Official Title: A Phase 1, Open-label, Positron Emission Tomography Study in Healthy Subjects to Determine the Relationship Between Plasma Concentration and Target Occupancy of ASN51 Following Repeated Oral Doses

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Statistical Analysis Plan

Clinical trial protocol title:	A phase 1, open-label, positron emission tomography study in healthy subjects to determine the relationship between plasma concentration and target occupancy of ASN51 following repeated oral doses.
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Based on:	Protocol version 2, dated 23 January 2023
Prepared by:	[redacted]

Version control history

Version	Reason for change
1, dated 22 May 2023	N/A
1.1, dated 12 Jun 2023	Updated a formatting error in section 12.1 in relation to Appendix A and Appendix B. Removed column “Study Day” from T14.2.1.1 as not required.

Table of Contents

1 List of abbreviations

λ_z	Terminal rate constant
AE	Adverse event
ANOVA	Analyses of variance
ANCOVA	Analysis of covariance
AUC	Area under concentration-time curve
AUC_{inf}	AUC from time zero to infinity
AUC_{tau}	AUC for the dosing interval
AUC_{last}	AUC from time zero to last measurable concentration
$\%AUC_{extrap}$	Percentage of AUC_{inf} extrapolated from from tlast to infinity
BMI	Body mass index
BQL	Below the limit of quantification
CI	Confidence interval
CL_{ss}/F	Apparent total body clearance at steady state
C_{max}	Maximum plasma concentration
C_{trough}	Trough concentration
CRF	Case report form
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Coefficient of variation
CVb	Between-subject CV
ECG	Electrocardiogram
FDA	Food and Drug Administration
HR	Heart rate
ICH	International Conference on Harmonization
IV	Intravenous
LSM	Least Square Means
MedDRA	Medical Dictionary for Regulatory Activities
N	Number of subjects
n	Number of observations used in analysis
PBMC	Peripheral blood mononuclear cell
PET	Positron emission tomography
PD	Pharmacodynamic
PK	Pharmacokinetic(s)
PR	Portion of the ECG from the beginning of the P wave to the beginning of the QRS complex, representing atrioventricular node function.
QD	Once a day
QRS	The QRS complex of the ECG reflects the rapid depolarization of the right and left ventricles
QT	Portion of the ECG between the onset of the Q wave and the end of the T wave, representing the total time for ventricular depolarization and repolarization.
QTc	Corrected portion of the ECG between the onset of the Q wave and the end of the T wave, representing the total time for ventricular depolarization and repolarization
QTcF	QTc interval with Fridericia's correction method
$R_{ac(AUC)}$	Accumulation ratio for AUC
$R_{ac(Cmax)}$	Accumulation ratio for Cmax
RO	Receptor Occupancy

RR	Portion of the ECG between consecutive R waves, representing the ventricular rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SRG	Safety Review Grouip
$t_{½}$	Terminal elimination half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum plasma concentration
V_Z/F	Apparent volume of distribution
V_T	Volume of distribution
WHO	World Health Organisation

2 Signatures

The following persons have read and agreed the content of this Statistical Analysis Plan:

[redacted] Head of Statistics, HMR	[redacted] Signature	Jun 14, 2023 Date
[redacted] Chief Investigator, HMR	[redacted] Signature	Jun 14, 2023 Date
[redacted] Asceneuron S.A	[redacted] Signature	Jun 13, 2023 Date

3 Introduction

This statistical analysis plan (SAP) is based on the current trial protocol (version 2, 23 January 2023). Where statistical methods differ substantially between this SAP and the protocol, that will be identified in this document.

This SAP describes the datasets and the statistical methods to be used for the reporting and analysis of all data collected during the trial except the PET data analysis which will be analysed and reported separately by Invicro.

If a future protocol amendment necessitates a substantial change to the statistical analysis of the trial data, this SAP will be amended accordingly. If, after database lock, additional analyses are required to supplement the planned analyses described in this SAP, those unplanned analyses will not be described in an amended SAP, but they will be identified in the integrated clinical study report (CSR). Any deviations from this SAP will be documented in the CSR.

This SAP has been written in consideration of the following guidelines:

- International Conference on Harmonization (ICH) E9, Guidance for Industry: Statistical Principles for Clinical Trials (ICH E9 1998)[1]; and
- ICH E3, Guidance for Industry: Structure and Content of Clinical Study Reports (ICH E3 1995)[2].

Pharmacokinetic (PK) analysis will be done using WinNonlin v8.1 or higher on a Windows PC. Statistical analysis will be done using SAS ® 9.4 or higher on a Windows PC.

4 Study objective(s) and endpoint(s)

4.1 Study objective(s)

4.1.1 Primary objective(s)

- To assess the pharmacodynamic (PD) response in peripheral blood mononuclear cells (PBMCs) following single and repeated oral doses of ASN51 in healthy subjects.
- To assess brain O-GlcNAcase occupancy using [^{18}F]-IMA601 positron emission tomography (PET), following repeated oral doses of ASN51 in healthy subjects.

4.1.2 Secondary objective(s)

- To assess the safety and tolerability of repeated oral doses of ASN51 in healthy subjects
- To assess the relationship between the plasma concentration of ASN51 and the time-course of brain O-GlcNAcase occupancy using [^{18}F]-IMA601 PET, following repeated oral doses of ASN51 in healthy subjects

- To assess the pharmacokinetics (PK) of repeated doses of ASN51 in healthy subjects
- To assess the trough O-GlcNAcase occupancy of ASN51 after repeated doses in healthy subjects
- To determine the effect of food on the PD response in PBMCs following repeated ASN51 dosing in healthy subjects

4.2 Study endpoint(s)

4.2.1 Primary endpoint(s)

PD:

- Protein O-GlcNAcylation in PBMCs
- [^{18}F]-IMA601 regional total volume of distribution (V_T) at each brain scan

4.2.2 Secondary endpoint(s)

Safety and tolerability:

- vital signs (blood pressure, pulse rate, tympanic temperature, and respiratory rate), 12-lead safety electrocardiogram (ECG), physical and neurological examination, laboratory safety tests (haematology, clinical chemistry, coagulation, and urinalysis), Columbia-Suicide Severity Rating Scale (C-SSRS), and adverse events (AEs)

PK:

- plasma concentration of ASN51 at the time of each postdose PET scan
- PK parameters including C_{max}, C_{max}/Dose, t_{max}, $t½$, λ_Z, AUC_{tau}, AUC_{last}, AUC_{inf}, AUC_{inf} /Dose, $\%AUC_{extrap}$, CL_{SS}/F, V_Z/F, C_{trough}, $R_{ac(Cmax)}$, $R_{ac(AUC)}$.

PD:

- Protein O-GlcNAcylation in PBMCs with or without prior feeding
- Trough [^{18}F]-IMA601 V_T

PK/PD:

- relationship between ASN51 plasma concentration, PBMC target engagement, and brain receptor occupancy (RO) over time

4.3 Statistical hypotheses

The trial is an exploratory one, and there are no null hypotheses to be tested.

5 Study design

This is a phase 1, open-label, dose escalation, PET study to investigate the brain occupancy of O-GlcNAcase, and the PD response in PBMCs, after repeated doses of ASN51 in healthy subjects.

Enrolment of up to 12 healthy subjects is planned, in up to 2 groups (Groups 1 and 2). Each group will consist of up to 6 subjects.

All subjects will receive once-daily (QD) doses of ASN51, by mouth, for 14 days: Group 1 will receive [redacted] ASN51 QD and Group 2 will receive [redacted] ASN51 QD. Group 2 will proceed only if the safety and tolerability of the previous dose level are acceptable, and the plasma concentrations of ASN51 are predicted to remain below the toxicokinetic limit, as determined by the Safety Review Group (SRG; see protocol section 8.5).

On Day 11, to evaluate the effect of food on PBMC response, subjects will receive ASN51 in the fed state following a United States Food and Drug Administration (FDA) high-fat breakfast. Subject fasting requirements are further detailed in protocol section 11.

In each group, 2 subjects will have a PBMC-only study design (section 5.1.1) and 4 will have a PBMC and PET scanning study design (section 5.1.2).

Schematic diagrams of each study design are in protocol section 8.2.

5.1.1 PBMC-only subjects

2 subjects in each of Groups 1 and 2 will not have PET scans during the study. They will:

- be screened within 28 days before their first dose of trial medication.
- be resident on ward from 1 day before their first dose (Day –1) until 6 days after their final dose (Day 20).
- return for a follow-up visit 9–11 days after their final dose of trial medication (Days 23–25).

5.1.2 PET subjects

4 subjects in each of Groups 1 and 2 will have PET scans during the study. PET subjects will:

- be screened within 21 days before imaging session 1 (see below).
- be resident on ward from 1 day before their first dose (Day –1) until 6 days after their final dose (Day 20); and have imaging sessions as described below.
- return for a follow-up visit 9–11 days after their final dose of trial medication (Day 23 ± 2 days), or 2–4 days after imaging session 3 (see below), whichever is later.

PET subjects will have up to 3 imaging sessions, as follows.

- *Imaging session 1*. Subjects will have a baseline PET scan between Day –7 and Day –3. Subjects will be admitted to the ward the day before their baseline PET scan, and be discharged the following day after their scan.
- *Imaging session 2*. Subjects will have an on-treatment PET scan at about 5 h postdose on Day 1.
- *Imaging session 3*. Subjects will have an on-treatment PET scan at 3–9 days after their final dose of ASN51:
  - 3 subjects per group on Day 17
  - 1 subject on Day 22 (± 1 day) (Group 1 only)
  - 1 subject on Day 23 (± 1 day) (Group 2 only)

The timing of on-treatment PET scans (imaging sessions 2 and 3) may be altered based on emerging data or study logistical requirements.

Subjects will receive an intravenous (IV) dose of the radiolabelled tracer, [^{18}F]-IMA601, at the start of each PET scan.

Arterial blood sampling will be done during each PET scan to quantify the parent tracer-related radioactivity over the course of the PET scan, and to establish a tracer metabolite-corrected plasma input function. The total arterial blood volume required for each tracer injection will not exceed 120 mL. Arterial cannulation and arterial blood sampling may be reduced or removed if analysis of PET data from previous subjects indicates that non-invasive analysis of the PET scan data can be done. If a non-invasive analysis is not possible, the use of an arterial cannula with each PET scan will continue through the study.

In the case of a technical failure (such as unsuccessful tracer synthesis), subjects may be asked to attend an additional on-treatment imaging session as described in section 12.2 of the protocol. However, no subject will have more than 3 PET scans and 3 doses of [^{18}F]-IMA601 during the study. See section 8.2 of the protocol for the design flow charts.

6 Time and events table

Please refer to section 12.1 of the protocol, version 2, dated 23 January 2023 and file note Ward 2.

7 Planned analyses

No interim analyses are planned. However, data will be reviewed for dose selection.

7.1 Interim analyses

No interim analyses are planned. However, safety and pharmacokinetic data from Group 1 will be reviewed before proceeding to Group 2.

7.2 Final analysis

The database will be locked once all subjects have completed the study, data have been entered, and queries resolved. The final analysis will be carried out following database lock.

7.2.1 Persons responsible for analysis

[redacted] Statistician

8 Sample size considerations

8.1 Sample size assumptions

Since this trial is hypothesis generating, no formal calculation of sample size is appropriate.

The sample size chosen is considered adequate to allow modelling of the relationship between ASN51 plasma concentrations and pharmacodynamic target engagement using an exploratory PBMC protein O-GlcNAcylation assay.

PET analyses of 8 subjects is sufficient to define the occupancy of O-GlcNAcase and is within the range generally accepted for PET studies.

9 Analysis populations

The following populations will be identified:

Safety population:	All subjects who received at least one dose of study drug
PET population:	All subjects in the safety population who had a baseline PET scan, at least 1 post-baseline PET scan, and a PK result immediately preceding a PET scan
PD analysis population:	All subjects in the safety population for who a PBMC measure is available.
PK analysis population:	The PK analysis population will consist of the subjects who provide evaluable data for the comparisons of interest. These subjects should have at least one quantifiable plasma concentration, should not have violated any major entry criterion likely to confound the PK analysis, and should not have deviated significantly from the protocol between enrolment and successful study completion

The primary endpoints will be analysed using the PET and PD populations. The secondary endpoints will be analysed using the Safety, PET and PD populations.

9.1 Analysis datasets

All analysis datasets will be based on observed data, except as outlined in Section 12.2.

10 Treatment comparisons

The treatment comparison of interest is study drug between ascending doses.

11 General considerations for data analyses

11.1 Data display treatment and other subgroup descriptors

The sort order for treatment groups will be study treatment in ascending dose order.

Listings of data will be sorted and displayed by treatment group, subject number, and also by date and time if applicable.

The treatment descriptions to be used on all tables and listings are:

Treatment Groups
[redacted] ASN51 (QD for 14 Days)
[redacted] ASN51 (QD for 14 Days)

11.2 Conventions for summary statistics and data displays

The minimum set of summary statistics for numeric variables will be: n, mean, standard deviation, median, minimum, and maximum. 95% confidence intervals (CI) will be presented where appropriate for data interpretation.

Categorical data will be summarised in frequency tables with n and percentage. Summaries of a categorical variable will include all recorded values.

The minimum and maximum values will be presented with the same number of decimal places as the raw data collected on the CRF (or to 3 significant figures for derived parameters less than 100 and as integers for values more than 99). The mean and percentiles (eg median) will be presented using one additional decimal place. The standard deviation and standard error will be presented using two additional decimal places.

12 Data handling conventions

12.1 Premature withdrawal and missing data

All subjects who withdraw prematurely from the study or study drug will be included in the statistical analyses.

If a subject completes the treatment period but has missing data, then this will be made apparent in the subject listings. Missing data will not be imputed except for as outlined in Section 12.2.

If the study is prematurely discontinued, all available data will be listed and a review will be carried out to assess which statistical analyses are still considered appropriate.

Data collected at unscheduled time points during the study will not be used in the summaries or data analyses. They will be included in the listings.

If time information (ie hours and/or minutes) for adverse events (AEs) or concomitant medication is missing, but the day is present, then the time will be calculated in days. If date information is partial or missing, then any derived times (eg AE start time from last study medication) will be listed as missing.

Conventions for handling missing plasma concentrations are given in Appendix B: Pharmacokinetic analysis

12.2 Derived and transformed data

Baseline will be considered to be the latest value obtained before study drug administration (eg Day 1, pre-dose; or Day –1 if not recorded at pre-dose; or screening if not recorded at pre-dose or on Day –1).

Laboratory data will be reported in standard units. Out-of-range laboratory tests may be repeated. If a test is out of-range at baseline and repeated before dosing, the latest repeat value before dosing will be used as baseline. However, if a test is out-of-range and repeated at any other time during the study, the out-of-range value (not the repeat value) will be included in statistical summaries.

Triplicate ECG and vital sign measurements will be made at screening and the mean of the three measurements for each subject will be used for analysis.

Triplicate PBMC measurements will be made and the mean of the three measurements for each subject will be used for analysis.

The PK parameters to be derived are given in Appendix B: Pharmacokinetic analysis.

12.3 Assessment windows

No assessment windows are defined for this report.

12.4 Vital signs reference ranges

The following vital signs ranges will be used:

Vital Sign	Range
Seated systolic blood pressure	90–140 mm Hg
Seated diastolic blood pressure	40–90 mm Hg
Seated pulse rate	40–100 beats/min
Tympanic temperature	35.5–37.8°C
Respiratory rate	10–16 breaths/min

13 Study population

13.1 Disposition of subjects

The disposition of all subjects in all populations will be summarised including: number of subjects by treatment; number completing the study, by treatment; and number withdrawn from the study. Screen failures will also be listed and summarised.

All subjects who withdraw or are withdrawn from the study will be listed, by treatment, with the reason for withdrawal.

A listing of analysis populations will be provided.

13.2 Protocol deviations

Before closing the database, data listings will be reviewed to identify any significant deviations and determine whether the data should be excluded from any analysis populations.

Major protocol deviations include subjects who:

- Entered the study even though they did not satisfy the entry criteria.
- Met the criteria for withdrawal from the study but were not withdrawn.
- Received the wrong treatment or incorrect dose.
- Received an excluded concomitant therapy.
- Received investigational product(s) past the expiration date.

In addition, subjects with minor time deviations (measurements taken outside the allowable windows) will be identified. Allowable time windows for pharmacokinetic samples and other procedures are given in 12.2 of the study protocol.

13.3 Demographic and baseline characteristics

Demographic and baseline characteristics (eg physical examination, vital signs and ECGs) will be listed and summarised.

Subjects who take concomitant medication will be listed. All non-trial medication will be coded using the latest version of the World Health Organisation (WHO) ATC index (version 2021 or higher).

Medical and surgical history data will also be listed. Medical and surgical history will be coded using the version of the Medical Dictionary for Regulatory Activities (MedDRA) current at the time of database lock.

13.4 Treatment compliance

Dates and times of dosing will be listed.

14 Safety analyses

Summaries and listings of safety data will use the safety population.

14.1 Extent of exposure

The dates and times of treatment dosing will be listed to indicate exposure to the study medication.

14.2 Adverse events

AEs will be coded using the version of the Medical Dictionary for Regulatory Activities (MedDRA) which is current at the time of database lock (version 25.1 or higher).

All AEs will be listed.

The number of subjects with at least one treatment-emergent adverse event (TEAE) per treatment will be tabulated by actual treatment and MedDRA system organ class. A TEAE is defined as an event emerging during treatment (having been absent pre-treatment) or that worsens after treatment[1].

For each of the following, the number of TEAEs and the number of subjects with TEAEs will be summarised by treatment:

- TEAEs, by system organ class and preferred term
- Drug-related ("possibly", "probably" or "definitely" as recorded by the investigator) TEAEs, by system organ class and preferred term

Subjects with more than one TEAE will be counted only once, at the greatest severity or causality, for each system organ class/preferred term. Multiple TEAEs in a subject will be counted once per system organ class and preferred term. AEs with missing severity and/or causality will be treated as severe and definitely related, respectively.

Summaries will be sorted by system organ class and decreasing total incidence of preferred term.

14.3 Deaths, serious adverse events and other significant adverse events

Deaths and serious adverse events (SAEs) will be listed separately (fatal events separate from non-fatal events). Other significant AEs, as identified by the investigator in the CRF, will be listed separately.

14.4 Adverse events leading to withdrawal from the study

AEs leading to withdrawal will be listed separately.

14.5 Clinical laboratory evaluations

Data from haematology, coagulation, urinalysis, and clinical chemistry will be summarised by treatment.

The laboratory tests with normal ranges that are different from the ranges most commonly used in the study (reference ranges) are listed in Appendix A: Laboratory tests with different ranges.

Data from haematology, coagulation, and clinical chemistry outside the normal ranges (used to assign clinical significance) and/or reference ranges (the most commonly used in the study) will be listed. Data outside the reference ranges will be summarised.

14.6 Other safety measures

14.6.1 Vital signs

Vital signs evaluation at each planned assessment, and change in vital signs from baseline (Day 1, pre-dose) at each planned post baseline assessment, will be summarised by actual treatment.

Vital signs data outside of the normal range will be listed and summarised.

A separate listing of vital sign findings, classified as clinically significant by the investigator will also be provided.

14.6.2 ECG

QT interval data will be presented using Fridericia's (QTcF) corrections.

ECG variables will be summarised by treatment and time point. Differences from baseline (Day 1 pre-dose) will be summarised by treatment and time point.

QTcF values > 450 msec, PR interval shortening < 110 msec, and PR interval prolongation >220 msec, and increases of QTcF from baseline of > 30 msec and > 60 msec, will be listed by treatment and timepoint and summarised. A separate listing of ECG findings classified as abnormal by the investigator will also be provided.

14.6.3 Physical examination

Abnormal physical and neurological examination findings will be listed.

14.6.4 Columbia-Suicide Severity Rating Scale (C-SSRS)

Positive C-SSRS data will be listed.

15 Pharmacokinetic analyses

The PK parameters to be derived are given in Appendix B: Pharmacokinetic analysis.

PK concentration data will be summarised using the PK analysis population.

Plasma concentrations and PK parameters will be listed and summarised, by treatment, using descriptive statistics. Individual and mean plasma concentration–time profiles will be presented graphically. All available data will be used to derive PK parameters in individual subjects.

For log–transformed parameters, the primary measure of central tendency will be the geometric mean[4]; for other parameters, it will be the arithmetic mean or median.

For all variables, N (number of subjects receiving the treatment/formulation in the population), n (number of observations), arithmetic mean, median, minimum, maximum, standard deviation (SD), %CV, and the 95% CI for the arithmetic mean will be provided. For log-transformed variables, all of the above plus the geometric mean, which is the anti-logged arithmetic mean of log-transformed variables, its 95% CI and the SD of the logs will be provided.

The between-subject CV will be calculated using:

1. %CVb = 100 * (SD/mean) with SD and mean of untransformed data
2. %CVb = 100 * $\sqrt{}$ (exp(SD)^2 -1) with SD of log-transformed data

15.1 Pharmacokinetic concentration data

Plasma concentrations will be listed and summarised by treatment.

Using actual sample times, linear and semi-logarithmic concentration-time plots will be prepared by treatment and synoptic linear and semi-logarithmic plasma concentration-time plots of ASN51 will be prepared for each Day. In addition to the plots of concentrations on PK days, separate plots of trough concentrations for ASN51 will be prepared. The same linear and logarithmic scales will be used for each subject. The linear and semi logarithmic plots for a given treatment will be presented on the same page.

Nominal blood sampling times will be used to calculate the mean (SD) drug concentrations at each time point.

Mean(+/- SD), and spaghetti plasma concentration versus time plots will be presented for ASN51 per treatment (synoptic plot) (normal scale and log-linear scale).

15.2 Pharmacokinetic parameters

The pharmacokinetic parameters will be listed and summarised by treatment.

16 Pharmacodynamic analyses

Protein O-GlcNAcylation in PBMCs at each planned assessment, and change in protein O-GlcNAcylation in PBMCs from baseline (Day 1, pre-dose) at each planned post baseline assessment, will be summarised by actual treatment using the PD population.

Time invariance of target engagement will be investigated by comparing the PD and PK/PD relationship over time.

Food effect on the PBMC assay will be investigated by comparing Day 11 and 14 PBMC data descriptively.

In addition to the descriptive statistics of the PBMC data (ie N, mean, median, SD, min, max, CV%), time-matched change from baseline PBMC parameters (Day 1 vs Day 14, and Day 11 vs Day 14) will be assessed using an Analyses of variance (ANOVA) approach. ANOVA will be performed on the natural log(ln)-transformed PBMC parameters. Each ANOVA will include calculation of least square means (LSM), the difference between LSM of the two conditions, and the standard error and 90% confidence interval (CI) associated with this difference. The LSM, difference in LSMs, and associated 90% CI will be back transformed to present geometric LSM, the ratio of geometric means, and associated 90% CI. The 90% CI of geometric mean ratio will be calculated to check whether it lies within the interval 0.70 to 1.43.

Furthermore, PBMC data and plasma concentration data of Day 1 and Day 14 will be investigated by a regression analysis, where the slopes and intercepts will be compared statistically for each treatment. The change from baseline of PMBC data will be analysed using analysis of covariance (ANCOVA). Time point, PK concentration and PK concentration by time point interaction will be fitted as fixed effects. PK concentration will be treated as a continuous covariate and time point will be fitted as a categorical covariate. The estimates, standard errors, associated 95% CI and P-values will be reported.

17 Changes from the protocol specified statistical analysis

After the study was submitted to the MHRA and ethics committee the following changes were made to the analyses:

- Various updates to scheduled timepoints have been made as document in file note ward 2.

18 References

1. International Conference on Harmonization, 1998. Statistical Principles for Clinical Trials – ICH Harmonised Tripartite Guideline. Guidance for Industry, E9, FDA federal register, Vol 63, 1998, p49583. Available at: http://www.fda.gov/cder/guidance.
2. International Conference on Harmonization, 1995. Structure and Content of Clinical Study Reports – ICH Harmonised Tripartite Guideline. Guidance for Industry, E3, FDA federal register, Vol 61, 1996, p37320. Available at: http://www.fda.gov/cder/guidance.
3. International Conference on Harmonisation, 2005. Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. Concept paper, Guidance for Industry, E14, Center for Drug Evaluation and Research (CDER). Available at: http://www.fda.gov/cder/guidance/6922fnl.htm.
4. Julious, SA & Debarnot, CAM (2000) "Why are Pharmacokinetic Data Summarised by Arithmetic Means?", Journal of Biopharmaceutical Statistics, 10 (1), p55-71

19 ATTACHMENTS

19.1 Table of contents for data display specifications

For overall page layout refer to Appendix C: Sample page .

The numbering in the tables below will take precedence over the numbering in the shells.

The following tables and figures will be produced (templates provided in Sections 19.2.1 and 19.2.2):

Table	Description	Population	Source Listing	Template (Shells below)
10.1	Summary of subject disposition	Safety	16.2.1.2 16.2.1.3 16.2.3.1	T_SD1
14.1	DEMOGRAPHIC DATA			
14.1	Summary of demographic characteristics	Safety	16.2.4.1	T_DM1
14.2	PHARMACOKINETIC AND PHARMACODYNAMIC DATA			
14.2.1.1	Summary of ASN51 plasma pharmacokinetic concentration-time data [units]	PK analysis	16.2.6.1.1	T_PK1
14.2.1.2	Summary of derived ASN51 plasma pharmacokinetic parameters	PK analysis	16.2.6.1.2 16.2.6.1.3	T_PK3
14.2.1.3	Summary of log-transformed derived ASN51 plasma pharmacokinetic parameters	PK analysis	16.2.6.1.2 16.2.6.1.3	T_PK4
14.2.2.1	Summary of plasma PBMC data (% above baseline)	PD analysis	16.2.6.2	T_VS1
14.2.2.2	Summary of analysis of time-matched change from baseline plasma PBMC data using analysis of variance (Day 1 vs Day 14 and Day 11 vs Day 14)	PD analysis	16.2.6.2	T_ANOVA1
14.2.2.3	Summary of ANCOVA analysis of PBMC and PK concentration to compare intercepts and slopes between Day 1 and Day 14	PD analysis	16.2.6.2	T_REGR
14.3	SAFETY DATA			
14.3.1.1	Overall summary of treatment-emergent adverse events	Safety	16.2.7.1	T_AE2
14.3.1.2	Summary of treatment-emergent adverse events	Safety	16.2.7.1	T_AE1
14.3.1.3	Summary of drug-related treatment-emergent adverse events	Safety	16.2.7.1	T_AE1
14.3.2.1	Listing of fatal adverse events	Safety	16.2.7.1	L_AE1_PG
14.3.2.2	Listing of non-fatal serious adverse events	Safety	16.2.7.1	L_AE1_PG
14.3.2.3	Listing of other significant adverse events	Safety	16.2.7.1	L_AE1_PG
14.3.3	Narratives of deaths, other serious and significant adverse events	Safety		-
14.3.4.1	Summary of laboratory values outside the reference range by treatment and planned relative time	Safety	16.2.8.1 16.2.8.2 16.2.8.3	T_LB1

Table	Description	Population	Source Listing	Template (Shells below)
14.3.4.2	Summary of laboratory values outside the reference range by treatment	Safety	16.2.8.1 16.2.8.2 16.2.8.3	T_LB3
14.3.5.1	Summary of chemistry laboratory values	Safety	16.4	T_LB2
14.3.5.2	Summary of haematology laboratory values	Safety	16.4	T_LB2
14.3.5.3	Summary of coagulation laboratory values	Safety	16.4	T_LB2
14.3.5.4	Summary of urinalysis results	Safety	16.4	T_UR1
14.3.6.1	Summary of vital signs	Safety	16.4	T_VS1
14.3.6.2	Summary of vital signs outside the normal range by treatment, planned relative time and parameter	Safety	16.2.9.1	T_VS2
14.3.6.3	Summary of vital signs outside the normal range by treatment and parameter (excluding baseline time point)	Safety	16.2.9.1	T_VS3
14.3.7.1	Summary of ECG values	Safety	16.4	T_EG2
14.3.7.2	Summary of QTcF and PR interval values outside the normal range by treatment, planned relative time and category	Safety	16.2.9.3	T_EG3
14.3.7.3	Summary of QTcF and PR interval values outside the normal range by treatment and category	Safety	16.2.9.3	T_EG4

Figure	Description	Population	Source Listing	Template (Shells below)
14.2	PHARMACOKINETIC AND PHARMACODYNAMIC DATA			
14.2.1	Individual ASN51 plasma concentration-time plots (linear and semi-log)	PK analysis	16.2.6.1.1	F_PK1
14.2.2	Mean (+/- SD) ASN51 plasma concentration-time plots (linear and semi-log)	PK analysis	16.2.6.1.1	F_PK2
14.2.3	Mean ASN51 plasma concentration-time plots (linear and semi-log)	PK analysis	16.2.6.1.1	F_PK2
14.2.4	Individual ASN51 plasma pre-dose concentration versus day	PK analysis	16.2.6.1.1	F_PK5
14.2.5	Mean (+/- SD) ASN51 plasma pre-dose concentration versus day	PK analysis	16.2.6.1.1	F_PK6

Figure	Description	Population	Source Listing	Template (Shells below)
14.3	SAFETY DATA			
14.3.1	Individual systolic blood pressure-time plots	Safety	16.4	F_SAF1
14.3.2	Individual diastolic blood pressure-time plots	Safety	16.4	F_SAF1
14.3.3	Individual heart rate-time plots	Safety	16.4	F_SAF1
14.3.4	Individual QTcF-time plots	Safety	16.4	F_SAF1

The following abbreviated listings will be produced (templates provided in Section 19.2.3):

Listing	Description	Template (Shells below)
16.2.1	Study dates & disposition of subjects	
16.2.1.1	Listing of study dates	L_SD1_PG
16.2.1.2	Listing of reasons for withdrawal	L_SD2_PG
16.2.1.3	Listing of subjects screened but not enrolled	L_SD3_PG
16.2.2	Protocol deviations	
16.2.2.1	Listing of subjects with inclusion/exclusion criteria deviations	L_DV1_PG
16.2.2.2	Listing of subjects with time deviations	L_TD1_PG
16.2.2.3	Listing of subjects with other protocol deviations	L_DV2_PG
16.2.3	Analysis sets, including subjects excluded from analysis	
16.2.3.1	Listing of analysis populations	L_AN1_PG
16.2.4	Demographic data & concomitant medication	
16.2.4.1	Listing of demographic characteristics	L_DM1_PG
16.2.4.2	Listing of concomitant medications	L_CM1_PG
16.2.4.3	Listing of medical history	L_MH1_X
16.2.5	Study drug administration	
16.2.5.1	Listing of exposure data	L_EX1_PG
16.2.6	Pharmacokinetic and pharmacodynamic data	
16.2.6.1.1	Listing of ASN51 plasma pharmacokinetic concentration-time data	L_PK1_PG

Listing	Description	Template (Shells below)
16.2.6.1.2	Listing of derived ASN51 plasma pharmacokinetic parameters	L_PK4_PG
16.2.6.1.3	Listing of derived ASN51 Ctrough (ng/mL) pharmacokinetic parameter	L_PK4_PG
16.2.6.1.4	Individual ASN51 plasma concentration-time plots for estimation of λz, with regression line	F_PK10
16.2.6.2	Listing of plasma PBMC data	L_PBMC_PG
16.2.7	Adverse events	
16.2.7.1	Listing of all adverse events	L_AE1_PG
16.2.7.2	Listing of serious adverse events	L_AE1_PG
16.2.7.3	Listing of adverse events leading to withdrawal from study	L_AE1_PG
16.2.8	Laboratory values	
16.2.8.1	Listing of clinical chemistry data outside the normal range	L_LB1_PG
16.2.8.2	Listing of haematology data outside the normal range	L_LB1_PG
16.2.8.3	Listing of coagulation data outside the normal range	L_LB1_PG
16.2.9	Vital signs, ECG variables, physical and neurological findings and C-SSRS	
16.2.9.1	Listing of vital signs outside the normal range	L_VS1_PG
16.2.9.2	Listing of clinically significant vital signs	L_VS2_PG
16.2.9.3	Listing of QTcF and PR interval values outside the normal range	L_EG1_PG
16.2.9.4	Listing of abnormal ECG findings	L_EG2_PG
16.2.9.5	Listing of abnormal physical examination findings	L_PE1_PG
16.2.9.6	Listing of abnormal neurological examination findings	L_NEURO_PG
16.2.9.7	Listing of positive Columbia-Suicide Severity Rating Scale data	L_CSS_PG

* ICH does not require full listings of lab data so only subjects with out-of-range values will be listed.

Complete listings of all data collected in this study will also be produced.

19.2 Data Display Specifications

Footnote “Note: Subjects received ASN51 in the fed state on Day 11 only” will be added to any outputs with Day 11

19.2.1 Table Outlines

Template T_SD1

Table 10.1 Summary of subject disposition

Characteristics	Status	Reason for Withdrawal	Treatment 1 (N=xx) n (%)	Treatment 2 (N=xx) n (%)	All Subjects n (%)
Screened population	Total				xx
	Included				xx
	Excluded	Not satisfying inclusion/exclusion criteria			xx
		Declined to participate			xx
		Other			xx
Safety population	Included		xx	xx	xx
	Completed		xx (xx)	xx (xx)	xx (xx)
	Withdrawn		xx (xx)	xx (xx)	xx (xx)
		Death	xx (xx)	xx (xx)	xx (xx)
		Adverse Events	xx (xx)	xx (xx)	xx (xx)
		Withdrawal by subject	xx (xx)	xx (xx)	xx (xx)
		Study terminated by Sponsor	xx (xx)	xx (xx)	xx (xx)
		Lost to follow-up	xx (xx)	xx (xx)	xx (xx)
		Other	xx (xx)	xx (xx)	xx (xx)
Alternative 1 (if applicable)	Included				
Alternative 2 (if applicable)	Included				

Source: Listing 16.2.xx

Note: Subjects received ASN51 in the fed state on Day 11 only

Programming notes: *Continued with all treatment groups*

Template T_DM1

Table 14.1 Summary of demographic characteristics

Variable	Statistics	Treatment 1 (N=xx)	Treatment 2 (N=xx)	All Subjects (N=xx)
Age (y)	n			
	Mean			
	SD			
	Median			
	Min			
	Max			
Sex (%)	Female			
	Male			
Race (%)	American Indian or Alaskan			
	Native			
	Asian			
	Black			
	Native Hawaiian or other			
	Pacific Islander			
	White			
	Other			
Ethnicity (%)	Hispanic or Latino			
	Not Hispanic or Latino			
Height (cm)	n			
	Mean			
	SD			
	Median			
	Min			
	Max			
Weight (kg)	n			
	Mean			
	SD			
	Median			
	Min			

Variable	Statistics	Treatment 1 (N=xx)	Treatment 2 (N=xx)	All Subjects (N=xx)
	Max			
BMI (kg/m2)	n			
	Mean			
	SD			
	Median			
	Min			
	Max			
Smoking	Never			
History (%)	Former			
	Current			
Cigarettes*	n			
(daily)	Mean			
	SD			
	Median			
	Min			
	Max			
Alcohol*	n			
(units/week)	Mean			
	SD			
	Median			
	Min			
	Max			

Source: Listing 16.2.xx

*includes only those subjects who smoke/drink alcohol

Template T_PK1

Table 14..2.xx Summary of ASN51 plasma pharmacokinetic concentration-time data [units]

Treatment	Planned Relative Time	n	No. Imputed	Mean	95% CI (Lower,Upper)	SD	%CVb	Median	Min	Max
Treatment 1	Pre-dose	x	x	xxxx.x	(xxxx.x,xxxx.x)		xx.x	xxxx.x	xxxx	xxxx
(N=xx)	30 min	x	x	xxxx.x	(xxxx.x,xxxx.x)	xx.xx	xx.x	xxxx.x	xxxx	xxxx
	1 h	x	x	xxxx.x	(xxxx.x,xxxx.x)	xx.xx	xx.x	xxxx.x	xxxx	xxxx
Treatment 2	Pre-dose	x	x	xxxx.x	(xxxx.x,xxxx.x)	xx.xx	xx.x	xxxx.x	xxxx	xxxx
(N=xx)	30 min	x	x	xxxx.x	(xxxx.x,xxxx.x)	xx.xx	xx.x	xxxx.x	xxxx	xxxx
	1 h	x	x	xxxx.x	(xxxx.x,xxxx.x)	xx.xx	xx.x	xxxx.x	xxxx	xxxx

Source: Listing 16.2.xx

Programming notes: *Continued with all dose levels and timepoints*
Column "No. Imputed" is not required for summary of PBMC data

Template T_PK3

Table 14..2.xx Summary of derived ASN51 plasma pharmacokinetic parameters

Parameter	Treatment	Study Day	n	Mean	95% CI (Lower,Upper)	SD	%CVb	Median	Min	Max
AUC_t (units)	Treatment 1 (N=xx)		xx	xxxx.xx	(xxxx.xx,xxxx.xx)	xx.xxx	xx.x	xxxx.xx	xxxx.x	xxxx.x
	Treatment 2 (N=xx)		xx	xxxx.xx	(xxxx.xx,xxxx.xx)	xx.xxx	xx.x	xxxx.xx	xxxx.x	xxxx.x
C_{max} (units)	Treatment 1 (N=xx)		xx	xxxx.xx	(xxxx.xx,xxxx.xx)	xx.xxx	xx.x	xxxx.xx	xxxx.x	xxxx.x
	Treatment 2 (N=xx)		xx	xxxx.xx	(xxxx.xx,xxxx.xx)	xx.xxx	xx.x	xxxx.xx	xxxx.x	xxxx.x

Source: Listing 16.2.xx

R_{ac} (AUC) = R_{ac} (AUC_{tau}) Day 14 / R_{ac}(AUC_{tau}) Day 1
R_{ac} (C_{max}) = R_{ac} (C_{max}) Day 14/R_{ac}(C_{max}) Day 1

Programming notes: *Continued with all dose levels, timepoints and parameters*

Template T_PK4

Table 14..2.xx Summary of log-transformed derived ASN51 plasma pharmacokinetic parameters {by group}

Parameter	Treatment	Study Day	n	Geom Mean	95% CI (Lower,Upper)	SD (logs)	%CVb
AUC_{last} (units)	Treatment 1 (N=xx)	x	x	xxxx.xx	(xxxx.xx,xxxx.xx)	xx.xxx	xx.xx
	Treatment 2 (N=xx)	x	x	xxxx.xx	(xxxx.xx,xxxx.xx)	xx.xxx	xx.xx
C_{max} (units)	Treatment 1 (N=xx)	x	x	xxxx.xx	(xxxx.xx,xxxx.xx)	xx.xxx	xx.xx
	Treatment 2 (N=xx)	x	x	xxxx.xx	(xxxx.xx,xxxx.xx)	xx.xxx	xx.xx

Source: Listing 16.2.xx

Programming notes: Continued with all dose levels, timepoints and parameters

Template T_ANOVA1

Table 14.2.xx Summary of analysis of time-matched change from baseline plasma PBMC data using analysis of variance -Day 1 vs Day 14 and Day 11 vs Day 14 (% above baseline)

		LS Means			Day 1 vs Day 14			Day 11 vs Day 14		
Treatment	Planned RelativeTime	Day 1	Day 11	Day 14	Geometric Mean Ratio	SE	90% CI	Geometric Mean Ratio	SE	90% CI
Treatment 1 (N=xx)	Pre-dose	NA	xxxx	xxxx	NA	NA	NA	x.xx	x.xx	x.xx
	8 h	xxxxx	xxxx	xxxx	x.xx	x.xx	(x.xx, x.xx)	x.xx	x.xx	(x.xx, x.xx)
	12 h	xxxxx	xxxx	xxxx	x.xx	x.xx	(x.xx, x.xx)	x.xx	x.xx	(x.xx, x.xx)
Treatment 2 (N=xx)	Pre-dose	NA	xxxx	xxxx	NA	NA	NA	x.xx	x.xx	x.xx
	8 h	xxxxx	xxxx	xxxx	x.xx	x.xx	(x.xx, x.xx)	x.xx	x.xx	(x.xx, x.xx)
	12 h	xxxxx	xxxx	xxxx	x.xx	x.xx	(x.xx, x.xx)	x.xx	x.xx	(x.xx, x.xx)

Source: Listing 16.2.xx

NA = not applicable

Template T_REGR

Table 14.2.xx Summary of ANCOVA analysis of PBMC and PK concentration to compare intercepts and slopes between Day 1 and Day 14

Treatment	Parameter	Estimate	SE	95% CI	P-Value
Treatment 1 (N=xx)	Intercept	xx.x	xx.xx	x.xxx	x.xxx
	PK Concentration	xx.x	xx.xx	x.xxx	x.xxx
	Day 1	xx.x	xx.xx	x.xxx	x.xxx
	Day 14	xx.x	xx.xx	x.xxx	x.xxx
	PK Concentration*Day 1	xx.x	xx.xx	x.xxx	x.xxx
	PK Concentration*Day 14	xx.x	xx.xx	x.xxx	x.xxx
Treatment 2 (N=xx)	Intercept	xx.x	xx.xx	x.xxx	x.xxx
	PK Concentration	xx.x	xx.xx	x.xxx	x.xxx
	Day 1	xx.x	xx.xx	x.xxx	x.xxx
	Day 14	xx.x	xx.xx	x.xxx	x.xxx
	PK Concentration*Day 1	xx.x	xx.xx	x.xxx	x.xxx
	PK Concentration*Day 14	xx.x	xx.xx	x.xxx	x.xxx

Source: Listing 16.2.xx

Programming notes: *Include timepoints: 8 h, 12h and 24 h*

Template T_AE2

Table 14.3.3.xx Overall summary of treatment-emergent adverse events

Number of Subjects with	Treatment 1 (N=xx) n (%)	Treatment 1 (N=xx) n (%)	All Subjects (N=xx) n (%)
Any TEAE	x (xx.x) [xx]	x (xx.x) [xx]	x (xx.x) [xx]
Any serious TEAE	x (xx.x) [xx]	x (xx.x) [xx]	x (xx.x) [xx]
Any TEAE leading to withdrawal	x (xx.x) [xx]	x (xx.x) [xx]	x (xx.x) [xx]
Any drug-related TEAE	x (xx.x) [xx]	x (xx.x) [xx]	x (xx.x) [xx]
Any TEAE with mild as worst severity	x (xx.x)	x (xx.x)	x (xx.x)
Any TEAE with moderate as worst severity			
Any TEAE with severe as worst severity			

Source: Listing 16.2.xx

n = number of subjects
[ ] = number of TEAEs

Programming notes: *Continued with all treatment groups*

Template T_AE1

Table 14.3.3.xx Summary of treatment-emergent adverse events

System Organ Class*	Preferred Term	Treatment 1 (N=xx) n (%)	Treatment 2 (N=xx) n (%)	All Subjects (N=xx) n (%)
Number of subjects with TEAEs		x (xx.x)	x (xx.x)	
Gastrointestinal disorders	Total number of subjects	x (xx.x)	x (xx.x)	
	Abdominal discomfort	x (xx.x) [xx]	x (xx.x) [xx]	
	Abdominal pain	x (xx.x) [xx]	x (xx.x) [xx]	
	-			
Nervous system disorders	Total number of subjects			
	Dizziness			
	Headache			
	-			
-	-			

Source: Listing 16.2.xx

n = number of subjects (subjects with >1 TEAE are counted only once per system organ class and preferred term)

[ ] = number of TEAEs

*Coded using MedDRA version xx.x

Programming notes: *Continued with all treatment groups*
SOCs and PTs are sorted in decreasing order of frequency
Presented for all applicable MedDRA system organ classes and terms.

Template T_LB1

Table 14.3.4.xx Summary of laboratory values outside the reference range by treatment and planned relative time

Laboratory Test (units)	Treatment	Planned Relative Time	n	H	L
	Treatment 1 (N=xx)				

Source: Listing 16.2.xx

H = Above reference interval, L = Below reference interval

Programming notes: Continued with all tests, treatment groups and time points. The summary is based on the reference ranges (most common ranges used)

Template T_LB3

Table 14.3.4.xx Summary of laboratory values outside the reference range by treatment

Laboratory Test (units)	Treatment	m	H	L	Overall*
	Treatment 1 (N=xx)				

Source: Listing 16.2.xx

H = Above reference interval, L = Below reference interval
Subjects only counted once per treatment per category

*Subjects only counted once per treatment

m = total number of results for that parameter

Programming notes: Continued with all tests, treatment groups and time points. The summary is based on the reference ranges (most common ranges used)

Template T_LB2

Table 14.3.5.xx Summary of chemistry laboratory values

										Change from Baseline					
Laboratory Test (units)	Treatment	Planned Relative Time	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
	Treatment 1 (N=xx)													

Source: Listing 16.2.xx

Programming notes: Continued with all treatments and time points

Template T_UR1

Table 14.3.5.xx Summary of urinalysis results

	Planned Relative		Treatment 1 (N=xx)		Treatment 2 (N=xx)	
Laboratory Test	Time	Result	n	(%)	n	(%)
	Time 1	Positive	X	x		
		Negative	X	X		
		Not Done	x			
	Time 2	Positive				
		Negative				
		Not Done				

Source: Listing 16.2.xx

Programming notes: Results recorded as received, e.g. Negative, Trace, etc; urine pH summarised as <5, 5-8, >8; specific gravity summarised as <=1.005, 1.006 - 1.010, 1.011 - 1.015, 1.016 - 1.020, 1.021 - 1.025, 1.026 - 1.029, >=1.030 Continued with all treatment groups and time points. The n's sum to N but the calculated percentages exclude Not Done.

Template T_VS1

Table 14.3.6.xx Summary of vital signs

									Change from Baseline					
Variable (units)	Treatment	Planned Relative Time	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Systolic Blood Pressure (mmHg)	Treatment 1 (N=xx)													

Source: Listing 16.2.xx

Programming notes: *Continued with all variables, treatments and time points*
Column "Variable" isn't required for summary of PBMC data
*For PBMC table, add footnote "*Note: Results at baseline (Day 1 Pre-dose) are set to 100%"

Template T_VS2

Table 14.3.6.xx Summary of vital signs outside the normal range by treatment, planned relative time and parameter

		Systolic Blood Pressure (mmHg)		Diastolic Blood Pressure (mmHg)		Heart Rate (beats/min)		Temperature (C)		etc	
Treatment	Planned Relative Time	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Treatment 1 (N=xx)	Time 1										
	Time 2										

Source: Listing 16.2.xx

Programming notes: *Continued with all treatments and parameters. n = total number of results for that parameter*

Template T_VS3

Table 14.3.6.xx Summary of Summary of vital signs outside the normal range by treatment and parameter (excluding baseline time point)

	Systolic Blood Pressure (mmHg)		Diastolic Blood Pressure (mmHg)		Heart Rate (beats/min)		Temperature (C)		etc		Overall*	
Treatment	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Treatment 1 (N=xx)												

Source: Listing 16.2.xx

Subjects only counted once per treatment per parameter

*Subjects only counted once per treatment

Programming notes: *Continued with all treatments and parameters. n = total number of resul ts for that parameter. Only include post-treatment time points*

Template T_EG2

Table 14.3.7.xx Summary of ECG values

									Change from Baseline					
Variable (units)	Treatment	Planned Relative Time	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Heart Rate (bpm)	Treatment 1 (N=xx)													
	Treatment 2 (N=xx)													
PR Interval (msec)	Treatment 1 (N=xx)													
	Treatment 2 (N=xx)													

Source: Listing 16.2.xx

Programming notes: *Continued with all treatment groups and time points. Do not summarise RR or QRS axis*

Template T_EG3

Table 14.3.7.xx Summary of QTcF and PR interval values outside the normal range by treatment, planned relative time and category

		QTcF (msec)										PR int. (msec)			
	Planned							>30-60		>60					
	Relative	451 – 480		481 – 500		> 500		Increase		Increase		<120		>220	
Treatment	Time	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Treatment 1	Time 1														
(N=xx)	Time 2														

Source: Listing 16.2.xx

Programming notes: *Continued with all treatments and time points. n = total number of results for that parameter*

Template T_EG4

Table 14.3.7.xx Summary of QTcF and PR interval values outside the normal range by treatment and category (excluding baseline time point)

	QTcF (msec)										PR int. (msec)					
	451 – 480		481 – 500		> 500		>30-60 Increase		>60 Increase		<120		>220		Overall*	
Treatment	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Treatment 1 (N=xx)																

Source: Listing 16.2.xx

Subjects only counted once per treatment per category

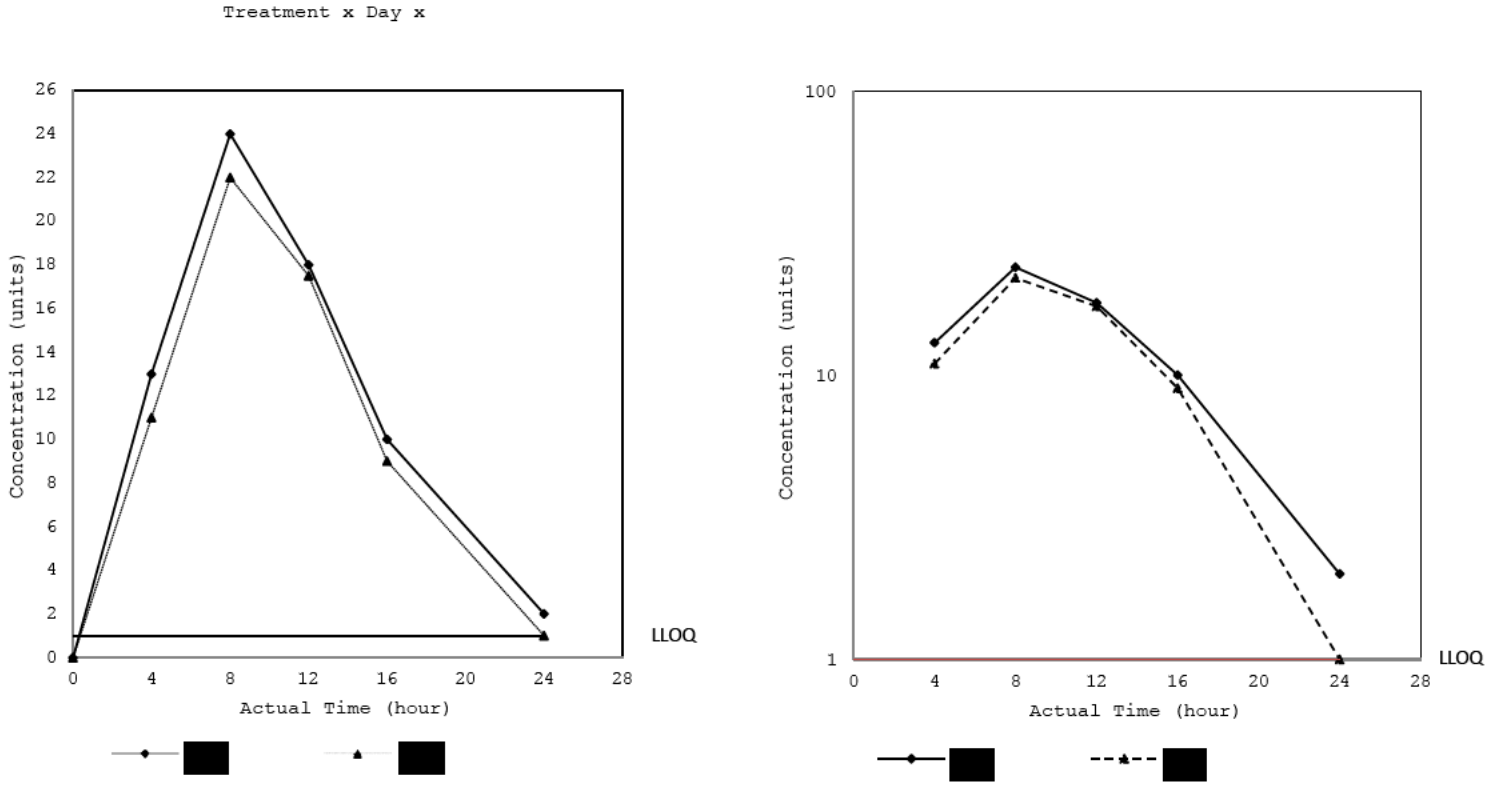
*Subjects only counted once per treatment

Programming notes: *Continued with all treatments and time points. n = total number of results for that parameter. Only include post-treatment time points*

19.2.2 Figure Outlines

Template F_PK1

Figure 14.2.xx Individual ASN51 plasma concentration-time plots (linear and semi-log)

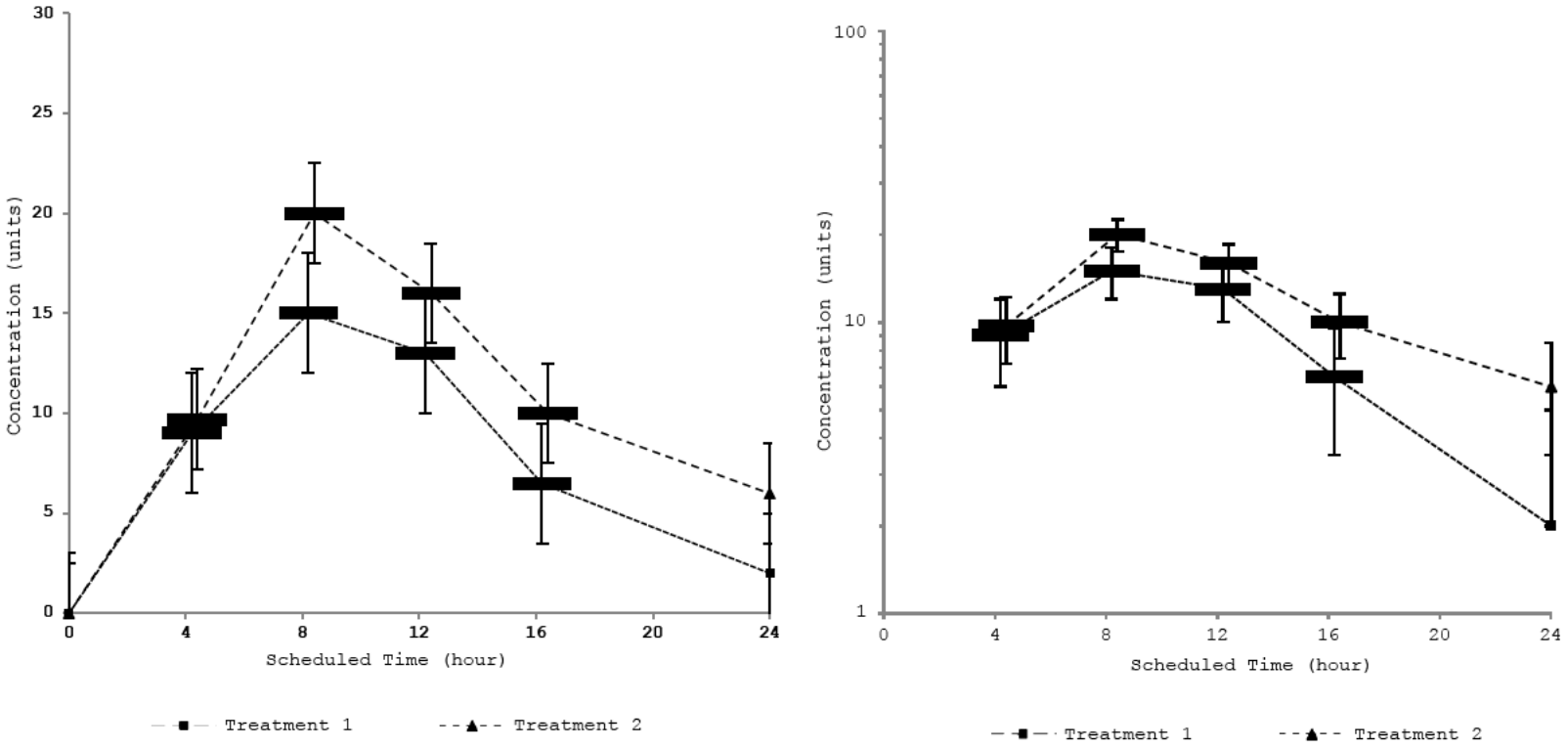


Programming notes: *Page by treatment and include all subjects on same page. First page will be Treatment 1 Day 1 followed by Treatment 1 Day 14 before treatment 2*

Template F_PK2

Figure 14.2.xx Mean (+/- SD) ASN51 plasma concentration-time plots (linear and semi-log)

Day x



Source: Listing 16.2.xx

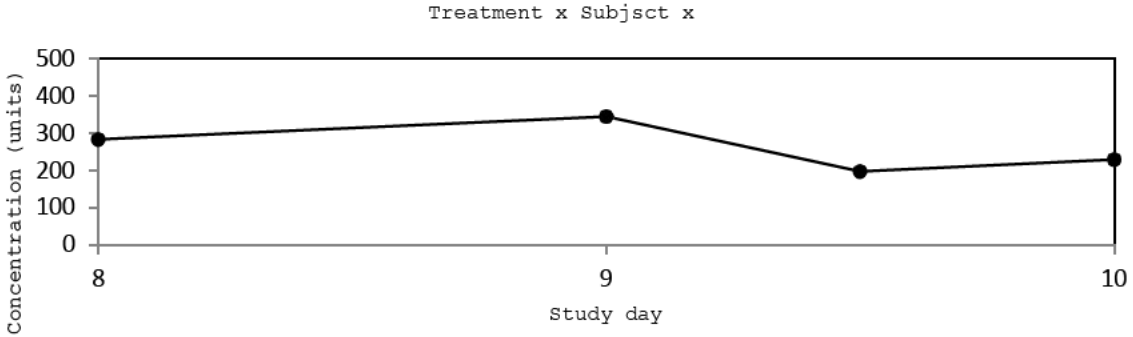
BQL values are imputed to zero

Programming notes: *Page by Day and offset treatment groups (to both sides of timepoint) to minimise overlapping error bars*

Remove error bars when producing plots without error bars

Template F_PK5

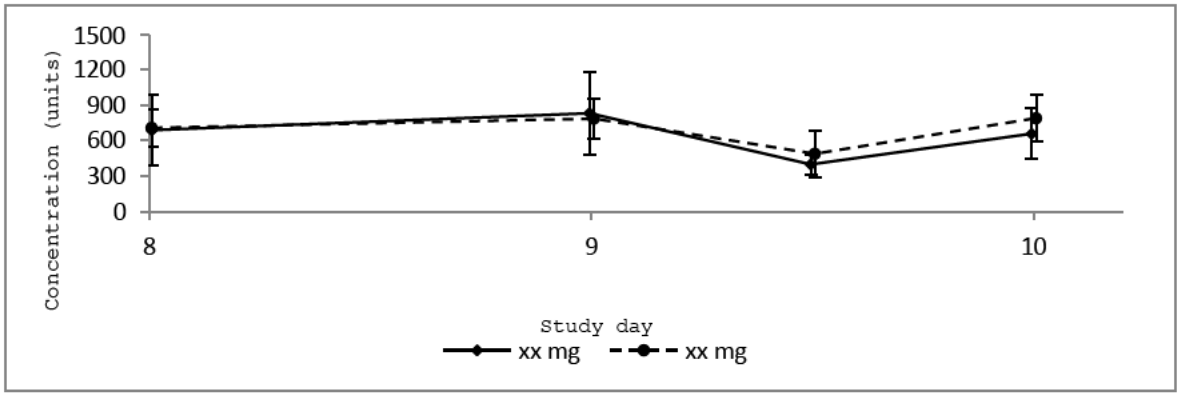
Figure 14.2.xx Individual ASN51 plasma pre-dose concentration versus day



Source: Listing 16.2.xx

Template F_PK6

Figure 14.2.xx Mean (+/- SD) ASN51 plasma pre-dose concentration versus day

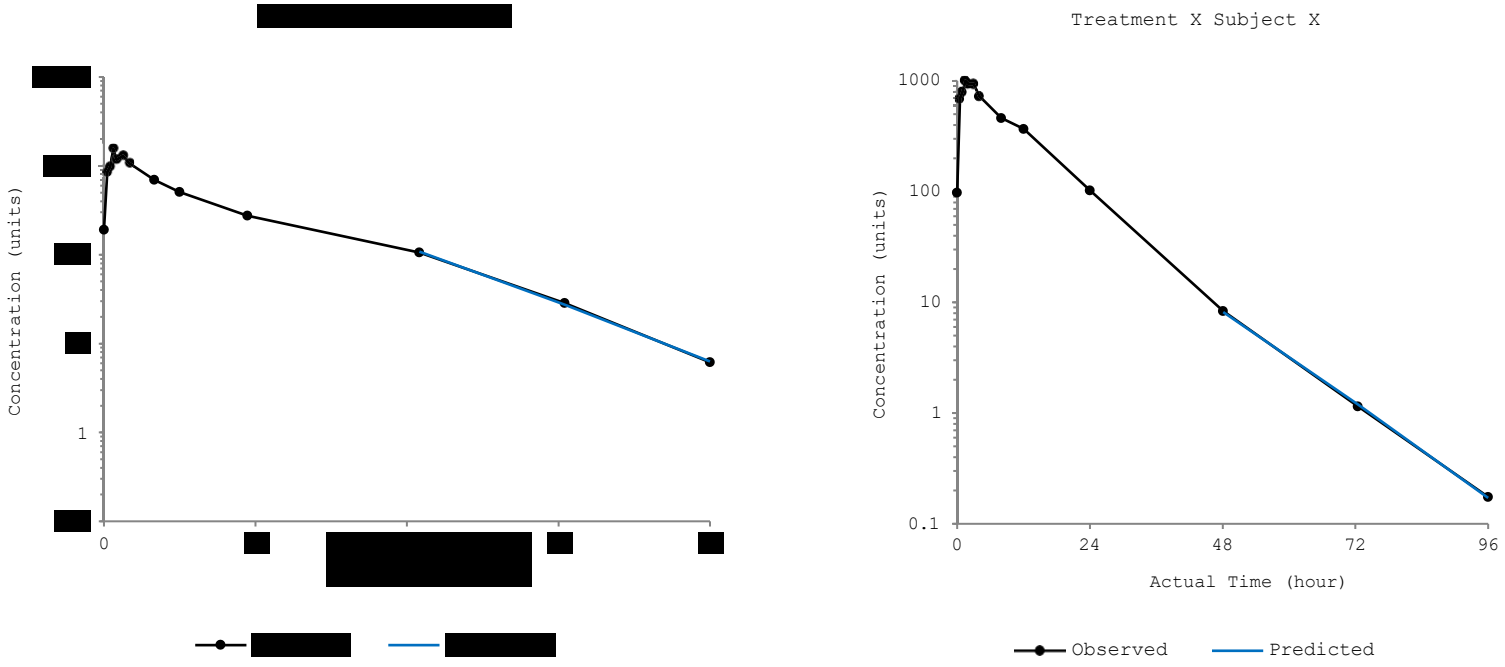


Source: Listing 16.2.xx

Programming notes: *Offset treatment groups (to both sides of timepoint) to minimise overlapping error bars*

Template F_PK10

Listing 16.2.xx Individual ASN51 plasma concentration-time plots for estimation of lambda-z, with regression line



Source: Listing 16.2.xx

Template F_SAF1

Figure 14.3.1 Individual systolic blood pressure-time plots

Treatment = Treatment 1 Days 1-13

Programming note: Plots are by treatment groups and Days. Add subject legend. The x-axis label will be "Planned Time Point".
The first page will be "Treatment 1 Days -13" followed by Treatment 1 Day 14 and Follow-up".
Continue with all parameters

19.2.3 Listing Outlines

Template L_SD1_PG

Listing 16.2.x.xx Listing of study dates

Treatment	Subject	Screening	Screening (MRI)	Imaging Session 1	Day 1	Day 14	Imaging Session 3	Follow Up

Template L_SD2_PG

Listing 16.2.x.xx Listing of reasons for withdrawal

Treatment	Subject	Date of Withdrawal	Study Day	Reason

Programming notes: *Reason for withdrawal is concatenation of reason and details*

Template L_SD3_PG

Listing 16.2.x.xx Listing of subjects screened but not enrolled

Screen Number	Date of Screen	Failure Category	Details

Template L_DV1_PG

Listing 16.2.x.xx Listing of subjects with inclusion/exclusion criteria deviations

Treatment	Subject	Type	Criterion
		Inclusion	
		Exclusion	

Template L_TD1_PG

Listing 16.2.x.xx Listing of subjects with time deviations

Treatment	Subject	Planned Relative Time	Procedure	Allowed deviation (h:min)	Actual deviation (h:min)	Time outside the deviation window (h:min)

Programming notes: *Only include time deviations which exceed the allowed deviation*

Template L_DV2_PG

Listing 16.2.x.xx Listing of subjects with other protocol deviations

Treatment	Subject	Protocol Deviation	Type of Deviation	Category

Template L_AN1_PG

Listing 16.2.x.xx Listing of analysis populations

Treatment	Subject	Safety Population	Population 1	Population 2	Etc.

Template L_DM1_PG

Listing 16.2.x.xx Listing of demographic characteristics

Treatment	Subject	Date of visit	Year of birth	Age (y)	Sex	Race	Ethnicity	Height (cm)	Weight (kg)	BMI (kg/m2)	Smoking History	Cigarettes (units)	Alcohol (units)
Treatment 1	[redacted]												

Programming notes: *A by-subject listing of demographic characteristics including:*

Template L_CM1_PG

Listing 16.2.x.xx Listing of concomitant medications

Treatment	Subject	Medication Class/ Medication Code*	Drug Name/ Indication	Dose/ Freq/Route	Date/time Started/ Date Stopped	Study Day Started/ Time Since Last Dose	Started Pre-Dose?	Ongoing Medication?

*Coded using WHOCC ATC/DDD Index vXX.X

Programming notes: *Include dose and units (e.g. [redacted])/Freq/Route*

Template L_MH1_X

Listing 16.2.x.xx Listing of medical history

Treatment	Subject	Category	System organ class*/Preferred term	Verbatim text	Clinical significance	Date Started	Date Stopped	End relative to Screening

*Coded using MedDRA version xx

Template L_EX1_PG

Listing 16.2.x.xx Listing of exposure data

Treatment	Subject	Start Date/ Start Time of Dose	Stop Date/ Stop Time of Dose	Duration (days)	Dose	Dose Unit	Formulation/Route	Frequency
Treatment 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Once

Note: Subjects received ASN51 in the fed state on Day 11 only

Template L_PK1_PG

Listing 16.2.6.xx Listing of ASN51 plasma pharmacokinetic concentration-time data

Treatment	Subject	{Add. time var.}	Date	Study Day	Planned Relative Time	Actual time (hh:mm)	Time Deviation (min)	Actual Relative Time (h)	Concentration (units)

Below the Limit of Quantification (BLQ) is < xx *units (e.g. 1 ng/mL)*

Programming notes: *Values below LLOQ are shown as* BLQ. Check LLOQ value in final PK spreadsheet.

Template L_PK4_PG

Listing 16.2.xx Listing of derived ASN51 plasma pharmacokinetic parameters

Treatment	Subject	Study Day	AUC_{inf} (units)	AUC_t (units)	C_{max} (units)	$t_{1/2}$ (units)	t_{max} (units)

Programming notes: *Continue with all parameters*
For Ctrough, report Days across and also include 1 dosing interval after the final dose

Template L_PBMC_PG

Listing 16.2.6.xx Listing of plasma PBMC data

Treatment	Subject	Date	Study Day	Planned Relative Time	PBMC pellet (% above baseline)

Note: Results at baseline (Day 1 Pre-dose) are set to 100%

Template L_AE1_PG

Listing 16.2.x.xx Listing of all adverse events

Treatment	Subject	System Organ Class* / Preferred Term/ Verbatim Text	Outcome/ Onset Date/Time/ Resolved Date/Time/ Duration	Study Day Started/ Time Since Last Dose	Severity/ Serious/ Withdrawal	Frequency/ Action Taken (1)/ Other Action Taken	Related to Study Drug/ Treatment Emergent?
Treatment 1	[redacted]	Gastrointestinal Disorders / Intestinal Spasm / Entero-spasm	Resolved/ [redacted]	Day x/ 10d 7h 3m	Mild/ No/ Yes	Intermittent/ Dose not changed/ None	Possibly/ Yes

(1) Action Taken with Study Treatment
*Coded using MedDRA vXX.X

Programming notes: *For the listing of "other significant AEs" include (from ICH E3) AEs leading to withdrawal, AEs leading to dose reduction (including drug withdrawn, interrupted, reduced or similar) and AEs with AEOSE=Y. If AEOSE has not been collected then use "Otherwise significant" in the CRF.*

Template L_LB1_PG

Listing 16.2.x.xx Listing of clinical chemistry data outside the normal ranges

Treatment	Subject	Laboratory test (units)	Planned Relative Time	Date/Time	Study Day	Value	Normal Interval*	RI	Clinically Significant?	Reference Interval#	RI
Treatment 1	[redacted]	Sodium (mmol/L)	Time 1	[redacted]	-1	135	137 - 145	L	N	134 - 142	
			Time 2	[redacted]	85	143	137 - 145			134 - 142	H
		ALT (U/L)	Time 1	[redacted]	-1	29.00	10.0 - 40.0			10.0 - 40.0	
			Time 2	[redacted]	85	70.00	10.0- 40.0	H	Y	10.0- 40.0	H

RI for Reference Interval flag, H = Above reference interval, L = Below reference interval

* Used for clinical significance assessment, #Based on most common reference ranges

Programming notes: *Lists only subjects with at least a high or low value in either of the ranges*

Template L_VS1_PG

Listing 16.2.x.xx Listing of vital signs outside the normal range

Treatment	Subject	Planned Relative Time	Date/Time	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Etc (units)
		24 H	[redacted]	63	148*	

* Value outside the normal range

Template L_VS2_PG

Listing 16.2.x.xx Listing of clinically significant vital signs

Treatment	Subject	Planned Relative Time	Date/Time	Vital Sign Finding	Comment on Clinical Significance

CS=Clinical Significance

Programming notes: *Lists only values with abnormal CS*

Template L_EG1_PG

Listing 16.2.x.xx Listing of QTcF and PR interval values outside the normal range

								QTcF (msec)	
Treatment	Subject	Planned Relative Time	Date/Time	Heart Rate (bpm)	PR Int. (msec)	QRS Dur. (msec)	QT Int. (msec)	Observed	Change from Baseline
		24 H	[redacted]	63	109*	78	390	452*	-6.5

* Value outside the normal range

Template L_EG2_PG

Listing 16.2.x.xx Listing of abnormal ECG findings

Treatment	Subject	Planned Relative Time	Date/Time	ECG Finding	Comment on Clinical Significance

Programming notes: *Lists only values with Normal variant='No' or with comment on ECG result*
ECG Finding contains Physician's Opinion from CRF and relates to whole trace (not individual parameters), e.g. Normal, Abnormal - NCS or Abnormal - CS

Template L_PE1_PG

Listing 16.2.x.xx Listing of abnormal physical examination findings

Treatment	Subject	Planned Relative Time	Date	Findings	Site	Details
Treatment 1	[redacted]			Abnormal - NCS		

Programming Notes: *List only findings with an 'abnormal' result. Findings is concatenation of result and clinical significance*
If subjects have multiple abnormal sites at a given time, create a separate row for each site.

Template L_NEURO_PG

Listing 16.2.x.xx Listing of abnormal neurological examination findings

Treatment	Subject	Planned Relative Time	Date	Examination	Assessment	Findings	Details
Treatment 1	[redacted]					Abnormal - NCS	

Programming Notes: *List only findings with an 'abnormal' result. Findings is concatenation of result and clinical significance*
If subjects have multiple abnormal sites at a given time, create a separate row for each site.

Template L_CSS_PG

Listing 16.2.x.xx Listing of positive Columbia-Suicide Severity Rating Scale data

Treatment	Subject	Planned Relative Time	Date/Time	Category	Question	Result

Appendix A: Laboratory tests with different ranges

Test	Unit	Sex	Normal ranges*	Reference ranges#
Haematocrit	L/L	F	0.333 – 0.45	0.311 – 0.446
Haemoglobin	g/L	F	113 – 150	100 – 150
Lymphocytes	10^9/L	Both	1 – 3.4	0.9 – 2.84
Mean corpuscular haemoglobin	Pg	Both	26.1 – 32.7	25 – 32.9
Mean corpuscular haemoglobin concentration	g/L	Both	321 – 355	317 – 350
Platelets	10^9/L	Both	120 – 326	145 – 350
Prothrombin time	sec	Both	9.4 – 13.5	10.2 – 13.9
Sodium	mmol/L	Both	137 – 145	134 – 142

* Used for clinical significance assessment, #Based on most common reference ranges

Appendix B: Pharmacokinetic analysis

1 Calculation Methods

1.1 Data Handling Conventions

1.1.1 Actual v Planned Times

Actual sample times will be used for the calculation of pharmacokinetic parameters and for individual concentration-time plots.

Planned sampling times will be used to calculate the concentration-time summary statistics and summary concentration-time plots.

1.1.2 Missing and BQL Concentrations

No missing values will be imputed.

For calculation of all pharmacokinetic parameters and individual profile plots, plasma concentrations below the limit of quantification of the assay (BQL) will be treated as missing (except BQL values observed before the maximum concentration, which will be taken as zero).

BQL values will be taken as zero for calculation of plasma concentration summary statistics unless they fall between two quantifiable concentrations in which case they will be treated as missing.

1.2 AUC Calculations

The AUC will be calculated by a combination of linear and logarithmic methods. The linear trapezoidal method will be employed for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method will be used for those arising from decreasing concentrations.

It is acceptable to include data from profiles with >20% extrapolated as long as at least 80% of the profiles in the study have <20% of the $AUC_{(0-\infty)}$ as extrapolated area. In this instance, individual plasma concentration-time profiles for which the extrapolated areas are >20% of $AUC_{(0-\infty)}$ will be identified.

It is unacceptable to use $AUC_{(0-\infty)}$ data if >40% of the AUC has been extrapolated, except in specific situations which should be carefully justified in the study report.

1.3 Lambda-z Calculations

The apparent terminal phase rate-constant (λ_z) will be estimated by linear regression of logarithmically transformed concentration versus time data. Only those data points which are judged to describe the terminal log-linear decline will be used in the regression.

During the analysis, repeated regressions are carried out using the last three points with non-zero concentrations, then the last four points, last five, etc. Points prior to C_{max} are not used. Points with a value of zero for the concentration are excluded. For each regression, an adjusted R^2 is computed. The λ_z using the regression with the largest adjusted R^2 is selected. If the adjusted R^2 does not improve, but is within 0.0001 of the largest adjusted R^2 value, the regression with the larger number of points is used. λ_z must be positive, and calculated from at least three data points.

A minimum number of three data points will be used in calculating λ_z.

1.4 Observed v Predicted Values

For parameters dependent on λ_z, the 'predicted' rather than the 'observed' parameters will be calculated.

The 'predicted' parameters are calculated using $\hat{C}_t$ (the predicted value of the concentration at time tn); whilst the 'observed' parameters use the last observed concentration.

1.5 Achievement of Steady-State

Achievement of steady state will be judged on the basis of visual interpretation of concentration-time plots.

2 Parameter Definitions

2.1 Plasma Parameters

Text Symbol	Definition	Calculation	Typical Units	Log Transform	WNL	CDISC Controlled Terminology	TFL Symbol
Concentrations during and after multiple dosing							
C_{trough}	Trough plasma concentration	Trough plasma concentration (measured concentration at the end of a dosing interval at steady state [taken directly before next administration, and at 1 dosing interval after the final dose]) obtained directly from the concentration-time data.	ng/mL	Y	-	CTROUGH	C_{trough}
Concentrations and times (Day 1 and after final dose)							
C_{max}	Maximum (peak) plasma concentration	Obtained directly from the concentration-time data.	ng/mL	Y	Cmax	CMAX	C_{max}
C_{max}/Dose	Dose-normalised C_{max}	Calculated as C_{max} /Dose administered	(ng/mL)/mg	Y	Cmax_D	CMAXD	C_{max}/D
t_{max}	Time to reach maximum (peak) plasma concentration	Obtained directly from the concentration-time data.	h	N	Tmax	TMAX	t_{max}
Half-life (after final dose)							
λ_z	Terminal rate constant	Estimated by linear regression of logarithmically transformed concentration versus time data.	1/h	Y	Lambda_z	LAMZ	λ_z
$t_{½}$	Terminal half-life	Calculated from the terminal slope of the log concentration-time curve, as follows: $t_{½} = \frac{\log_e 2}{l_z}$	h	Y	HL_Lambda_z	LAMZHL	$t_{1/2}$

Text Symbol	Definition	Calculation	Typical Units	Log Transform	WNL	CDISC Controlled Terminology	TFL Symbol
Areas under the curve (Day 1 and after final dose)							
AUC_{τ}	Area under the plasma concentration-time curve during a dosing interval (t)	Calculated using the trapezoidal method.	h*ng/mL	Y	User specified area	AUCTAU	AUC_{tau}
Areas under the curve (after final dose)							
AUC_{last}	Area under the plasma concentration-time curve from time zero to time of last measurable concentration	Calculated using the trapezoidal method.	h*ng/mL	Y	AUClast	AUCLST	AUC_{last}
AUC_{∞}	Area under the plasma concentration-time curve from time zero to infinity	Calculated using the trapezoidal method for the interval 0 to t_{last} (time t_{last} is the time at which the last non-zero level was recorded), plus the area under the exponential curve from t_{last} to infinity, calculated as follows: $AUC_{t-\infty} = \frac{C_t}{\lambda_z}$ where $\hat{C}_t$ is the predicted value of the concentration at t_{last}.	h*ng/mL	Y	AUCINF_pred	AUCIFP	AUC_{inf}
AUC_{∞}/Dose	Dose-normalised AUC_{∞}	Calculated as AUC_{∞}/Dose administered	(h*ng/mL)/mg	Y	AUCINF_D_pred	AUCIFPD	AUC_{inf}/D
$\%AUC_{extrap}$	Percentage of AUC_{∞} extrapolated from from t_{last} to infinity	$\%AUC_{extrap} = \frac{100 \times AUC_{t-\infty}}{AUC_{\infty}}$	%	N	AUC_%EXTRAP_pred	AUCPEP	$\%AUC_{extrap}$
Clearance and volume of distribution (after final dose)							
CL_{SS}/F	Apparent total clearance from plasma after oral administration	Calculated using the following formula: $CL_{SS}/F = \frac{Dose}{AUC_{\tau}}$	L/h	Y	Clss_pred (actually derives Clss_F_pred for oral dose)	CLFTAU	CL_{SS}/F
V_z/F	apparent volume of distribution after non-intravenous administration calculated at steady state [3]	Calculated at steady state will be calculated using the following formula: $V_z/F = \frac{Dose}{\lambda_z \bullet AUC_{\tau}}$	L	Y	Vz_pred (actually derives Vz_F_pred for oral dose)	VZFTAU	V_z/F
Accumulation ratios							
$R_{ac(AUC)}$	Accumulation ratio for AUC	Calculated from AUC_t at steady state and AUC_t after single dose	-	N	-	ARAUC	$R_{ac(AUC)}$
$R_{ac(Cmax)}$	Accumulation ratio for C_{max}	Calculated from C_{max} at steady state and C_{max} after single dose	-	N	-	ARCMAX	$R_{ac(Cmax)}$

Appendix C: Sample page layout

Asceneuron S.A.: ASN51-103 Page x of y*

Population: [Pop]

Table *[number] [title]*

Column headers

Main body of output

Source: Listing *[16.2.xx]*

Footnotes about the table or listing text go here.

Program: *[Prog Name]* [Date] HMR 22-012

Produced By: *[Username]*

*y = last page of individual output

Font size will be Arial 9.5pt. The following margins will be used: Left: 1", Right: 1", Top: 1", Bottom: 1"

ASN51-103 (HMR 22-012) SAP v1.1 (13JUN2023)

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