsor.

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

The definition of what constitutes source data and its origin can be found in the monitoring plan.

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

The sponsor or designee will perform monitoring to confirm that data entered on the eCRF by authorized site 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 clinical study will be open for recruitment of participants.

The first act of recruitment is the first site activated and will be the study start date.

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

Reasons for the early closure of a study site by the sponsor or investigator may 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 CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11. Publication Policy

The results of this study may 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.

Protocol-specific requirements for the inclusion and exclusion of participants are detailed in Section 5.1 and Section 5.2, respectively.

Additional tests may 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 Safety Laboratory Tests

Laboratory test	Parameters		
Hematology	RBC count platelet count hemoglobin hematocrit	RBC indices: MCV MCH	WBC count with differential: neutrophils eosinophils lymphocytes basophils monocytes
Serum chemistry	ALT AST albumin[a] BUN bilirubin (total and direct) creatinine	GFR glucose potassium sodium calcium chloride bicarbonate	total protein[a] creatine kinase HbA1C HDL LDL triglycerides C-reactive protein
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase • Microscopic examination (if blood or protein is abnormal) • Urine protein quantitative analysis (if protein is abnormal)		
Pregnancy testing	Highly sensitive serum hCG pregnancy serum test at screening and urine test at other time points (as needed for WOCBP potential, defined in Section 10.4.1)		
Other tests	• SARS-CoV-2 nasopharyngeal swab test (PCR) (if applicable) • HBV, HCV, HIV (refer to exclusion criterion 4 and Sections 10.2.1.2, 10.2.1.3, and 10.2.1.4, respectively) • Menopausal test (FSH) if applicable (to confirm non-WOCBP status) • IgG[a] (to verify exclusion criterion 11)		

[a] This result will be blinded postbaseline.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; GFR=glomerular filtration rate; HbA1C=glycated hemoglobin; HBV=hepatitis B virus; hCG=human chorionic gonadotropin; HCV=hepatitis C virus; HDL=high-density lipoprotein; IgG=immunoglobulin G; LDL=low-density lipoprotein; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PCR=polymerase chain reaction; RBC=red blood cell; WBC=white blood cell; WOCBP=women of childbearing potential

10.2.1. Other Screening Tests

10.2.1.1. SARS-CoV-2

Participants will be tested for SARS-CoV-2 if they are symptomatic or if applicable law requires testing; if applicable, a negative PCR test (central or local laboratory) is required within 72 hours before enrollment and should occur regardless of a participant's vaccination status.

10.2.1.2. Hepatitis B Virus

Active acute or chronic HBV is exclusionary. Participants with an active acute or chronic HBV at screening will be excluded from the study.

The serologic marker combinations shown in Table 7 will be used to identify an active HBV infection.[17]

Table 7: Interpretation of Hepatitis B Serological Test Results

Test result			
HBsAg	Anti-HBc	Anti-HBs	**Interpretation**
Positive	Positive	Negative	An active HBV infection is exclusionary
Negative	Positive	Negative	A low-level chronic HBV infection with impaired liver function is exclusionary[a]

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

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

10.2.1.3. Hepatitis C Virus

An active acute or chronic HCV infection is exclusionary. The HCV antibody serologic test will identify an active infection as indicated in Table 8.

Table 8: Interpretation of the Hepatitis C Antibody Test

HCV Ab test result	Interpretation
Positive	An active acute or chronic HCV infection is exclusionary unless an RNA test indicates HCV negative

Ab=antibody; HCV=hepatitis C virus

10.2.1.4. Human Immunodeficiency Virus

HIV-positive is permissible if all of the following conditions are met:

- CD4 ≥ 200 cells/mm^3 (Table 9, Section 5.2 exclusion criterion 4.d)
- Viral load is < 200 copies/mm^3 or undetectable (Table 9, Section 5.2 exclusion criterion 4.c)
- Participant is receiving stable antiretroviral therapy for at least 3 months (minimally) before screening

- AIDS-defining condition is absent

AIDS-defining conditions include the following:

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

Table 9: Interpretation of HIV Test Results

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

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

10.3.1. Definition of AE

AE Definition

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

Events to Be Collected as AEs

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

Events NOT to Be Collected as AEs

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen

10.3.2. Definition of SAE

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

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 should be considered serious.
- Hospitalization for elective treatment of a preexisting condition that did not worsen from screening will not be collected as an AE.

Results in persistent or significant disability/incapacity

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

Is a congenital anomaly/birth defect

Other situations:

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

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

AE and SAE Recording

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

Assessment of Severity

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

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

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

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

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

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

Assessment of Causality

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

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

Follow-up of AEs and SAEs

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

10.3.4. Reporting of SAEs and AESIs

SAE and AESI Reporting

- All SAEs and AESIs will be recorded on the AE form of the eCRF. SAEs will also be recorded on the paper SAE report form.
- The investigator or designated site staff will ensure all entered data are consistent.

- An 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 should be faxed or emailed to the sponsor's designee (refer to the Serious Adverse Event Reporting details on page 2 of this protocol).

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Women of Childbearing Potential Definition

A 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 WOCBP

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[18] acceptable methods are permitted for efgartigimod studies:

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

10.4.2.2. Male Contraception

All nonsterilized male participants must use this method from signing of the ICF until the date of the last dose of IMP.

An acceptable method of contraception is a condom with either cap, diaphragm, or sponge with spermicide (efgartigimod studies only).

Males cannot donate sperm while receiving IMP.

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; if applicable, a negative PCR test (central or local laboratory) is required within 72 hours before enrollment and should occur regardless of a participant's vaccination status.

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

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

Additional testing for COVID-19 beyond what is listed in the SoA (Section 1.3) 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 should be performed as indicated in the SoA (Section 1.3). If assessments cannot be performed because of 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
- Protocol-required laboratory assessments

10.6. Appendix 6: Home Study Visits

A home nurse may travel to the participant's home to conduct study visits and perform activities in the SoA (Section 1.3), or the participant may attend an alternative location, as determined by the site investigator. For each home visit, the investigator or designee will confer with the participant via an audio or video interview to elicit answers regarding 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 performed 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 10: ESSDAI: Domain and Item Definitions and Weights

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
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	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]

Table 10: ESSDAI: Domain and Item Definitions and Weights (Continued)

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
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	[redacted]	[redacted]

Table 10: ESSDAI: Domain and Item Definitions and Weights (Continued)

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	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]

Table 10: ESSDAI: Domain and Item Definitions and Weights (Continued)

[redacted]	[redacted]	[redacted]
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	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]

Source: Seror et a, 2011l[8]

[redacted]

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 11.

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 11: 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[19] (or van Bijsterfeld score of ≥ 4[20]) 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[21,b]	1

Source: Shiboski et al[22]
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.[23]

[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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