Official Title: A Phase 1, Open-Label, Positron Emission Tomography Study in Healthy Adult Subjects to Determine the Relationship Between Plasma Concentration and Brain Target Occupancy of ASN51 Following a Single Oral Dose

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Statistical Analysis Plan

Clinical trial protocol title:	A Phase 1, Open-Label, Positron Emission Tomography Study in Healthy Adult Subjects to Determine the Relationship Between Plasma Concentration and Brain Target Occupancy of ASN51 Following a Single Oral Dose
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Based on:	Protocol version 2.0, 19 May 2021
Prepared by:	[redacted]

Table of Contents

1 List of abbreviations

λ_z	Terminal rate constant
AE	Adverse event
AUC	Area under concentration-time curve
AUC_{inf}	AUC from time zero to infinity
AUC_t	AUC from time zero to time t
AUC_{last}	AUC from time zero to last measurable concentration
BMI	Body mass index
BQL	Below the limit of quantification
CI	Confidence interval
C_{max}	Maximum plasma concentration
CRF	Case report form
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
HR	Heart rate
ICH	International Conference on Harmonization
IMP	Investigational medicinal product
MedDRA	Medical Dictionary for Regulatory Activities
N	Number of subjects
n	Number of observations used in analysis
PCI	Potential clinical importance
PD	Pharmacodynamic(s)
PET	Positron emission tomography
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.
Q1	Lower quartile
Q3	Upper quartile
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.
QTcB	QTc interval with Bazett’s correction method
QTcF	QTc interval with Fridericia's correction method
RO	Receptor occupancy
RR	Portion of the ECG between consecutive R waves, representing the ventricular rate
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SEM	Standard error of mean
SRC	Safety Review Committee
$t_{½}$	Terminal elimination half-life

TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum plasma concentration
V_T	Regional total volume of distribution
WHO	World Health Organisation

2 Signatures

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

[redacted] PhD Principal Statistician, HMR	[redacted] Signature	Nov 22, 2021 Date
[redacted] MBBS Principal Investigator, HMR	[redacted] Signature	Nov 24, 2021 Date
[redacted] M.D. [redacted] Clinical Development and Translational Medicine	[redacted] Signature	Nov 17, 202 Date

3 Introduction

This statistical analysis plan (SAP) is based on the current trial protocol (version 2.0, 19 May 2021). 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 analysis of the PK-RO which will be done 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 v8.3 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 brain O-GlcNAcase occupancy using [^{18}F] IMA601 PET, following a single oral dose of ASN51

4.1.2 Secondary objective(s)

- 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 a single oral dose of ASN51
- To assess the single dose safety and tolerability of ASN51 in healthy adult subjects under fasted conditions

4.2 Study endpoint(s)

4.2.1 Primary endpoint(s)

- Pharmacodynamic (PD): [^{18}F]-IMA601 regional total volume of distribution (VT) at each brain scan.

4.2.2 Secondary endpoint(s)

- Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs) up to follow-up
- Serious Adverse Events (SAEs) up to 4 weeks after last administration
- Laboratory tests
- Vital signs
- ECG
- Physical examination
- Pharmacokinetic (PK): plasma concentration of ASN51 at the time of each post-dose PET scan.
- PK/PD: relationship between ASN51 exposure and receptor occupancy.

4.3 Statistical hypotheses

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

5 Study design

This is an open-label, adaptive-design PET study to investigate the occupancy of O-GlcNAcase by ASN51 after single oral doses in healthy adult male and female subjects (aged 25-55 years, inclusive). The study schema is depicted in Figure 2 of the protocol.

Up to 10 subjects will be enrolled. Each subject will have up to 3 imaging sessions, with one scan in each session. In the first imaging session, subjects will have 240 ml of water followed by a baseline PET scan approximately 2 h later. In the second and third imaging sessions, subjects will receive a single oral dose of ASN51 with 240 ml of water, followed by an on-treatment PET scan. Safety and pharmacokinetic data of the SAD study ASN51-101 will be assessed by the Safety Review Committee (SRC) prior to the dosing of the first subject(s) to determine the first dose level to be administered in session 2 after the baseline session 1 and the timing of the PET scans in relation to the study drug administration time. At most 2 subjects will be dosed on the same study day. For subsequent sessions, the dose level and the time of the PET scan in all imaging session 2 and 3 will be determined after review of the results from

the first on-treatment PET scan, including the PK data. Subjects will receive an intravenous dose of the radiolabelled tracer, [^{18}F]-IMA601, at the start of each PET scan.

This study will have an adaptive design: to adequately evaluate the exposure versus receptor occupancy (RO) relationship, various doses of ASN51 of up to 85% of the highest well-tolerated dose level in the preceding SAD study ASN51-101, and the timing of on-treatment PET scans may be altered based on emerging data or study logistical requirements. On-treatment PET scans may be scheduled up to 48 h post-dose.

After each on-treatment PET scan, the SRC will review available RO, PK, safety and tolerability data, before selecting the dose and PET scan timings for imaging session 3. 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 145 mL. Arterial cannulation and arterial blood sampling may be reduced or removed if analysis of PET data from previous subjects indicates that noninvasive 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.

Subjects will be screened within 21 days before their baseline PET scan. Their on-treatment PET scans will be within 7 days of their baseline scan with an interval of 7–14 days between imaging sessions 2 and 3. Subjects will be confined for 72 h after the study drug administration in sessions 2 and 3. After the baseline scan in session 1 without study drug administration, subjects may leave the unit in the evening. In the case of a technical failure (such as unsuccessful tracer synthesis), subjects may be asked to attend an additional on-treatment imaging session, in which they will receive a third oral dose of ASN51. There will be at least 7 days between each dose of ASN51. Subjects will not have more than 3 PET scans or 3 doses of ASN51 during the study. Subjects will have a follow-up visit at the research unit 7 days (± 3 days) after imaging session 3 (Day 8).

6 Time and events table

Please refer to Table 1 of the protocol, version 2.0, dated 19 May 2021

7 Planned analyses

7.1 Interim analyses

No interim analyses are planned.

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

The trial is hypothesis generating, so no formal calculation of sample size is appropriate. The sample size of at most 10 subjects is considered adequate to allow modelling of the relationship between ASN51 plasma concentrations and the occupancy of O-GlcNAcase and is within the range generally accepted for PET studies. Enrolment of subjects into the study will be stopped as soon as the brain O-GlcNAcase occupancy versus ASN51 plasma concentrations is sufficiently characterized in opinion of the SRC.

9 Analysis populations

The following populations will be identified

All-treated set:	This analysis set includes all randomised subjects who received study drug (at least one dose).
Safety set:	This analysis set includes subjects from the all-treated set who had at least one safety assessment post-baseline. The safety set will be employed in the analysis of tolerability and safety variables.
PET population:	The PET population will consist of randomised subjects who receive study medication, have a baseline PET scan, at least one post-baseline PET scan, and a PK result immediately preceding PET scan.

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.

In all populations, treatment will be assigned based upon the treatment subjects actually received.

The primary endpoint will be analysed using the PET population.

9.1 Analysis datasets

All analysis datasets will be based on observed data, except as outlined in Section 11.2.

10 Data display treatment and other subgroup descriptors

The treatment groups will be sorted in ascending dose order. When a total column is included, it immediately follows the treatment groups which it aggregates.

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

xx mg ASN51

10.1 Conventions for summary statistics and data displays

The minimum set of summary statistics for numeric variables will be: n, mean, standard deviation (or standard error mean [SEM]), 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, Q1, and Q3) will be presented using one additional decimal place. The standard deviation and standard error will be presented using two additional decimal places.

11 Data handling conventions

11.1 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 11.2.

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 A: Pharmacokinetic Analysis.

11.2 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 vital sign measurements will be made at screening 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 A: Pharmacokinetic Analysis.

11.3 Assessment windows

No assessment windows are defined for this report.

11.4 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	50–95 mm Hg
Seated heart rate	45–100 beats/min
Respiration rate	10–16 breaths/min
Tympanic temperature	35.5–37.8°C

12 Study population

12.1 Disposition of subjects

The disposition of all subjects in the safety population will be summarised including: number of subjects randomised; number completing the study, by treatment; and number withdrawn from the study.

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.

12.2 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 HMR Trial Procedures Summary.

12.3 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) Drug Global dictionary current at the time of the database lock (version September 2021 or higher).

Medical and surgical history will also be listed.

12.4 Treatment compliance

Dates and times of dosing will be listed.

13 Safety analyses

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

13.1 Extent of exposure

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

13.2 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 24.0 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 group:

- TEAEs, by system organ class and preferred term
- Drug-related ("related" 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.

13.3 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.

13.4 Adverse events leading to withdrawal from the study

AEs leading to withdrawal will be listed separately.

13.5 Clinical laboratory evaluations

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

Data from haematology, coagulation and clinical chemistry outside the normal range will be listed separately and summarised.

13.6 Other safety measures

13.6.1 Vital signs

Vital signs evaluation at each planned 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.

13.6.2 ECG

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

ECG variables will be summarised by treatment and time point.

QTcF and QTcB values > 450 msec, PR interval shortening < 120 msec, and PR interval prolongation >220 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.

13.6.3 Physical examination

Abnormal physical examination findings will be listed.

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

Positive C-SSRS data will be listed.

14 Pharmacokinetic analyses

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

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

14.1 Pharmacokinetic concentration data

The plasma concentrations and dose-normalised plasma concentrations of ASN51 will be listed and summarised by treatment.

Using actual sample times, linear and semi-logarithmic plasma concentration-time plots will be prepared by treatment and synoptic linear and semi-logarithmic dose-normalised plasma concentration-time plots of ASN51 will be prepared. Both Session 2 and Session 3 profiles will be included on the same plot. The same linear and logarithmic scales will be used for each subject. The linear and semi-logarithmic plots for a given subject will be presented on the same page.

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

Mean dose normalised plasma concentration versus time plots will be presented for ASN51 per treatment (synoptic plot) (normal scale and log-linear scale).

14.2 Pharmacokinetic parameters

The pharmacokinetic parameters of ASN51 will be listed and summarised by treatment.

If there is a quantifiable plasma concentration of the baseline PK sample of session 3, that value will be used in addition for the calculation of the PK parameters for session 2.

15 Pharmacodynamic analyses

15.1 PET analysis data

Start and end date of each PET scan will be listed together with the scan start/stop time and the Dose drawn up, Dose administered, Residual 1, and Residual 2.

[18F]-IMA601 regional total volume of distribution (V_T) at each brain scan will be listed for each session and for change from baseline.

The RO values will be listed for sessions 2 and 3, respectively, together with the plasma concentration of ASN51 at the time of the start of each post-dose PET scan; which will be calculated by log-linear interpolation from the two closest PK data points by subject and treatment.

These concentration data will be transferred to Invicro for the PK-RO analysis. The PK-RO analysis will be provided by Invicro and sent to HMR for the inclusion in the CSR.

16 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

17 ATTACHMENTS

17.1 Table of contents for data display specifications

For overall page layout refer to Appendix B: 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 Section 17.2.1 and 17.2.2):

Table	Description	Population	Source Listing	Template (Shells below)
10.1	Summary of subject disposition	Safety	16.2.1.2 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 DATA			
14.2.1	Summary of derived ASN51 plasma pharmacokinetic concentration-time data (units) by treatment	PK Analysis	16.2.6.1.1	T_PK1
14.2.2	Summary of derived ASN51 plasma pharmacokinetic parameters by treatment	PK Analysis	16.2.6.1.2	T_PK3
14.2.3	Summary of log-transformed derived ASN51 plasma pharmacokinetic parameters by treatment	PK Analysis	16.2.6.1.2	T_PK4
14.3	SAFETY DATA			
14.3.1.1	Summary of treatment-emergent adverse events	Safety	16.2.7.1	T_AE1
14.3.1.2	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 normal range by treatment and planned relative time	Safety	16.2.8.1 16.2.8.2 16.2.8.3	T_LB1
14.3.4.2	Summary of laboratory values outside the normal 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

Table	Description	Population	Source Listing	Template (Shells below)
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
14.3.7.1	Summary of ECG values	Safety	16.4	T_EG2
14.3.7.2	Summary of QTcF, QTcB and PR interval values outside the normal range by treatment, planned relative time and category	Safety	16.2.9.3	T_EG3

Figure	Description	Population	Source Listing	Template (Shells below)
14.2	PHARMACOKINETIC 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	Individual ASN51 dose-normalised plasma concentration-time plots (linear and semi-log)	PK Analysis	16.2.6.1.1	F_PK1
14.2.3	Mean (+/- SD) ASN51 plasma concentration-time plots (linear and semi-log)	PK Analysis	16.2.6.1.1	F_PK2
14.2.4	Mean (+/- SD) ASN51 dose-normalised plasma concentration-time plots (linear and semi-log)	PK Analysis	16.2.6.1.1	F_PK2

The following abbreviated listings will be produced (templates provided in Section 17.2.3):

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
16.2.2	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

Listing	Description	Template (Shells below)
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 and surgical history	L_MH1_PG
16.2.5	Study drug administration	
16.2.5.1	Listing of exposure data	L_EX1_PG
16.2.6	Pharmacokinetic and pharmacodynamics data	
16.2.6.1.1	Listing of ASN51 plasma pharmacokinetic concentration-time data	L_PK1_PG
16.2.6.1.2	Listing of derived ASN51 plasma pharmacokinetic parameters	L_PK4_PG
16.2.6.1.3	Individual ASN51 plasma concentration-time plots for estimation of λz, with regression line	F_PK10
16.2.6.2.1	Listing of regional total volume of distribution of [18F]-IMA601 data	L_PD1
16.2.6.2.2	Listing of receptor occupancy and plasma concentration data of ASN51	L_PD2
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 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, QTcB 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

Listing	Description	Template (Shells below)
16.2.9.6	Listing of positive Columbia-Suicide Severity Rating Scale data	L_CSS_PG

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

17.2 Data display specifications

17.2.1 Table outlines

Note: Summary statistics for continuous data will only be provided for treatments where n>1

Template T_SD1

Table 10.1 Summary of subject disposition

Population	Status	Reason for Withdrawal	Treatment 1 (N=xx) n (%)	Treatment 2 (N=xx) n (%)	Etc	All Subjects (N=xx) n (%)
All-treated	Included		xx (xx)	xx (xx)		xx (xx)
Safety	Included		xx	xx		xx
	Completed		xx (xx)	xx (xx)		xx (xx)
	Withdrawn					
		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

Programming notes: *Continued with all treatment groups*
Remove column "Reason for Withdrawal" if no subject withdrew
Add a footnote about n=4 for the [redacted] *dose group*

Template T_DM1

Table 14.1 Summary of demographic characteristics

Variable	Statistics	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	
	Max	

Variable	Statistics	All Subjects (N=xx)
BMI (kg/m2)	n	
	Mean	
	SD	
	Median	
	Min	
	Max	
Smoker	Former	
History (%)	Never	
Alcohol*	n	
(units/week)	Mean	
	SD	
	Median	
	Min	
	Max	
Caffeine*	n	
(cups daily)	Mean	
	SD	
	Median	
	Min	
	Max	
Optional (units)		

Source: Listing 16.2.xx

*includes only those subjects who drink caffeine/alcohol

Programming notes: Continued with all treatment groups and additional demographic characteristics

Template T_PK1

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

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

Template T_PK3

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

Parameter	Treatment	{Additional time variables}	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

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 treatment

Parameter	Treatment	{Additional time variables}	n	Geom Mean	95% CI (Lower,Upper)	SD (logs)	%CVb
AUC_{last} (units)	Treatment 1 (N=xx)			xxxx.xx	(xxxx.xx,xxxx.xx)	xx.xxx	xx.xx
	Treatment 2 (N=xx)			xxxx.xx	(xxxx.xx,xxxx.xx)	xx.xxx	xx.xx
C_{max} (units)	Treatment 1 (N=xx)			xxxx.xx	(xxxx.xx,xxxx.xx)	xx.xxx	xx.xx
	Treatment 2 (N=xx)			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_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 (%)	Etc	All Subjects (N=xx)
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 v 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 normal range by treatment, planned relative time

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

Source: Listing 16.2.xx

H = Above reference interval, L = Below reference interval
m = number of subjects with results for that parameter

Programming notes: Continued with all tests, treatment groups and time points.

Template T_LB3

Table 14.3.4.xx Summary of laboratory values outside the normal 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 double flag

*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.

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

Template T_VS1

Table 14.3.6.xx Summary of vital signs

Variable (units)	Treatment	Planned Relative Time	n	Mean	SD	Median	Min	Max
Systolic BP (mmHg)	Treatment 1 (N=xx)							

Source: Listing 16.2.xx

Programming notes: Continued with all variables, treatments and time points

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_EG2

Table 14.3.7.xx Summary of ECG values

Variable (units)	Treatment	Planned Relative Time	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, QTcB and PR interval values outside the normal range by treatment, planned relative time and category

		QTcF (msec)						QTcB (msec)						PR int. (msec)			
	Planned Relative	451 – 480		481 – 500		> 500		451 – 480		481 – 500		> 500		<120		>220	
Treatment	Time	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Treatment 1	Time 1																
(N=xx)	Time 2																
	Time 3																

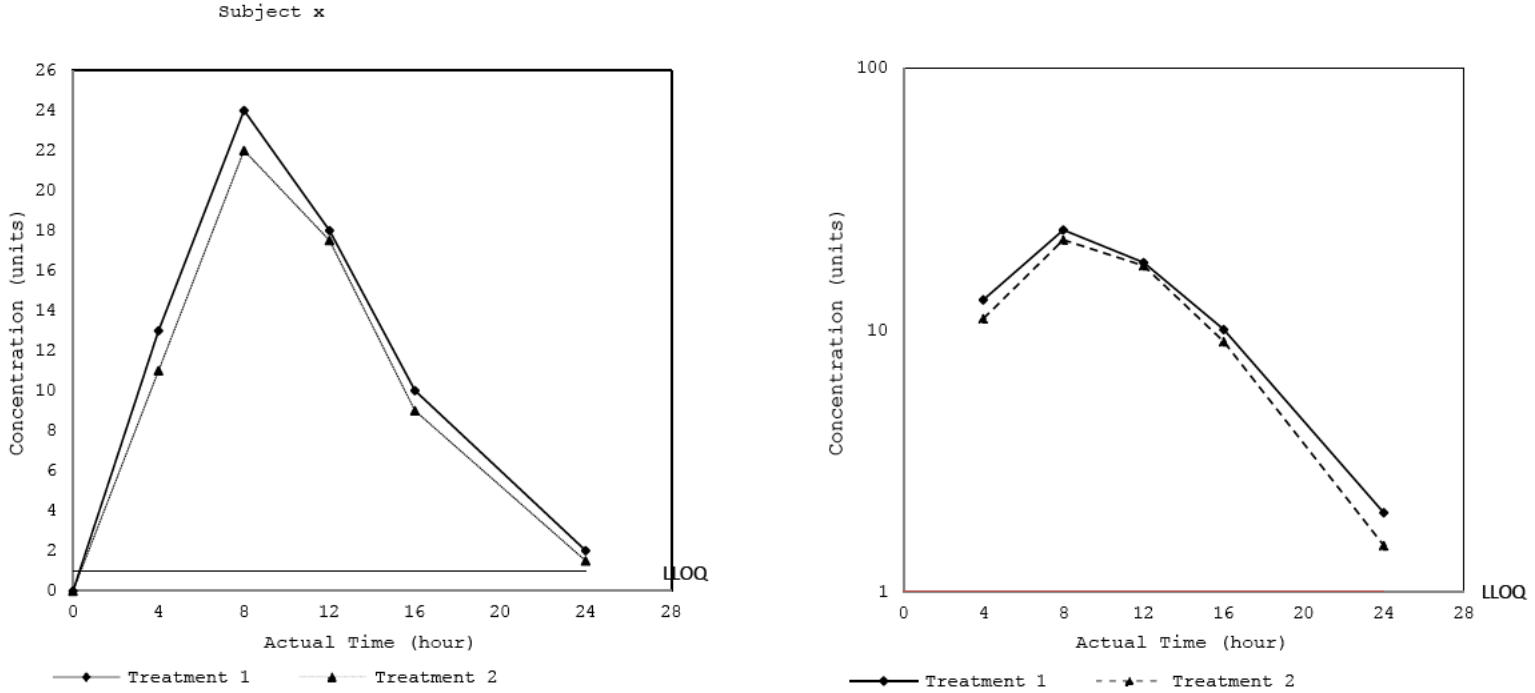
Source: Listing 16.2.xx

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

17.2.2 Figure outlines

Template F_PK1

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

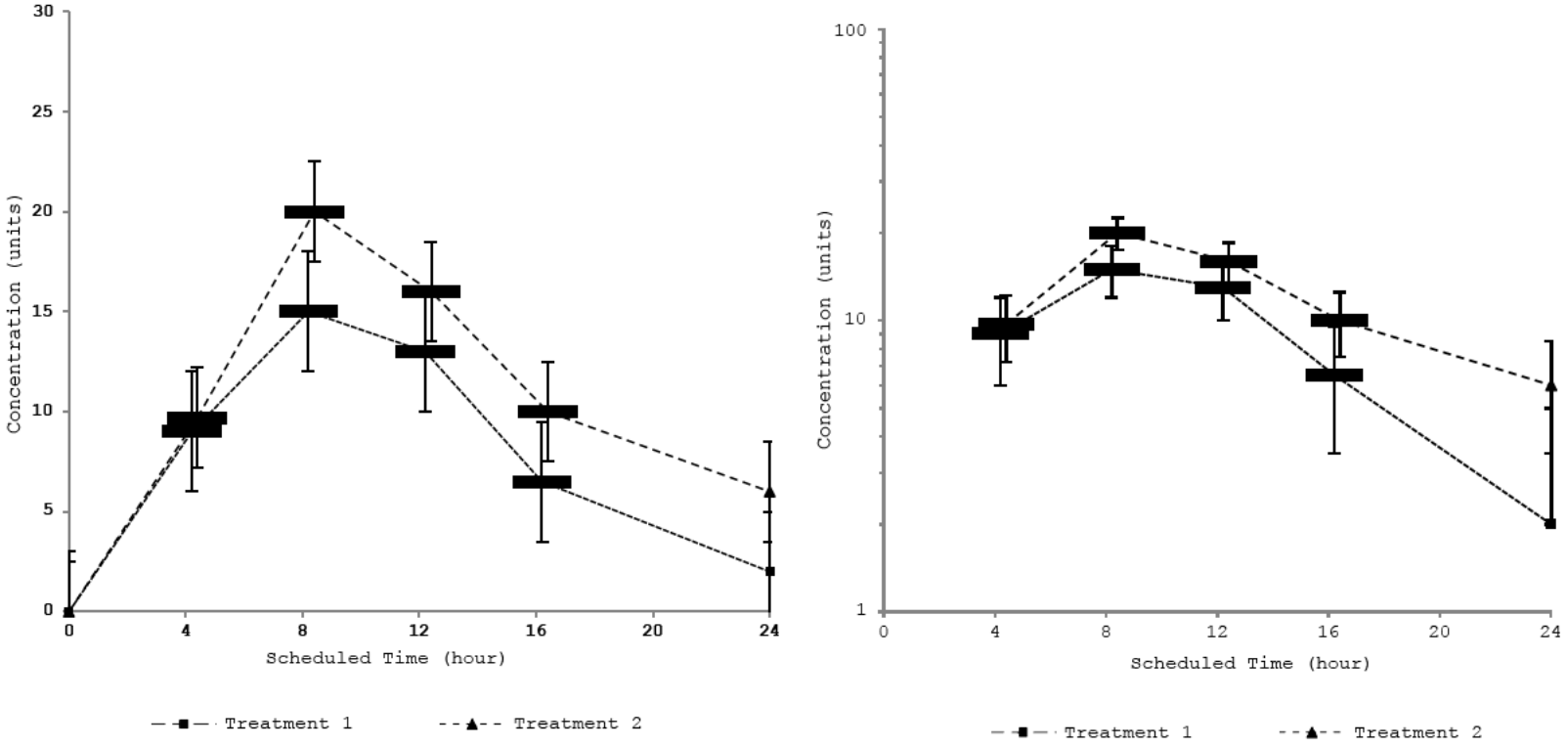


Source: Listing 16.2.xx

Programming notes: *For dose-normalised plot, the y-axis label will be "Dose-normalised concentration (units)"*

Template F_PK2

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



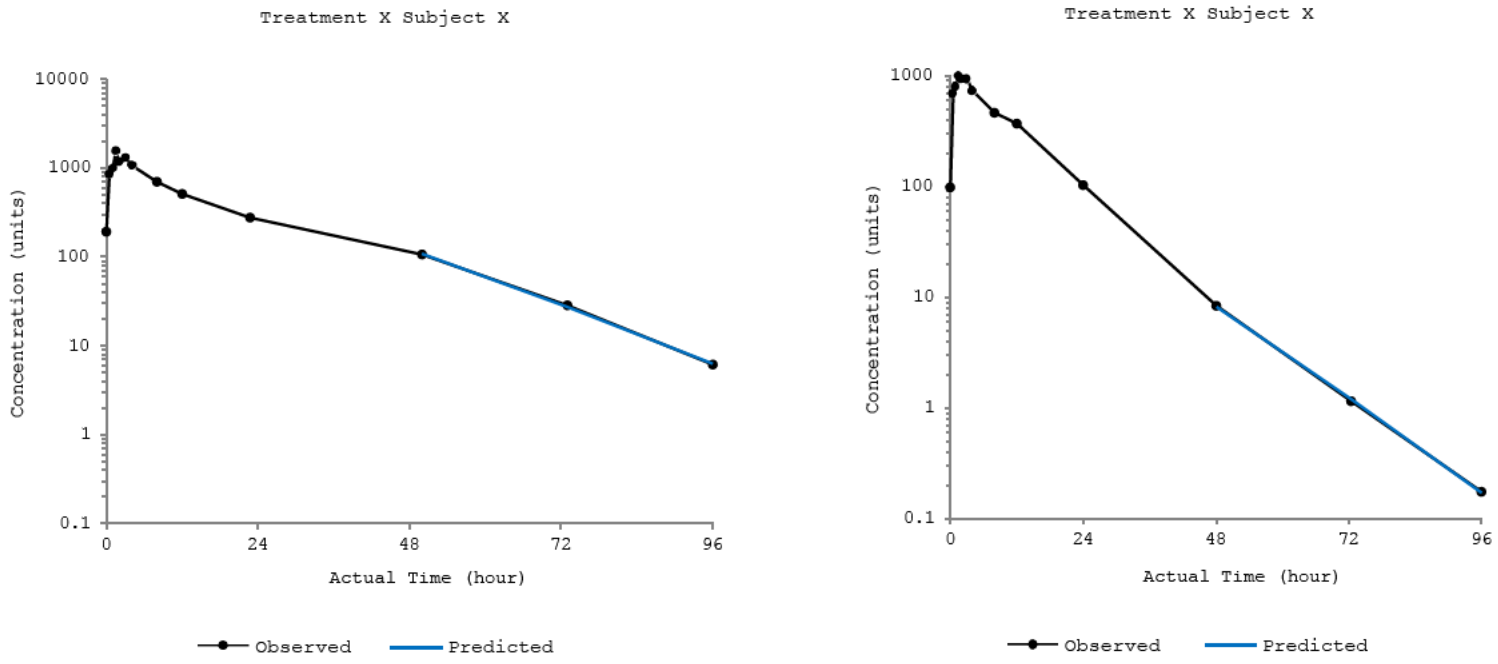
Source: Listing 16.2.xx

BLQ values are imputed to zero

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

Template F_PK10

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



Source: Listing 16.2.xx

17.2.3 Listing outlines

Template L_SD1_PG

Listing 16.2.x.xx Listing of study dates

Subject	Sequence*	Screening	Period 1	Period 2	Period 3	Follow Up
[redacted]	xxx					

Programming notes: *Lists dates for screening, each dosing period and follow up*
Add footnotes for the sequences

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_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

Subject	Sequence*	Date of visit	Year of birth	Age (y)	Sex	Race	Ethnic origin	Height (cm)	Weight (kg)	BMI (kg/m2)	Etc (units)

*A = 0 mg ASN51, B = xx mg ASN51, C = xx mg ASN51, D = xx mg ASN51,

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

Treatment

Subject

Date of visit

Year of birth

Age

Sex

Race / Ethnic Origin

Height (if collected only once during the study)

Weight (if collected only once during the study)

Smoking History

Alcohol Consumption

Additional study-specific demography characteristics included on the CRF

Template L_CM1_PG

Listing 16.2.x.xx Listing of concomitant medications

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

*Coded using WHODrug Global vXX.X

Programming notes: ** only include this column and the footnote if coding used*
Include dose and units (e.g. [redacted]

Template L_MH1_PG

Listing 16.2.x.xx Listing of medical and surgical history

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

*Coded using MedDRA vXX.X

Template L_EX1_PG

Listing 16.2.x.xx Listing of exposure data

Treatment	Subject	Start Date/ Start Time of Dose	Dose	Dose Unit	Formulation/ Route	Frequency
Treatment 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	2xday

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 for each analyte.

Template L_PK4_PG

Listing 16.2.xx Listing of derived ASN51 plasma pharmacokinetic parameters

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

Programming notes: *Continue with all parameters*

Template L_PD1

Listing 16.2.xx Listing of [18F]-IMA601 data regional total volume of distribution

Treatment	Subject	Scan number	{Add. time var.}	Start Date/ Start Time of PET scan	Stop Date/ Stop Time of PET scan	Dose drawn up	Residual 1	Residual 2	Brain Region	V_T (units)	Change from baseline V_T (units)

Template L_PD2

Listing 16.2.xx Listing of receptor occupancy and plasma concentration data of ASN51

Treatment	Subject	Scan number	{Add. time var.}	Start Date/ Start Time of PET scan	Stop Date/ Stop Time of PET scan	Concentration at start of PET scan	Occupancy (%)

Programming notes: *Concentration at start of PET scan will be calculated using the closest time before start of PET scan and the closest time after PET scan*

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		Gastrointestinal Disorders / Intestinal Spasm / Entero-spasm	Resolved/ 34d 4h 5m	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 range

Treatment	Subject	Laboratory test (units)	Planned Relative Time	Date/Time	Study Day	Value	Reference Interval	RI	Clinically Significant?
Treatment 1	[redacted]	Alk Phos (U/L)	Time 1	[redacted]	-1	64.00	32.0 - 92.0		
			Time 2	[redacted]	85	84.00	32.0 - 92.0		
		ALT (U/L)	Time 1	[redacted]	-1	29.00	10.0 - 40.0		
			Time 2	[redacted]	85	70.00	10.0- 40.0	H	Y

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

Programming notes: *Lists only subjects with at least a high or low value*

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

Programming notes: *Lists only values with abnormal CS*

Template L_EG1_PG

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

Treatment	Subject	Planned Relative Time	Date/Time	Heart Rate (bpm)	PR Int. (msec)	QRS Dur. (msec)	QRS Axis (deg)	QT Int. (msec)	QTcF (msec)	QTcB (msec)
		24 H	[redacted]	63	148	78	50	390	452*	396

* 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	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	Site	Details

Programming Notes: *List only findings with an 'abnormal' result.*
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: Pharmacokinetic analysis

1 Calculation methods

1.1 Data handling conventions

1.1.1 Missing and BLQ concentrations

No missing values will be imputed.

For all PK assessments (calculation of parameters, and individual profile plots) BQL values will be taken as missing with the exception of the predose value, where a BLQ value 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.

2 Parameter definitions

2.1 Plasma parameters

Text Symbol	Definition	Calculation	Typical Units	Log Transform	WNL	CDISC Controlled Terminology	TFL Symbol
Concentrations and times							
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 AUC to infinity	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							
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: $t_{½} = \frac{\log_e 2}{\lambda_z}$	h	Y	HL_Lambda_z	LAMZHL	$t_{1/2}$
Areas under the curve							
AUC_{last}	Area under the plasma concentration-time curve from time zero to time of last measurable concentration	The area under the concentration-time curve from zero time (pre-dose) to the time of last quantifiable concentration will be calculated using the (specified) trapezoidal method.	h*ng/mL	Y	AUClast	AUCLST	AUC_{last}
AUC_{last}/Dose	Dose-normalised AUC from time zero to last measurable concentration	The dose-normalised AUC from time zero to last measurable concentration will be calculated as AUC_{last}/Dose Administered	(h*ng/mL)/mg	Y	-	AUCLSTD	AUC_{last}/D
AUC_{∞}	Area under the plasma concentration-time curve from time zero to infinity	Calculated using the (specified) 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:	h*ng/mL	Y	AUCINF_pred	AUCIFP	AUC_{inf}

Text Symbol	Definition	Calculation	Typical Units	Log Transform	WNL	CDISC Controlled Terminology	TFL Symbol
		$AUC_{t-\infty} = \frac{C_t}{\lambda_z}$ where $\hat{C}_t$ is the predicted value of the concentration at t_{last}.					
AUC_∞/Dose	Dose-normalised AUC to infinity	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	$\%AUC_{extrap}$

Appendix B: Sample page layout

Asceneuron S.A.: ASN51-102 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 21-001

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"

Signature: [redacted]

Email: [redacted]

Signature: [redacted]

Email: [redacted]

ASN51-102 (HMR 21-001) SAP v1 (17Nov2021)

Final Audit Report 2021-11-24

Created:	2021-11-18
By:	[redacted]
Status:	Signed
Transaction ID:	CBJCHBCAABAAdXvkO_3E8PfoQULrGjJ-KjMBj5CZarF6

"ASN51-102 (HMR 21-001) SAP v1 (17Nov2021)" History

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