16.1.9. Documentation of Statistical Methods

Document	Date
Statistical analysis plan – v3.0	02 May 2024

STATISTICAL ANALYSIS PLAN

Protocol No. ARGX-113-2104

A phase 2 randomized, double-blinded, placebo-controlled study to evaluate the efficacy and safety of efgartigimod IV in adult patients with post–COVID-19 postural orthostatic tachycardia syndrome (POTS)

-

AUTHORS: [redacted]

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V2.0 (02 May 2024) for Protocol ARGX-113-2104.

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
0.1	05May202	[redacted]	Not Applicable – First Version
0.2	19/10/2023	[redacted]	Added estimand and ICE sections as appropriate. Exploratory endpoints updated in section 2 Indication of delivery type entered through out. Up-date on [redacted] test analysis for 5 post dose records
1.0	03/01/2024	[redacted]	Added text to explain not as protocol details, and new derivations for concomitant medications
2.0	29/01/2024	[redacted]	Update to missing imputation method, to allow for MAR of placebo (ICE and non ICE) and treatment non ice subjects
3.0	10/4/2024	[redacted]	Inclusion of windows for IGG, and enlargement of windows for safety and efficacy windows. New definition for baseline of variables from data collected from questionnaires, HUTT analysis changed to the change from baseline per visit to the maximum value obtained during the visit. Primary and secondary analysis for COMPASS and Maps have been exchanged.

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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
[redacted]	[redacted]
FAS	full analysis set

FPA	Final Planned Analysis
HR	heart rate
IAWK12	Interim Analysis Week 12
IAWK24	Interim Analysis Week 24
ICF	informed consent form
IgG	immunoglobulin G
IMP	investigational medicinal product
IRR	infusion related reactions
LLN	lower limit of normal
MaPS	Malmö POTS symptom score
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
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 Measurement Information System	Patient-Reported Outcomes
[redacted]	[redacted]
PT	preferred term
QTc	corrected QT interval
QTcB	Bazett's corrected QT interval
QTcF	Fridericia's corrected QT interval
[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
UN	unstructured covariance structure
VAS	visual analog scale

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-113-2104. 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 3.0, dated 25 July 2023.

2. Study Objectives and Endpoints

Table A: Objectives

Objectives	Endpoints
Primary	
• Evaluate the efficacy of efgartigimod in reducing the severity of post-COVID-19 POTS symptoms. • Evaluate the safety and tolerability of efgartigimod in patients with post-COVID-19 POTS	• Change from baseline to week 24 in the Composite Autonomic Symptom Score 31 (COMPASS 31) (2-week recall version) • Change from baseline to week 24 in the Malmö POTS Symptom Score (MaPS) • Incidence and severity of adverse events (AEs), incidence of SAEs, changes in laboratory test results, vital signs, and electrocardiogram (ECG) results
Secondary	
• Evaluate the efficacy of efgartigimod on patient global assessment of disease activity and fatigue	• Change from baseline to week 24 in the Patient Global Impression of Severity (PGI-S) • Patient Global Impression of Change (PGI-C) at week 24 • Change from baseline to week 24 in the Patient-Reported Outcomes Measurement

	Information System (PROMIS) Fatigue Short Form 8a • Change from baseline to week 24 in the PROMIS Cognitive Function Short Form 6a
• Assess the pharmacodynamic (PD) effect of efgartigimod	• Absolute values, changes from baseline, and percent reduction from baseline in total IgG levels
• Assess the pharmacokinetic (PK) profile of efgartigimod	• Efgartigimod serum concentration-time profile
• Assess the immunogenicity of efgartigimod	• Incidence and prevalence of antidrug antibodies (ADA) against efgartigimod
Exploratory	
• [redacted]	• [redacted] • [redacted] • [redacted] • [redacted] • [redacted] • [redacted]
[redacted]	[redacted]

	[redacted]

Table B: Estimands

Objectives	Estimands
Primary	
The estimand is the difference between treatment arms in change from baseline to week 24 in COMPASS-31 and MaPS irrespective of whether stopping IMP or using prohibited medication.	Treatment conditions Efgartigimod or placebo irrespective of study treatment discontinuation and/or prohibited medication.
	Population Randomized participants with post–COVID-19 postural orthostatic tachycardia syndrome as defined in FAS
	Variable (endpoint) Change from baseline to week 24 in COMPASS-31/MaPS
	Intercurrent events Early discontinuation of study treatment Use of any prohibited medications
	Summary measure Difference in LS means, corresponding 95% CI and p-value

.

For the Main estimand:

The available data occurring on or after ICEs will be analyzed as observed (Treatment policy). The reasoning of treatment policy is to estimate the COMPASS-31 and MaPS response based on the available data and data will be analyzed as it is (regardless of the intercurrent event occurring).

For Supportive analysis of estimands

Composite Variable strategy: Assessment on or after ICEs will be treated missing and imputed assuming MNAR delta adjustment imputation. The rationale behind composite strategy is, discontinue of study treatment or use of prohibited medications will affect the COMPASS-31 and MaPS response.

3. STUDY DESIGN

3.1. General Description

This study aims to evaluate the efficacy and safety of weekly infusions of efgartigimod IV 10 mg/kg compared to matched-placebo IV in adult participants with post–COVID-19 POTS. This is a randomized, double-blinded, placebo-controlled, parallel-group, phase 2 study. The total study duration is approximately 36 weeks comprising:

- Screening period of approximately 4 weeks
- Treatment period of 24 weeks
- Follow-up period of approximately 8 weeks (56 days ± 3 days) for participants who do not roll over to the open-label extension (OLE) study ARGX-113-2105

42 participants are planned to be randomized to estimate the treatment effect at week 24.

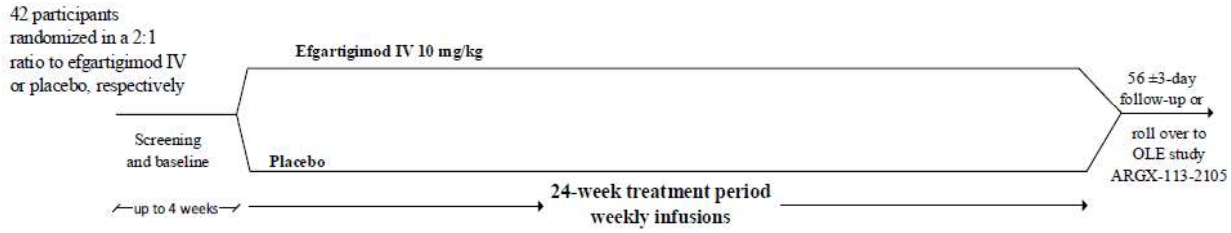
The end of study is defined as the date of the last participant's last visit of treatment period or follow-up period or early discontinuation visit (EDV), as applicable.

Treatment and Dosing:
The study population is adult patients with new-onset POTS post–COVID-19. Participant eligibility for trial participation is evaluated based on inclusion/exclusion criteria during screen period. Eligible participants will receive weekly infusions of efgartigimod IV 10 mg/kg or matching placebo in a 2:1 ratio according to randomization. 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.
Investigational medicinal product (efgartigimod or matching placebo) will be administered during the treatment period in an approximately 1-hour IV infusion once weekly by site staff or a home nurse. IMP administration at home will not commence until after 3 doses have been administered on-site. Any participant who misses a scheduled dose (±2 days) will wait to receive the next scheduled dose.

The final dose is to be administered at week 23. At week 24, eligible participants may roll over into a single-arm OLE ARGX-113-2105. Participants permanently discontinuing IMP will be ineligible to roll over into the OLE study.

Blinding:
This study is double-blinded, and the sponsor/designee, participants, and investigators are blinded to IMP treatment assignment. Investigator can determine whether unblinding of the IMP assignment is necessary in emergencies. The date and reason for the unblinding should be recorded.

Table C: Study Overview



IV=intravenous; OLE=open-label extension

3.2.Sample Size

The anticipated width of the 95% CI of the treatment difference on changes from baseline in COMPASS 31 is estimated as follows:
The SD of COMPASS 31 at a single time point in subjects living with POTS is assumed to be approximately [redacted] with mean score of [redacted] As the COMPASS 31 scale has favourable test-retest reliability, the Pearson correlation between 2 measurements is assumed to be a minimum of [redacted]
From this, it is estimated that the within-subject SD on COMPASS 31 is approximately [redacted], from which the SD on the change from baseline is derived to be approximately [redacted]
Therefore, the anticipated width (half-width) of the 95% CI is approximately [redacted] assuming complete data, which could increase to [redacted] when applying a conservative dropout rate of [redacted]%. With an anticipated 95% CI half-width [redacted] COMPASS 31 data from approximately 42 participants will provide sufficient precision to estimate the treatment effect at week 24.

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

The protocol mentions mixed model repeated measures as the method of analyzing the Primary endpoints, however the protocol does not mention estimands or Intercurrent events. The SAP considers estimands and intercurrent events. As a result, the main analysis method will be using the mixed model repeated measures and ANCOVA after applying MNAR to missing data from the intercurrent events will be used as supplementary analysis.

The baseline for Questionnaire responses will be the final assessment before the initial administration of IMP up until 3 days post IMP, recorded under baseline visit. The information obtained through this method will be used to inform the development of Phase 3 trials.

4. PLANNED ANALYSES

The following analyses will be performed for this study:

- Interim Analysis at the end of treatment phase
- 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 either completed the week 12 assessments or discontinued the study prior to week 24. A further interim will be carried out at 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 week 12 will be based on the unblinded treatment groups by a separate unblinded team who is otherwise not involved within the trial. 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.

Access to data will be controlled by access rights to folders where data is stored and manipulated within IQVIA and access to the sFTP used for data transfer.

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 randomized participants who received at least one dose of IMP and classified as Planned Treatment.

5.3.Safety Analysis Set [SAF]

The safety analysis set (SAF) will contain all randomized participants who received at least one dose of IMP. Data from these participants will be classified according to actual treatment received. The actual treatment arm will be the same as the planned treatment arm unless the participant received IMP other than the planned one

for the whole study.

5.4.PK Analysis Set [PKAS]

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

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

6. GENERAL CONSIDERATIONS

6.1.Reference Start Date and Study Day

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

- Reference start date is defined as the day of the first dose of IMP.
- If the date of the event is on or after the reference date, then:
  - Study Day = (date of event – reference date) + 1.
- If the date of the event is prior to the reference date, then:
  - Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day. Date implies a complete date having day, month and year available. Unless otherwise specified, the *study day* will remain missing when it cannot be calculated due to absence or incompleteness of the concerned and/or reference dates.

In case the participant never received IMP, the date/time of randomization will be used instead of first IMP administration date/time.
End of study (EOS) is defined as date of participant's last visit. This is date of treatment period completion and/or safety follow-up or early discontinuation visit.
End of treatment (EOT) is defined as date of treatment completion or date of permanent discontinuation of IMP.

6.2. Baseline

Unless otherwise specified, baseline is defined as the last available non-missing measurement taken prior to reference start date/time.
Assessments performed on the same day as the first IMP administration but without time information collected or with time information exactly equal to the time of first IMP administration and which are planned predose will be considered as predose.
For parameters related to questionnaires, baseline assessment is the last evaluable assessment before the initial administration of IMP up until within 3 days after IMP, collected gathered during the baseline visit for questionnaires. It includes COMPASS 31, MaPS, PGIC, PGIS, PROMIS (Cognitive Function Short Form 6a, Fatigue Short Form 8a, Global Health Scale score) and EQ-5D-5L.
In case the participant never received IMP, the date/time of randomization will be used instead of first IMP administration date/time.
Adverse Events (AEs) and medications commencing on the reference start date will be considered post-baseline unless otherwise indicated based on available start date/time combination or collected electronic case report form (eCRF) information that identifies the individual event/medication as starting prior to first IMP administration.

6.3. Windowing Conventions

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

Table D: Non-efficacy Analysis Visit Definition

	Target Day	Assigned Study Day (Inclusive)		Week Assigned
		From	To	
Treatment	1	screening	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] An assessment before the first administration of IMP will be allocated to baseline.

[b] Post baseline visit Day 1.

[c] considers value of x, starting from 1 to up until 16 to get visit windows for Week 9 to Week 24.

Note: After treatment period ends, safety follow-up will be of approximately 8 weeks (56 days ± 3 days) for participants who do not roll over to the OLE study ARGX-113-2105.

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

Table E: Serum Chemistry and hematology, Physical examination, Analysis Visit Definition

	Target Day	Assigned Study Day (Inclusive)		Week Assigned
		From	To	
Treatment	1	Screening	1[a]	Baseline
	29	1[b]	57	Week 4
	85	58	127	Week 12
	169	128	178	Week 24
Safety Follow-up	Final dose + 56 days	(Final dose + 56 days) - 3 days	(Final dose + 56 days) + 3 days	Week xx+ 56 days

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

[b] Post baseline visit Day 1.

Table F: Immunogenicity, Analysis Visit Definition

	Target Day	Assigned Study Day (Inclusive)		Week Assigned
		From	To	
Treatment	1	screening	1[a]	Baseline
	8	1[b]	18	Week 1
	29	19	57	Week 4
	85	58	127	Week 12
	169	128	178	Week 24
Safety Follow-up	Final dose + 56 days	(Final dose + 56 days) - 3 days	(Final dose + 56 days) + 3 days	Week xx+ 56 days

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

[b] Post baseline visit Day 1.

Table G: ECG, Analysis Visit Definition

	Target Day	Assigned Study Day (Inclusive)		Week Assigned
		From	To	
Treatment	1	screening	1[a]	Baseline
	8	1[b]	46	Week 1
	85	47	127	Week 12
	169	128	178	Week 24
Safety Follow-up	Final dose + 56 days	(Final dose + 56 days) - 3 days	(Final dose + 56 days) + 3 days	Week xx+ 56 days

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

[b] Post baseline visit Day 1.

Table H: 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	screening	3	Baseline
15	4	22	Week 2
29	23	43	Week 4
57	44	71	Week 8
85	72	106	Week 12
127	107	148	Week 18
169	149	178	Week 24

Baseline will be the last assessment before the first administration of IMP (primary consideration) or up to and including 3 days post IMP.

For Modified COMPAS and PROMIS Fatigue efficacy assessments, the following window will be considered:

Target Day	Assigned Study Day (Inclusive)		Week Assigned
	From	To	
1	Screening	3	Baseline
15	4	22	Week 2
29	23	57	Week 4
85	58	127	Week 12
169	128	178	Week 24

Baseline will be the last assessment before the first administration of IMP (primary consideration) or up to and including 3 days post IMP.

Note : Original Compass assessments are not to be included in the baseline calculation..

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

Target Day	Assigned Study Day (Inclusive)		Week Assigned
	From	To	
1	screening	3	Baseline
15	4	22	Week 2
29	23	57	Week 4
85	58	106	Week 12
127	107	148	Week 18
169	149	178	Week 24

Baseline will be the last assessment before the first administration of IMP (primary consideration) or up to and including 3 days post IMP.

For PROMIS (Cognition, [redacted] and [redacted] efficacy assessments, the following window will be considered:

Target Day	Assigned Study Day (Inclusive)		Week Assigned
	From	To	
1	screening	3	Baseline

29	4	57	Week 4
85	58	127	Week 12
169	128	178	Week 24

Baseline will be the last assessment before the first administration of IMP (primary consideration) or up to and including 3 days post IMP.

[redacted]

Target Day	Assigned Study Day (Inclusive)		Week Assigned
	From	To	
1	screening	1[a]	Baseline
85	1[b]	127	Week 12
169	128	178	Week 24

[a] An assessment before the first administration of IMP will be allocated to baseline.
[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] Q[redacted] [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 post final dose 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 to efficacy and safety, see appropriate section of the applicable endpoints.
Missing efgartigimod concentrations will not be imputed.

7.2.Output Presentation

For continuous variables, full descriptive statistics will only be presented if there are at least 2 non-missing observations. Alternatively, only the number of non-missing data points and mean are shown. 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 95% Confidence interval 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 IAWK12, IAWK24 and FPA and/or the study along with the reason for discontinuation will be summarized using the FAS for both the IAWK12, IAWK24 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 randomized, completed, or discontinued the study for the IAWK12, IAWK24 and FPA.
- number and percentage of participants for each study discontinuation reason or the IAWK12, IAWK24 and FPA.
- number and percentage of participants discontinuing treatment but continuing study assessments for the IAWK12, IAWK24 and FPA.
- number and percentage of participants who roll over to OLE study ARGX-113-2105 for the FAS, IAWK12, IAWK24 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 IAWK12, IAWK24 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)
- Baseline BMI (kg/m^2)
- Time since diagnosis (years) - calculated relative to date of consent.
- SARS-CoV-2
- Active stand test (HR on 10-minute stand)
- Head-up tilt test

Summary statistics including n, mean, median, SD, Q1, Q3, minimum and maximum will be presented for continuous variables such as age, height, weight, BMI, time since diagnosis, active stand test (HR on 10-minute stand) and head-up tilt test. Frequency counts and percentages will be presented for categorical variables such as sex, race, ethnicity, and SARS-CoV-2.

All demographic data and baseline characteristics will be listed.

9.1. Derivations

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

- Percent reduction = (baseline-actual)*100/baseline

10. Medical History

Surgical and Medical History & Concomitant illnesses information will be presented for the SAF. Medical History and Concomitant illnesses will be coded using the latest version of MedDRA (medical dictionary for regulatory activities).

- Medical History conditions are defined as those conditions which stop prior to or at screening. Hence, any medical history abnormalities/conditions and any event including medical history for COVID and POTS before or at screening will be presented as Medical History.
- Concomitant illnesses which started prior to or at screening 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.

Details collected as a part of the medical history must include but are not limited to all previous treatment/therapy for COVID-19 and post–COVID-19 POTS.

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.

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.
- Concomitant therapy: the therapy was taken on or after the first dose date.

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 IAWK12, IAWK24 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 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 will be summarized using descriptive statistics. All IMP administration data will be listed. Participants with an overdose of IMP will be listed.

12.1. Derivations

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

13. STUDY MEDICATION COMPLIANCE

The infusion is given once a week by site staff or delegate. At least, the first 3 doses of IMP (at baseline, week 1 and 2 or subsequent if previous doses are missed) must be administered on-site.
The compliance will be summarized descriptively. Compliance will be further categorized as <80, 80-100, >100.

13.1. Derivations

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

expected will be based on participants expecting study drug infusion/administration of eCRF page "Exposure – Infusion" irrespective of dosing received. Only visits up to treatment discontinuation are considered in the compliance calculation.

14. Efficacy Outcomes

14.1. Primary Efficacy

14.1.1. Primary Efficacy Variables & Derivations

The primary efficacy variables are:

- Change from baseline to week 24 in the Composite Autonomic Symptom Score 31 (COMPASS 31)
- Change from baseline to week 24 in the Malmö POTS Symptom Score (MaPS)

Efficacy endpoints will be analyzed using the FAS for IAWK12 and IAWK24 (Note data will be used for all subjects up to the cut of date for IAWK12, the data will not be truncated to week 12 therefore the change from baseline to week 24 ANCOVA will contain a subset of the subjects available at week 12 cut off,, whereas the MMRM will contain all subjects within the cutoff regardless of where they are within the trial up to week 24 .)

Estimand for primary analysis is as defined in Table B. The estimand is the difference between treatment arms in change from baseline to week 24 in COMPASS-31 and MaPS irrespective of stopping IMP or using prohibited medication. Missing data due to withdrawal of consent/loss to follow-up will be imputed based on subjects remaining in the study, irrespective of whether those subjects discontinued study treatment or used prohibited medications later than the imputation.

Intercurrent Events (ICE) are early discontinuation of study treatment and use of any prohibited medications.

14.1.1.1. Change from baseline to week 24 in the Composite Autonomic Symptom Score 31 (COMPASS 31) (2-week recall version)

The primary objective of the study is to evaluate the efficacy of efgartigimod in reducing the severity of post-COVID-19 POTS symptoms.

For change from baseline to week 24 in COMPASS 31 (2-week recall version) and MaPs, between treatment group difference will be analyzed using longitudinal mixed model repeated measures (MMRM). Without

imputation of intercurrent events.

The model will be implemented in SAS using the MIXED procedure and will include the change from baseline in COMPASS31 as the dependent variable and baseline value of COMPASS31, interaction of baseline value with visit as covariates. Fixed effects in the model will be treatment, visit and treatment by visit interactions. The visits included in the model will be weeks 2, 4, 12 and 24. All data will be included for subject in the IAWK12 even if it is for visits after week 12.

Within-subject correlation will be modeled by assuming an unstructured variance covariance matrix, and the Kenward-Roger degrees of freedom method will be used.

If the default Newton–Raphson algorithm used by SAS PROC MIXED fails to converge, the following steps will be taken to avoid lack of convergence while maintaining an unstructured variance:

The Fisher scoring algorithm (via the SCORING=5 option of the PROC MIXED statement) will be used to obtain the initial values of covariance parameters.

If the above fails, the no-diagonal factor analytic structure will be used, which effectively performs the Cholesky decomposition via the TYPE=FA0(V) option of the REPEATED statement, where V is the total number of distinct visits in the response vector (counting only rows where all model components are non-missing).

If all of the above fail, the variance-and-correlations parameterization will be attempted using TYPE=UNR.

In case if model does not converge after all of the above steps, following covariance structures will be tested for convergence (in order) ANTE(1), TOEPH, ARH(1), CSH, TOEP, AR(1), and CS.

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

Sample SAS code to be considered as below (SAS code is regarded as “draft” until fully validated at the analysis stage):

```
proc mixed data=COMPASS31 method=REML;
      class BCOMPASS31 ARMCD VISIT USUBJID;
      model change = BCOMPASS31 ARMCD VISIT BCOMPASS* VISIT
      ARMCD*VISIT/ddfm=kenwardroger;
      repeated VISIT / type=un subject = USUBJID;
      lsmeans ARMCD*VISIT / pdiff cl;
      ods output lsmeans = lsm;  * contains the adjusted means;
      ods output diffs = dif;  * contains treatment differences;
```

```
run;
```

For change from baseline to week 24 in MaPS, between treatment group difference will be analyzed using MMRM, except with change from baseline in MaPS as the dependent variable and baseline value of MaPS as covariate.

The visits included in the model will be weeks 2, 4, 8, 12, 18 and 24.

14.1.1.2. Change from baseline to week 24 in the Malmö POTS Symptom Score (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 in MaPS score, analysis will be presented similar to analysis proposed for COMPASS 31. Summary statistics will be provided in terms of absolute value and changes from baseline for each visit using FAS for IAWK12 and IAWK24. All data will be included for subject in the IA even if it is for visits after week 12.

For change from baseline to week 24 in MaPS, between treatment group difference will be analyzed using ANCOVA as presented in section 14.1.1.1, except with change from baseline in MaPS as the dependent variable and baseline value of MaPS as covariate.

14.1.1.3. Supplementary Analysis of Primary Efficacy Variables

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 original version of COMPASS 31 (longer recall) will be administered at screening and the modified version (2-week recall) will be administered at baseline and all other time points. The modified COMPASS 31 version used in the ARGX-113-2104 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 supplementary primary efficacy analysis will be performed for the FAS for IAWK12 and IAWK24. Summary statistics will also be provided in terms of absolute value and changes from baseline for each visit where no imputation performed on missing data.

The estimand uses the composite approach, and is the difference between treatment arms in change from baseline to week 24 in COMPASS-31 and MaPS with outcomes after stopping IMP and /or using prohibited medication imputed as gaining no further benefit over and above that of the control arm.

Treatment Condition: Efgartigimod or placebo assuming less efficacious outcome post ICE
Population: Randomized participants with post–COVID-19 postural orthostatic tachycardia syndrome as defined in FAS.
Variable/Endpoint(s): Change from baseline to week 24 in the Composite Autonomic Symptom Score 31/change from baseline to week 24 in the Malmö POTS Symptom Score (MaPS)
Intercurrent Events (ICE): Composite Approach, with Imputation using MNAR model delta adjustment imputation.
Delta adjustment will be applied to only treatment arm and ICE occurred; no delta adjustment will be performed for placebo arm. Any missing data other than ICE in treatment arm will be imputed using MAR assumption. Missing data under placebo arm will be imputed assuming MAR , irrespective of ICEs. The result will be created assuming delta=3, 4, 5. Further sensitivity analysis can be performed with different deltas.

a. Early discontinuation of study treatment
b. Use of any prohibited medications

Population-level summary: Change from baseline mean difference between placebo and efgartigimod in COMPASS-31 and MaPS presenting Difference in LS means, corresponding 95% CI and p-value using the FAS.

ICE	Approach for dealing with the ICE
Discontinuation of study treatment	Composite approach: scores after treatment discontinuation in participants who discontinue treatment and refused to stay in the study will in the case of both the experimental arm and the control arm be imputed being modelled as gaining no further benefit over and above that of the control arm.
Use of any prohibited medication	Composite approach: assessments after visit x, if the ICE has taken place at visit x will in the case of both the experimental arm and the control arm be imputed being modelled as gaining no further benefit over and above that of the control arm.

Explicit details regarding the imputation of missing values are provided via sample SAS code that is intended to demonstrate the application of these strategies. Minor alterations to SAP code may be performed. Example code for generating the missing imputed data is as follows:

Identify ICE 1 and ICE 2,
Seperate patient and ICE , this data will be mergred before applying MNAR

perform MI using MCMC, to impute only the non-monotone missing values (IMPUTE=MONOTONE)

```
PROC MI DATA=DIA NIMPUTE=500 SEED=9453 OUT=DIA_mono;
  VAR trt BASVAL change_1-change_4 ;
  MCMC CHAIN=SINGLE NBITER=200 NITER=100 IMPUTE=MONOTONE;
RUN;
```

Merge ICEs patient wise
Apply MAR for Placebo treated patient with or without ICE it will be

```
PROC MI DATA=DIA_mono_(where=(trt=0)) NIMPUTE=1 SEED=4648 OUT=DIA_imputed_MAR;
                                   by _imputation_;
  VAR trt BASVAL change_1-change_4;
  CLASS trt;
  MONOTONE REGRESSION;
RUN;
```

Apply MNAR only for those ICE under treatment arm who have intercurrent event other than 'study treatment discontinuation'.

```
PROC MI DATA=DIA_mono_(where=(trt=1)) NIMPUTE=1 SEED=4648 OUT=DIA_imputed_MNAR;
                                    by _imputation_;
  VAR BASVAL  change_1-change_4;
  CLASS  ICE;
  MONOTONE REGRESSION;
  mnar adjust(change_2 / delta=3 adjustobs=(ICE='2'));  /*ICE=2 means other than ' study treatment
discontinuation' */
  mnar adjust(change_3 / delta=3 adjustobs=(ICE='2'));
  mnar adjust(change_4 / delta=3 adjustobs=(ICE='2'));
RUN;
```

If the above methodology is unable to be undertaken due to the small sample sizes expected at week 12 analysis or subsequently at week 24, the ANCOVA analysis will be undertaken on observed data only, For the change from baseline to 24 weeks for both the COMPASS 31 analysis an ANCOVA will also be calculated using the FAS by the Proc Mixed procedure, example code is:

```
Ods output estimates =est;
proc mixed data=COMPASS31 method=REML;
      class BCOMPASS31 ARMCD ;
      model change = BCOMPASS31 ARMCD /solution;
      LSMEANS trt / diff=control('0') cl;
            ODS OUTPUT Diffs=lsdiffs LSMeans=lsm solutionF=Parms;
            BY visit _imputation_;
run;
```

(i.e using week 24 data only.)

Combine the imputations using proc MIanalysis

```
proc mianalyze parms(classvar=full)=lsdiffs;
                                   BY visit;
    class trt ;
    modeleffects trt;
ods output ParameterEstimates=MIAN_lsdiffs;
run;
```

14.2. Secondary Efficacy

The secondary efficacy analyses will be performed for the FAS.

14.2.1. Secondary Efficacy Variables & Derivations

14.2.1.1. Change from baseline (CFB) to week 24 in the Patient Global Impression of Severity (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 IAWK12 and IAWK24.

Table I: 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 IAWK12 and IAWK24..

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).

The proportion of efgartigimod and placebo participants with improvement at week 24 will be compared using, a fisher's exact test, based on observed data for both the 1 week recall and 2 week recall results using the FAS for the IAWK12 and IAWK24.

14.2.1.2. Patient Global Impression of Change (PGI-C) at week 24

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 IAWK12and IAWK24.

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").

The proportion of efgartigimod and placebo participants with improvement at week 24 will be compared using a fisher's exact test, based on observed data for IAWK12 and IAWK24 using the FAS.

14.2.1.3. Change from baseline to week 24 in the Patient-Reported Outcomes Measurement Information System (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.

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 IAWK12 and IAWK24 using the FAS.

For change from baseline to week 24 in PROMIS Fatigue Short Form 8a, between treatment group difference will be analysed using longitudinal mixed model repeated measures (MMRM) as presented in section 14.1.1.1, using FAS except with change from baseline in PROMIS Fatigue as the dependent variable and baseline value

of PROMIS Fatigue as covariate. The visits included in the model will be baseline, weeks 2, 4, 12 and 24.

14.2.1.4. Change from baseline to week 24 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 IAWK12 and IAWK24. T-score will be descriptively summarized to present absolute value and changes from baseline for each visit.

For change from baseline to week 24 in PROMIS Cognitive, between treatment group difference will be analysed using longitudinal mixed model repeated measures (MMRM) as presented in section 14.1.1.1, except with change from baseline to week 24 in PROMIS Fatigue as the dependent variable and baseline value of PROMIS Cognitive as covariate using FAS for the IAWK12 and IAWK24. The visits included in the model will be baseline, weeks 4, 12 and 24.

14.3. Exploratory Efficacy

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.

14.3.1. [redacted]

[redacted]

[redacted]

14.3.2. [redacted]

[redacted]

14.3.3. [redacted]

[redacted]

14.3.4. [redacted]

[redacted]

14.3.5. [redacted]

[redacted]

14.3.6. [redacted]

[redacted]

15. PHARMACODYNAMIC ANALYSIS

Pharmacodynamic (PD) effect of efgartigimod will be assessed via, Total IgG. PD analyses will be performed

in the SAF for the IAWK12, IAWK24 and FPA.

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 postbaseline value

Additionally, lines chart showing change in Total IgG over time will be prepared.

- Charts of IgG % change from Baseline by time for each Subject will be generated for the IAWK12 and IAWK24.
- The mean values to week 12 will be charted by line plot with SE (error bars) by week and by treatment for the IAWK12.

All PD data will be listed.

16. 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, 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).

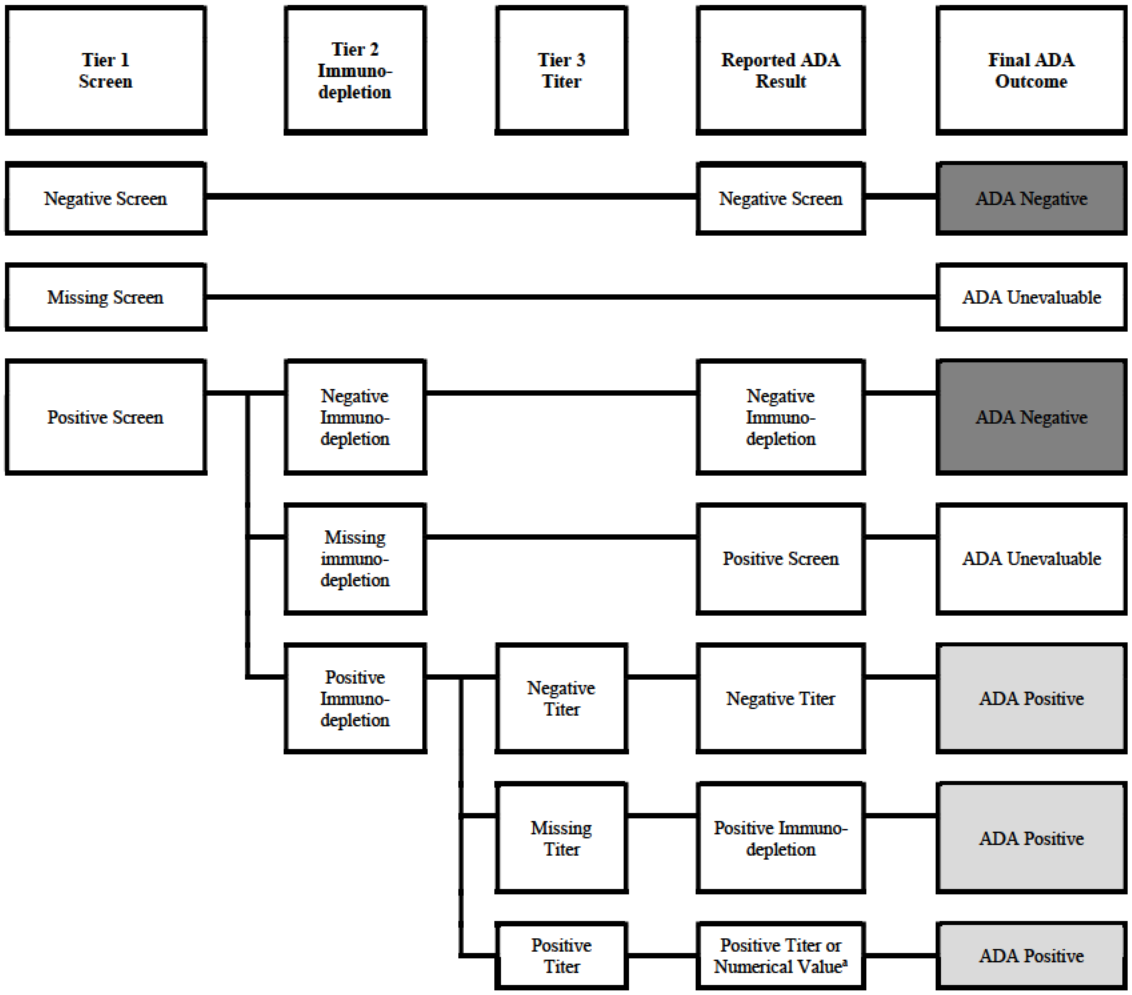
If available, a titer result will be reported for the ADA confirmed positive samples. However, a titer result is not always available:

- 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 J: Participant Classification for ADA Against Efgartigimod

Participant ADA classification / **Baseline ADA sample status**	Highest[a] postbaseline sample status: ADA negative	ADA positive (missing titer[b])	**ADA positive (negative titer[c] or numerical titer value)**		ADA unevaluable
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", 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.

17. BIOMARKER ANALYSIS

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

[redacted], where a shift table might be prepared using the SAF for the FPA only.

- [redacted]

18. Safety Outcomes

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 laboratory test results,
- vital signs, and
- electrocardiogram (ECG) results

These endpoints will be assessed and reported based on the SAF.
There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

18.1. Adverse Events

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

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

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

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

AE onset and duration will be calculated as follows when start and stop dates are fully known:
AE onset day (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 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 implantsand 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, and the number of events and the event rate per 100 PYFU, for the SAF at the IAWK12, IAWK24 and FPA for the following;;

-
- TEAEs (IAWK12, IAWK24 and FPA)
- Serious TEAEs (IAWK12, IAWK24 and FPA)
- Grade ≥3 TEAEs (IAWK12, IAWK24 and FPA)
- Fatal TEAEs

- Treatment-related TEAEs according to the Principle Investigator (IAWK12, IAWK24 and FPA)
- Procedures-related TEAEs (FPA Only)
- Serious treatment-related TEAEs (IAWK12, IAWK24 and FPA)
- TEAEs leading to IMP discontinuation (IAWK12, IAWK24 and FPA)
- TEAEs leading to IMP interruption
- TEAEs of special interest (IAWK12, IAWK24 and FPA)
- IRRs (IAWK12, IAWK24 and FPA)

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

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

All AEs, including pretreatment events will be listed.

18.1.1. All TEAEs

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

- TEAEs
- Serious TEAEs
- Nonserious TEAEs
- Grade ≥3 TEAEs

TEAEs by worst toxicity (FPA Only)

- Treatment-related TEAEs
- Procedure-related TEAEs
- Serious treatment-related TEAEs
- TEAEs leading to IMP discontinuation

- TEAEs of special interest by worst outcome
- IRRs
- Serious IRR (IAWK12, IAWK24 and FPA)
-

18.2. Laboratory Evaluations

Results from the central laboratory will be included in the reporting of this study for serum chemistry and hematology, coagulation, urinalysis, serology (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.

Table K: 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, albumin, blood urea nitrogen, creatinine, glucose, potassium, chloride bicarbonate, 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 (as needed for WOCBP potential, defined in Section 10.4.1 of the protocol)
Specialty laboratory tests:	CRP, ESR, TSH

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 IAWK12, IAWK24 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 IAWK12, IAWK24 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 IAWK12, IAWK24 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

18.2.1. Laboratory Specific Derivations

All datapoints obtained after informed consent up to 60 days after IMP discontinuation or database cutoff will be considered.
The following abnormality categories will be defined:

- Low: value < lower limit of normal range
- Normal: lower limit of normal range ≤ value ≤ upper limit of normal range
- High: value > upper limit of normal range
    - Notes:
    - Classification will be done in standardized units, using non imputed values and limits.
    - For the worst-case analysis visits, as defined in section 6.4, an additional category low + high is defined in case there are both low and high post-baseline values.

Toxicity grades will be computed according to the National Cancer Institute (NCI) common toxicity criteria for

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

Only lab parameters specified within the protocol will be 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.

18.3. ECG Evaluations

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

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

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

The following summaries will be provided for ECG data:

ECG parameters will be summarized using descriptive statistics at each analysis visit 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.

18.3.1. ECG Abnormal Criteria

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

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

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

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.

18.4. 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.

18.4.1. Vital Signs Abnormal Criteria

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

Variable	Unit	Low	Normal	High
SBP	mmHg	< 90	90-150	> 150
DBP	mmHg	< 45	45 – 90	> 90
Heart rate	Bpm	< 40	40 – 100	> 100
Body temperature	˚C	< 35.8	35.8 – 37.5	> 37.5

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

18.5. Physical Examination

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.

19. PHARMACOKINETIC ANALYSIS

PK analyses will be performed in the PKAS.

At IMP administration visits, PK blood samples will be collected pre-dose (within the 2 hours before IMP infusion) and post-dose (within the 30 minutes after the end of the infusion).

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. 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).
- When post-dose samples are collected following the occurrence of incomplete or incorrect dosing.
- 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.

20. REFERENCES

1. Dobson, A. J. (2002). An introduction to generalized linear models, 2nd ed. Chapman & Hall/CRC.
2. ICH-E3 Structure and Content of Clinical Study Reports – Step 4: 30 Nov 1995.
3. ICH Topic E6 (R2) Guideline for Good Clinical Practice – Step 4: 9 Nov 2016.
4. ICH Topic E9 Statistical Principles for Clinical Trials – Step 4: September 1998.
5. ICH Topic E9 (R1) Statistical Principles for Clinical Trials, Addendum on Estimands and Sensitivity Analysis is Clinical Trials – Step 4: November 2019.
6. ICH guideline E14: the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (R3) – questions and answers: January 2016.
7. Guideline on Missing Data in Confirmatory Clinical Trials - CHMP, 2 July 2010

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA Output Conventions

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

Dates & Times

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

Presentation of Treatment Groups

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

Treatment Group for Tables, Listings and Figures
Efgartigimod
Placebo

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

Listings

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

- Randomized treatment group (or treatment received if it's a safety output), first by active dose [by ascending dose group] and then control/ placebo
- Center-participant ID,
- Date (where applicable),

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

APPENDIX 2. TOXICITY GRADES

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

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
Sodium low	mmol/L	<LLN-130	-	<130-120	<120
	mEq/L	<LLN-130	-	<130-120	<120

Paramater	Unit	Grade 1	Grade 2	Grade 3	Grade 4
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 concomitantOr else, assign as Concomitant and Prior.
	Missing	If start date <= study med start date and if study medication is Ongoing,then assign it as prior and concomitant both. If it is not Ongoing, then assign it to Prior only.
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	If start date <= study med start date and if study medication is Ongoing,then assign it as prior and concomitant both. Check out for month and year as well in this case. If it is not Ongoing, then assign it to Prior only.

START DATE	STOP DATE	ACTION
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant
	Partial	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitantOr else, assign as Concomitant and Prior.
	Missing	Assign as concomitant and prior.