16.1.9. Documentation of Statistical Methods

Document	Date
Statistical analysis plan – v3.0	12 Feb 2024

STATISTICAL ANALYSIS PLAN

Protocol No. ARGX-113-2106

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 (pSS)

AUTHORS: [redacted]

VERSION NUMBER AND DATE: V3.0, 12FEB2024

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Template No.: CS_TP_BS016 Revision 7 Reference: CS_WI_BS005
Effective Date: 01Nov2021

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V3.0 (Dated 12FEB2024) for Protocol ARGX-113-2106.

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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Position:	Director, Biostatistics		

Document: [redacted]
Author: [redacted]
Version Number: V2.0
Version Date: 31JAN2024
Template No.: CS_TP_BS016 Revision 7
Reference: CS_WI_BS005
Effective Date: 01Nov2021

Company:	IQVIA

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	10JAN2024	[redacted]	Not Applicable – First Version
2.0	31JAN2024	[redacted]	The Changes to Planned Analysis section updated : 1. The secondary endpoint is changed to Exploratory endpoint. 2. [redacted] Also, SAS code for MI was added for Supplemetary Estimand.
3.0	12FEB2024	[redacted]	1. Changed condition for one of the CRESS component as it was typo which is mentioned below: From : RF : ≥ 25% increase in rheumatoid factor (RF) from baseline To: RF : ≥ 25% decrease in rheumatoid factor

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			(RF) from baseline. 2. Added visit window for RF, IGG and Clinical laboratory tests for programming purpose.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Expansion
ACR	American College of Rheumatology
ADA	antidrug antibody(ies)
AE	adverse event
AESI	adverse event of special interest
[redacted]	[redacted]
BLQ	below limit of quantitation
C3	complement component 3
C4	complement component 4
CI	confidence interval
clinESSDAI	clinical EULAR Sjögren's syndrome disease activity index
CRESS	Composite of Relevant Endpoints for Sjögren's Syndrome
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
ECG	electrocardiogram
eCOA	Electronic Clinical Outcome Assessment
eCRF	electronic case report form
EDV	early discontinuation visit
efgartigimod IV	efgartigimod formulation for intravenous administration
eGFR	estimated glomerular filtration rate
EOT	End of Treatment
[redacted]	[redacted]
ESSDAI	EULAR Sjögren's syndrome disease activity index
ESSPRI	EULAR Sjögren's Syndrome Patient Reported Index
EULAR	European Alliance of Associations for Rheumatology
FAS	Full Analysis set
FcRn	neonatal crystallizable fragment receptor

Abbreviation	Expansion
GM	geometric mean
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IA	interim analysis
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
[redacted]	[redacted]
[redacted]	[redacted]
IgG	immunoglobulin G
[redacted]	[redacted]
IMP	investigational medicinal product
IRR	Infusion-related reaction
IRT	interactive response technology
IV	intravenous
LLN	Lower Limit Normal
MCS	Mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
MMRM	Mixed Model Repeated Measure
NCI	National Cancer Institute
OLE	open-label extension
OSS	ocular staining score
[redacted]	[redacted]
PCR	polymerase chain reaction
PCS	Physical component summary
PD	pharmacodynamic(s)

Abbreviation	Expansion
PDMP	Protocol Deviations Management Plan
[redacted]	[redacted]
PK	pharmacokinetic(s)
PKAS	pharmacokinetic analysis set
pSS	primary Sjögren's syndrome
PT	preferred term
[redacted]	[redacted]
RNA	Ribonucleic acid
SAE	serious adverse event
SAF	Safety analysis set
SAP	statistical analysis plan
SD	standard deviation
[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
SWSF	stimulated whole salivary flow
TEAE	treatment-emergent adverse event
ULN	Upper Limit Normal
UWSF	unstimulated whole salivary flow
[redacted]	[redacted]
WHO DRUG	World Health Organization Drug Dictionary
WOCBP	women of childbearing potential

1. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and conventions to be used in the presentation and analysis of efficacy, safety, pharmacodynamics (PD), pharmacokinetics (PK), and immunogenicity data for Protocol ARGX-113-2106. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

The statistical analysis will process and present the results following the ICH standards, in particular the ICH-E3, ICH-E6, and ICH-E9 guidelines[1,2,3]. This SAP is based on protocol version 2.0, dated 05 Dec 2022.

2. STUDY OBJECTIVES AND ENDPOINTS

Table A : Objectives

Objectives	Endpoints
Primary	
To evaluate the effect of efgartigimod IV compared to placebo on CRESS	• Proportion of Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS) responders on ≥ 3 of 5 items at week 24 (refer to Section 8.2.1 of protocol). The 5 items are: – Systemic disease activity: clinical EULAR Sjögren's syndrome disease activity index (clinESSDAI) – Patient-reported symptoms: EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) – Tear gland function: Schirmer's test and ocular staining score (OSS) – Salivary gland function: unstimulated whole salivary flow (UWSF) rate and salivary gland ultrasonography (SGUS) – Serology [serum - immunoglobulin G (IgG) and/or rheumatoid factor (RF)]
Secondary	
To evaluate the effect of efgartigimod IV compared to placebo on the histology of the	• Change in the relative counts of lymphocytic infiltrate (stained for CD45) at week 24 • Change in B/B+T cell ratio at week 24

Objectives	Endpoints
parotid gland (selected sites only)	
To evaluate the safety of efgartigimod IV compared to placebo in participants with pSS	• Incidence and severity of Treatment-emergent adverse event (TEAEs), adverse events of special interest (AESIs), and serious adverse events (SAEs) by System Organ Class (SOC) and Preferred Term (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 EULAR Sjögren's syndrome disease activity index (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 Sjögren's Tool for Assessing Response (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

Objectives	Endpoints
	autoantibodies in serum: – Anti-Ro/SS-A – Anti-La/SS-B
To evaluate the immunogenicity of efgartigimod IV	• Incidence and prevalence of antidrug antibody(ies) (ADA) against efgartigimod in serum
Exploratory	
[redacted]s	• [redacted] • [redacted]
[redacted]	• [redacted] • [redacted] • [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]

Table B : Estimands

Objectives		
	Main	Supplementary

The primary estimand for the study is the proportion of CRESS responders on ≥ 3 of 5 items at week 24 in efgartigimod IV compared to placebo, considering the participant who discontinued study treatment or used any prohibited medications.	Treatment conditions Efgartigimod or placebo, taking into account study treatment discontinuation and/or prohibited concomitant medication.	Treatment conditions Efgartigimod or placebo in the scenario where study treatment discontinuation and/or prohibited concomitant medication would not have occurred.
	Population Adult participants with pSS, per ACR/EULAR 2016 classification criteria, with at least a moderate level of systemic disease activity (ESSDAI ≥ 5) as defined by Inclusion and Exclusion criteria.	Population Adult participants with pSS, per ACR/EULAR 2016 classification criteria, with at least a moderate level of systemic disease activity (ESSDAI ≥ 5) as defined by Inclusion and Exclusion criteria.
	Variable (endpoint)Proportion of CRESS responders on ≥ 3 of 5 items at week 24.	Variable (endpoint) Proportion of CRESS responders on ≥ 3 of 5 items at week 24.

	Intercurrent events (Composite Variable Strategy) • Early withdrawal of study treatment • Use of any prohibited concomitant medications	Intercurrent events (Hypothetical Strategy strategy). • Early withdrawal of study treatment • Use of any prohibited concomitant medications
	Summary measure The proportion of responders and its 95% Wilson score CI will be calculated using binomial distribution for treatment and placebo. Also, CMH will be used The participants with ICEs will be considered as Non-Responders.	Summary measure The proportion of responders and its 95% Wilson score CI will be calculated using binomial distribution for treatment and placebo. Also, CMH will be used. If the planned hypothetical approach is not feasible due to data sparsity, then data will be analyzed as observed.

Abbreviations: ICE= Intercurrent Event , CI= Confidence Intervals.

Where the strategies are described as follows in the sequence, these strategies will be applied:

For the Main estimand:

Composite Variable strategy: Assessment on or after ICEs will be treated as Non responder. The rationale behind composite strategy is, discontinue of study treatment or use of prohibited concomitant medications will affect the CRESS response.

For the supplementary estimand:

Hypothetical strategy: Any early discontinuation or taking prohibited concomitant medication is observed- then the assessment will be set to missing and the missing binary outcomes will be imputed, assuming that they are missing at random. The aim of hypothetical strategy is to address the effect in an alternative hypothetical setting where subject neither discontinued or no prohibited concomitant medication available.

If the planned hypothetical approach is not feasible due to data sparsity, then available data occurring on or after ICEs will be analyzed as observed (Treatment policy). The reasoning of treatment policy is to estimate the CRESS response based on the available data and data will be analyzed as it is (regardless of the intercurrent event occurring).

For both main and supplementary estimand, additional sensitivity analysis will be performed using CMH considering IgG as stratification factor.

3. STUDY DESIGN

3.1. General Description

This study aims to evaluate the efficacy and safety of infusions of efgartigimod, a human neonatal crystallizable fragment receptor (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.

This is a randomized, double-blinded, placebo-controlled, phase 2, multicenter study, with an open-label extension (OLE) 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 (after final dose)

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 using interactive response technology (IRT) to receive efgartigimod IV 10 mg/kg or placebo in a 2:1 ratio, respectively.

Treatment and Dosing:

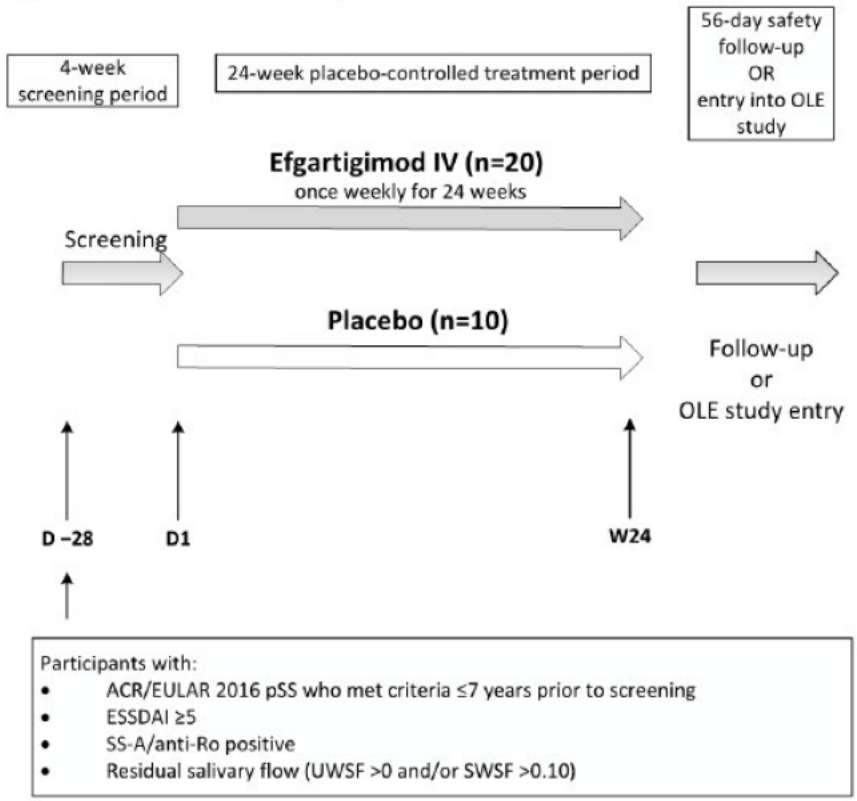
Upon confirmation of eligibility at baseline, the participant will be randomized, stratified by IgG value at screening (> 16.0 g/L or ≤ 16 g/L).

All participants will receive efgartigimod IV 10 mg/kg or placebo once weekly for 24 weeks during the treatment period. Treatment 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 a single-arm OLE study.

This is a double-blinded study. The IRT will be programmed with blind-breaking instructions.

Figure 1: 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

3.2. Sample Size

Participants are 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[4].

Therefore the target sample size should provide sufficient precision of the efgartigimod treatment effect at week 24 for planning future studies.

3.3. Schedule of Activities

Schedule of activities can be found in Section 1.3 of the protocol.

3.4. Changes to Analysis from Protocol

1. For this SAP, Estimand are defined for the study in Table B. The primary estimand for the study is to assess the proportion of CRESS responders on ≥ 3 of 5 items at week 24 in efgartigimod IV compared to placebo, considering the participant who discontinued study treatment or used prohibited concomitant medication.
2. The histology of the parotid gland (Immunohistochemistry- The relative counts of lymphocytic infiltrate (stained for CD45), B/B+T cell ratio) will be considered as – Exploratory endpoint and not as secondary endpoint.
3. [redacted]
4. Data for the following biomarker endpoints will be received and processed by the sponsor:
    a. Autoantibodies in serum including Anti-Ro/SS-A and Anti-La/SS-B
    b. [redacted]
    c. [redacted]
    d. [redacted]

[redacted]

e. The histology of the parotid gland (Immunohistochemistry- The relative counts of lymphocytic infiltrate (stained for CD45), B/B+T cell ratio).

f. [redacted]

g. [redacted]

h. [redacted]

4. PLANNED ANALYSES

The following analyses will be performed for this study:

1. Interim Analysis at the end of treatment phase
2. Final Analysis

4.1. Data Monitoring Committee

There will be no Data monitoring Committee for this study.

4.2. Interim Analysis

One interim analysis (IA) will take place for this study once all the participants have either completed the week 24 assessments or discontinued the study prior to week 24. The results of the interim analysis will be based on unblinded treatment groups.

Derivations and definitions for the interim analysis will be based on those required for the final analysis contained in this SAP, unless deviations are stated within the text. The list of outputs provided with the full set of output templates (planned for the final analysis) will highlight which of these outputs will also be provided for the interim

analysis.

The interim analysis will be performed by IQVIA Biostatistics following authorization of this SAP, database lock, analysis sets and unblinding of treatment. The IQVIA study team, including those responsible for creating the programs to produce the outputs for the interim analysis, will remain unblinded. The Unblinding Plan will have all the details about Unblinded Team members.

4.3. Final Analysis

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following authorization of this SAP, database lock, analysis sets and unblinding of treatment.

Pharmacokinetic analysis is being performed by the IQVIA PK group in conjunction with the IQVIA Biostatistics group. PK concentration listings and summary statistics are described in this SAP. A separate PK analysis plan will be prepared to describe planned population PK/PD analysis.

5. ANALYSIS SETS

Agreement and authorization of participants included/excluded from each analysis set for IA and Final Analysis, will be conducted prior to the unblinding of the study.

5.1. Enrolled Analysis Set [ENR]

The enrolled analysis set (ENR) will contain all participants who provided informed consent.

5.2. Full Analysis Set [FAS]

The full analysis set (FAS) will contain all randomized participants who received at least one dose of IMP and classified as Planned Treatment.

5.3. Safety Analysis Set [SAF]

The safety analysis set (SAF) will have - All participants exposed to IMP. Participants will be assigned in the

efficacy analyses according to the IMP they received. Data from these participants will be classified according to actual treatment received. The actual treatment arm will be the same as the planned treatment arm unless the participant received IMP other than the planned one for the whole study.

5.4. Efficacy Analysis Set [EAS]

The efficacy set contains all subjects from the FAS that are, based on pre-randomization information, eligible for efficacy evaluation.

5.5. PK Analysis Set [PKAS]- efgartigimod

The PK analysis set (PKAS) used for the descriptive summaries of efgartigimod serum concentrations will consist of all randomized participants who receive at least one dose of efgartigimod and have at least 1 measured concentration of efgartigimod at a scheduled PK time point after start of dosing without protocol violations or events with potential to affect the PK concentration. Participants in this population will be used for all PK summaries.

When using the FAS, participants will be classified according to their planned treatment arm. For analyses performed on the SAF or PKAS, the actual treatment arm will be considered. The actual treatment arm will be the same as the planned treatment arm unless the participant received IMP other than the planned one for the whole study.

6. GENERAL CONSIDERATIONS

6.1. Reference Start Date and Study Day

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events. It will appear in every listing where an assessment date or event date appears.

Reference start date is defined as the day of the first dose of IMP.

- If the date of the event is on or after the reference date, then:
    - Study Day = (date of event – reference date) + 1

- If the date of the event is prior to the reference date, then:
    - Study Day = (date of event – reference date)

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day

Date implies a complete date having day, month and year available. Unless otherwise specified, the study day will remain missing when it cannot be calculated due to absence or incompleteness of the concerned and/or

reference dates.

In case the participant never received IMP, the date/time of randomization will be used instead of first IMP administration date/time.

End of study (EOS) is defined as date of participant's last visit. This is date of treatment period completion and/or safety follow-up or early discontinuation 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 treatment period in this study at week 24.
- Participants not rolling over to the OLE study will have completed this study after the Safety Follow-up visit (SFV) or Early Discontinuation visit (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).

End of treatment (EOT) is defined as date of treatment completion or date of permanent discontinuation of IMP.

6.2. Baseline

Unless otherwise specified, baseline is defined as the last available non-missing measurement taken prior to reference start date/time.

Assessments performed on the same day as the first IMP administration but without time information collected or with time information exactly equal to the time of first IMP administration and which are planned predose will be considered as predose. For parameters related to questionnaires, the baseline is the last value before or at the day of first administration of the IMP, independent of the time of administration. In case the participant never received IMP, the date/time of randomization will be used instead of first IMP administration date/time.

Adverse Events (AEs) and medications commencing on the reference start date will be considered post-baseline

unless otherwise indicated based on available start date/time combination or collected electronic case report form (eCRF) information that identifies the individual event/medication as starting prior to first IMP administration.

6.3. Windowing Conventions

All assessments, including unscheduled assessments, will be allocated to an analysis visit window. Tables and listings will be based on analysis windows defined below. Allocations of assessments will be performed using their relative day.

Table C: Non-efficacy Analysis Visit Definition

Phase	Target Day	Assigned Study Day (Inclusive)		Week Assigned
		From	To	
		-28	-2	Screening
Treatment	1		1[a]	Baseline
	8	1[a]	11	Week 1
	15	12	18	Week 2
	22	19	25	Week 3
	29	26	32	Week 4
	36	33	39	Week 5
	43	40	46	Week 6
	50	47	53	Week 7
	57	54	60	Week 8
Treatment	57 + (x*7)	57 + (x*7) - 3	57 + (x*7) + 3	Week 8+x [b]

Safety Follow-up	Final dose + 56 days	(Final dose + 56 days) - 3 days	(Final dose + 56 days) + 3 days	Week xx+ 56 days

[a] An assessment on day 1 before the first administration of IMP will be allocated to baseline.

[b] considers value of x, starting from 1 to up until 16 to get visit windows for Week 9 to Week 24. The above Table C contains visit window for assessments at every week. Kindly refer respective visit window table for other assessments.

Some parameters which are not collected at every visits, visit window will be combined (by extending window with previous or subsequent visits).

For e.g. Week 3 is not protocol scheduled visit for RF, IGG and Brief Physical Examination. Hence, visit window can be combined with Week 2 and Week 4. The non-missing value closest to the target day will be used in the analysis in case of multiple observations.

Table C: Non-efficacy Analysis Visit Definition (continued:)

Phase	Target Day	Assigned Study Day (Inclusive)		Week Assigned
		From	To	
		-28	-2	Screening
Treatment	1		1	Baseline
	8	1[a]	11	Week 1
	15	12	22	Week 2
	29	23	43	Week 4
	57	44	71	Week 8
	85	72	99	Week 12
	113	100	127	Week 16

	141	128	156	Week 20
	169	157	184	Week 24
	EDV	Final Dose - 9 days	Final Dose + 9 days	Final Dose +/- 9 days

Note: After treatment period ends, safety follow-up will be of approximately 7 weeks (56 days ± 3 days) for participants who do not roll over to the Open Label Extension (OLE) study ARGX-113-2211.

For Clinical laboratory assessments (Including Pregnancy and Urinalysis) , we do not have week 2 visit, as in that case the following window.

Table C: Non-efficacy Analysis Visit Definition (continued:)

	Target Day	Assigned Study Day (Inclusive)		Week Assigned
		From	To	
		-28	-2	Screening
	1		1	Baseline
	8	1[a]	11	Week 1
	29	12	43	Week 4
	57	44	71	Week 8
	85	72	99	Week 12
	113	100	127	Week 16
	141	128	156	Week 20
	169	157	184	Week 24

	EDV	Final Dose - 9 days	Final Dose + 9 days	Final Dose +/- 9 days

Table D: Efficacy Analysis Visit Definition

For efficacy assessments, wider window will be considered as follows

Target Day	Assigned Study Day (Inclusive)		Week Assigned
	From	To	
1		1[a]	Baseline
113	85	141	Week 16
169	142	176	Week 24
EDV	Final Dose - 9 days	Final Dose + 9 days	Final Dose +/- 9 days

*Subject who permanently discontinue the treatment , assessment will be collected at IMP discontinued visit which will be performed at next scheduled visit after discontinuation. EDV: EDV visits will be performed within 7 days post final dose for those subjects who discontinue study permanently.

[a] An assessment on day 1 before the first administration of IMP will be allocated to baseline.

Questionnaires given on the day of the first administration of IMP (pre-administration or post-administration) are allocated to baseline.

Per parameter and analysis window, the non-missing value closest to the target day will be used in the analysis. If more than one non-missing value is located at the same distance from the target day, then the one latest in time will be selected for analysis. The value latest in time will be identified using, in order of preference, the assessment time, and the visit label.

6.4. Worst-case

A worst-case analysis visit will be created for parameters for which abnormalities and/or toxicity grades (e.g., labs,

vital signs, ECGs) are defined to summarize values considered as the worst-case. For abnormalities worst-case is derived per parameter and in case both the lowest and the highest values are considered abnormal, a participant can have two worst-case analysis visits for a same parameter. For toxicity grades the worst-case is the value associated with the highest toxicity grade and is derived per parameter and toxicity direction (hypo / hyper).

All non-missing post-baseline values, including unscheduled assessments will be considered when deriving the worst-case analysis visit.

6.5. Treatment-emergent Abnormality/Toxicity

A treatment-emergent abnormality/toxicity (for laboratory assessments, vital signs, or ECGs) is defined as any postbaseline abnormality/toxicity that was not present at baseline (e.g. hemoglobin normal at baseline and grade 1 postbaseline; glucose low at baseline and high postbaseline; QTcF [450; 480] ms at baseline and >500 ms postbaseline).

6.6. Statistical Tests

The default significance level will be 5%; CIs will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses. P-values for comparing treatment groups should be interpreted as supportive summary statistics.

6.7. Values below or Above the Quantification Limit

ADA against efgartigimod: titer of positive ADA samples reported as “negative titer” (refer to Section 16) will be imputed by 1. Listings will always present “negative titer”.

Safety and PD values expressed as below (or above) the quantification limit will be imputed by the value of the quantification limit itself. For participants with a baseline PD value below/above the quantification limit, the PD parameter will be excluded from the statistical analyses involving change and percent change from baseline. Listings will always show the non-imputed values.

Pharmacokinetic concentrations below the lower quantification limit will be reported in the listings as BLQ. For descriptive statistical analysis, all BLQ values will be set to zero. Listings will always present BLQ.

6.8. Common Calculations

For quantitative measurements, change from baseline will be calculated as:

- Change from baseline at Visit X = Value at Visit X – baseline value

A percent change from baseline can be calculated as;

- Percent change from baseline at Visit X = (actual value at Visit X -baseline value) *100/baseline value

6.9. Software Version

All analyses will be conducted using SAS version 9.4 or higher.

7. STATISTICAL CONSIDERATIONS

7.1. Missing Data

For imputation of missing values related to efficacy and safety, see appropriate section of the applicable endpoints.

Missing efgartigimod concentrations will not be imputed.

7.2. Output Presentation

For continuous variables, full descriptive statistics will only be presented if there are at least 2 non-missing observations. Alternatively, only the number of non-missing data points and mean are shown.

Descriptive statistics for safety and efficacy will include the number of non-missing data points, the arithmetic mean, the standard deviation (SD), the median, minimum, Q1, Q3, maximum, and for efficacy the standard error (SE) and 95% CI may be provided in addition (refer to output templates for details).

Mean, Q1, Q3 and median will be presented with one more decimal place than the measured values. SE and SD will be presented with two more decimal places than the measured values. Minimum and maximum will be presented with the same number of decimal places as the measured values.

Descriptive statistics for PD parameters will include the number of non-missing data points, the arithmetic mean, the

SD, the SE, the 95% CI, the median, minimum, Q1, Q3, and maximum. Descriptive statistics of total IgG levels will be presented in µg/mL.

Serum PK concentrations will be summarized using descriptive statistics for n>2 by study day and nominal time point using N (sample size), n (available data), arithmetic mean, SD, geometric mean, mean coefficient of variation (CV), CV%, the geometric CV%. minimum, median and maximum.

Concentrations that are BLQ will be treated as zero for the computation of descriptive statistics. If the calculated arithmetic mean concentration is BLQ then it shall be reported in outputs as BLQ; the corresponding SD and CV shall be reported as not determined (ND); minimum, median, and maximum shall be reported as BLQ if applicable. If at least one BLQ value is reported at a specific time point, the geometric mean and geometric CV% for that time point will not be calculated. In addition, if more than half of the values per time point are BLQ, the arithmetic mean will be reported as BLQ and SD, CV%, GM, [geometric SD], and geometric CV% will not be calculated. If n≤2, only N, n, minimum, and maximum will be reported.

For the reporting of descriptive statistics for PK data, the mean and SD will be presented to one digit more precision than the source data except values ≥1000 which will be presented without the decimals and rounded to the nearest integer. The minimum, median, and maximum will be presented to the same precision as the source data. Coefficient of variation will always be reported to 1 decimal place. Individual serum concentrations will be reported as received by the bioanalytical laboratory.

Descriptive statistics for immunogenicity titer values will include the number of observed values, arithmetic mean, SE, 95% CI, median, Q1, Q3, minimum, maximum, the geometric mean, and geometric CV%.

For event-type safety data, the number and percentage of participants with an event will be shown. The denominator will be all participants in the analysis set per treatment.

For frequency tabulations and cross-tabulations, the denominator will be the number of participants per treatment arm. For tables where results are shown by analysis visit, the denominator will be the number of participants per treatment arm and analysis visit. Missing values will not be included in the denominator count when computing percentages. For cross-tabulation of post-baseline results versus baseline results, a “missing” category will be shown for baseline results, if applicable. Percentages will be presented with 1 decimal place.

Appendix 1 shows conventions for presentation of data in outputs.

7.3. Multiple Comparisons/ Multiplicity

No multiple comparison adjustment or alpha sharing to be considered.

8. DISPOSITION AND WITHDRAWALS

All participants who provide informed consent will be accounted for in this study.

8.1. Disposition

The number of participants will be summarized for FAS and EAS. The number of participants per country and site will also be provided using the FAS. The number of participants who completed or discontinued the treatment and/or the study along with the reason for discontinuation will be summarized using the FAS.

Participant disposition and withdrawals will be presented for the FAS.

Data will be tabulated at least for:

- Number of participants in each analysis sets.
- number and percentage of participants randomized, completed, or discontinued the study.
- number and percentage of participants for each study discontinuation reason.
- number and percentage of participants discontinuing treatment but continuing study assessments.
- number and percentage of participants who roll over to OLE study ARGX-113-2211.

Participants not rolling over to the OLE study will have completed this study after the Safety Follow-up (SFV) or Early Discontinuation Visit (EDV).

A listing of participant disposition will be prepared to present information about treatment allocation, treatment discontinuation and study discontinuation.

8.2. Protocol Deviations

Frequency counts and percentages of participants with protocol deviations will be summarized, by class of deviations and overall using the FAS as per PDMP.

A listing will be prepared containing types of deviations and class along with additional information concerning all protocol deviations as available.

9. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and other baseline characteristics will be summarized using descriptive statistics for the FAS.

The following demographic and other baseline characteristics will be reported for this study:

- Age (years) - calculated relative to date of consent
- Age Category (18 - <65 years, 65 - <75 years and >= 75 years).
- Sex
- Race
- Ethnicity
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- Time since PSS diagnosis (years) - calculated relative to date of consent
- Anti-Ro/SS-A positive
- Anti-La/SS-B positive
- UWSF- Salivary Flow Rate
- SWSF – Salivary flow Rate
- SGUS
- OSS- Right Eye and Left Eye
- Schirmer- Right Eye and Left Eye
- Schirmer <5mm/5min in at least one eye
- [redacted]
- ESSDAI Total score
- ESSDAI ≥10
- clinESSDAI score
- ESSPRI score
- [redacted]
- Time since ACR-EULAR Classification time - Duration calculated relative to date of consent

- Baseline IgG
- [redacted]
- [redacted]

Summary statistics including n, mean, median, SD, minimum and maximum will be presented for all continuous variables listed above. Frequency counts and percentages will be presented for categorical variables such as sex, race and ethnicity.

All demographic data and baseline characteristics will be listed as well.

9.1. Derivations

- BMI (kg/ m^2) = weight (kg)/ height $(m)^2$
- Time since diagnosis is defined as (date of ICF – date of diagnosis) / 365.25. Partially missing date of diagnosis will be imputed as follows:
    - Missing day of diagnosis will be imputed with 1.
    - Missing day and month of diagnosis will be imputed with 1JAN.

10. MEDICAL HISTORY

Surgical and Medical History & Concomitant Illnesses information will be presented for the SAF.

Medical History and Concomitant Illnesses will be coded using the latest version of MedDRA (medical dictionary for regulatory activities).

- Medical/ Surgical History conditions are defined as those conditions which stop prior to or at screening. Hence, any medical history abnormalities/conditions and any before randomization date will be presented as Medical History.
- Concomitant Illnesses which started prior to or at screening and are ongoing during the study will be reported. These are also recorded in Medical History page of the eCRF.
- Frequency and percentage of participants with findings of Medical history and concomitant illnesses will be presented by SOC and PT.

11. PRIOR AND CONCOMITANT THERAPY

All therapies will be coded using WHO-DRUG and presented for the SAF. Anatomical Therapeutic Chemical (ATC) selection is performed. ATC coding up to level 4 is available in the clinical database.

See Appendix 3 for handling of partial and missing dates for medications.

In the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case; i.e. concomitant.

Based on their start and stop dates, therapies will be allocated to 1 or both of the following categories:

- 'Prior' therapies are therapies which strictly started prior to the first dose date of IMP.
- 'Concomitant' therapies are therapies which are taken on or after the first dose date of IMP.

If the start and/or stop date is incomplete or missing, the therapy will be allocated to both categories unless the available parts of the start and/or stop date provide evidence that the therapy was not administered during the specific period.

Prior and concomitant therapies will be tabulated by ATC class (level 1 and 3) and generic term.

Certain medications or treatments are not permitted during the periods listed in Table 4 of protocol.

All prior and concomitant therapies will be listed.

12. STUDY MEDICATION EXPOSURE

Exposure to IMP in days will be summarized for the SAF.

The infusion start date/time and infusion end date/time of each dose administered along with total dose administered at each visit will be recorded. The date of first study infusion will be taken from the eCRF "Exposure - Infusion" form. The date of last study infusion will be taken from the eCRF "End of Treatment" form. Interruptions, compliance, and dose changes are not taken into account for duration of exposure.

As per protocol, a variation of more than 10% of the amount of 10 mg/kg will be considered an overdose. Overdose information is as collected in "Exposure – Infusion" page of eCRF.

The number of administrations of IMP per participant and the compliance will be summarized descriptively. The total treatment administration duration will be summarized using descriptive statistics. All IMP administration data will be listed. Participants with an overdose of IMP will be listed.

12.1. Derivations

- Total treatment administration duration (days) = date of last IMP administration – date of first IMP administration + 1.
- Number of administrations = Number and percentage of participants receiving 1,2,3 etc. administrations overall.

13. STUDY MEDICATION COMPLIANCE

The infusion is given once a week by site staff or delegate. At least, the first 3 doses of IMP (at baseline, week 1 and 2 or subsequent if previous doses are missed) must be administered on-site.

The compliance will be summarized descriptively. Compliance will be further categorized as <80, 80-100, >100.

13.1. Derivations

Compliance is defined as: 100* (number of doses received/number of doses expected).

Number of doses expected will be based on participants expecting study drug infusion/administration on eCRF page "Exposure – Infusion" irrespective of dosing received.

Only visits up to treatment discontinuation are considered in the compliance calculation.

14. EFFICACY OUTCOMES

14.1. Primary Efficacy

The primary efficacy analyses will be performed for the EAS.

14.1.1. Primary Efficacy Variables & Derivations

The primary endpoint is the derived response of CRESS response on ≥ 3 of 5 items at week 24.

The CRESS composite measures below mentioned assessments which are developed to assess treatment efficacy in participants with pSS:

1) Systemic disease activity: clinESSDAI

2) Patient-reported symptoms: ESSPRI

3) Tear gland function: Schirmer's test and OSS

4) Salivary gland function: UWSF rate and SGUS

5) Serology (serum IgG and/or RF)

The primary efficacy endpoint is the proportion of responders on ≥ 3 non-missing of 5 items at week 24 using CRESS.

CRESS consists of the following items, with definitions of treatment response and lower disease activity:

1) Systemic disease activity: This will be measured with clinESSDAI (Seror [a], et al., 2016)[9].

The clinESSDAI consists of 11 domains, related to organ involvement (cutaneous, pulmonary, renal, articular, muscular, peripheral nervous system, central nervous system, hematological, glandular, constitutional, and lymphadenopathic).

The ClinESSDAI includes all ESSDAI domains except the biological domain.

Table E: Domain Weights of ClinESSDAI

Domain (activity level)	ClinESSDAI Weights
Constitutional (0-2)	4
Lymphadenopathy (0-3)	4
Glandular (0-2)	2

Domain (activity level)	ClinESSDAI Weights
Articular (0-3)	3
Cutaneous (0-3)	3
Pulmonary (0-3)	6
Renal (0-3)	6
Muscular (0-3)	7
Peripheral nervous system (0-3)	5
Central nervous system (0-3) [Seror 2015]	5
Hematological (0-3)	2
Biological (0-2)	NA*
Score total	0-135

*NA: Not Applicable

The activity levels of each domain (range: 0-3 points or 2 points) are multiplied by their respective weights (range: 1-7 points) to obtain the total score. The final score, the sum of all domain scores, falls between 0 (no disease activity) and 135. For CNS, score values indicates (0= None, 2=Moderate and 3= High). If a domain score is missing, final score will not be calculated.

These 11 components are present in database and these components gradings are multiplied by their weights as mentioned in table above at database level. The values for each domain are obtained from CRF and then the Total Score consisting of 11 components is available at database level and hence, no score derivation is required.

Responder with low disease activity (clinESSDAI score of < 5 points) is obtained at week 24[5].

2) Patient-reported symptoms: This will be measured with ESSPRI.

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

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).” These individual 3 item scores are obtained from eCOA.

The ESSPRI Total score is derived by summation of all the three numeric scores and then averaging the same. If any of the three numeric scores are missing, the total score will be missing.
The ESSPRI total score ranges from 0 to 10, with higher scores indicating more symptoms.

Higher score in ESSPRI reflects more severe symptomatology.

Clinically meaningful response is defined as a decrease of ≥ 1 point or ≥ 15% from baseline.

3) Tear gland function: This will be measured with Schirmer’s test and OSS.

The Schirmer’s test measures total tear secretion is used to identify aqueous-deficient dry eye, the type of dry eye primarily associated with Sjögren’s syndrome. In the absence of anesthesia, the Schirmer test measures reflex tearing, while the test performed with anesthesia measures basal tear secretion.

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. 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.

- 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, to be presented as stable.
- For the tear gland analysis, (Schirmer’s test, OSS) mean scores of both eyes are used.

  Here, the mean value calculated for both the eyes at each visit will be considered and CRESS response will be derived.

  .

These values for Schirmer’s test and OSS are obtained from eCRF data.

4) Salivary gland function: This will be measured with UWSF and SGUS.

The following parameters and grades are considered for measure of SGUS parameter:

(1) Parenchymal echogenicity compared to thyroid parenchyma, graded 0–1

(2) homogeneity, graded 0–3

(3) presence of hypoechoic areas in parenchyma, graded 0–3

(4) presence of hyperechoic foci, graded 0–3 in parotid glands and 0–1 in submandibular glands

(5) clearness of the salivary gland border, graded 0–3

Table F: Salivary gland Function grades

Salivary Gland Type			
Parotid (left)	**Parotid (right)**	**Submandibular (left)**	**Submandibular (right)**
Parenchymal echogenicity compared to thyroid parenchyma, graded 0–1	Parenchymal echogenicity compared to thyroid parenchyma, graded 0–1	Parenchymal echogenicity compared to thyroid parenchyma, graded 0–1	Parenchymal echogenicity compared to thyroid parenchyma, graded 0–1
homogeneity, graded 0–3	homogeneity, graded 0–3	homogeneity, graded 0–3	homogeneity, graded 0–3
presence of hypoechoic areas in parenchyma, graded 0–3	presence of hypoechoic areas in parenchyma, graded 0–3	presence of hypoechoic areas in parenchyma, graded 0–3	presence of hypoechoic areas in parenchyma, graded 0–3
presence of hyperechoic foci, graded 0–3 in parotid glands	presence of hyperechoic foci, graded 0–3 in parotid glands	presence of hyperechoic foci, graded 0–1 in submandibular glands	presence of hyperechoic foci, graded 0–1 in submandibular glands
clearness of the salivary gland border, graded 0–	clearness of the salivary gland border, graded 0–	clearness of the salivary gland border, graded 0–3	clearness of the salivary gland border, graded 0–3

3	3		
Score Range – 0 to 13	Score Range – 0 to 13	Score Range – 0 to 11	Score Range – 0 to 11

The overall ultrasound score is calculated by summation of the grades for the 5 above mentioned parameters - for all 4 major salivary glands. The overall ultrasound score can range from 0 to 48.

If any parameter is not assessed, the whole score cannot be derived, no substitutes for missing data.

Responder for salivary gland function has two components:

- 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

Unstimulated whole salivary flow (UWSF) will be measured as ml per minute.

5) Serology: It is measured with serum IgG and RF

For the biological domain, levels of rheumatoid factor (RF), and IgG are measured based on blood sample examined in the laboratory. TThe amount of RF antibody will be measured in - (IU/ml) [(IU/ml] and IgG will be assessed in (g/L).

A responder for biological domain is defined as follows:

- A response is defined as ≥ 10% reduction in IgG from baseline or
- A response is defined as ≥ 25% decrease in rheumatoid factor (RF) from baseline

Primary Analysis

Main Estimand Strategy: This is based on a composite endpoint strategy. This estimand is intended to provide an estimate of the treatment effect in the absence of prohibited concomitant medication use in a population without treatment discontinuation.

Analysis methodology: The test of proportions will be conducted at a two-sided level alpha of 0.05 with no adjustment for multiplicity. Based on the CRESS response, participants will be categorized as responders versus non-responders and a 95% Wilson Score CI for the proportion of CRESS responders will be presented for both treatment groups.

The proportion of responders and its 95% Wilson score CI will be calculated using binomial distribution. To perform this in SAS, [redacted]

[redacted]

The common odds ratio will be provided, along with the 95% CI. For above analysis, in the event of missing values for the primary endpoint, assessments on or after ICEs will be treated as Non-Responders as per primary estimand composite strategy.

Intercurrent events Data after study drug discontinuation and prohibited concomitant medication will be excluded and set to missing.

Missing Data not related to intercurrent events: There will be no imputation performed on missing data, not related to intercurrent events.

Here, the numerator will include participants which are responders. Participants who are taking prohibited concomitant medications or early discontinue study treatment, are considered as Non-Responders. The denominator will include all participants irrespective of any ICEs occurred.

Supplementary Estimand Strategy: This is based on hypothetical strategy. Any early discontinuation or taking prohibited concomitant medication is observed- then the assessment will be set to missing and the missing binary outcomes will be imputed, assuming that they are missing at random. The aim of hypothetical strategy is to address the effect in an alternative hypothetical setting where subject neither discontinued or no prohibited concomitant medication available.

Analysis set: Efficacy Analysis set.

Analysis Methodology:

The SAS procedure MI will be used and the details of MI procedure will be stated in the dataset specification document. The missing binomial outcomes will be imputed by multiple imputation method with the assumption of monotone missing pattern and logistic regression method. Multiple imputations would be conducted based on CRESS response (Yes/ No). To reduce the sampling variability from the imputation process, 500 datasets will be generated.

Here in this case the numerator will include all the participants which are responders (imputed and actual responders) and the denominator will include all participants in FAS population.

In the estimation step, separate analysis will be performed using the statistical method mentioned for the primary endpoint statistical analysis.

Because the imputation of missing data is a key aspect to the analysis of the data, explicit details regarding this imputation are provided via sample SAS code that is intended to demonstrate the application of these strategies.Minor alterations to SAP code may be performed.

Example code for imputation of binary outcome which will be used for imputation by logistic regression is as follows:

[redacted]

[redacted]

Document: [redacted]

Author: [redacted]

Version Number: V2.0

Version Date: 31JAN2024

Template No.: CS_TP_BS016 Revision 7

Reference: CS_WI_BS005

Effective Date: 01Nov2021

[redacted]

Document: [redacted]
Author: [redacted]
Version Number: V2.0
Version Date: 31JAN2024
Template No.: CS_TP_BS016 Revision 7
Reference: CS_WI_BS005
Effective Date: 01Nov2021

[redacted]

The values obtained from back transformed dataset, will be used for reporting Unadjusted Odds Ratio and CIs.

If the planned hypothetical approach is not feasible due to data sparsity, then available data occurring on or after ICEs will be analyzed as observed (treatment policy).In this case, the numerator will include all the participants which are responders (actual responders only) and the denominator will be participants in EAS population.

Missing data unrelated to ICEs , will not be imputed.

14.2. Secondary Efficacy

The secondary efficacy analyses will be performed for the EAS and will be analyzed on data observed.

14.2.1. Secondary Efficacy Variables & Derivations & Analyses.

14.2.1.1 Proportion of Participants with Minimal Clinically Important Improvement in ESSDAI: Iimprovement of ≥ 3 Points in ESSDAI Score at Week 24 and Proportion of Participants with Low Disease Activity: ESSDAI Score of < 5 at Week 24

As explained in Section 14.1.1, the ESSDAI (Seror [a], et al., 2015)[10] 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.

Table G: Domain Weights of ESSDAI

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

Each domain is scored on a range of values depending on their activity level, which can include 3 or 4 levels, into a scale from 0: No, 2: Moderate, 3: High.t

For ESSDAI, the activity levels of each domain (range: 0-3 points or 0-2 points) are multiplied by their respective weights (range: 1-6 points) to obtain the total score. The final score, the sum of all domain scores, falls between 0 (no disease activity) and, theoretically, 123 (higher disease activity). ESSDAI cannot be assessed if any domain is missing.

The Biological domain for post baseline visits will be derived using following variables at analysis level:

Biological [1]	No=0	Absence of any of the following biological features
	Low=1	Clonal component and/or hypocomplementemia (low C4 or C3 or CH50) and/or hypergammaglobulinemia or high IgG level between 16 and 20 g/L
	Moderate=2	Presence of cryoglobulinemia and/or hypergammaglobulinemia or high IgG level > 20 g/L, and/or recent onset hypogammaglobulinemia or recent decrease of IgG level (< 5 g/L)

The proportion of efgartigimod and placebo participants with improvement of >= 3 points in score and the proportion of participants having ESSDAI score of <5 at week 24 will be provided, along with 95% Wilson Score CIs by each IgG stratum at screening (> 16.0 g/L or ≤ 16 g/L) for both treatment groups and for each of these two endpoints.

14.2.1.2 Proportion of Participants with Minimal Clinically Important Improvement in clinESSDAI: Improvement of ≥ 3 Points in clinESSDAI Score at Week 24 and Proportion of oParticipants with Low Disease Activity: clinESSDAI score of < 5 at Week 24

As explained in Section 14.1.1of SAP, the ClinESSDAI includes all ESSDAI domains except the biological domain.

The proportion of efgartigimod and placebo participants with improvement of >= 3 points in clinESSDAI score and the proportion of participants having clinESSDAI score of <5 at week 24 will be provided, and along with 95% Wilson Score CIs by each IgG stratum at screening (> 16.0 g/L or ≤ 16 g/L) for both treatment groups and for each of these two endpoints.

14.2.1.3 Proportion of Participants with Minimal Clinically Important Improvement in ESSPRI: Decrease of 1 Point or ≥ 15% at Week 24

The Information on the derivation of ESSPRI total score is provided in Section 14.1.1.

The proportion of participants with decrease of 1 point or >= 15% in ESSPRI total score at week 24 will be provided and along with 95% Wilson Score CIs by each IgG stratum at screening (> 16.0 g/L or ≤ 16 g/L) for both treatment groups and for each of these two endpoints.

14.2.1.4 Change in ESSDAI Score, clinESSDAI Score and ESSPRI Score at Week 24

These scores will be descriptively summarized for actual scores and changes from baseline scores for each visit and by treatment.

For change from baseline to week 24 for ESSDAI, clinESSDAI and ESSPRI scores, between treatment group difference will be analyzed using longitudinal mixed model repeated measures (MMRM).

[redacted]

To estimate the difference between the efgartigimod and placebo in mean change from baseline to Week 24, a treatment-by-visit interaction contrast will be constructed (i.e., the treatment group contrast at Week 24). On the basis of this analysis, LS means, SE with 95% CI for placebo and efgartigimod will be reported, along with difference in LS means of efgartigimod vs placebo (with SE), 95% 2-sided CI. 2-sided p-value for testing differences between treatment groups will also be presented. Inference will be based on the precision of the

estimation rather than hypothesis testing.

[redacted]

14.2.1.6 Proportion of Participants with STAR Score of ≥ 5 at Week 24

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

The details of each of the components remains the same as explained in Section 14.1.1.This composite measure contains 5 domains (like CRESS):

- Systemic activity: If participant has clinESSDAI score decreased by ≥ 3 points at week 24, in that case the participant will be scored with 3 points
- Patient-reported outcome: If participant has ESSPRI score decrease of at least 1 point or ≥ 15% at week 24, in that case the participant will be scored with 3 points
- Lacrimal gland function (assessed by Schirmer's test or OSS)

Here there are two criteria associated w.r.t Schirmer's test:

- If Schirmer's test is ≤5 mm at baseline (abnormal) in at least 1 eye, a response is defined as an increase of at least 5 mm from baseline.
- If Schirmer's scores are normal in both eyes at baseline, a response is defined as no change to abnormal.

Also, there are two criteria associated w.r.t OSS:

- If OSS score ≥ 3 points at baseline (abnormal) in at least 1 eye, a response is defined as a decrease of at least 2 points from baseline.
- If OSS scores are normal in both eyes at baseline, a response is defined as no change to abnormal.

If either of the Schirmer's test or OSS assessment criteria are met, 1 point is assigned.

- Salivary gland function

Here there are two criteria associated w.r.t 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

If either of the UWSF or SGUS assessment criteria are met, 1 point is assigned.

- Biological (assessed by IgG or RF): 1 point is assigned if,
  - IgG: ≥ 10% reduction
  - RF: ≥ 25% decrease

The proportion of participants with STAR score of >= 5 points at week 24 will be provided and along with 95% Wilson score CIs by each IgG stratum at screening (> 16.0 g/L or ≤ 16 g/L) for both treatment groups and for this endpoint in an identical manner to the primary endpoint.

14.3. Exploratory Efficacy

The exploratory efficacy analyses will be performed for the EAS.

In each Section 14.3.x that relates to continuous parameters, the actual and change from baseline to week 24 analysis; for each visit will be descriptively summarized only.

14.3.1. [redacted]

[redacted]

14.3.2. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

14.3.3. [redacted]

[redacted]

[redacted]

[redacted]

14.3.4. [redacted]

[redacted]

[redacted]

14.3.5. [redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

14.3.6. [redacted]

[redacted]

[redacted]

14.3.7. [redacted]

[redacted]

14.3.8. [redacted]

[redacted]

14.3.9. [redacted]

[redacted]

[redacted]

14.3.10. [redacted]

[redacted]

14.3.11. [redacted]

[redacted]

14.4. Additional Efficacy Analysis

The below mentioned endpoints will be performed as sensitivity analysis:

14.4.1. Proportion of participants with MCII in clinESSDAI defined as improvement of ≥ 4 points in clinESSDAI at week 24

As explained in Section 14.1.1 of SAP, the ClinESSDAI includes all ESSDAI domains except the biological domain.

The proportion of efgartigimod and placebo participants with MCII in clinESSDAI of >= 4 points in clinESSDAI score at week 24 will be provided, along with 95% Wilson score CIs and by each IgG stratum at screening (> 16.0 g/L or ≤ 16 g/L) for both treatment groups, in an identical manner to the primary endpoint.

14.4.2. Proportion of participants with MCII in ESSDAI defined as improvement of ≥ 4 points in ESSDAI at week 24

As explained in Section 14.1.1 , the ESSDAI (Seror [a], et al., 2015)10 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.

The proportion of efgartigimod and placebo participants with MCII in ESSDAI of >= 4 points in at week 24 will be provided, along with 95% Wilson score CIs and by each IgG stratum at screening (> 16.0 g/L or ≤ 16 g/L) for both treatment groups, in an identical manner to the primary endpoint.

14.4.3. Proportion of participants with MCII in ESSPRI defined as decrease of ≥ 1.5 points

The Information on the derivation of ESSPRI total score is provided in Section 14.1.1.

The proportion of participants with decrease of >= 1.5 points in ESSPRI total score at week 24 will be provided and along with 95% Wilson score CIs and by each IgG stratum at screening (> 16.0 g/L or ≤ 16 g/L) for both treatment groups, in an identical manner to the primary endpoint.

15. PHARMACODYNAMIC ANALYSIS

PD analyses will be performed in the SAF. PD endpoints include IgG autoantibodies. PD endpointswill be summarized using descriptive statistics at each analysis visit. Actual values, changes from baseline, and percent

change from baseline will be presented. In addition to the planned time points, the following time points will also be shown:

- Maximum drop from baseline
- Minimum postbaseline value

Additionally, a line chart showing percent change in Total IgG, over time will be prepared. If appropriate, the graphic presentation of percent change over time may be presented for all PD endpoints combined. All PD data will be listed.

16. IMMUNOGENICITY ANALYSIS

Incidence and prevalence of ADAs against efgartigimod will be assessed in the SAF. ADAs to efgartigimod is measured at the time points specified in the schedule of activities of protocol, primarily at baseline, week 2, 4, 8, 12, 16, 24, EDV and SFV.

Immunogenicity samples are analyzed in a 3-tiered approach:

- All samples are evaluated in the ADA screening assay and are scored ADA screening positive (tier 1) or negative.
- If a sample is scored positive in the ADA screening assay, it is further evaluated in the confirmatory assay (tier 2) and is scored confirmed positive (positive immuno-depletion) or confirmed negative (negative immuno-depletion).
- If a sample is scored as confirmed positive, the samples are further characterized in the ADA titration assay (to determine titer).

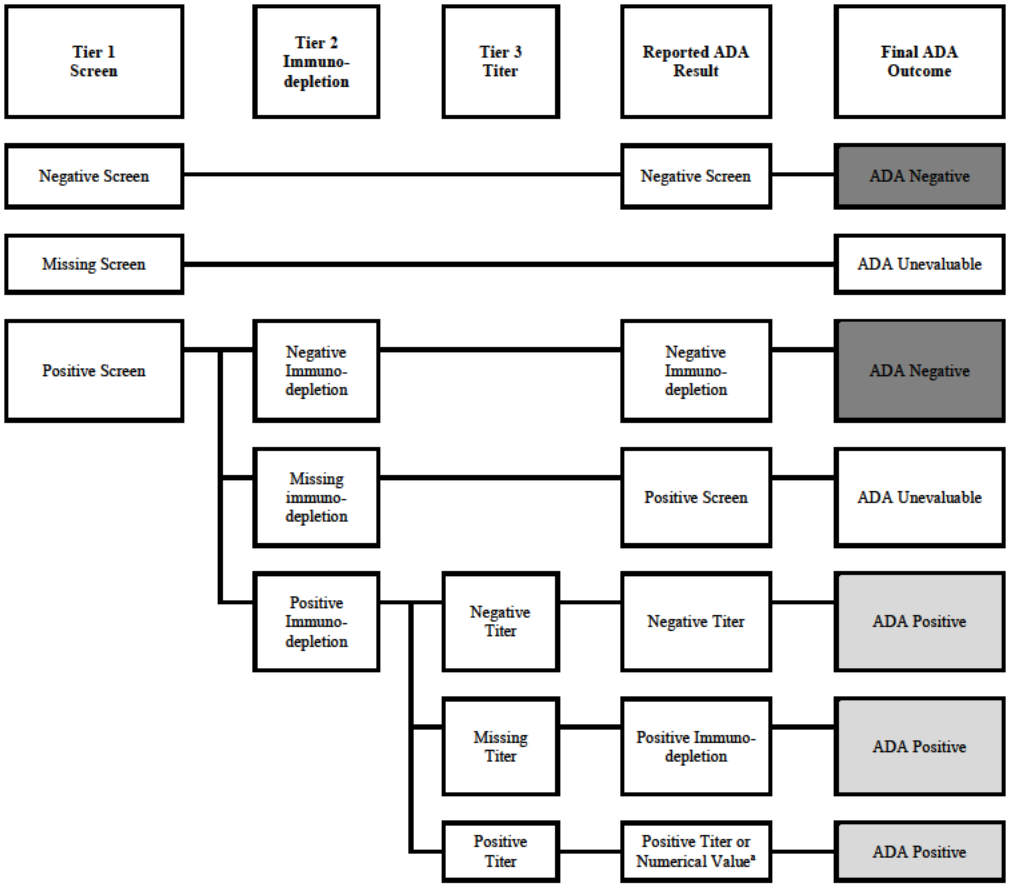
If available, a titer result will be reported for the ADA confirmed positive samples. However, a titer result is not always available:

- If the ADA confirmed positive sample could not be run in the titration assay (e.g., due to insufficient sample volume/quality to perform the titer analysis), the result will be described as “positive immuno-depletion”, and the sample should be considered ADA positive.
- If a sample is negative in the titration assay, it will be reported as “negative titer”, but it should be considered ADA positive because it was confirmed positive in the second tier.
- If a sample could not be analyzed or reported as “positive screen”, the ADA sample status is ADA unevaluable

An overview of this 3-tiered approach and all possible ADA sample results that will be reported by the laboratory is

given below. From these reported ADA sample results, a final ADA sample status must be derived during the statistical analysis, as presented in the final column ("Final ADA Outcome"):

Figure 2: ADA Sample Status



[a] "Positive titer" is reported if it was not possible to retrieve a numerical value.

Participant Classification for ADA Against Efgartigimod

TableH below gives an overview of how the ADA participant classification will be derived, starting from the participant baseline ADA sample status.

Table H: Participant Classification for ADA Against Efgartigimod

	Highest[a] postbaseline sample status				
Participant ADA classification	ADA negative	ADA positive (missing titer[b])	**ADA positive (negative titer[c] or numerical titer value)**		ADA unevaluable
Baseline ADA sample status					
ADA negative	ADA negative	Treatment-induced ADA	Treatment-induced ADA		*ADA unevaluable*
ADA positive (missing titer[b])	Treatment-unaffected ADA	*ADA unevaluable*	*ADA unevaluable*		*ADA unevaluable*
ADA positive (negative titer[c] or numerical titer value)	Treatment-unaffected ADA	*ADA unevaluable*	**Titer <4x baseline titer:** Treatment-unaffected ADA	**Titer ≥4x baseline titer:** Treatment-boosted ADA	*ADA unevaluable*
ADA unevaluable	*ADA unevaluable*	*ADA unevaluable*	*ADA unevaluable*		*ADA unevaluable*

[a] Highest sample status, with order (from low to high): ADA unevaluable, ADA negative, ADA positive ("positive immuno-depletion" or "positive titer"), ADA positive with titer <1 ("negative titer"), ADA positive with titer ≥1 (numerical value selecting the sample with highest titer).
[b] Samples with missing titer will have a reported ADA result of "positive immuno-depletion" or "positive titer".
[c] Results reported as "negative titer", i.e. titer value <1 will be set to a value of 1.

The following definitions will be used in the summary tables:

- ADA evaluable participant = participant classified in any of following categories: ADA negative, treatment-unaffected ADA, treatment-induced ADA, or treatment-boosted ADA. The first 2 categories are classified as "ADA negative", and the latter 2 are classified as "ADA positive".
- ADA incidence = percentage of participants with treatment-induced or treatment-boosted ADA (denominator: number of evaluable participants).
- ADA prevalence = percentage of participants with treatment-unaffected ADA, treatment-induced ADA, or treatment-boosted ADA (denominator: number of evaluable participants).
- ADA unevaluable participant = participant classified as ADA unevaluable or with missing baseline ADA sample or without postbaseline ADA samples (in case no ADA data are available at all, the participant cannot

be classified)

Note: A 4-fold difference in titer values is considered significant if a 2-fold serial dilution is applied (= 2 times the dilution factor).

Frequency tabulations (number and percentages) will be provided with ADA negative/positive/unevaluable samples per visit.

Frequency tabulations (number and percentages) will be provided in 1 table for:

- ADA unevaluable Participants
- ADA baseline positive/negative/unevaluable samples
- Participants per ADA participant classification
- Prevalence and incidence of ADA

Correlation tables by ADA against efgartigimod participant classification will be provided for the following parameters:

- Mean drug concentration over time
- Mean percent change from baseline in [total IgG]
- ClinESSDAI score at over time
- TEAEs by MedDRA SOC and PT
- Serious TEAEs by MedDRA SOC and PT
- Injection/infusion-related reactions

ADA against efgartigimod titer values will be summarized using descriptive statistics by ADA participant classification at each analysis visit.

All available data for ADA against efgartigimod will be listed, while also showing the ADA sample status and participant classification.

17. BIOMARKER ANALYSIS

Frequency tabulations (number and percentages) for categorical variables and summary statistics for continuous variables will be provided in terms of actual value and changes from baseline for each visit.

For the below mentioned biomarkers- data will be analyzed:

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

18. SAFETY OUTCOMES

In order to assess the long-term safety and tolerability of efgartigimod in participants, the below safety endpoints are considered within the secondary objectives.

- Incidence and severity of TEAEs
- Incidence and severity of AESIs
- Incidence and severity of SAEs
- changes in clinical laboratory safety results
- vital signs, and
- electrocardiogram (ECG) results

These endpoints will be assessed and reported based on the SAF.

There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

18.1. Adverse Events

AEs and SAEs will be collected as defined in the Section 10.3 of the protocol. AEs will be coded using latest version of Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary. AEs will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. For each AE, start and stop date/times are collected as well as severity, a seriousness flag, treatment-relatedness, relatedness to procedures, action taken towards the study drug and outcome.

Treatment-emergent adverse events (TEAEs) are defined as AEs with onset on or after the first administration of IMP up to and including 60 days after the last IMP administration before the event (refer to schematic).

D1: IMP start	D40: Start IMP interruption		D120: IMP restart	D160: Start IMP disc		D240: Study disc
IMP			IMP			
TE: D1-D40	TE: D40+60 days	Non-TE: D101-119	TE:D120-D160	TE: D160+60 days	Non-TE: >D220	

AEs will be considered treatment-emergent based on their start date/time. If the AE start date/time is incomplete or missing, the AE will be considered treatment-emergent unless the available part of the AE start or stop date/time provide evidence that the event did not occur within 60 days from last IMP administration before the event.

AE onset and duration will be calculated as follows when start and stop dates are fully known:

- AE onset day (versus first administration)
  - AE start date ≥ date of first administration: AE start date – date of first administration + 1 day.
  - AE start date < date of first administration: AE start date – date of first administration.
- AE duration (days) =
  - AE end date – AE start date + 1 day.
  - study discontinuation date – AE start date + 1 day (when the AE start date is fully known but the AE is not resolved at the end of the study). In this case the duration will be presented as ">x days".

An AE for which the study drug was discontinued is defined as an AE with action taken "drug withdrawn".

Severity is classed as mild/ moderate/ severe/ life-threatening/ death. If a participant reports a TEAE more than once within that SOC/ PT, the AE with the worst-case severity will be used in the corresponding severity summaries.

Relationship, as indicated by the Investigator, is classed as "not related" or "related". If a participant reports the same AE more than once within that SOC/ PT, the AE with the worst-case relationship to IMP will be used in the corresponding relationship summaries.

AEs leading to discontinuation of IMP will be identified by using the "Action taken with Efgartigimod/Placebo due to adverse event" from the AE page of the eCRF.

Adverse event of special interest (AESI) can be serious or nonserious, related, or unrelated to the IMP or study

procedures. Infections are considered AESIs and are defined as events with a PT that falls under the MedDRA SOC *'Infections and infestations'*.

Infusion related reactions (IRRs) are defined as all AEs with a MedDRA PT that is listed in either:

- MedDRA Hypersensitivity SMQ broad selection.
- MedDRA Anaphylactic reaction SMQ broad selection.
- MedDRA Extravasation events (injections, infusions and implants) SMQ broad selection, excluding implants.

and occurs within 48 hours of an infusion/injection, or within 2 days if the AE start time is not available. In case of partially missing AE start date, the AE will be considered an IRR, unless the available parts of the AE start date provide evidence it did not occur within 48 hours of an infusion/injection.

Any deaths during the study are recorded on the "Deaths Details" page of the eCRF. A death case is defined as an AE with outcome 'fatal'. Fatal events will be presented in a summary table presenting overall TEAEs and a data listing along with primary cause of death.

Summary tables will only include TEAEs. However, all AEs reported during the study will be listed. Summary tables by SOC and PT will be sorted alphabetically.

An overview table of AEs will be presented by treatment to show number and percentage of participants with at least one event, the number of events, and the event rate per 100 PYFU for the following;

- TEAEs
- Serious TEAEs
- Grade ≥3 TEAEs
- Fatal TEAEs
- Treatment-related TEAEs according to the Principal Investigator
- Procedures-related TEAEs
- Serious treatment - related TEAEs
- TEAEs leading to IMP discontinuation
- TEAEs leading to IMP interruption
- TEAEs of special interest
- IRRs

The overview table will also include a 95% Agresti- Min CI (in case of <30 participants in each group) or a 95% Newcombe CI (in case of ≥30 participants in each group) CI for the difference in AE rate between efgartigimod and placebo.

The event rate per 100 PYFU is defined as 100 * the number of events divided by the sum of the follow-up time during which an event is considered treatment-emergent of all participants per treatment arm expressed in years (i.e. divided by 365.25).

All AEs, including pretreatment events will be listed.

18.1.1. All TEAEs

Summary tables will only include TEAEs and will be presented by System Organ Class (SOC) and Preferred Term (PT) for each treatment group. Table will contain number and percentage of participants with at least one event and the number of events (except for TEAEs by worst toxicity) for TEAE. These outputs will be provided for:

- TEAEs
- Serious TEAEs
- Nonserious TEAEs
- Grade ≥3 TEAEs
- TEAEs by worst toxicity
- Treatment-related TEAEs
- Procedure-related TEAEs
- Serious treatment-related TEAEs
- TEAEs leading to IMP discontinuation
- TEAEs of special interest
- IRRs
- Serious IRRs

18.2. Laboratory Evaluations

Results from the central laboratory will be included in the reporting of this study for serum chemistry and hematology, coagulation, urinalysis, serology (e.g. viral marker testing), and specialty laboratory parameters. A list of laboratory assessments to be included in the outputs is included in Appendix 2 (Table 6) of the protocol.

These are mainly as follows.

Laboratory Assessments

Hematology	RBC count, platelet count, hemoglobin, hematocrit, MCV, MCH, WBC count with differential: neutrophils, eosinophils, lymphocytes, basophils, monocytes
Serum chemistry	ALT, AST, albumin, blood urea nitrogen, creatinine, eGFR, glucose, potassium, chloride, bicarbonate, sodium, total protein, calcium, bilirubin (total and direct) 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,)
Other tests	SARS-CoV-2 nasopharyngeal swab test (PCR) (if applicable) HBV, HCV, HIV Menopausal test (FSH) if applicable (to confirm non-WOCBP status) IgG[a]

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

Normal ranges are available as provided by the central laboratory and results will be presented in standardized units unless specified otherwise. Clinically significant changes occurring during the study are recorded as an AE.

Quantitative laboratory measurements reported as "< X", i.e. BLQ, or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

Continuous laboratory parameters will be summarized using descriptive statistics of actual values and changes from baseline at each analysis visit. Categorical parameters will only be listed.

The following summaries will be provided for laboratory data:

- Continuous laboratory parameters to be summarized using descriptive statistics of actual values and changes from baseline at each analysis visit.
- Laboratory toxicity grades to be presented as cross-tabulations of the toxicity at each postbaseline analysis visit and at the worst-case analysis visit versus the baseline toxicity.
- Laboratory abnormalities as cross-tabulations of the abnormality at each postbaseline analysis visit and at the worst-case analysis visit versus the baseline abnormality. The number of participants with treatment-emergent abnormalities will also be shown. The denominator for the percentage is the total number of participants per treatment arm and per analysis visit in the SAF.
- Listing of participants with any post-baseline abnormality or toxicity grade ≥1.

18.2.1. Laboratory Specific Derivations

All datapoints obtained after informed consent up to 60 days after IMP discontinuation or database cutoff will be considered.

- The following abnormality categories will be defined:
  - Low: value < lower limit of normal range
  - Normal: lower limit of normal range ≤ value ≤ upper limit of normal range
  - High: value > upper limit of normal range

- Notes:
  - Classification will be done in standardized units, using non imputed values and limits.
  - For the worst-case analysis visits, as defined in Section 6.4, an additional category low + high is defined in case there are both low and high post-baseline values.

Toxicity grades will be computed according to the National Cancer Institute (NCI) common toxicity criteria for adverse events (CTCAE) toxicity grading list (version 5.0). The implementation of these toxicity grades for analysis is presented in appendix 2. Only the parameters described in appendix 2 will be computed, according to the declared limits for each grade.

Only lab parameters specified within the protocol will be analysed and, only those both in the protocol and in appendix 2 will be considered for toxicity. All others that are in the protocol and not in appendix 2, but have High/Low/Normal will be presented in the abnormality table.

18.3. ECG Evaluations

Results from the central ECG (Electrocardiogram) Reading Centre will be included in the reporting of this study. Single 12-lead ECG(s) will be obtained using an ECG machine. The following ECG parameters will be reported for this study:

- HR (bpm)
- PR Interval (msec)
- QRS Interval (msec)
- RR Interval (msec)
- QT Interval (msec)
- QTcF Interval (msec)
- QTcB Interval (msec)

All datapoints obtained after informed consent up to 60 days after IMP discontinuation or database cutoff will be considered.

The following summaries will be provided for ECG data:

- ECG parameters will be summarized using descriptive statistics at each analysis visit.
- Abnormalities of the actual values will be presented as cross-tabulations of the abnormality at each postbaseline analysis visit and at the worst-case analysis visit versus the baseline abnormality. Numbers and cumulative

numbers (QTc only) of participants with treatment-emergent abnormalities will also be shown. The denominator for the percentage is the total number of participants per treatment arm and per analysis visit.

- Abnormalities of the QTc changes will be presented as tabulations of the change abnormality at each postbaseline analysis visit and at the worst-case analysis visit. Cumulative numbers of participants with change abnormalities will also be shown. The denominator for the percentage is the total number of participants per treatment arm and per analysis visit.
- All ECG data will be listed, but only for participants with any postbaseline abnormality.

18.3.1. ECG Abnormal Criteria

Abnormal quantitative ECG measurements will be identified in accordance with the following predefined abnormal criteria for HR, QRS and PR interval:

	HR (bpm)	**PR (ms)**	**QRS (ms)**
Low	<40	<120	-
Normal	40-100	120-220	0-120
High	>100	>220	>120

Note: For the worst-case analysis visit, as defined in Section 6.4, an additional category "low + high" is defined if there are both low and high postbaseline values.

Actual values for QT interval, QTcB interval and QTcF will be classified as:

- Actual values:
  - ≤ 450 (normal)
  -]450; 480]
  -]480; 500]
  - > 500
- Changes from baseline:
  - ≤ 30 (normal)
  -]30; 60]
  - > 60

Note: The worst-case, as defined in Section 6.4, is the highest postbaseline value and associated change.

18.4. Vital Signs

The following Vital Signs measurements will be reported for this study:

- Sitting / Supine Systolic Blood Pressure (mmHg)
- Sitting / Supine Diastolic Blood Pressure (mmHg)
- Sitting / Supine Pulse Rate (bpm)
- Respiratory Rate (breaths/min)
- Body Temperature (^{o} C)

Vital signs parameters will be summarized using descriptive statistics at each analysis visit. Abnormalities will be presented as cross-tabulations of the abnormality at each post-baseline analysis visit.

All datapoints obtained after informed consent up to 60 days after IMP discontinuation or database cutoff will be considered.

The following summaries will be provided for vital signs data:

- Vital signs parameters will be summarized using descriptive statistics at each analysis visit.
- Abnormalities will be presented as cross-tabulations of the abnormality at each postbaseline analysis visit and at the worst-case analysis visit versus the baseline abnormality.
- All vital signs data will be listed, but only for participants with any postbaseline abnormality.

18.4.1. Vital Signs Abnormal Criteria

Abnormal quantitative Vital Signs measurements will be identified in accordance with the following predefined abnormal criteria.

Variable	Unit	Low	Normal	High
SBP	mmHg	< 90	90-150	> 150
DBP	mmHg	< 45	45 – 90	> 90
Heart rate	Bpm	< 40	40 – 100	> 100

Variable	Unit	Low	Normal	High
Body temperature	°C	< 35.8	35.8 – 37.5	> 37.5

Note: For the worst-case analysis visits, as defined in Section 6.4, an additional category "low + high" is defined if there are both low and high postbaseline values.

18.5. Physical Examination

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.

Brief physical examination will include weight, assessments of gastrointestinal, pulmonary, cardiovascular, and respiratory systems; and general appearance.

All datapoints obtained after informed consent up to 60 days after IMP discontinuation or database cutoff will be considered. Physical examination abnormalities will be listed.

19. PHARMACOKINETIC ANALYSIS

PK analyses will be performed in the PKAS.

At IMP administration visits, PK blood samples will be collected predose (within the 2 hours before IMP infusion).

A listing of PK blood sample collection times, derived sampling time deviations, and concentrations will be provided. A subject listing of all concentration-time data will be presented by study day and scheduled time point.

Serum concentrations will be summarized using descriptive statistics for efgartigimod. The pharmacokineticist will determine a strategy for dealing with data affected by protocol deviations or events which may impact the quality of PK concentration data on a case-by-case basis with input from the study physician, as needed. Examples of protocol deviations or events include, but may not be limited to the following:

- When a predose sample is taken after IMP administration.

- When the most recent IMP administration before the scheduled predose PK sample or any other scheduled PK sample (ie, week 24 sample)is missed (not applicable for Day 1).
- Samples are collected following the occurrence of incomplete or incorrect dosing for the most recent prior dose administration Any administration. Any event related to sample collection, handling and storage that affects the integrity of the samples and/or the bioanalytical results.
- When predose PK samples are taken outside the visit windows.
    - The study visit windows are ±2 days

In the case of an important protocol deviation or event, the PK data collected may be excluded from the summaries and a reason for the exclusion of the data point will be added in the appropriate listing.

Figures of geometric mean concentration-time data (±SD on linear plot, as appropriate) may be presented for efgartigimod on linear and semi-logarithmic scales. Individual participant concentration-time data will be graphically presented on linear and semi-logarithmic scales. Individual concentrations which are BLQ will be displayed as zero in the graphic presentations on linear scale; but will not be plotted on semi-logarithmic scale. Means which fall below the BLQ will also be displayed as zero in the graphic presentations on the linear scale, but will not be plotted on semi-logarithmic scale.

The strategy for the population PK analysis and any related exposure-response modeling utilizing the efgartigimod concentration and IgG data collected from this study will be outlined separately in the PK analysis plan.

20. REFERENCES

1. ICH-E3 Structure and Content of Clinical Study Reports – Step 4: 30 Nov 1995.
2. ICH Topic E6 (R2) Guideline for Good Clinical Practice – Step 4: 9 Nov 2016.
3. ICH Topic E9 Statistical Principles for Clinical Trials – Step 4: September 1998.
4. ICH Topic E9 (R1) Statistical Principles for Clinical Trials, Addendum on Estimands and Sensitivity Analysis is Clinical Trials – Step 4: November 2019.Arends S, de Wolff L, van Nimwegen JF, et al.
5. Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS): development and validation of a novel outcome measure. Lancet Rheumatol. 2021;3(8):E553-E562.
6. [redacted]

7. [redacted]
8. [redacted]
9. ClinESSDAI User guidelines (Seror [a], et al., 2016).
10. ESSDAI User guidelines (Seror [a], et al., 2015).

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA Output Conventions

Outputs will be presented according IQVIA Standard conventions. Kindly refer to output templates for additional information.

Dates & Times

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

Presentation of Treatment Groups

For outputs, treatment groups will be represented as follows and in the given order:

Treatment Group for Tables, Listings and Figures
Efgartigimod
Placebo

In the demographics and analysis, an overall total will be added to summarize all participants over treatments. Overall totals will be shown last.

Listings

All listings will be ordered by the following (unless otherwise indicated in the template):

- Randomized treatment group (or treatment received if it's a safety output), first by active dose [by ascending dose group] and then control/ placebo
- Center-participant ID
- Date (where applicable)
- For listings where non-randomized participants are included, these will appear in a category after the randomized treatment groups labeled 'Not Randomized'

APPENDIX 2. TOXICITY GRADES

The table below shows how the CTCAE, v5.0: 27 Nov 2017 will be implemented in the analysis.

Parameter	Unit	Grade 1	Grade 2	Grade 3	Grade 4
Alanine amino transferase		>1-3 *ULN	>3-5 *ULN	>5-20 *ULN	>20 *ULN
Albumin	g/L	<LLN-30	<30-20	<20	-
	g/dL	<LLN-3	<3-2	<2	-
Alkaline phosphatase		>1.0-2.5 *ULN	>2.5-5.0 *ULN	>5.0-20.0 *ULN	>20.0 *ULN
Aspartate amino transferase		>1-3 *ULN	>3-5 *ULN	>5-20 *ULN	>20 *ULN
Bilirubin (total)		>1.0-1.5 *ULN	>1.5-3.0 *ULN	>3.0-10.0 *ULN	>10.0 *ULN
Calcium (ionized) low	mmol/L	<LLN-1.0	<1.0-0.9	<0.9-0.8	<0.8
	mg/dL	<LLN-4.0	<4.0-3.6	<3.6-3.2	<3.2
Calcium (ionized) high	mmol/L	>ULN-1.5	>1.5-1.6	>1.6-1.8	>1.8
	mg/dL	>ULN-6.0	>6.0-6.4	>6.4-7.2	>7.2
Calcium (corrected) low	mmol/L	<LLN-2.00	<2.00-1.75	<1.75-1.50	<1.50
	mg/dL	<LLN-8	<8-7	<7-6	<6
Calcium (corrected) high	mmol/L	>ULN-2.9	>2.9-3.1	>3.1-3.4	>3.4
	mg/dL	>ULN-11.5	>11.5-12.5	>12.5-13.5	>13.5
Cholesterol	mmol/L	>ULN-7.75	>7.75-10.34	>10.34-12.92	>12.92
	mg/dL	>ULN-300	>300-400	>400-500	>500
Creatine kinase		>1.0-2.5 *ULN	>2.5-5.0 *ULN	>5.0-10.0 *ULN	>10.0 *ULN
Creatinine		>1.0-1.5 *ULN	>1.5-3.0 *ULN	>3.0-6.0 *ULN	>6.0 *ULN
Glucose (fasting) low	mmol/L	<LLN-3.0	<3.0-2.2	<2.2-1.7	<1.7
	mg/dL	<LLN-55	<55-40	<40-30	<30
Lipase		>1.0-1.5 *ULN	>1.5-2.0 *ULN	>2.0-5.0 *ULN	>5.0 *ULN
Potassium low	mmol/L	-	<LLN-3.0	<3.0-2.5	<2.5
	mEq/L	-	<LLN-3.0	<3.0-2.5	<2.5
Potassium high	mmol/L	>ULN-5.5	>5.5-6.0	>6.0-7.0	>7.0

Parameter	Unit	Grade 1	Grade 2	Grade 3	Grade 4
	mEq/L	>ULN-5.5	>5.5-6.0	>6.0-7.0	>7.0
Sodium low	mmol/L	<LLN-130	-	<130-120	<120
	mEq/L	<LLN-130	-	<130-120	<120
Sodium high	mmol/L	>ULN-150	>150-155	>155-160	>160
	mEq/L	>ULN-150	>150-155	>155-160	>160
CD4 count	giga/L	<LLN-0.50	<0.50-0.20	<0.20-0.05	<0.05
	counts/m m^3	<LLN-500	<500-200	<200-50	<50
Lymphocytes (absolute count) low	giga/L	<LLN-0.80	<0.80-0.50	<0.50-0.20	<0.20
	counts/m m^3	<LLN-800	<800-500	<500-200	<200
Lymphocytes (absolute count) high	giga/L	-	>4-20	>20	-
	counts/m m^3	-	>4000-20000	>20000	-
Neutrophils (absolute count) low	giga/L	<LLN-1.5	<1.5-1.0	<1.0-0.5	<0.5
	counts/m m^3	<LLN-1500	<1500-1000	<1000-500	<500
Platelets	giga/L	<LLN-75	<75-50	<50-25	<25
	counts/m m^3	<LLN-75000	<75000-50000	<50000-25000	<25000
White blood cells	giga/L	<LLN-3	<3-2	<2-1	<1
	counts/m m^3	<LLN-3000	<3000-2000	<2000-1000	<1000

CTCAE= Common Terminology Criteria for Adverse Events; LLN=lower limit of normal; ULN=upper limit of normal

Note: In case ULN/LLN is higher/lower than the upper/lower limit of grade 1 (or even higher grades), ULN/LLN will be ignored and only the fixed values of CTCAE will be considered.

Values within normal ranges will be presented as Grade 0 for Toxicity outputs.

APPENDIX 3. ALGORITHM FOR PRIOR /CONCOMITANT MEDICATIONS

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant
	Partial	If only day is missing: compare Month and year from start and stop date based on rule described below: If stop date < study med start date, assign as prior If stop date >= study med start, assign as concomitantOr else, assign as Concomitant and Prior. If day and month are missing please compare the year and implement rules described above.
	Missing	Assign as concomitant and prior.
Partial	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant
	Partial	If only day is missing: compare Month and year from start and stop date based on rule described below: If stop date < study med start date, assign as prior If stop date >= study med start, assign as concomitantOr else, assign as Concomitant and Prior. If day and month are missing please compare the year and implement rules described above.
	Missing	Assign as concomitant and prior.

START DATE	STOP DATE	ACTION
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant
	Partial	If only day is missing: compare Month and year from start and stop date based on rule described below: If stop date < study med start date, assign as prior If stop date >= study med start, assign as concomitantOr else, assign as Concomitant and Prior. If day and month are missing please compare the year and implement rules described above.
	Missing	Assign as concomitant and prior.