STATISTICAL ANALYSIS PLAN

Protocol No. ARGX-113-2105

Open-Label Extension Study to Evaluate the Long-term Safety and Efficacy of Efgartigimod in Adult Patients with Post-COVID-19 Postural Orthostatic Tachycardia Syndrome (PC-POTS) who Completed Study ARGX-113-2104

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V0.1 (Dated 23 FEB 2024) for Protocol ARGX-113-2105.

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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, Statistical Services		
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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	24 April 2024	[redacted]	Not Applicable – First Version

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Term
[redacted]	[redacted]
ADA	antidrug antibody(ies)
AE	adverse events
AESI	adverse events of special interest
BLQ	below the limit of quantification
bpm	beats per minute
CI	confidence interval
COMPASS 31	Composite Autonomic Symptom Score
eCRF	Electronic case report form
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DBP	diastolic blood pressure
ECG	electrocardiogram
EDV	early discontinuation visit
ENR	Enrolled Analysis Set
EoS	end of study
EoT	end of treatment
FAS	full analysis set
FPA	Final Planned Analysis
[redacted]	[redacted]
IA	Interim Analysis

ICF	informed consent form
IgG	immunoglobulin G
IMP	investigational medicinal product
IRR	Infusion/injection related reactions
LLN	lower limit of normal
MaPS	Malmö POTS symptom score
MedDRA	Medical Dictionary for Regulatory Activities
msec	millisecond
NCI	National Cancer Institute
ND	not determined
OLE	open-label extension
PD	pharmacodynamic(s)
PGI-C	Patient Global Impression – Change
PGI-S	Patient Global Impression – Severity
PK	pharmacokinetic(s)
PKAS	pharmacokinetic analysis set
POTS	postural orthostatic tachycardia syndrome
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	preferred term
QTc	corrected QT interval
QTcB	Bazett's corrected QT interval
QTcF	Fridericia's corrected QT interval
Q2W	Every 2 weeks
QW	Once weekly

[redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SAF	safety analysis set
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SFV	safety follow-up visit
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
ULQ	upper limit of quantification
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-113-2105. 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. This SAP is based on protocol version 2.0 (Amendment 1), dated 23 February 2024.

2. STUDY OBJECTIVES AND ENDPOINTS

Objectives

Objectives	Endpoints
Primary	
• Evaluate the long-term safety of efgartigimod in patients with post-COVID-19 POTS	• Incidence and severity of AEs and AESIs, incidence of SAEs, changes in clinically significant laboratory test results (per investigator judgment), vital signs, and ECG results
Secondary	
• Evaluate the long-term efficacy of efgartigimod in reducing the severity of PC-POTS symptoms	• Change from baseline to week 24 and week 48 in COMPASS 31 (modified) • Change from baseline to week 24 and week 48 in MaPS
• Evaluate the long-term efficacy of efgartigimod on patient global assessment of symptom experience, fatigue, and cognitive function	• Change from baseline to week 24 and week 48 in PGI-S • PGI-C at week 24 and week 48 • Change from baseline to week 24 and 48 in the PROMIS Fatigue Short Form 8a • Change from baseline to week 24 and 48 in the PROMIS Cognitive Function Short Form 6a
• Assess the PD effect of efgartigimod	• Absolute values, changes from baseline, and percent reduction from baseline in total IgG levels over the 48-week treatment period

• Assess the exposure to efgartigimod	• Efgartigimod serum trough concentrations over the 48-week treatment period
• Assess the immunogenicity of efgartigimod	• Incidence and prevalence of ADA against efgartigimod over the 48-week treatment period
Exploratory	
• [redacted]	• [redacted]
• [redacted]	• [redacted]

[redacted] ADA=antidrug antibodies; AE=adverse event; AESI=adverse events of special interest; COMPASS=Composite Autonomic Symptom Score; ECG=electrocardiogram; [redacted] IgG=immunoglobulin G; MaPS=Malmö POTS Symptom Score; PC-POTS=post-COVID-19 postural orthostatic tachycardia syndrome; PD=pharmacodynamic; PGI-C=Patient Global Impression of Change; PGI-S=Patient Global Impression of Severity; PROMIS=Patient-Reported Outcomes Measurement Information System; [redacted]; SAE=serious adverse event

3. STUDY DESIGN

3.1. General Description

Study ARGX-113-2105 (2105) is a long-term, single-arm, open-label, multicenter extension of the ARGX-113-2104 (2104) study, designed to evaluate the long-term safety of efgartigimod IV in adult patients with PC-POTS. Participants will be enrolled from both active and placebo arms of the 2104 study and will receive efgartigimod IV 10 mg/kg in the extension study without knowledge of their prior treatment arm. To be eligible to enroll in this study, participants must have completed the 24-week treatment period of the 2104 study and must not have permanently

discontinued the IMP in that study.

The treatment period of this study is 48 weeks. Participants will receive efgartigimod (10 mg/kg) by IV infusion QW for the first 4 weeks (induction dosing period), and then Q2W for 42 weeks (maintenance dosing period). Participants will return for a safety follow-up visit approximately 56 days after the last dose of IMP administration. The total study duration is approximately 386 days comprising:

- Treatment period of 48 weeks:
  - Induction dosing period: 4-week period of QW efgartigimod IV dosing from day 1 (baseline) to day 22 (week 3)
  - Maintenance dosing period: 42-week period from day 29 (week 4) to day 323 (week 46) Q2W. Participants will receive efgartigimod IV doses Q2W, with the first dose of this period administered on day 29 (week 4). If clinically indicated (e.g., the participant loses PC-POTS symptom control), the participant and investigator, based on the participant-reported reason for the request and physical examination, can jointly decide to return to QW dosing. Participants who switch back to QW dosing will not be allowed to switch back to Q2W dosing during the study. Participants who switch must attend an unscheduled visit. The decision to switch to QW dosing and the date of the switch should be recorded in the eCRF.
  - End of treatment visit on week 48.

- Safety follow-up period starting after last dose of IMP, with a safety follow-up visit approximately 56 days after the last dose of IMP administration.

Visit Frequency:
A minimum of 8 study site visits over the 48-week treatment period and 56-day follow-up period is planned (baseline, weeks 1, 2, 4, 12, 24, 48, and the SFV); all other visits may be conducted by home health care service, or telemedicine visit.

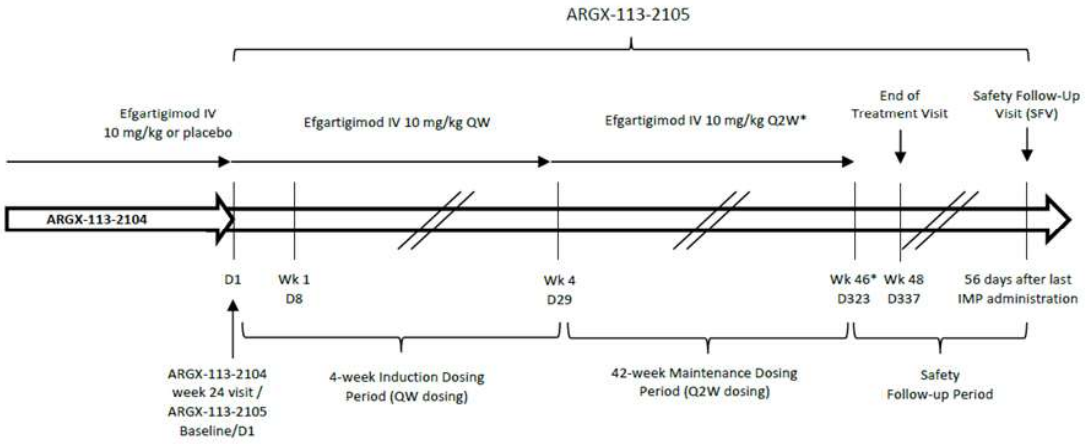
End-of-Study Definition:
The end-of-study is defined as the date of the last participant's last visit.
A participant will have completed the study if the SFV has been completed. The SFV will occur 56 ±3 days after the participants final IMP administration.

Treatment and Dosing:
The treatment period of this study is 48 weeks. Participants will receive efgartigimod (10 mg/kg) by IV infusion QW for the first 4 weeks (induction dosing period), and then once Q2W for 44 weeks (maintenance dosing period).
Efgartigimod will be administered during the treatment period in an approximately 1-hour IV infusion by site staff or a home nurse. If clinically indicated (e.g., the participant loses PC-POTS symptom control), the participant and investigator, based on the participant-reported reason for the request and physical examination, can jointly decide to return the participant to QW dosing during the maintenance dosing period. Participants who switch back to QW dosing

will not be allowed to switch back to Q2W dosing during the study. Participants who switch must attend an unscheduled visit.
The decision to switch to QW dosing and the date of the switch should be recorded in the eCRF. The final dose for participants who remain on Q2W dosing will be administered at week 46 (day 323). The final dose for participants who switch back to QW dosing during the maintenance dosing period will be administered at week 47 (day 330). The end of treatment visit occurs on week 48 (day 337).
The 10 mg/kg efgartigimod dose is based on body weight, and the maximum total dose per efgartigimod infusion is 1200 mg for participants who weigh ⩾120 kg. The dose level will be recalculated if a participant's weight has changed (increased or decreased) by more than 10% from baseline. Otherwise, dose modifications are not permitted.
IMP infusions must occur at the site for a minimum of 3 consecutive visits (baseline visit and the week 1 and 2 visits) before home infusions are allowed. If doses are missed at 1 or more of these visits, then dosing at subsequent visits will also be on-site. IMP administration at home will not commence until after 3 doses have been administered on-site.

Blinding:
This study is open label, and the sponsor/designee, participants, and investigators will remain blinded to laboratory variables as detailed in the unblinded plan until such time as 2104 becomes unblinded, this is to stop 2104 inadvertently becoming unblinded.

Study Overview



Abbreviations: D = day; IV = intravenous; QW = once weekly; Q2W = every 2 weeks; Wk = week.
* During the maintenance dosing period, the participant and investigator (based on the participant-reported reason for the request and physical examination) can jointly decide to return the participant from Q2W to QW dosing. The final dose for participants who remain on Q2W dosing will be administered at week 46 (day 323). The final dose for participants who switch back to QW dosing during the maintenance dosing period will be administered at week 47 (day 330).

3.2.Sample Size

The results of this study will not be used inferentially. No formal sample size calculation is performed. Approximately 38 participants are expected to roll over to this OLE study and receive efgartigimod IV 10 mg/kg, assuming approximately 90% of participants in the parent study (ARGX-113-2104) will be eligible to enrol in this OLE study.
Note: Enrolled means the participant agrees to participate in the clinical study by completing the informed consent process, and having fully completed the parent study (2104).

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

4. THE, BASELINE IS DEFINED AS THE LAST AVAILABLE NON-MISSING MEASUREMENT FROM THE PARENT STUDY 2104. PLANNED ANALYSES

The following analyses will be performed for this study:

- Interim Analysis
- Final Analysis

4.1.Data Monitoring Committee

There will be no Data monitoring Committee for this study.

4.2.Interim Analysis

One interim analysis will take place for this study once all the participants have completed the week 24 assessments on 2104 or discontinued the study prior to week 24. Interim analyses identified in this SAP will be performed by IQVIA Biostatistics following authorization of this SAP, database lock and analysis sets. The results of interim analysis will be based on the unblinded data. Section 9.4 of the protocol can be referred to for reference of interim analysis.

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.

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 Clinical Pharmacology Department in conjunction with BIOS group, PK concentration listings and summary statistics will be described in this SAP. A separate modeling and simulation 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 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 enrolled participants.

5.3. Safety Analysis Set [SAF]

The safety analysis set (SAF) will contain all enrolled participants who exposed to study intervention.

5.4. PK Analysis Set [PKAS]

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.

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 informed consent 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.
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 per parameter from the parent study 2104. Refer to appendix 1 baseline for details.
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.
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.
The baseline visit for Study 2105 will be conducted after the participant has finished in 2104 and completed week 24

analysis. All baseline assessments will be performed before first administration of efgartigimod IV in ARGX-113-2105, if applicable. Assessments do not need to be repeated if they are performed as part of 2104.

6.3. Windowing Conventions

All assessments, including unscheduled assessments, will be allocated to analysis visit window. Tables and listings will be based on analysis window defined below and the schedule in section 1.3 of the protocol. Allocations of assessments will be performed using their relative day and only for the scheduled visit windows.

Non-efficacy Analysis Visit Definition

	Target Day	Assigned Study Day (Inclusive)		Week Assigned
		From	To	
Treatment	1		1[a]	Baseline
	8	1[b]	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
	57 + (x*7)	57 + (x*7) - 3	57 + (x*7) + 3	Week 8+x [c]
Safety Follow-up	Final dose + 56 days	(Final dose + 56 days) - 3 days	(Final dose + 56 days) + 3 days	Week xx+ 56 days

[a] Last available non-missing measurement from the parent study 2104.

[b] Post baseline visit Day 1.

[c] considers value of x, starting from 1 to up until 40 to get visit windows for Week 9 to Week 48.

Note: After treatment period ends, safety follow-up will be of approximately 8 weeks (56 days ± 3 days) .
Some parameters which are not collected at every visits, visit window will be combined (by extending window with previous or subsequent visits).

Serum Checmistry and hematology, Physical examination, Analysis Visit Definition

	Target Day	Assigned Study Day (Inclusive)		Week Assigned
		From	To	
Treatment	1		1[a]	Baseline
	29	1[b]	57	Week 4
	85	58	127	Week 12
	169	128	253	Week 24
	337	254	340	Week 48
Safety Follow-up	Final dose + 56 days	(Final dose + 56 days) - 3 days	(Final dose + 56 days) + 3 days	Week xx+ 56 days

[a] Last available non-missing measurement from the parent study 2104[b] Post baseline visit Day 1.

Immunogenicity, Analysis Visit Definition

	Target Day	Assigned Study Day (Inclusive)		Week Assigned
		From	To	
Treatment	1		1[a]	Baseline
	8	1[b]	18	Week 1
	29	19	57	Week 4
	85	58	127	Week 12
	169	128	253	Week 24
	337	254	340	Week 48
Safety Follow-up	Final dose + 56 days	(Final dose + 56 days) - 3 days	(Final dose + 56 days) + 3 days	Week xx+ 56 days

[a] Last available non-missing measurement from the parent study 2104[b] Post baseline visit Day 1.

ECG, Analysis Visit Definition

	Target Day	Assigned Study Day (Inclusive)		Week Assigned
		From	To	

Treatment	1		1[a]	Baseline
	85	1[b]	127	Week 12
	169	128	253	Week 24
	337	254	340	Week 48
Safety Follow-up	Final dose + 56 days	(Final dose + 56 days) - 3 days	(Final dose + 56 days) + 3 days	Week xx+ 56 days

[a] Last available non-missing measurement from the parent study 2104[b] Post baseline visit Day 1.

Efficacy Analysis Visit Definition

For MAPS efficacy assessments, the following window will be considered:

Target Day	Assigned Study Day (Inclusive)		Week Assigned
	From	To	
1		1	Baseline
15	2	22	Week 2
29	23	36	Week 4
43	37	50	Week 6
57	51	64	Week 8
71	65	78	Week 10
85	79	99	Week 12
113	100	127	Week 16
141	128	155	Week 20
169	156	211	Week 24
253	212	295	Week 36
337	296	340	Week 48

Last available non-missing measurement from the parent study 2104

For COMPAS efficacy assessments, the following window will be considered:

Target Day	Assigned Study Day (Inclusive)	

	From	To	Week Assigned
1		1	Baseline
15	2	22	Week 2
29	23	43	Week 4
57	44	71	Week 8
85	72	127	Week 12
169	128	211	Week 24
253	212	295	Week 36
337	296	340	Week 48

Last available non-missing measurement from the parent study 2104

For PGI-S, PGI-C and PROMIS Fatigue efficacy assessments, the following window will be considered:

Target Day	Assigned Study Day (Inclusive)		Week Assigned
	From	To	
1		1	Baseline
15	2	22	Week 2
29	23	57	Week 4
85	58	106	Week 12
169	149	178	Week 24
337			Week 48

Last available non-missing measurement from the parent study 2104

For PROMIS Cognition efficacy assessments, the following window will be considered:

Target Day	Assigned Study Day (Inclusive)		Week Assigned
	From	To	
1		1	Baseline
29	2	57	Week 4
85	58	127	Week 12
169	128	253	Week 24

337	254	240	Week 48

Last available non-missing measurement from the parent study 2104

[redacted]:

Target Day	Assigned Study Day (Inclusive)		Week Assigned
	From	To	
1		1[a]	Baseline
85	1[b]	127	Week 12
169	128	253	Week 24
337	254	340	Week 48

[a] Last available non-missing measurement from the parent study 2104

[b] Post baseline visit Day 1.

Subject who permanently discontinue the treatment, assessment (COMPASS 31, MaPs, PGI-S and PGI-C, PROMIS, Exit Interview, [redacted]) will be collected at IMP discontinued visit which will be performed at next scheduled visit after discontinuation: EDV visits will be performed within 7 days of last contact with participant for those subjects who discontinue study permanently.

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, the visit label, or group identifier (if applicable). Windowing will be applied to the data prior to any missing data calculations. Questionnaire Total scores and other assessments closest to the target date will be considered for questionnaires.

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 to 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 (eg, 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 5%; confidence intervals (CIs) will be 95% 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" 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 safety, see appropriate section of the applicable endpoints.
Other missing values 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. In tables by analysis visit, only analysis visits with at least 10 participants (overall) will be 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.

Descriptive statistics for PK serum concentrations will include the number of observed values, arithmetic mean, SD, median, minimum and maximum, CV%, the GM, and geometric CV%. Serum concentrations will be reported as received by the bioanalytical laboratory.

Descriptive statistics for PK concentrations will be presented with 3 significant digits in µg/mL for efgartigimod (where appropriate), except values ≥1000 which will be presented without the decimals and rounded to the nearest integer. If at least one BLQ value is reported at a specific time point, the GM 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, and geometric CV% will not be calculated.

Descriptive statistics for immunogenicity titer values will include the number of observed values, arithmetic mean, SE, 95% CI, median, Q1, Q3, minimum, maximum, the GM, 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 ENR for the Final Planned Analysis (FPA). The number of participants per country and site will also be provided using the SAF for the FPA. The number of participants who completed or discontinued the treatment using the SAF, for IA and FPA and/or the study along with the reason for discontinuation will be summarized using the FAS for both the IA and FPA.

Participant disposition and withdrawals will be presented for the FAS set.
Data will be tabulated at least for;

- participants each analysis sets for the FPA
- number and percentage of participants who roll over from OLE study 2104 for the FAS, IA and FPA.
- number and percentage of participants completed, or discontinued the study for the IA and FPA.
- number and percentage of participants for each study discontinuation reason or the IA and FPA.
- number and percentage of participants discontinuing treatment but continuing study assessments for the IA and FPA.

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 for the FPA.
- 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 for IA and FPA.
The following demographic and other baseline characteristics will be reported for this study:

- Age (years) - calculated relative to date of consent - overall
  - 18-<65 years
  - 65-<75 years
  - >=75 years
- Sex
  - Childbearing potential for female subjects only
- Race
- Ethnicity
- Base line weight (kg)
- Height (cm) Measured at screening for 2104
- Baseline BMI (kg/m^2)

Summary statistics including n, mean, median, SD, Q1, Q3, minimum and maximum will be presented for continuous variables such as age, height, weight, BMI and [redacted] 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.

9.1. Derivations

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

10. MEDICAL HISTORY

Surgical and Medical History & Concomitant illnesses information will be presented for the SAF.
Refer to the criteria in Appendix 1 for which Surgical and Medical History collects in POTS will be added into POTS-

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

- Medical History conditions are defined as those conditions which stop prior to or at Baseline. Hence, any medical history abnormalities/conditions and any event before or at Wk 24 2104 will be presented as Medical History.
- Concomitant illnesses which started prior to or at wk 24 2104 date and are ongoing during the study will be reported. These are also recorded in Medical History page of the eCRF.
- Medical history and concomitant illnesses will be presented by SOC and PT.

Frequency and percentage of participants with findings by SOC and PT will be presented for FPA only.

11. THERAPIES

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.
Refer to the criteria in Appendix 1 for which Prior and Concomitant Therapies collects in POTS will be added into POTS-OLE.
See Appendix 3 for handling of partial and missing dates for medications.

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

- Prior therapy: the therapy strictly started before the first dose date in this 2105 study
- Concomitant therapy: the therapy was taken on or after the first dose date in this 2105 study

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. All prior and concomitant therapies will be listed.

12. STUDY MEDICATION EXPOSURE

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

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 Study 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. Overdosed information is as collected in "Exposure – Infusion" page of eCRF.

The total treatment administration duration, the duration on weekly infusions, two weekly infusions, and reverting back to one weekly infusion will be summarized using descriptive statistics. The Number of administrations in total, and per dosing regime will be summarized using descriptive statistics.
Compliance will be further summarized by visit for each of the three regimens. 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 on specific dosing regime – date of first IMP administration on specific dosing regime + 1.
-
- Number of administrations = Number and percentage of participants receiving 1,2,3 etc.
-

13. STUDY MEDICATION COMPLIANCE

The study includes a 48-week treatment period in which all patients will initially receive QW doses of efgartigimod (10 mg/kg) by IV infusion. After 4 weeks of this induction dosing period, participants will be switched to a less frequent dosing regimen (Q2W), for the maintenance dosing period, although if clinically indicated the participant can be returned to QW dosing.
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.
All IMP administration data will be listed.

13.1. Derivations

Compliance is defined as: 100* (number of doses received/number of doses expected) for each dosing regime and total. Number of doses expected will be based on participants expecting study drug infusion/administration of eCRF page "Exposure – Infusion" irrespective of dosing received. Only visits up to treatment discontinuation are considered in the compliance calculation. When a subject has reverted to weekly doses, this will be considered a separate regime

to the initial weekly dose regime.

14. PRIMARY ANALYSIS

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

- Incidence and severity of AEs
- incidence of SAEs,
- changes in clinically significant laboratory test results,
- vital signs, and
- electrocardiogram (ECG) results
-

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

14.1. Adverse Events

AEs and SAEs will be collected as defined in the section 10.3 of the protocol. Refer to the criteria in Appendix 1 for which AEs collects in POTS will be added into POTS-OLE. 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 in this 2105 study 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 (vs. 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/injection 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 to show number and percentage of participants with at least one event, and the number of events and the event rate per 100 PYFU, for the SAF at the IA and FPA for the following;

- TEAEs (IA and FPA)
- Serious TEAEs (IA and FPA)
- Grade ≥3 TEAEs (IA and FPA)
- Fatal TEAEs
- Treatment-related TEAEs according to the Principle Investigator (IA and FPA)
- Procedures-related TEAEs (FPA Only)
- Serious treatment-related TEAEs (IA and FPA)
- TEAEs leading to IMP discontinuation (IA and FPA)
- TEAEs leading to IMP interruption
- TEAEs of special interest (IA and FPA)
- IRRs (IA and FPA)

IRRs

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

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.

14.1.1. All TEAEs

Summary tables will only include TEAEs and will be presented by System Organ Class (SOC) and Preferred Term (PT) for each treatment regimen and total. 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 (FPA Only)

- Treatment-related TEAEs
- Procedure-related TEAEs
- Serious treatment-related TEAEs
- TEAEs leading to IMP discontinuation or interruption.
- TEAEs of special interest by worst outcome
- IRRs
- Serious IRR (IA and FPA)

14.2. Laboratory Evaluations

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

Laboratory Assessments

Hematology	RBC count, platelet count, hemoglobin, hematocrit, RBC indices: MCV, MCH, %reticulocytes WBC count with differential: neutrophils, eosinophils, lymphocytes, basophils, monocytes
Serum chemistry	ALT, AST, albumin[a], blood urea nitrogen, creatinine, glucose, potassium, chloride bicarbonate, sodium, total protein[a], calcium, bilirubin (total and direct)
Routine urinalysis	Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase, microscopic examination (if blood or protein is abnormal)
Pregnancy testing	Urine test (as needed for WOCBP potential, defined in Section 10.4.1 of the protocol)
Specialty laboratory tests:	CRP, ESR, TSH

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell; TSH=thyroid stimulating hormone; WBC=white blood cell; WOCBP=women of childbearing potential

[a] Results will be blinded up to and including the date of database lock on 2104, so as not to unblind 2104 prematurely.

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 descriptive summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings. For Toxicity grades the <X and >X will be represented within the scores.
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 for SAF at the IA and FPA.
- 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 for SAF at the IA and FPA.
- Laboratory abnormalities as cross-tabulations of the abnormality at each postbaseline analysis visit and at the worst-case analysis visit versus the baseline abnormality for SAF at the IA and FPA.
- 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.

14.2.1. Laboratory Specific Derivations

All datapoints obtained after informed consent up to 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 analyzed 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.

14.3. 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 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 for the SAF for FPA only.
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 in the SAF for FPA only.
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 in the SAF. Produced for the FPA only.
All ECG data will be listed, but only for participants with any postbaseline abnormality.

14.3.1. 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.

Absolute 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.

14.4. Vital Signs

The following Vital Signs measurements will be reported for this study for SAF at the IA and FPA.:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)
- Respiratory Rate (breaths/min)
- Oral Temperature (ºC)

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.

14.4.1. 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
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.

14.5. Physical Examination

Physical examination will be assessed as defined within protocol. 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.

15. SECONDARY ANALYSIS

15.1. Efficacy Variables & Derivations

The efficacy variables are:

- Change from baseline to week 24 and week 48 in the Composite Autonomic Symptom Score 31 (COMPASS 31, modified)
- Change from baseline to week 24 and week 48 in the Malmö POTS Symptom Score (MaPS)
- Change from baseline to week 24 and week 48 in the Patient Global Impression of Severity (PGI-S)
- Patient Global Impression of Change (PGI-C) at week 24 and week 48
- Change from baseline to week 24 and 48 in the Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form 8a
- Change from baseline to week 24 and 48 in the PROMIS Cognitive Function Short Form 6a

For analyses of change from baseline, the baseline is defined as the latest measurement prior to enrollment in the OLE study. Efficacy endpoints will be analyzed using the FAS for IA and FPA.
No estimands have been defined for this study.

15.1.1. Change from baseline to week 24 and week 48 in the Composite Autonomic Symptom Score 31 (COMPASS 31) (modified)

COMPASS 31 questionnaire is to evaluate the severity and distribution of autonomic symptoms in various autonomic nerve disorders. The 31-item questionnaire addresses 6 domains: orthostatic intolerance, vasomotor, secretomotor, bladder, pupillomotor, and gastrointestinal-mixed upper and diarrhea. The modified version (2-week recall) will be used throughout the study. The modified COMPASS 31 version used in the ARGX-113-2105 study modified the recall period to 2 weeks in contrast with the original COMPASS 31.
Participants are asked to respond to each of the item question using different, response options depending on each item, based on their perceived symptoms experience over the last 2 weeks. The response options are different depending on item content and vary from dichotomous to 7-point scale options. The modified COMPASS 31 has 6 domains that sum up to a total score of 0 to 100. Higher scores indicate a more severe degree of autonomic symptoms.

The modified COMPASS 31, scoring algorithm for each domain and total scores will be provided by external vendor. This total score will be considered for change from baseline analysis.

The analysis will be performed for the FAS for IA and FPA. Summary statistics will be provided in terms of absolute value and changes from baseline of 2105 study for each visit where no imputation performed on missing data. The

summary statistics for the change from baseline of 2105 study in COMPASS 31 score at each visit will also be presented by a longitudinal graph by parent treatment group.

Further charts will be produced showing the summary statustics for the change from baseline of 2105 study in COMPASS 31 score at each visit in a longitudinal graph by parent treatment group and by reverted back to QW group and non-reverted group.

For the measuring reduction in severity of COMPASS 31, summary statistics and plots for change from the parent study baseline will also be presented.

The COMPASS 31 score will also be presented by visit for 2 subgroups, subgroups are defined as changing back at any time from Q2W to QW dosing regimen (Y/N).

15.1.2. Change from baseline to week 24 and week 48 in the MaPS

The MaPS score consists of 12 questions that will assess symptom burden related (tachycardia, palpitations, dizziness, presyncope) and unrelated to orthostatic intolerance (GI symptoms, insomnia, concentration difficulties). Participants will grade their symptoms for the past 7 days using a 11-point scale ranging from 0 (no symptoms) to 10 (worst possible). The items will be summed to yield a total score with a maximum value of 120 points, with higher scores indicating more severe symptoms. This total score will be derived programmatically.

For change from baseline to week 24 and week 48 in MaPS score, analysis will be presented similar to analysis proposed for COMPASS 31, MaPS will also be presented by visit for 2 subgroups (switch back from Q2W to QW=Y/N). All data will be included for subject in the IA even if it is for visits after week 24.

Additionally, a worsening will be defined as having 2 consecutive MAPS measures that are $\geq$ 10 points higher than baseline, in absence of infection/AEI. The number and percentage of patients who entered OLE and had a worsening condition will be calculated and presented by parent study treatment arm.

15.1.3. Change from baseline (CFB) to week 24 and week 48 in the PGI-S

Patient Global Impression of Severity (PGI-S):

- Severity of symptoms over the past week (1-week recall)
- overall experience of symptoms over the past 2 weeks (2-week recall)

are both rated on a 4-point type Likert scale, with scores ranging from 1 (none), 2(mild), 3(moderate) and 4 (severe).

Positive PGIS change (1, 2, 3) indicates worsening, while negative PGIS change (−1, −2, −3) indicates improvement while considering change from baseline to week 24 for both 1 week recall and 2 week recall results separately using the FAS for the IA.

PGIS Change

Improved 3 categories	CFB = -3
Improved 2 categories	CFB =-2
Improved 1 categories	CFB =-1
No Change	CFB =0
Worsened 1 category	CFB =+1
Worsened 2 categories	CFB =+2
Worsened 3 categories	CFB = +3

The number and percentage of participants with each PGI-S score will be summarized by treatment and time point, for the FAS. Number and percentages will also be presented for CFB categories for both 1 week recall and 2 week recall responses separately using the FAS for the IA.

These PGI-S score will further define as Improvement (with CFB as -3, -2 or -1), No Change (with CFB as 0) and Worsening (with CFB as +1, +2, +3).

15.1.4. PGI-C at week 24 and week 48

The Patient Global Impression of Change (PGI-C) is a single item designed to capture the subject's perception of change in their overall symptom severity. Overall change in symptoms from the start of IMP to time point is rated on a 7-point Likert scale, with scores ranging from Much Better (1), Somewhat Better (2), A Little Better (3), No change (4), A Little Worse (5), Somewhat Worse (6), and Much Worse (7).

The number and percentage of participants with each PGI-C score will be summarized by treatment and time point, for the FAS for IA and FPA.

These PGI-C score will further define as Improvement (those reporting "Much better", "Somewhat better", or "A little better"), No Change (those reporting "No change") and Worsening (those reporting "A little worse", "Somewhat worse" or "Much worse").

15.1.5. Change from baseline to week 24 and week 48 in the PROMIS Fatigue Short Form 8a

PROMIS Fatigue Short Form 8a assesses the impact and perceived fatigue during the last 7 days, through 8-question scale with scores ranging from 1 to 5. Scores are converted to a T-score and received within the eCOA transfers. Higher scores indicate higher fatigue levels. A decrease in score (negative change from baseline) indicates improvement in fatigue.

The number and percentage of participants with each PROMIS score will be summarized by treatment and time point, for the FAS. T-scores will be descriptively summarized to present absolute value and changes from baseline for each visit for IA and FPA using the FAS.

15.1.6. Change from baseline to week 24 and week 48 in the PROMIS Cognitive Function Short Form 6a

PROMIS Cognitive Function Short Form 6a assesses the frequency of cognitive difficulties experienced in the past 7 days. The questionnaire comprises 6 questions on subjective cognitive difficulties regarding a participant's concentration, memory, language, mental acuity, and perceived changes in cognitive functioning. The participant marks their response on a 5-point Likert scale, with lower scores indicating worse perceived cognitive functioning. Scores are converted to a T-score and received within the eCOA data transfers.

The number and percentage of participants with each individual PROMIS score will be summarized by treatment and time point, for the FAS for the IA. T-score will be descriptively summarized to present absolute value and changes from baseline for each visit.

15.2. Pharmacodynamic Analysis

Pharmacodynamic (PD) effect of efgartigimod will be assessed via Total IgG. PD analyses will be performed in the SAF for IA and FPA.
Two analyses will be presented, one using the baseline of the parent study (2104); and the other using the baseline of the present OLE study (2104 week 24 visit/ARGX-113-2105 baseline/day 1).

Total IgG will be summarized using descriptive statistics at each analysis visit. Absolute values, changes from baseline, and percent reduction 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 post baseline value

All PD data will be listed.

15.3. Pharmacokinetic Analysis

PK analyses will be performed in the PKAS.
At IMP administration visits, PK blood samples will be collected pre-dose, at visits where IMP is not administered (Week 48 and at unscheduled visits) the PK sample can be collected at any time during the visit.
A listing of PK blood sample collection times, derived sampling time deviations, and concentrations will be provided for the PKAS for FPA only.
Serum concentrations will be summarized using descriptive statistics for efgartigimod including the change from baseline and percent reduction. 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 GM and geometric CV% for that time point will not be calculated. 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 pre-dose PK sample is missed (not applicable for Day 1).
- Any event related to sample collection, handling and storage that affects the integrity of the samples and/or the bioanalytical results.
- When pre-dose PK samples are taken outside the visit windows.
- The study visit windows are ±2 days.

In the case of a protocol deviation or event which may impact the quality of PK, 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.
The strategy for the population PK analysis and any related exposure-response modeling utilizing the efgartigamod concentration and IgG data collected from this study will be outlined separately in the modeling data analysis plan.

15.4. Immunogenicity Analysis

Incidence and prevalence of antidrug antibodies (ADA) against efgartigimod will be assessed in the SAF for the FPA. ADAs to efgartigimod is measured at the time points specified in the schedule of activities of protocol, primarily at baseline, week 1, 4, 12, 24, 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).

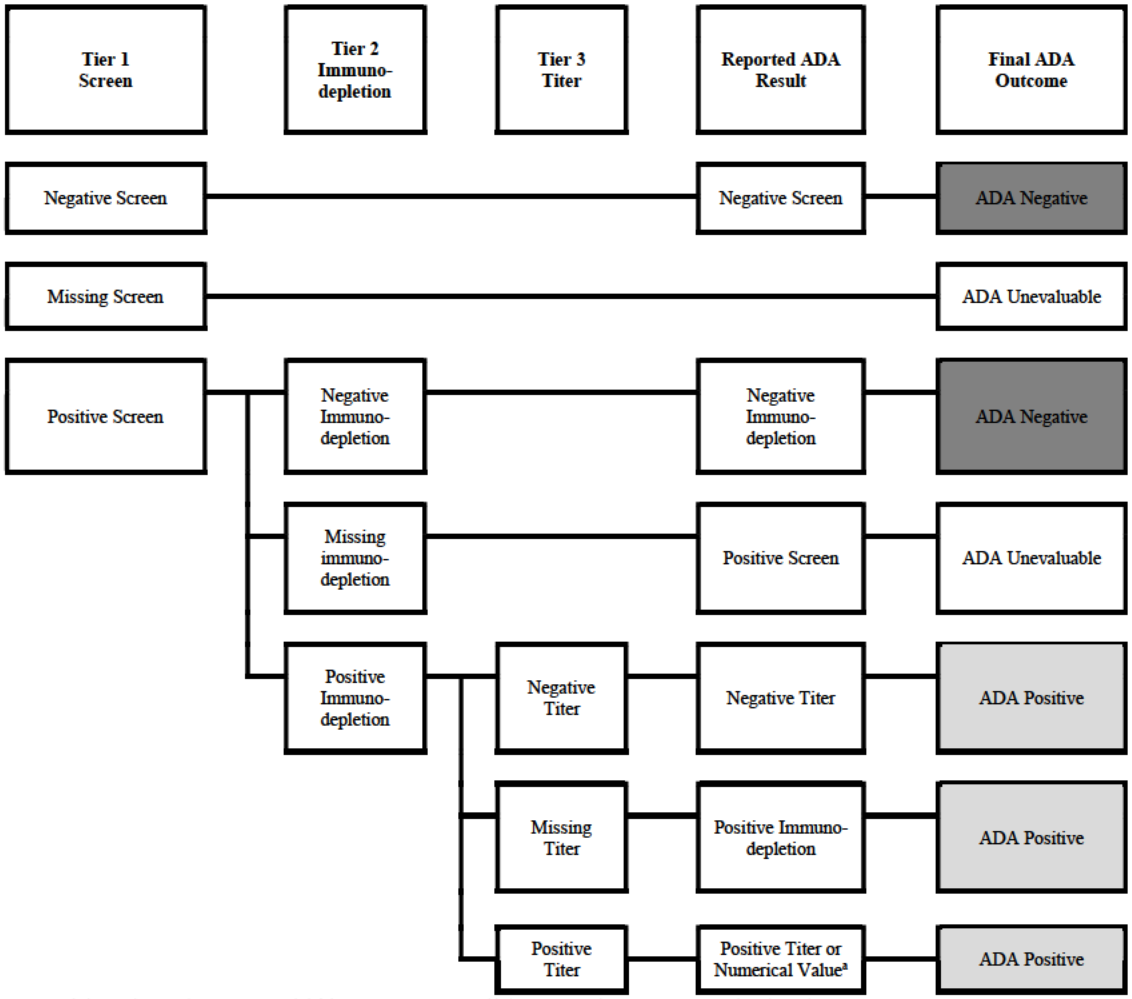
- If a sample is scored as confirmed positive, the samples are further characterized in the ADA titration assay (to determine titer).

If available, a titer result will be reported for the ADA confirmed positive samples. However, a titer result is not 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 1: ADA Sample Status



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

Participant Classification for ADA Against Efgartigimod

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

Table E Participant Classification for ADA Against Efgartigimod

Participant ADA classification	Highest[a] postbaseline sample status: 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*

Error! Reference source not found. 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).

Error! Reference source not found. Samples with missing titer will have a reported ADA result of "positive immuno-depletion" or "positive titer".

Error! Reference source not found. Results reported as "negative titer", ie, 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]
- COMPASS-31 and MaPS
- 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.

15.5. Change of Dosing Regimen and Analysis

If clinically indicated, the participant and investigator, based on the participant-reported reason for the request and physical examination, can jointly decide to return the participant to QW dosing during the maintenance dosing period. Participants who switch back to QW dosing will not be allowed to switch back to Q2W dosing during the study.

The number and percentage of participants on Q2W and QW dosing will be summarized by visit for the SAF, number and percentage of participants switch from Q2W to QW at any time will also be summarized by parent study treatment

arm.
Summary statistics will be provided for time from first infusion to switch back to QW dosing for FAS. A Kaplan-Meier plot for the time to switch back to QW will also be provided by parent study treatment arm, the number of subjects at risk at each timepoint and probability of staying on Q2W will be presented. Subjects that do not enter the maintenance dosing period will not be included in this analysis.
The definition of events and censoring:

- Subjects in maintenance dosing period (Q2W for 42 weeks) switch back to QW will be the event.
- If subject does not have the event up to the end of study, the subject will be censored at the date of whichever occurs first, the last dose date or cut-off date.

15.5.1. Derivations

- Time from first infusion to switch back to QW dosing (days) = date of first IMP administration – date of first switch back to QW dosing administration + 1.

16. EXPLORATORY ANAYSIS

The exploratory efficacy analyses and QoL will be performed for the FAS.

Summary statistics will be provided in terms of absolute value and changes from baseline for each visit.

16.1. [redacted]

[redacted]

16.2. [redacted]

[redacted]

16.3. [redacted]

[redacted]

16.4. [redacted]

[redacted]

16.5. [redacted]

[redacted]

[redacted]

17. 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 guideline E14: the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (R3) – questions and answers: January 2016.

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

In the general characteristics analysis, an overall total will be added to summarize all participants over subgroups. Overall totals will be shown last.

Listings

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

- Treatment group (or treatment received if it's a safety output)
- Center-participant ID,
- Date (where applicable),

For listings where non-enrolled participants are included, these will appear in a category after the enrolled treatment groups labeled 'Not Randomized'.

Baseline

Baseline for these data will integrate from the latest non-missing data of 2104 to baseline visit of 2105.

Description	Source
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
Physical Examination	EDC data: PE1
ECG	EDC data: EG Non-EDC data: ECG
Laboratory Assessment - Hematology and Chemistry	EDC data: LB Non-EDC data: Q^2S (and RBM)
Laboratory Assessment: Immunogenicity Sample	EDC data: LB_IMMUNO Non-EDC data: Q^2S (and RBM)
Laboratory Assessment: Biomarker Sample	EDC data: LB_MI_BIO Non-EDC data: Q^2S (and RBM)
Lab Page - Urinalysis	EDC data: LB1 Non-EDC data: Q^2S (and RBM)
Lab Page - TSH/CRP/ESR	EDC data: LB2 Non-EDC data: Q^2S (and RBM)
Pharmacokinetics Concentration	EDC data: PC1 Non-EDC data: PK
Pharmacodynamics	EDC data: PD Non-EDC data: Q^2S (and RBM)
Pregnancy Testing	EDC data: PREG
ADA	Non-EDC data: ADA
eCOA	Non-EDC data: eCOA

Baseline for these data will use 2105 baseline data

Description	**Source**
Vital Sign	EDC data: VS
Adverse Events	EDC data: AE
Prior and Concomitant Medications	EDC data: CM
Medical History	EDC data: MH
Date of Visit	EDC data: VIS
Study Continuation	EDC data: STDYCON
Pandemic Visit Impact	EDC data: VIS_PAND
IRT	Non-EDC data: IRT

Criterias of prior/concomitant medications, Medical history and AEs from POTS to POTS-OLE

POTS Form	**Criteria when met in POTS, the respective record will be added into POTS-OLE**
Adverse Event (Eg. HEADACHE)	• Outcome = Recovering/Resolving or Not Recovered/Not Resolved or Unknown • Prior and Concomitant Medications = Ongoing with Indication = Adverse Event (HEADACHE)

Medical History (Eg. HEADACHE)	• Ongoing • Prior and Concomitant Medications = Ongoing with Indication = Medical History (HEADACHE)
Related Procedures/Surgeries (Eg. Cataract extraction)	• Ongoing • Prior and Concomitant Medications = Ongoing with Indication = Related Procedures/Surgeries (Cataract extraction)
Prior and Concomitant Medications	• Ongoing

APPENDIX 2. TOXICITY GRADES

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

Paramater	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
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
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
	mEq/L	>ULN-5.5	>5.5-6.0	>6.0-7.0	>7.0

Paramater	Unit	Grade 1	Grade 2	Grade 3	Grade 4
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
Lymphocytes (absolute count) low	giga/L	<LLN-0.80	<0.80-0.50	<0.50-0.20	<0.20
	counts/mm^3	<LLN-800	<800-500	<500-200	<200
Lymphocytes (absolute count) high	giga/L	-	>4-20	>20	-
	counts/mm^3	-	>4000-20000	>20000	-
Neutrophils (absolute count) low	giga/L	<LLN-1.5	<1.5-1.0	<1.0-0.5	<0.5
	counts/mm^3	<LLN-1500	<1500-1000	<1000-500	<500
Platelets	giga/L	<LLN-75	<75-50	<50-25	<25
White blood cells	giga/L	<LLN-3	<3-2	<2-1	<1
	counts/mm^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 , values within normal ranges will be presented as Grade 0 for toxicity outputs.

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.

APPENDIX 3. ALGORITHM FOR PRIOR /CONCOMITANT MEDICATIONS AND ADVERSE EVENTS:

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 stop date < study med start date, assign as prior If stop date >= study med start, assign as concomitant Or else, assign as Concomitant and Prior.
	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 stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Or else, assign as Concomitant and Prior.
	Missing	Assign as concomitant and prior.
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant
	Partial	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Or else, assign as Concomitant and Prior.
	Missing	Assign as concomitant and prior.

DocuSign

Certificate Of Completion

[redacted]

Record Tracking

Status: Original [redacted] Location: DocuSign

6/3/2024 3:39:01 AM [redacted]

Signer Events	Signature	Timestamp

[redacted]

Signer Events	Signature	Timestamp
[redacted]		
In Person Signer Events	**Signature**	**Timestamp**
Editor Delivery Events	**Status**	**Timestamp**
Agent Delivery Events	**Status**	**Timestamp**
Intermediary Delivery Events	**Status**	**Timestamp**
Certified Delivery Events	**Status**	**Timestamp**
Carbon Copy Events	**Status**	**Timestamp**
[redacted]		
Witness Events	**Signature**	**Timestamp**
Notary Events	**Signature**	**Timestamp**

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	6/3/2024 3:42:49 AM
Certified Delivered	Security Checked	6/3/2024 8:04:29 AM
Signing Complete	Security Checked	6/3/2024 8:05:12 AM
Completed	Security Checked	6/3/2024 8:05:16 AM

Payment Events	Status	Timestamps
Electronic Record and Signature Disclosure		

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PDF Reader:	Acrobat® or similar software may be required to view and print PDF files
Screen Resolution:	1024 x 768 Recommended
Enabled Security Settings:	Allow per session cookies
Mobile Signing:	• Apple iOS 7.0 or above • Android 4.0 or above

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