STATISTICAL ANALYSIS PLAN

ARGX-113-2211

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

AUTHOR: [redacted]

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[redacted]

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V2.0 (Dated 27 Mar 2025) for Protocol ARGX-113-2211.

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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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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from First Authorized Version
1.0	30MAY2024	[redacted]	Not Applicable – First Authorized Version
1.1	28Jan2025	[redacted]	Updated the baseline definition for ECG parameters. Updated section on medical history, physical examination, enrollment failures, compliance, and study medical exposure
2.0	24 March 2025	[redacted]	Update window section to remove EDV as a separate window and clarify the table titles. Update wording to describe the dosing regimen.

[redacted]

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LIST OF ABBREVIATIONS

Abbreviation	Term
ADA	antidrug antibody(ies)
AE	adverse event
AESI	adverse event of Special interest
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
DBP	diastolic blood pressure
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
GM	geometric mean
HBV	hepatitis B virus
HCV	hepatitis C virus

[redacted]

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]
IgG	immunoglobulin G
[redacted]	[redacted]
IMP	investigational medicinal product
IRR	Infusion-related reaction
IV	intravenous
LLN	Lower Limit Normal
MCS	Mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
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)
PDMP	Protocol Deviations Management Plan
[redacted]	[redacted]
PI	Principal Investigator
PK	pharmacokinetic(s)
PKAS	pharmacokinetic analysis set
pSS	primary Sjögren's syndrome
PT	preferred term
PYFU	patient years of follow-up

[redacted]

QW	once weekly
Q2W	every 2 weeks
RF	rheumatoid factor
RNA	Ribonucleic acid
SAE	serious adverse event
SAF	Safety analysis set
SAP	statistical analysis plan
SBP	systolic blood pressure
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
[redacted]	[redacted]
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

DEFINITIONS OF TERMS

Term	Definition
Non-responder	Participant who does not have a reduction in ClinESSDAI score of ≥3 points and/or a change in score that alters their disease severity category
Responder	Participant who has a reduction in ClinESSDAI score of ≥3 points and/or a change in score

[redacted]

Term	Definition
	that reclassifies their disease from moderate severity to mild severity
Therapeutic failure	Participant who are non-responder at week 24. This participant will discontinue study treatment
Enrolled	The participant agrees to participate in the clinical study by completing the informed consent process.

[redacted]

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-113-2211. 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 V1.0, dated 24FEB2023.

2. STUDY OBJECTIVES AND ESTIMANDS

Table A : Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the long-term safety of efgartigimod in patients with pSS	• Incidence and severity of adverse event (AEs) and adverse events of Special interest (AESIs), incidence serious adverse events (SAEs), changes in laboratory test results, vital signs, and electrocardiogram (ECG) results
Secondary	
• To evaluate effect and assess long-term effect of efgartigimod on durability of CRESS response	• Proportion of Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS) responders on ≥ 3 of 5 items at weeks 24 and 48 (refer to Section 8.2.1 of the 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)

[redacted]

Objectives	Endpoints
• To evaluate the effect of efgartigimod on clinical efficacy parameters	• Proportion of participants with minimal clinically important improvement from baseline in ESSDAI: improvement of ≥ 3 points in ESSDAI score at weeks 24 and 48 • Proportion of participants with low disease activity: ESSDAI score of < 5 at weeks 24 and 48 • Proportion of participants with minimal clinically important improvement from baseline in clinESSDAI: improvement of ≥ 3 points in clinESSDAI score at weeks 24 and 48 • Proportion of participants with low disease activity: clinESSDAI score of < 5 at weeks 24 and 48 • Proportion of participants with minimal clinically important improvement from baseline in ESSPRI: decrease of ≥ 1 point or ≥ 15% at weeks 24 and 48 • Change from baseline in ESSDAI score at weeks 24 and 48 • Change from baseline in clinESSDAI score at weeks 24 and 48 • Change from baseline in ESSPRI score at weeks 24 and 48
• To evaluate the effect of efgartigimod on STAR	• Proportion of Sjögren's Tool for Assessing Response (STAR) responders (score of ≥ 5) at weeks 24 and 48 when compared to baseline
• To assess the pharmacodynamics (PD) effect of efgartigimod	• Values, changes from baseline, and percent reduction from baseline in total IgG levels in serum over the 48-week treatment period • Values, changes from baseline, and percent reduction from baseline in autoantibodies in serum over the 48-week treatment period: – Anti-Ro/SS A – Anti-La/SS B
• To assess the exposure to efgartigimod	• Efgartigimod serum concentrations over the 48-week treatment period
• To assess the immunogenicity of efgartigimod	• Incidence and prevalence of antidrug antibody(ies) (ADA) against efgartigimod over the 48-week treatment period
Exploratory	
[redacted]	

Objectives	Endpoints
[redacted]	

No estimands have been defined for this study.

[redacted]

3. STUDY DESIGN

3.1. General Description

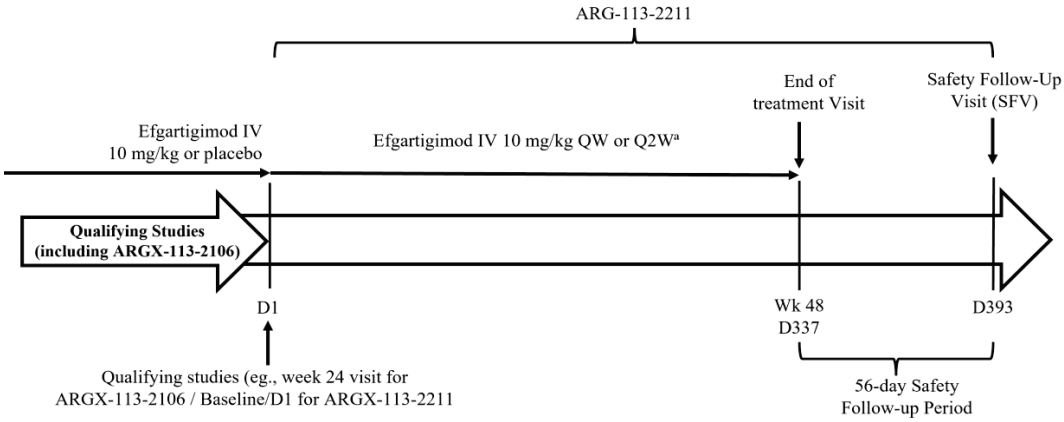
This is a long-term, single-arm, open-label, multicenter extension of pSS qualifying efgartigimod studies designed to evaluate the long-term safety of efgartigimod in adult patients with pSS. Participants will be enrolled from both active and placebo arms of qualifying efgartigimod studies and receive efgartigimod intravenous (IV) 10 mg/kg over 48 weeks in the extension study without knowledge of their treatment assigned in the qualifying study. To be eligible to enroll in this study, participants must have completed the treatment period of the qualifying study and must not have permanently discontinued the investigational medicinal product (IMP) in that study.
Participants will receive efgartigimod 10 mg/kg by IV infusion either every 2 weeks (Q2W) or once weekly (QW). The dosing regimen is based on whether the participant is a responder or non-responder on day 1. ClinESSDAI assessments to determine responder status using the baseline will be conducted on day 1 and weeks 16 and 24. Responders will receive IV infusions Q2W. Non-responders will receive an infusion QW until such time that they are considered to be responders. If a participant is not a responder at week 24, they will be evaluated by the principal investigator (PI) for therapeutic failure.

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

If the participant and/or investigator consider there to be a reduction in therapeutic effect once the patient has switched to Q2W, the participant will return for an unscheduled visit during which a clinESSDAI, a blood sampling for pharmacokinetic (PK) and ADA will be collected.
If there has been an increase in clinESSDAI score of ≥ 3 points and/or a change in score that reclassifies their disease from mild severity to moderate severity the participant will switch to QW dosing regimen and will remain on this dose regimen for the remainder of the treatment period.
Investigational medicinal product (IMP) infusions must occur at the site for a minimum of 3 consecutive visits (for QW dosing regimen: baseline visit and the week 1 and 2 visits; for Q2W dosing regimen: baseline visit and the week 2 and 4 visits) before home infusions are allowed. If doses are missed at 1 or more of these visits, then dosing at subsequent visits will also be on-site. IMP administration at home will not commence until after 3 consecutive doses have been administered on-site.
Participants will return for a follow-up visit approximately 56 days after the final IMP administration.

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

Figure 1: Study Overview



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

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

[redacted]

3.2. Sample Size

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

3.3. Schedule of Events

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

3.4. Changes to Analysis from Protocol

The Biomarker data will not be analyzed due to the lack of available data to BIOS.

4. PLANNED ANALYSES

The following analyses will be performed for this study:

- An interim analysis (IA) will be conducted when all subject's complete week 16 or discontinue prior to week 16. If required, more IA will be conducted based on sponsor's discretion.
- Final Analysis

4.1. Data Monitoring Committee (DMC)

There will be no DMC for this study.

4.2. Interim Analysis

One interim analysis will take place after all enrolled subjects of ARGX-112-2211 study complete week 16 or discontinue prior to week 16.

The interim analysis will be performed by IQVIA Biostatistics following authorization of this SAP, database lock, and analysis sets.

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, and analysis sets.

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.

5. ANALYSIS SETS

Agreement and authorization of subjects included/excluded from each analysis set will be conducted prior to database lock.

5.1. Full Analysis Set [FAS]

The full analysis set (FAS) will contain all enrolled subjects in the OLE study.

5.2. Safety Analysis Set [SAF]

The safety analysis set (SAF) will have – All FAS subjects who have been administered study treatment during the OLE.

5.3. PK Analysis Set [PKAS]- efgartigimod

The PK analysis set (PKAS) used for the descriptive summaries of efgartigimod serum concentrations will consist of all enrolled 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.

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 start date, then:
    - Study Day = (date of event – reference start date) + 1.
- If the date of the event is prior to the reference start date, then:
    - Study Day = (date of event – reference start date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings.

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 enrolled will be used instead of first IMP administration date/time.
End of study (EOS) is defined as date of participant's last visit. A participant will have completed the study if the SFV assessments have been completed.
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 from the parent study 2106. Refer to appendix 1 baseline for details. These baseline observations could be either from week 24 or prior visits of ARGX-113-2106. All baseline assessments will be performed before first administration of efgartigimod in ARGX-113-2211, if applicable. The baseline of ECG parameters should come from the same date. If an individual

ECG parameter is not reported on the latest date prior to 1st IMP infusion within the extension study, leave blank. Assessments do not need to be repeated if they are performed as part of the last visit of the qualifying study. 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 enrolled 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 B: Non-efficacy Analysis Visit Definition (immunogenicity)

Phase	**Target Day**	**Assigned Study Day (Inclusive)**		Week Assigned
		From	To	
Treatment	Not applicable [a]			Baseline
	15	1[a]	22	Week 2
	29	23	43	Week 4
	57	44	71	Week 8
	85	72	99	Week 12
	113	100	141	Week 16
	169	142	211	Week 24
	253	212	295	Week 36
	337	296	Up to the date of SFV.	Week 48
Safety Follow-up	NA	NA	NA	SFV

[redacted]

[a] Last available non-missing measurement from the parent study ARGX-113-2106.
For QW regimen, the final dose will be administrated at week 47. For Q2W regimen, the final dose will be administered at week 46.
After treatment period ends, safety follow-up will be approximately 7 weeks (56 days ± 3 days) will be summarized separately.

The above Table B contains visit window for every assessment's visited (e.g., Immunogenicity). Refer to respective visit window table for other assessments.

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

For e.g. Week 2 are not protocol scheduled visit for brief physical examination (symptom driven), vital signs, electrocardiogram (ECG), clinical laboratory assessments, total IgG, anti-Ro/SS-A, anti-La/SS-B autoantibodies. Hence, visit window can be combined with baseline and week 4. The non-missing value closest to the target day will be used in the analysis in case of multiple observations.

Table B: Non-efficacy Analysis Visit Definition for brief physical examination (symptom driven), vital signs, electrocardiogram (ECG), clinical laboratory assessments, total IgG, anti-Ro/SS-A, anti-La/SS-B autoantibodies.

Phase	Target Day	Assigned Study Day (Inclusive)		Week Assigned
		From	To	
Treatment	Not applicable [a]			Baseline
	29	2	43	Week 4
	57	44	71	Week 8
	85	72	99	Week 12
	113	100	141	Week 16
	169	142	211	Week 24
	253	212	295	Week 36
	337	296	Up to the date of SFV.	Week 48
Safety Follow-up	NA	NA	NA	SFV

[redacted]

For Urinalysis, we do not have week 2, week 4, week 8, week 12 visit, as in that case the following window:

Table B: Non-efficacy Analysis Visit Definition for Urinalysis.

Phase	Target Day	Assigned Study Day (Inclusive)		Week Assigned
		From	To	
Treatment	Not applicable [a]			Baseline
	113	2	141	Week 16
	169	142	211	Week 24
	253	212	295	Week 36
	337	296	Up to the date of SFV.	Week 48
Safety Follow-up	NA	NA	NA	SFV

For Urine pregnancy testing, we only have Baseline, and Safety Follow-up schedules the following window:

Table B: Non-efficacy Analysis Visit Definition for Urine Pregnancy testing.

Phase	Target Day	Assigned Study Day (Inclusive)	Week Assigned

[redacted]

		From	To	
Treatment	Not applicable [a]			Baseline
Safety Follow-up	NA	NA	NA	SFV

a Last available non-missing measurement from the parent study ARGX-113-2106.

For efficacy assessments (e.g., ClinESSDAI), wider window will be considered as follows:

Table C: Efficacy Analysis Visit Definition for ClinESSDAI.

Target Day	Assigned Study Day (Inclusive)		Week Assigned
	From	To	
Not applicable [a]			Baseline
113	2	141	Week 16
169	142	197	Week 24
225	198	239	Week 32
253	240	267	Week 36
281	268	295	Week 40
309	296	323	Week 44
337	324	Until study discontinuation	Week 48

a Last available non-missing measurement from the parent study ARGX-113-2106.

Note: ClinESSDAI will only be conducted at weeks 32, 36, 40, and 44 if the participant is a non-responder at week 24 and not considered a therapeutic failure by the PI.

[redacted]

a Last available non-missing measurement from the parent study ARGX-113-2106.

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.

[redacted]

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 significant level will be (10%); confidence intervals (CIs) will be 90% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

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:

- Test 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.

[redacted]

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 Presentations

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 90% 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 90% 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 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 one or 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 and shall be reported as not determined (ND); minimum, median, and maximum shall be reported as BLQ if applicable. If n≤2, only N, n, minimum, and maximum will be reported.

[redacted]

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, 90% 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.
For frequency tabulations and cross-tabulations, the denominator will be the number of participants. For tables where results are shown by analysis visit, the denominator will be the number of participants 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.
Summaries will be provided both for the overall study population as well as grouped according to treatment received in the parent study AGRX-113-2106 (efgartigimod or placebo). 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 subjects who provide informed consent will be accounted for in this study.

8.1. Disposition

The number of participants will be summarized for FAS. 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.
The enrollment failures will be summarized using number of participants who signed the informed consent form.

[redacted]

Data will be tabulated at least for:

- Number of participants in each analysis sets.
- number and percentage of participants enrolled, 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.

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

8.2. Protocol Deviations

The number and percentage of subjects with protocol deviations will be summarized, by class of deviations and overall using the FAS as per Protocol Deviations Management Plan (PDMP).
A listing will be prepared containing types of deviations and class along with additional information concerning all protocol deviations as available.
For protocol deviations, only PDs related to the study will be reported. No deviations will be forwarded from the main study.

9. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and other baseline characteristics will be summarized using descriptive statistics for the FAS.
The baseline visits for study ARGX-113-2211 will be conducted after the participant has completed the qualifying study (i.e., week 24 visit ARGX-113-2106). 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
- Childbearing potential for female subjects only (Yes, No)
  - If No, then reason (Post-Menopausal, Premenarchal, Surgically Sterile, Other)
- Weight (kg)
- Height (cm) [obtained from Argenx – 113-2106]
- BMI (kg/m^2)

[redacted]

- 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
- RF
- ESSDAI Total score
- ESSDAI ≥10
- clinESSDAI score
  - Is patient a responder (Yes, No)
  - Dosing Regimen (QW, Q2W)
- ESSPRI score
- MFI Score
- SF-36 Score [Physical Component Score (PCS) and Mental Component Score (MCS)]
- Baseline IgG
- [redacted]
- [redacted]

Summary statistics including n, mean, median, SD, minimum and maximum will be presented for all continuous variables listed above. The number and percentage of subjects will be presented for categorical variables such as sex.

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

9.1. Derivations

- BMI (kg/ m^2) = weight (kg)/ height $(m)^2$

Weight is from Argenx -113-2211 baseline, while height is from Argenx-113-2106

10. 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.
Any medication that the participant is receiving at the time of enrollment or receives during the study will be recorded in "Prior and Concomitant Medications" page of the eCRF. The concomitant medications listed in previous study of ARGX-113-2106 which are "Ongoing" will be considered for OLE study.
See Appendix 3 for handling of partial and missing dates for medications.
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 in this study 2211.
- 'Concomitant' therapies are therapies which are taken on or after the first dose date of IMP in this study 2211.

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.

11. 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, temporary discontinuation, compliance, and dose changes are not considered for duration of exposure.

Table D: Treatment Administered Duration and the number of Administered doses.

The treatment exposure into different dosing regimen are described in the below table:

Classification based Dosing	Regime pattern

[redacted]

Participants continuing QW (QW)	Start : QW During the study : QW End of study at week 48 : QW
Participants switching to and continuing Q2W (Q2W)	Start : Q2W During the study : Q2W End of study at week 48 : Q2W
Participants switching to Q2W at start of OLE and switching to QW (SQW)	Start : Day 1- Q2W During the study : The participant becomes a non-responder at week 16, 24, 32, 36, 40, 44, or an unscheduled visit where which a clinESSDAI result has resulted a non-responder outcome End of study at Week 48 : QW
Participants continuing QW and switching to Q2W later during OLE (SQ2W)	Starts: Day 1 – QW During the study: the study the participant becomes a responder at week 16, 24, 32, 36, 40, 44, or an unscheduled visit where which a clinESSDAI result has resulted a responder outcome -Q2W End of study at week 48 : Q2W

The above definitions do not consider authorized temporary discontinuation of treatment.

Note the disease worsening is only recorded on the ECRF on weeks 24, 32, 40 and 44 or unscheduled. For more accurate interpretation of the regimen the actual imp allocation must be considered. Where a scheduled imp allocation has not occurred due to procedure or a missed visit, it will be considered as being undertaken for the purpose of checking the regimen period. Note: further detail may be required depending on the data received and this will be detailed within the ADAM Specifications.

Treatment Administration Duration will be defined overall from Start Day 1 to end of treatment or end of study.

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.

[redacted]

The number of administrations of IMP per participant and the compliance will be summarized descriptively overall, summing the different doses from the different regimens. 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.

11.1. 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.

12. STUDY MEDICATION COMPLIANCE

The infusion is given once a week by site staff or delegate. At least, the first 3 doses of IMP (for QW dosing regimen: baseline visit and the week 1 and 2 visits; for Q2W dosing regimen: baseline visit and the week 2 and 4 visits; or subsequent if previous doses are missed) must be administered on-site.

Compliance will be calculated for Q2W participants who continued Q2W dosing regimen throughout the study. The dosing regimen of other participants will be listed in the listing.

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

12.1. 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.

13. EFFICACY OUTCOMES

13.1. Efficacy Endpoints

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

[redacted]

13.1.1. Proportion of CRESS Responders on ≥3 of 5 items at Week 24 and 48

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 efficacy endpoint is the proportion of responders on ≥ 3 non-missing of 5 items at week 24 and 48 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)[8].

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
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*

[redacted]

Domain (activity level)	ClinESSDAI Weights
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 and 48[4].

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 electronic clinical outcome assessment (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

[redacted]

- 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

[redacted]

clearness of the salivary gland border, graded 0–3	clearness of the salivary gland border, graded 0–3	clearness of the salivary gland border, graded 0–3	clearness of the salivary gland border, graded 0–3
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. The 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.

The proportion of participants with CRESS responders on ≥3 of 5 items at week 24 and 48 will be provided along with exact 90% CIs.

13.1.2. Proportion of Participants with Minimal Clinically Important Improvement in ESSDAI: Improvement of ≥ 3 Points in ESSDAI Score at Week 24 and 48 & Proportion of Participants with Low Disease Activity: ESSDAI Score of < 5 at Week 24 and 48

As explained in Section 14.2.1.1, the ESSDAI (Seror [a], et al., 2015)[9] 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

[redacted]

Domain (activity level)	ESSDAI Weights
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, 1: Low, 2: Moderate, 3: High.

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 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 exact 90% CIs and for each of these two endpoints.

[redacted]

13.1.3. Proportion of Participants with Minimal Clinically Important Improvement in clinESSDAI: Improvement of ≥ 3 Points in clinESSDAI Score at Week 24 and 48 & Proportion of Participants with Low Disease Activity: clinESSDAI score of < 5 at Week 24 and 48

As explained in Section 14.2.1.1of SAP, the ClinESSDAI includes all ESSDAI domains except the biological domain.
The proportion of participants with improvement of >= 3 points in clinESSDAI score and the proportion of participants having clinESSDAI score of <5 at week 24 and 48 will be provided, along with exact 90% CIs and for each of these two endpoints.

13.1.4. Proportion of Participants with Minimal Clinically Important Improvement in ESSPRI: Decrease of 1 Point or ≥ 15% at Week 24 and 48

The Information on the derivation of ESSPRI total score is provided in Section 14.2.1.1.
The proportion of participants with decrease of 1 point or >= 15% in ESSPRI total score at week 24 and 48 will be provided and along with exact 90% CIs for each of these two endpoints.

13.1.5. Change in ESSDAI Score, clinESSDAI Score and ESSPRI Score at Week 24 and 48

These scores will be descriptively summarized for actual scores and changes from baseline in ESSDAI, clinESSDAI, and ESSPRI at scheduled timepoint of week 16, 24, 36 and 48. In addition, the same analysis in clinESSDAI and ESSDAI will be assessed for three subgroups (mutually exclusive) based on the dosing regimen defined below.

- For patients continuing QW: the population that patients continuing QW is defined as those continue QW throughout the study.
- For patients switching to Q2W: the population that patients switching to Q2W is defined as that switch from QW to Q2W at any timepoint.
- For patients switching back to QW from Q2W: the population that patients switching back to QW from Q2W is defined as those switches from Q2W to QW at any timepoint.

Plots of mean changes from the OLE baseline will be presented along with their 90% confidence intervals at each scheduled timepoint of week 16, 24, 36 and 48 for ESSDAI, clinESSDAI, and ESSPRI. Box and Whisker plots will also be presented for the change from OLE baseline for each scheduled timepoint.

13.1.6. Proportion of Participants with STAR Score of ≥ 5 at Week 24 and 48

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 14.2.1.1. This composite measure contains 5 domains (like CRESS):

- Systemic activity: If participant has clinESSDAI score decreased by ≥ 3 points at week 24 and 48, 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 and 48, 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 16, 24, 36 and 48 will be provided and along

[redacted]

with exact 90% CIs.

[redacted]

13.2. [redacted]

[redacted]

13.2.5 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

13.2.7 [redacted]

[redacted]

13.2.8. [redacted]

[redacted]

[redacted]

[redacted]

13.2.9. [redacted]

[redacted]

13.2.10. [redacted]

[redacted]

13.2.11. [redacted]

[redacted]

[redacted]

13.2.12. [redacted]

[redacted]

13.2.13. [redacted]

13.2.14. [redacted]

[redacted]

[redacted]

[redacted]

13.3 [redacted]

[redacted]

13.3 [redacted]

[redacted]

13.3 [redacted]

[redacted]

13.3. [redacted]

[redacted]

[redacted]

13.3.5 [redacted]

[redacted]

14. PHARMACODYNAMIC ANALYSIS

PD analyses will be performed in the SAF. PD endpoints include total IgG, Anti-Ro/SS-A, and anti-La/SS-B. PD endpoints will 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 at baseline, week 4, 8, 12, 16, 24, 36, 48, and SFV, 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, Anti-Ro/SS-A, and anti-La/SS-B, 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.

15. 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, 36, 48 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

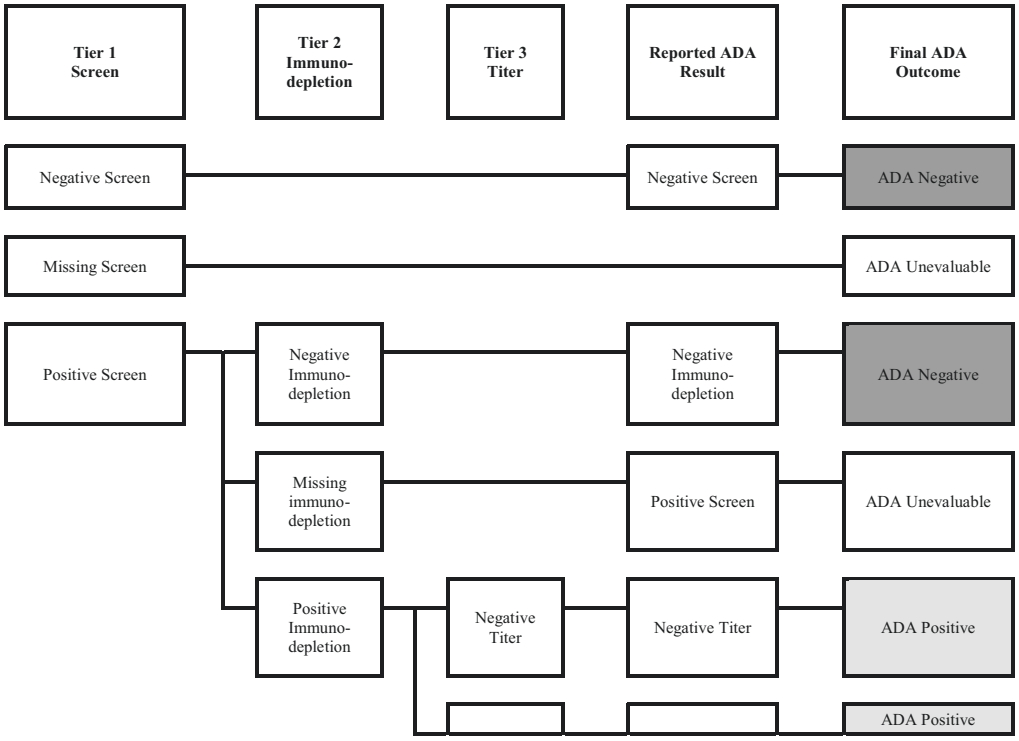
[redacted]

always available:

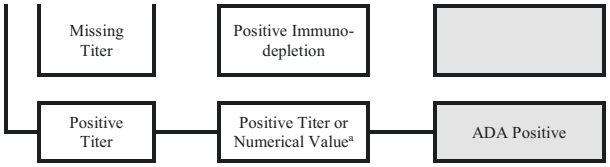
- If the ADA confirmed positive sample could not be run in the titration assay (e.g., due to insufficient sample volume/quality to perform the titer analysis), the result will be described as “positive immuno-depletion”, and the sample should be considered ADA positive.
- If a sample is negative in the 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



[redacted]



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

Participant Classification for ADA Against Efgartigimod

Table G 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-

[redacted]

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.

[redacted]

16. [redacted]

[redacted]

17. SAFETY OUTCOMES

17.1. Primary Safety Outcomes

To assess the long-term safety and tolerability of efgartigimod in participants, the below safety endpoints are considered within the primary 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.

17.1.1. Adverse Events

AEs and SAEs will be collected as defined in the Section 10.3 of the protocol. Also, the AEs listed in previous study of ARGX-113-2106 which are “Ongoing” will be included for OLE study. 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

[redacted]

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 IMP discontinuation will be identified if "Drug withdrawn" is collected by using the "Action taken with Efgartigimod due to adverse event" from the AE page of the eCRF.
AEs leading to IMP interruption will be identified if "Drug interrupted" is collected by using the "Action taken with Efgartigimod due to adverse event" from the AE page of the eCRF.
Adverse event of special interest (AESsI) 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:

[redacted]

- 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 patient years of follow-up (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 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 expressed in years (i.e. divided by 365.25).
Some examples using the efgartigimod cut-off of 60 days:
With 'the follow-up time during which an event is considered treatment-emergent' we mean the following:

- If a participant received medication from Sept 1 until Sept 30, then the follow-up time during which events are considered treatment-emergent is from Sept 1 until 60 days after Sept 30. So, the follow-up time is 90 days.
- If a participant received only medication on Sept 1, then the follow-up time for this participant is 61 days.

[redacted]

If a participant has no meaningful interruptions (ie, no interruptions of more than 60 days), the follow-up time during which an event is considered treatment-emergent is equal to (last dose date – first dose date + 1) + 60.

Example:

- Subject 1 has 2 TEAEs and a treatment duration (last dose date – first dose date +1) of 15 days => follow-up time = 15 + 60.
- Subject 2 has 1 TEAE and a treatment duration of 45 days => follow-up time = 45 + 60.

Then the event rate per 100 PYFU is calculated as: 100 * (2+1) / [(15+60+45+60)/365.25)].
The actual duration of the event does not play any role in the derivation of event rate.

All AEs, including pretreatment events will be listed.

17.1.1.1. All TEAEs

Summary tables will only include TEAEs and will be presented by System Organ Class (SOC) and Preferred Term (PT). 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

17.1.2. Laboratory Evaluations

Results from the central laboratory will be included in the reporting of this study for serum chemistry and

[redacted]

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, %reticulocytes, WBC count with differential: neutrophils, eosinophils, lymphocytes, basophils, monocytes
Serum chemistry	ALT, AST, GGT, alkaline phosphatase, albumin, creatinine, potassium, BUN, CRP, glucose, sodium, total protein, calcium, bilirubin (total and direct)
Routine urinalysis	Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase, microscopic examination (if blood or protein is abnormal)
Pregnancy testing	Urine test at baseline and other time points (as needed for WOCBP potential, defined in Section 10.4.1 of the protocol)

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

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

[redacted]

abnormalities will also be shown. The denominator for the percentage is the total number of participants and per analysis visit in the SAF.

- Listing of participants with any post-baseline abnormality or toxicity grade ≥1.

17.1.2.1. Laboratory Specific Derivations

All datapoints obtained after informed consent up to 60 days after IMP discontinuation 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.

17.1.3. 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)

[redacted]

- QTcB Interval (msec)
- Axis (^{0})

All datapoints obtained after informed consent up to 60 days after IMP discontinuation 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 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 and per analysis visit.
- All ECG data will be listed, but only for participants with any postbaseline abnormality.

17.1.3.1. ECG Abnormal Criteria

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

Table I: Criteria to Define ECG Abnormalities

	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:

[redacted]

- ≤ 30 (normal)
-]30; 60]
- > 60

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

17.1.4. Vital Signs

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

- Sitting / Supine Systolic Blood Pressure (SBP) (mmHg)
- Sitting / Supine Diastolic Blood Pressure (DBP) (mmHg)
- Sitting / Supine Pulse Rate (bpm)
- Respiratory Rate (breaths/min)
- Body Temperature (^{0} C)
- Weight (Kg)

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 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.

17.1.4.1. Vital Signs Abnormal Criteria

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

Table JI: Criteria to Define Vital Sign Abnormalities

	Pulse rate (bpm)	SBP (mmHg)	DBP (mmHg)	Temperature (°C)
Low	<40	<90	<45	<35.8
Normal	40-100	90-150	45-90	35.8-37.5
High	>100	>150	>90	>37.5

[redacted]

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.

17.2. Other Safety Outcomes

17.2.1. Physical Examination

Brief physical examination will include weight (recorded on eCRF Vital Signs), assessments of gastrointestinal, pulmonary, cardiovascular, and respiratory systems; and general appearance.
All datapoints obtained after informed consent up to 60 days after IMP discontinuation will be considered. Physical examination abnormalities will be listed with the AE's.

18. 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) and post-dose (within 30 minutes after the end of IMP infusion) at baseline and week 16.
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.
- Postdose samples are collected following the occurrence of incomplete or incorrect dosing for the most recent prior dose 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

[redacted]

and a reason for the exclusion of the data point will be added in the appropriate listing.

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.

19. 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. Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS): development and validation of a novel outcome measure. Lancet Rheumatol. 2021;3(8):E553-E562.

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

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