Statistical Analysis Plan

Clinical trial protocol title:	A Phase 1, Randomized, Open-Label, Parallel-Group, Relative Bioavailability Study to Investigate the Pharmacokinetics, including Food Effect, as well as the Safety and Tolerability of Single Doses of New Immediate Release Tablet Formulations of Emodepside (BAY 44-4400), compared to Oral Solution, in Healthy Male Subjects
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CRO details:	Hammersmith Medicines Research Cumberland Avenue London NW10 7EW
Sponsor details:	DNDi, Chemin Louis Dunant, 15, 1202 Geneva Switzerland Phone: +41 22 906 9230
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Prepared by:	Helen Topping

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1 List of abbreviations

λ_z	Terminal rate constant
AE	Adverse Event
ANOVA	Analysis of variance
AUC	Area under concentration-time curve
AUC_{0-t}	AUC from time zero to time t
AUC_{0-t}/Dose	AUC from time zero t to time t, corrected for dose
$AUC_{0-t,norm}$	AUC from time zero t to time t, corrected for dose and body weight
AUC_{last}	AUC from time zero to last measurable concentration
BMI	Body Mass Index
BP	Blood Pressure
BQL	Below the limit of quantification
CI	Confidence Interval
C_{max}	Maximum Plasma Concentration
C_{max}/Dose	C_{max} corrected by dose
$C_{max, norm}$	C_{max} corrected by dose and body weight
CRF	Case Report Form
CTR	Clinical Trial Report
ECG	Electrocardiogram
HMR	Hammersmith Medicines Research
HR	Heart Rate
ICH	International Conference on Harmonization
IR	Immediate Release
LLOQ	Lower Limit of Quantification
LSF	Liquid Service Formulation
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time
MRT_{last}	Mean residence time at last measurable concentration
N	Number of subjects
n	Number of observations used in analysis
PCI	Potential clinical importance
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
RR	Portion of the ECG between consecutive R waves, representing the ventricular rate

SAP	Statistical Analysis Plan
SD	Standard deviation
SRG	Safety Review Group
$t_{1/2}$	Terminal elimination half-life
$t_{1/2,0\text{-}t}$	Dominant half-life
TEAE	Treatment-Emergent Adverse Event
t_{max}	Time to maximum plasma concentration

2 Signatures

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

Helen Topping ***Senior Statistician, HMR***	PP Signature	28 MAR 2018 Date
Dr Jeremy Dennison ***Principal Investigator, HMR***	J.M.T.S.D Signature	28 MAR 2018 Date
Jean-Yves Gillon ***Head of Translation, DNDi***	 Signature	27 March 2018 Date
Frédéric Monnot ***Filarial Team Leader, DNDi***	 Signature	27 March 2018 Date

3 Introduction

This Statistical Analysis Plan (SAP) is based on the current trial protocol (version 3, 1 February 2018). 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.

The randomisation code will not be broken before this SAP is finalised. 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 analysis will be done using WinNonlin v7 on a Windows PC. Statistical analysis will be done using SAS® 9.3 on a Windows PC.

4 Study Objective(s) and Endpoint(s)

4.1 Study Objective(s)

4.1.1 Primary Objective

To investigate the pharmacokinetics, including relative bioavailability and food effect, of two new immediate release (IR)-tablet formulations of emodepside in comparison to the liquid service formulation (LSF) oral solution.

4.1.2 Secondary Objectives

To investigate and compare safety and tolerability of single oral doses of emodepside formulations in healthy subjects.

4.2 Study Endpoint(s)

4.2.1 Primary Endpoint

- Based on the plasma concentration–time data, the following PK parameters of emodepside will be calculated:
  - Main: $AUC_{0\text{-}7d}$, $AUC_{0\text{-}7d}$/Dose, C_{max}, C_{max}/Dose

4.2.2 Secondary Endpoints

- Safety and Tolerability Variables:
  - Adverse Events (AEs)
  - Physical and neurological examination findings
  - Vital signs (BP and HR),
  - 12-lead ECG (HR, PR, QRS, QTcB, QTcF), will be analysed ad hoc for safety and for the final data base and report by central reading
  - Clinical laboratory tests
    - Haematology: haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), platelets, reticulocytes, white blood cells (WBC) including differential, red blood cells (RBC);
    - Coagulation: activated partial thromboplastin time (aPTT), prothrombin time (PT);
    - Biochemistry: serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), creatine kinase (CK), amylase, lipase, glucose, cholesterol (HDL, LDL, total), triglycerides, creatinine, urea, uric acid, bilirubin (total and conjugated), total protein, sodium, potassium, calcium, chloride and magnesium;
    - Urinalysis: by dipstick – glucose, ketone bodies, specific gravity, occult blood, pH, proteins, leucocytes, bilirubin, urobilinogen, nitrites, and microscopy (reflex).

4.2.3 Exploratory Endpoints

- Pharmacokinetic:
  - $AUC_{0\text{-}7d,norm}$, $C_{max,norm}$, $t_{1/2,0\text{-}24h}$, $t_{1/2,0\text{-}7d}$, t_{max}, MRT, points terminal

4.3 Statistical Hypotheses

Except for the analysis of pharmacokinetic data, no formal statistical testing will be done.

5 Study Design

This is a single-centre, open-label, randomized, parallel-group relative bioavailability study in healthy men. The study will be done in 2 parts, as follows:

- Part 1 – single oral doses of 5 mg emodepside will be tested:
  - Part 1a – the LSF (reference formulation) and 2 new IR-tablet formulations (test formulations) will be administered in the fasted state.
  - Part 1b – the 2 new IR-tablet formulations will be administered in the fed state (high-fat, high-calorie meal).
- Part 2 – single oral doses of 10 mg (2 x 5 mg) emodepside will be tested: depending on the results from Part 1, one or both IR-tablet formulations will be administered in the fasted state.

The treatments in each study part are summarised in Table 1.

Table 1. Planned treatments by dose, formulation and condition

Part	Treatment	Formulation, dose and condition	Number of subjects
Part 1a	A	5 mg emodepside LSF, fasted	12
	B	5 mg emodepside IR-tablet #406, fasted	12
	C	5 mg emodepside IR-tablet #416, fasted	12
Part 1b	D	5 mg emodepside IR-tablet #406, fed	12
	E	5 mg emodepside IR-tablet #416, fed	12
Part 2	F*	2 x 5 mg emodepside IR-tablet #406, fasted	12
	G*	2 x 5 mg emodepside IR-tablet #416, fasted	12

* one or both treatments may be tested, depending on results from Part 1

Up to 84 healthy volunteers will be enrolled, in up to 7 treatment arms made up of 12 subjects each.

The 36 subjects in Part 1a will be randomised to one of 3 treatments (A, B or C). The 24 subjects in Part 1b will be randomised to one of 2 treatments (D or E). Parts 1a and 1b may proceed in parallel, or may be done sequentially.

After at least 10 subjects in each arm have received treatment in Part 1, and data up to 72 h after dosing are available, there will be a Dose Decision Meeting to determine which treatment(s) will be tested in Part 2 (see section 7.5).

In Part 2, either treatment F, G or both F and G will be tested. There will be 12 subjects enrolled for each treatment tested. If both treatments are tested, they will be done in parallel, and subjects will be randomised to one of the 2 treatments.

The study will be performed in a single site specialized in Phase 1 studies.

6 Time and Events Table

Procedure	Screening	Inpatient																		Follow-up	
	Day –28 to –2	Day –1	Day 0													Day 1		Day 2	Day 3	Day 5	Day 7
		hours	*–1*	*0*	*0.25*	*0.5*	*1*	*1.5*	*2*	*2.5*	*3*	*4*	*6*	*8*	*12*	*24*	*36*	*48*	*72*	*120*	*168*
Subject demographics and informed consent	X																				
Inclusion/exclusion criteria - Eligibility check	X	X																			
Medical history/prior medication	X																				
Inpatient stay		←																	→		
Administration of emodepside[1]				X																	
Outpatient visit	X																			X	X
Drugs of abuse screen	X	X																			
Alcohol breath test	X	X																			
Physical and neurological examination[2]	X	X							X							X	X	X	X	X	X
Vital signs[3]	X		X			X	X	X	X		X	X		X	X	X	X	X	X	X	X
12-lead safety ECG[4]	X		X			X	X	X	X		X	X		X	X	X		X	X	X	X
Laboratory safety tests[5,6]	X		X													X		X	X	X	X
Serology[7]	X																				
Blood samples for assay of emodepside[6]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE questioning[8]	←																			→	

1. Subjects in Part 1a and Part 2 will fast for 10 h before until at least 4 h after dosing. Subjects in Part 1b will be given a high-calorie, high-fat breakfast approximately 30 min before dosing, which they must finish at least 5 min before dosing. Standard meals will be served at approximately 5 h (lunch), 8 h (snack) and 12 h (dinner) after dosing on Day 0. Procedures scheduled at the same time as a meal will be completed before the meal.
2. A full physical examination will be done at Screening and Follow-up. A brief (symptom-directed) physical examination and short neurological examination will be undertaken at all other time points. Any abnormalities will trigger a full neurological examination and/or opening of an AE as appropriate. Height, weight and body mass index (BMI) will be assessed at screening, and weight will be assessed on Day –1.
3. Vital signs will comprise supine blood pressure and heart rate. Subjects should rest in the supine position for at least 10 min before vital signs measurements. Vital signs will be measured in triplicate at screening and pre-dose (–1 h); single measurements at all other time points. Body temperature will be measured on day -1.

4. Subjects should rest in the supine position for 10 min before ECG measurements. Measurement in triplicate at screening and pre-dose (–1 h); single measurements all other time points.
5. Blood and urine samples for clinical laboratory safety tests (haematology, biochemistry, coagulation and urinalysis).
6. Subjects should rest in the supine position for 10 minutes before blood is drawn (if possible).
7. Serology tests will comprise HIV 1 & 2 and hepatitis B & C.
8. Adverse event monitoring will be done throughout the study, but scheduled questioning will be done at the time points of scheduled blood draws.

7 Planned Analyses

7.1 Interim Analyses

The decision to go ahead with one or both treatments in Part 2 (10mg [2 x 5mg] of IMP) will be made based on the safety, tolerability and PK of the treatments in Part 1 (5mg of IMP).

The dose decision will be made by the Safety Review Group (SRG) at the Safety Review Meeting. The treatments will not be decided until the SRG has reviewed the safety, tolerability and PK data of at least 10 subjects per treatment. Safety, tolerability and PK data up to a minimum of 72 h post-dose should be reviewed before a decision can be made.

7.1.1 Persons responsible for analysis

Toni Mitchell (HMR)	Statistician
Nick Jackson (HMR)	SAS Programmer

7.2 Final Analysis

Each part of the study (Part 1 and Part 2) will have a separate database and will be analysed and reported separately. Each database will be locked once all subjects have completed, data have been entered, all queries resolved and protocol deviations identified for that part of the study. Final analyses will be carried out following database lock for each individual part of the study.

7.2.1 Persons responsible for analysis

Helen Topping (HMR)	Statistician
Nick Jackson (HMR)	SAS Programmer
Duyen Unsworth (HMR)	Data Manager

8 Sample Size Considerations

8.1 Sample Size Assumptions

No formal statistical sample size estimation has been performed, due to the exploratory nature of this study.

10 subjects per treatment arm is considered sufficient to examine the safety and tolerability of emodepside, as well as the PK after single doses. However, 12 subjects will be recruited and enrolled per treatment arm to ensure a minimum of 10 evaluable subjects complete the study.

9 Analysis Populations

The following populations will be identified:

Safety Population:	All subjects who received at least one dose of IMP.
PK Concentration Population:	All subjects who received at least one dose of IMP and for whom a PK sample has been analysed.
PK Parameter Population:	All subjects in the PK Concentration Population for whom PK parameters can be derived.

In all populations, treatment will be assigned based upon the treatment subjects actually received, regardless of the treatment to which they were randomized.

The primary endpoint will be analysed using the PK Parameter population.

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 test (IR-tablet formulations) versus reference (LSF).

11 General Considerations for Data Analyses

11.1 Data Display Treatment and Other Subgroup Descriptors

The sort order for treatment groups will be treatment 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	Short Description
Emodepside LSF 5 mg [fasted]	LSF 5 mg [fasted]
Emodepside IR-tablet #406 5 mg [fasted]	IR #406 5 mg [fasted]
Emodepside IR-tablet #416 5 mg [fasted]	IR #416 5 mg [fasted]
Emodepside IR-tablet #406 5 mg [fed]	IR #406 5 mg [fed]
Emodepside IR-tablet #416 5 mg [fed]	IR #416 5 mg [fed]
Emodepside IR-tablet #406 10 mg [fasted]	IR #406 10 mg [fasted]
Emodepside IR-tablet #416 10 mg[fasted]	IR #416 10 mg [fasted]

11.2 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), median, minimum, and maximum. 95% confidence intervals 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 (e.g. 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.

12 Data Handling Conventions

12.1 Premature Withdrawal and Missing Data

All subjects who withdraw prematurely from the study and received the 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 (i.e. hours and/or minutes) for adverse events 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 (e.g. AE start time from last study medication) will be listed as missing.

Conventions for handling missing plasma concentrations are given in Appendix B.

12.2 Derived and Transformed Data

Baseline will be considered to be the latest value obtained before study drug administration (e.g. Day 0, pre-dose; or Day -1 if not recorded pre-dose; or Screening if not recorded elsewhere (e.g. body weight)).

Laboratory data will be reported in standard units. Out-of-range laboratory tests may be repeated. If a test is out-of-range at a baseline time point 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 pre-dose on Day 0 and the mean of the three measurements for each subject will be used as their baseline value for that session.

The pharmacokinetic parameters to be derived are given in Appendix B.

12.3 Assessment Windows

No assessment windows are defined for this report.

12.4 Values of Potential Clinical Importance

Any laboratory value outside the reference interval for that variable will be flagged with an 'H' if it is higher than the reference interval, and with an 'L' if it is lower. Additionally, if, during the course of the trial, a variable changes from baseline (Day 0 pre-dose) by more than a predetermined amount (as defined by the Principal Investigator, Appendix A), that value will receive a flag 'I' if increased, or 'D' if decreased. Therefore, if a value both falls outside the reference interval and alters from the baseline value by more than the predetermined amount, it will attract a double flag and will be considered to be potentially clinically important.

A vital signs result will be considered to be of potential clinical importance if it falls outside the relevant range below:

Vital Sign	**Range**
Supine/semi-recumbent systolic blood pressure	85–160 mm Hg
Supine/semi-recumbent diastolic blood pressure	40–90 mm Hg
Supine/semi-recumbent heart rate	35–100 beats/min
Respiration rate	8–20 per min
Oral temperature	35.5–37.8°C

QT, QTcB or QTcF > 450 msec and increases in QT, QTcB or QTcF from baseline (Day 1 pre-dose) of > 30 msec will be considered to be potentially clinically important.

13 Study Population

13.1 Disposition of Subjects

The disposition of all subjects in the safety population will be summarized including: number of subjects randomized (or treated, for non-randomised groups); number completing the study, by treatment; and number discontinued from the study. The number of subject in each analysis population will be summarized by treatment.

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 section 8.8 of the study protocol.

13.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics (e.g. 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 version of the WHODrug Global that is current when the database is locked.

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

Adverse events will be coded using the version of the Medical Dictionary for Regulatory Activities (MedDRA) which is current at the time of database lock (version 20.1 or higher).

All adverse events will be listed.

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

For each of the following, the number of adverse events and the number of subjects with adverse events will be summarised:

- TEAEs by system organ class and preferred term
- TEAEs by system organ class, preferred term and severity
- 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. Adverse events with missing severity and/or causality will be treated as severe and 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 will be listed separately (fatal events separate from non-fatal events). Other significant adverse events, as identified by the investigator in the CRF, will be listed separately.

14.4 Adverse Events Leading to Withdrawal from the Study

Adverse events leading to withdrawal will be listed separately.

14.5 Clinical Laboratory Evaluations

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

Urinalysis parameters will also be listed

All laboratory values of potential clinical importance will be listed and all related laboratory results (i.e. haematology or clinical chemistry) for subjects with values of potential clinical importance will be listed, separately. Frequencies of laboratory values of potential clinical importance 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 0 pre-dose in the current treatment period) at each planned post-baseline assessment (with or without potential clinical significance) will be summarised by actual treatment.

Vital signs data of potential clinical importance will be listed.

14.6.2 ECG

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

ECG data will be summarised by treatment and time point. Differences from baseline (Day 0 pre-dose) will be summarised by treatment and time point.

The number of subjects with a potentially clinically important ECG value will be summarised by actual treatment and time point, giving the numbers of subjects with QT, QTcB or QTcF > 450 msec, > 480 msec and > 500 msec, and the numbers of subjects with increases in QT, QTcB or QTcF from baseline of > 30 msec and > 60 msec[3]. A supporting listing of all subjects with an ECG value of potential clinical importance and a separate listing of ECG findings classified as abnormal by the Investigator will also be provided.

14.6.3 Physical and neurological examination

Abnormal physical and neurological examination findings will be listed.

15 Pharmacokinetic Analyses

Analytical Services International Ltd, London, U.K will measure the plasma concentrations of emodepside. The pharmacokinetic analysis will be done by HMR. Pharmacokinetic parameters will be calculated using WinNonlin, version 7 or higher.

The pharmacokinetic parameters to be derived are given in Appendix B.

PK Concentration data will be summarised using the PK concentration population. PK parameters will be summarised using the PK Parameter population.

For log normally distributed 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, SD, %CV, and the 95% confidence interval 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% confidence interval 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

The plasma concentrations will be listed and summarised by treatment. Individual and mean plasma concentration–time profiles will be presented graphically.

15.2 Pharmacokinetic Parameters

The pharmacokinetic parameters will be listed and summarised by treatment.

To assess the relative bioavailability, analysis of variance (ANOVA) models will be fitted to the tablet (test) and solution (reference) data with the logarithm of the pharmacokinetic parameters $AUC_{0\text{-}7d}$/Dose or C_{max}/Dose as the dependent variable, and formulation as a fixed effect. The point estimates least squares (LS)-means and 90% confidence intervals for the ratios "B/A" and "C/A" will be calculated in Part 1a. In Part 2, "F/A" and/or "G/A" will be calculated. The acceptance range 80 – 125% will be applied for these assessments.

In part 1, to assess the effect of food, ANOVA models will be fitted to the data with the logarithm of the pharmacokinetic parameters $AUC_{0\text{-}7d}$/Dose or C_{max}/Dose as the dependent variable, and fed (test) or fasted (reference) as a fixed effect. The point estimates and 90% confidence intervals for the ratios "D/B" and "E/C" will be calculated. The acceptance range 80 – 125% will be applied for the assessment of a potential food effect.

To assess dose proportionality, for each tablet type, exploratory ANOVA models will be fitted to the relevant fasted data in Parts 1 and 2 with the logarithm of the pharmacokinetic parameters $AUC_{0\text{-}7d}$ or C_{max} as the dependent variable and dose as a fixed effect. The ratios "F/B" and/or "G/C" will be calculated, with their 95% confidence interval.

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 C.

Tables, figures and listings will be labelled A (for Part 1) and B (for Part 2), e.g. 14.1A, 14.1B. Separate tables will be produced for Parts A and B.

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 AND PHARMACODYNAMIC DATA			
14.2.1	Summary of Emodepside Plasma Pharmacokinetic Concentration-Time Data (ng/mL)	PK Concentration	16.2.6.1	T_PK1
14.2.2	Summary of Derived Emodepside Plasma Pharmacokinetic Parameters	PK Parameter	16.2.6.2	T_PK3
14.2.3	Summary of Log-Transformed Derived Emodepside Plasma Pharmacokinetic Parameters	PK Parameter	16.2.6.2	T_PK4
14.2.4	Summary of Relative Bioavailability of Emodepside	PK Parameter	16.2.6.2	T_PK6
14.2.5	Assessment of the Effect of Food on the PK of Emodepside	PK Parameter	16.2.6.2	T_PK6
14.2.6	Summary of Dose Proportionality Analysis of Emodepside	PK Parameter	16.2.6.2	T_PK8
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 Treatment-Emergent Adverse Events by Severity	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	Summary of Laboratory Values of Potential Clinical Importance	Safety	16.2.8.1 16.2.8.3	T_LB1
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 Values	Safety	16.4	T_LB2
14.3.5.4	Summary of Urinalysis Dipstick Results	Safety	16.2.8.5	T_UR1
14.3.6	Summary of Vital Signs	Safety	16.4	T_VS1
14.3.7.1	Summary of ECG Values	Safety	16.4	T_EG2

Table	Description	Population	Source Listing	Template (Shells below)
14.3.7.2	Summary of ECG Values and Changes in ECG Values of Potential Clinical Importance	Safety	16.2.9.2	T_EG3

Figure	Description	Population	Source Listing	Template (Shells below)
14.3	PHARMACOKINETIC AND PHARMACODYNAMIC DATA			
14.2.1	Individual Emodepside Plasma Concentration-Time Plots (Linear and Semi-log)	PK Concentration	16.2.6.1	F_PK1
14.2.2	Geometric mean (+/- SD) Emodepside Plasma Concentration-Time Plots (Linear and Semi-log)	PK Concentration	16.2.6.1	F_PK2
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
14.3.5	Individual QTcB-Time Plots	Safety	16.4	F_SAF1

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

Listing	Description	Template (Shells below)
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
16.2.5	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	Listing of Emodepside Plasma Pharmacokinetic Concentration-Time Data	L_PK1_PG
16.2.6.2	Listing of Derived Emodepside Plasma Pharmacokinetic Parameters	L_PK4_PG
16.2.6.3	Individual Emodepside Plasma Concentration-Time Plots (log scale) for Estimation of λz, with Regression Line	F_PK10
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 Abnormalities of Potential Clinical Importance	L_LB1_PG
16.2.8.2	Listing of All Clinical Chemistry Laboratory Data for Subjects with PCI Abnormalities*	L_LB2_PG
16.2.8.3	Listing of Haematology Abnormalities of Potential Clinical Importance	L_LB1_PG
16.2.8.4	Listing of All Haematology Laboratory Data for Subjects with PCI Abnormalities*	L_LB2_PG
16.2.8.5	Listing of Urinalysis Data	L_URI_PG
16.2.9	Vital signs, ECG variables, physical and neurological findings	
16.2.9.1	Listing of Vital Signs of Potential Clinical Importance	L_VS1_PG
16.2.9.2	Listing of ECG Values of Potential Clinical Importance	L_EG1_PG

Listing	Description	Template (Shells below)
16.2.9.3	Listing of Abnormal ECG Findings	L_EG2_PG
16.2.9.4	Listing of Abnormal Physical Examination Findings	L_PE1_PG
16.2.9.5	Listing of Abnormal Neurological Examination Findings	L_NE1_PG

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

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

17.2 Data Display Specifications

17.2.1 Table Outlines

Template T_SD1

Table 10.1 Summary of Subject Disposition

Population	Status	Reason for Withdrawal	Treatment 1 n (%)	Treatment 2 n (%)	Etc	All Subjects n (%)
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)
		Physician decision	xx (xx)	xx (xx)		xx (xx)
		Protocol violation	xx (xx)	xx (xx)		xx (xx)
		Pregnancy	xx (xx)	xx (xx)		xx (xx)
		Study terminated by Sponsor	xx (xx)	xx (xx)		xx (xx)
		Lost to follow-up				
		Other	xx (xx)	xx (xx)		xx (xx)
Alternative 1 (if applicable)	Included		xx (xx)	xx (xx)		xx (xx)
Alternative 2 (if applicable)	Included		xx (xx)	xx (xx)		xx (xx)

Source: Listing 16.2.xx

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)	Etc	All Subjects (N=xx)
Age (y)	n				
	Mean				
	SD				
	Median				
	Min				
	Max				
Gender	n				
	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				

Variable	Statistics	Treatment 1 (N=xx)	Treatment 2 (N=xx)	Etc	All Subjects (N=xx)
	Min				
	Max				
BMI (kg/m2)	n				
	Mean				
	SD				
	Median				
	Min				
	Max				
Smoker	n				
	%				
Cigarettes*	n				
(daily)	Mean				
	SD				
	Median				
	Min				
	Max				
Alcohol*	n				
(units/week)	Mean				
	SD				
	Median				
	Min				
	Max				
Xanthine*	n				
(units/week)					
	Mean				
	SD				
	Median				
	Min				
	Max				

*includes only those subjects who smoke/drink alcohol/drink beverages containing xanthine

Source: Listing 16.2.xx

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

Template T_PK1

Table 14..2.xx Summary of Emodepside Plasma Pharmacokinetic Concentration-Time Data [units]

Treatment (N=xx)	Planned Relative Time	n	No. Imputed	Mean	95% CI	SD	%CVb	Median	Min	Max
Treatment 1 (N=xx)	1h									
Treatment 2 (N=xx)										

Source: Listing 16.2.xx

Programming notes: *Continued with all dose levels and timepoints*
Means, SD, CI and CV should only be calculated if ≥2/3 individual values are >LLOQ

Template T_PK3

Table 14..2.xx Summary of Derived Emodepside Plasma Pharmacokinetic Parameters

Parameter	Treatment (N=xx)	n	Mean	95% CI	SD	%CVb	Median	Min	Max
AUC_{last} (units)									
C_{max} (units)									

Source: Listing 16.2.xx

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

Template T_PK4

Table 14..2.xx Summary of Log-Transformed Derived Emodepside Plasma Pharmacokinetic Parameters

Parameter	Treatment (N=xx)	n	Geom Mean	95% CI	SD (logs)	%CVb
AUC_{last}(units)						
C_{max} (units)						

Source: Listing 16.2.xx

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

Template T_PK6

Table 14.2.xx Summary of Relative Bioavailability of Emodepside

			LSMeans		Test vs Reference	
Parameter	Test Formulation	Reference	Test	Ref	Ratio (%)	90% CI
C_{max}/Dose (units)	#406 5 mg	LSF	xx.x	xx.x	xxxx.x	xxxx.x, xxxx.x
	#416 5 mg		xx.x	xx.x	xxxx.x	xxxx.x, xxxx.x
$AUC_{0\text{-}7d}$/Dose (units)	#406 5 mg	LSF	xx.x	xx.x	xxxx.x	xxxx.x, xxxx.x
	#416 5 mg		xx.x	xx.x	xxxx.x	xxxx.x, xxxx.x

Source: Listing 16.2.xx

Programming notes: *For bioavailability In part 1a calculate values for "B/A" and "C/A"*
In part 2 calculate values for "F/A" and "G/A"
For food effect calculate for part 1 only values for "D/B" and "E/C"

Template T_PK8

Table 14.2.xx Summary of Dose Proportionality Analysis of Emodepside

		10mg vs 5 mg	
Formulation	Parameter	Ratio (%)	95% CI
#406 5 mg	C_{max}(units)	xxxx.x	xxxx.x, xxxx.x
	AUC_{0-7d}(units)	xxxx.x	xxxx.x, xxxx.x

Source: Listing 16.2.xx

Programming notes: *Continue with all formulations. Calculate "F/B" and/or "G/C"*

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
Number of subjects with AEs		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			
	↓			
↓	↓			

n = number of subjects (subjects with ≥1 adverse event are counted only once per system organ class and preferred term
[ ] = number of adverse events
Based on MedDRA version xx.x

Source: Listing 16.2.xx

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 of Potential Clinical Importance

Laboratory Test (units)	Treatment	Planned Relative Time	n	Double Flags HI	Double Flags LD
	Treatment 1 (N=xx)				

H = Above reference interval, L = Below reference interval, I = Increase from baseline greater than pre-defined limit, D = Decrease from baseline greater than pre-defined limit

Source: Listing 16.2.xx

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

Template T_LB2

Table 14.3.5.xx Summary of Chemistry Laboratory Values

Laboratory Test (units)	Treatment	Planned Relative Time	n	Mean	SD	Median	Min	Max	Change from Baseline n	Change from Baseline Mean	Change from Baseline SD	Change from Baseline Median	Change from Baseline Min	Change from Baseline 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 Dipstick Results

Laboratory Test	Planned Relative Time	Result	Treatment 1 (N=xx) n	Treatment 1 (N=xx) %	Treatment 2 (N=xx) n	Treatment 2 (N=xx) %
	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 summarized as <5, 5-8, >8*
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 BP (mmHg)	Treatment 1 (N=xx)													

Source: Listing 16.2.xx

Programming notes: *Continued with all variables, treatments and 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 ECG Values and Changes in ECG Values of Potential Clinical Importance

Variable	Treatment	Planned Relative Time	451 – 480 msec		481 – 500 msec		> 500 msec		>30-60 msec Increase		>60 msec Increase	
			n	%	n	%	n	%	n	%	n	%
QT interval	Treatment 1	Time 1										
	(N=xx)	Time 2										
		Time 3										
	Treatment 2	Time 1										
	(N=xx)	Time 2										
		Time 3										
QTcB interval	Treatment 1	Time 1										
	(N=xx)	Time 2										
		Time 3										
	Treatment 2	Time 1										
	(N=xx)	Time 2										
		Time 3										
QTcF interval	Treatment 1	Time 1										
	(N=xx)	Time 2										
		Time 3										

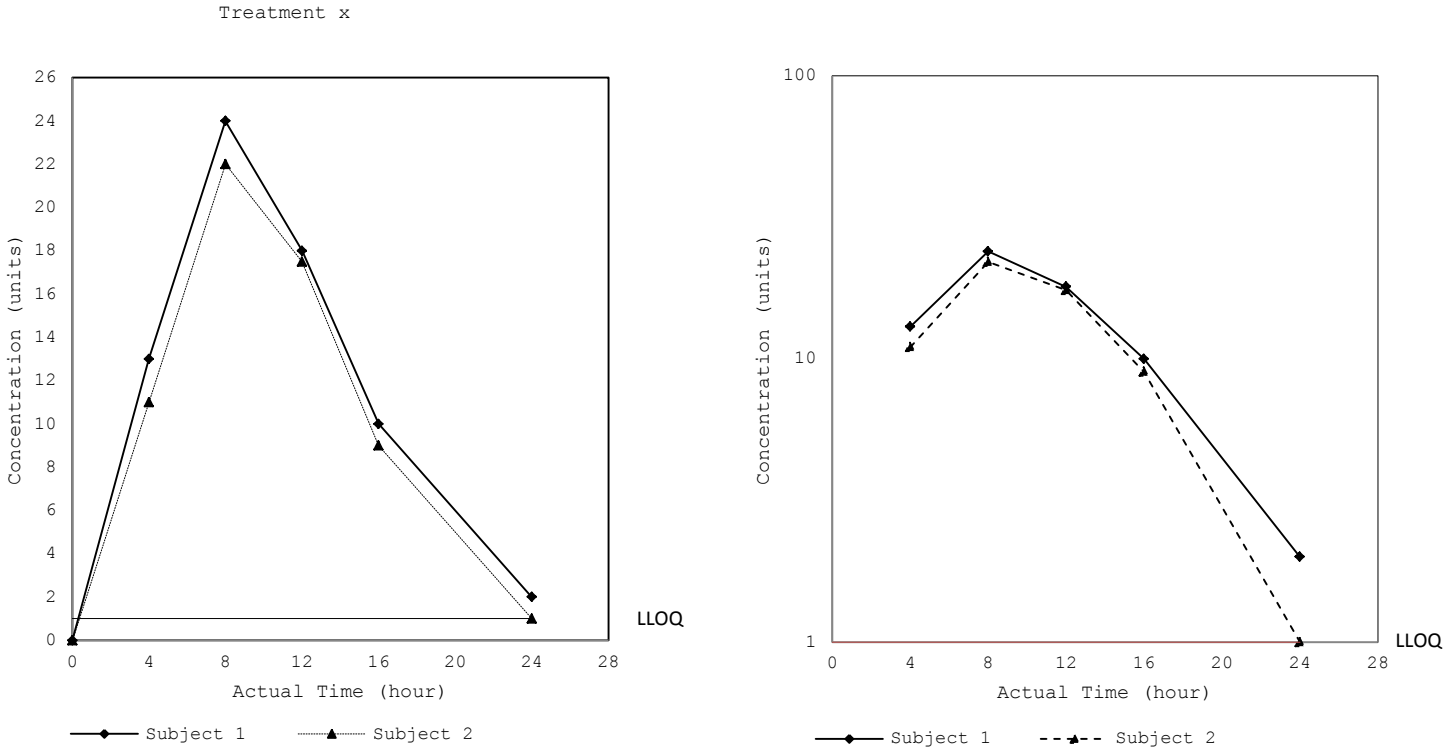
Source: Listing 16.2.xx

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

17.2.2 Figure Outlines

Template F_PK1

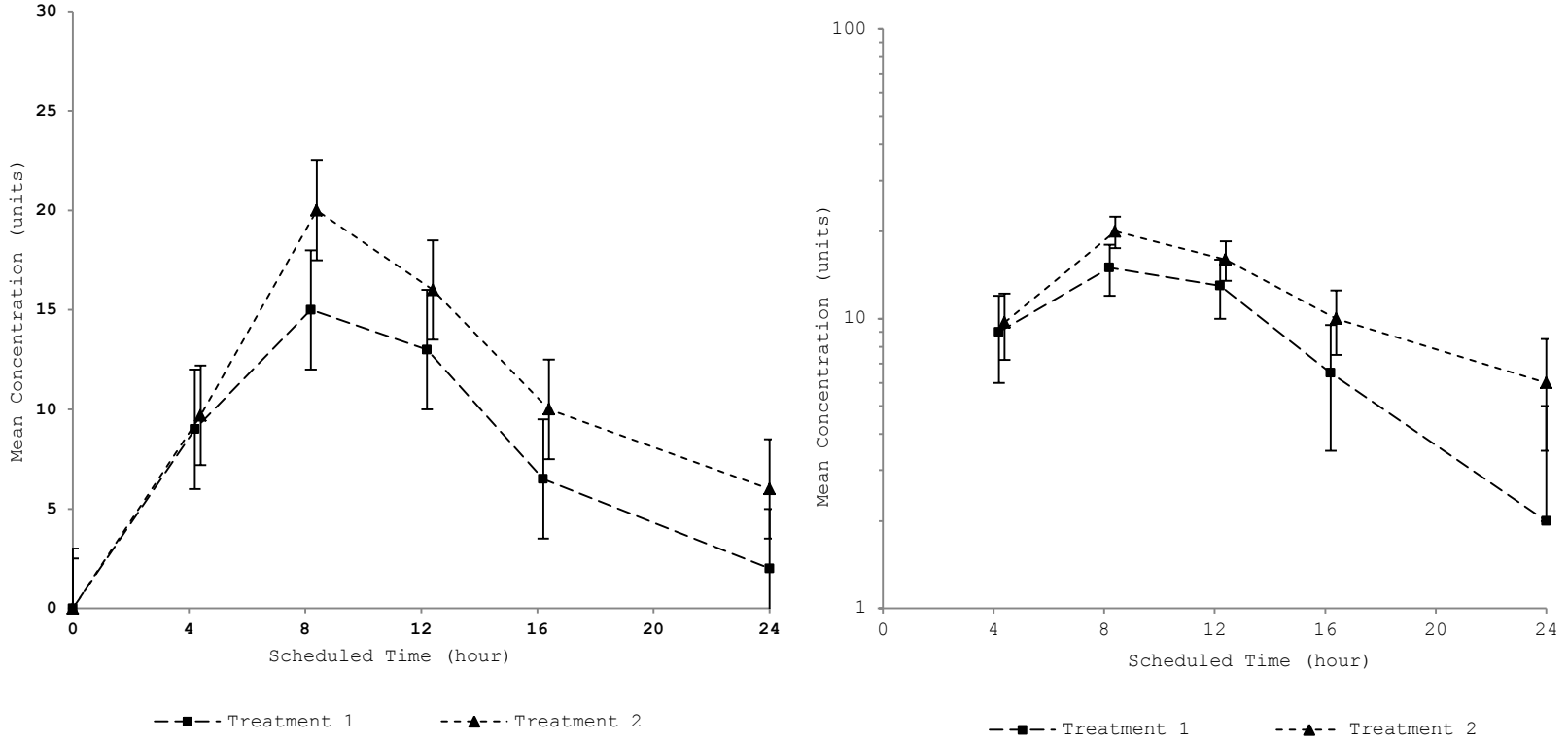
Figure 16.2.4 .xx Individual Emodepside Plasma Concentration-Time Plots (Linear and Semi-log)



Programming note: Plot will include all subjects for a given treatment group

Template F_PK2

Figure 16.2.4.xx Geometric mean (+ SD) of Emodepside Plasma Concentration-Time Plots (Linear and Semi-log)



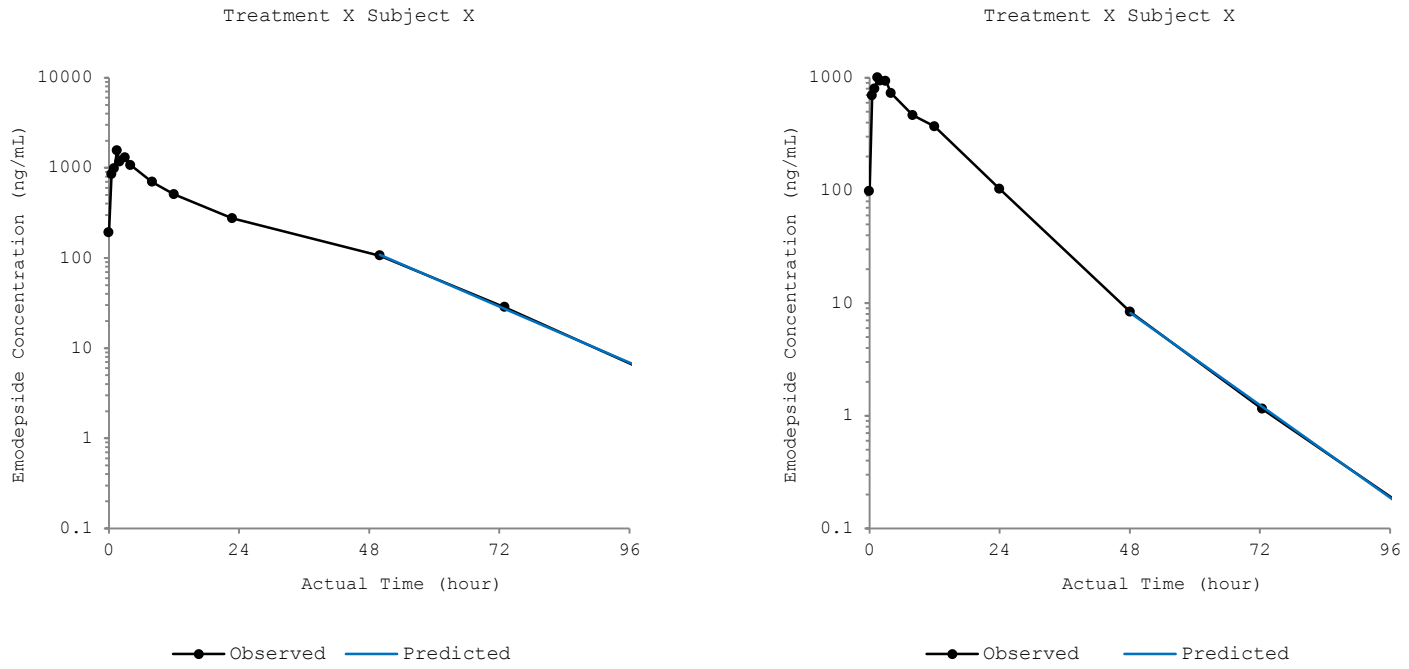
BLQ values are imputed to zero

Programming note: The SD is the geometric standard deviations

In Part 1, the following treatment comparisons will be plotted separately: LSF vs #406 5mg [fasted] and #416 5 mg [fasted], LSF vs #406 5 mg [fed] and #416 5 mg [fed], LSF vs #406 5mg [fasted] and #406 5 mg [fed], LSF vs #416 5 mg [fasted] and #416 5 mg [fed].

Template F_PK10

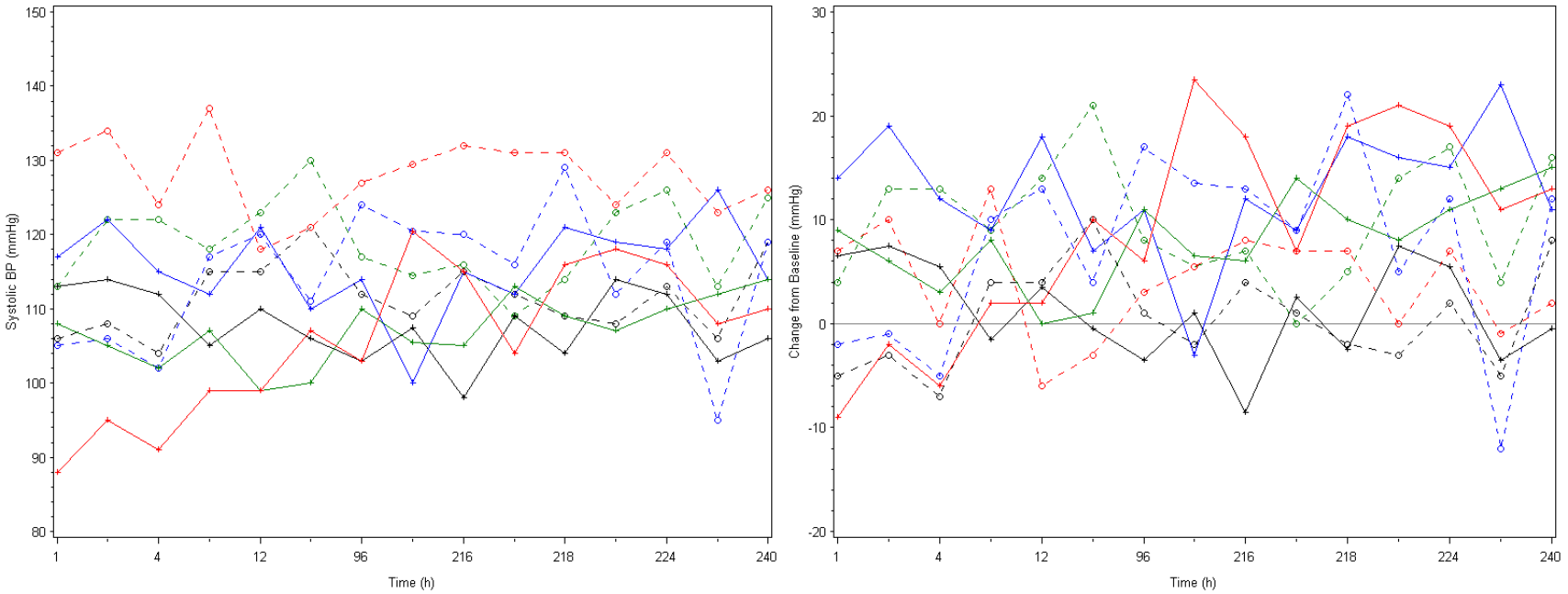
Figure **16.2.**xx Individual Emodepside Plasma Concentration-Time Plots (log scale) for Estimation of Lambda-z, with Regression Line



Template F_SAF1

Figure 14.3.1 Individual Systolic Blood Pressure-Time Plots

Treatment = x



Programming note: Plots are by treatment groups
Continue with all parameters

17.2.3 Listing Outlines

Template L_SD1_PG

Listing 16.2.x.xx Listing of Study Dates

Treatment	Subject	Screening	First dose	Follow Up

Programming notes: *Lists dates for screening, each dosing period and 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_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)

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

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	Date of birth	Age (y)	Gender	Race	Ethnic origin	Height (cm)	Weight (kg)	BMI (kg/m2)	Etc (units)
Treatment 1 ↓											

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

Treatment

Subject

Date of visit

Date of birth

Age

Gender

Race / Ethnic Origin

Height (if collected only once during the study)

Weight (if collected only once during the study)

Smoking History

Alcohol Consumption

Xanthine

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	Time Since Last Dose	Started Pre-Trial?	Ongoing Medication?

Coded using WHODrug Global version xx.x*

Programming notes: ** only include this column and the footnote if coding used*
Include dose and units (e.g. 5 mg)/Freq/Route

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	Dur-ation (days)	Dose	Dose Unit	Formulation/ Route	Frequency
Treatment 1	1001	01JAN2002 23:59	15FEB2002 15:30	46	25	mg	Tablet/ Oral	2xday

Template L_PK1_PG

Listing 16.2.4.xx Listing of Emodepside 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 (hh:mm)	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

Template L_PK4_PG

Listing 16.2.4.xx Listing of Derived Emodepside Pharmacokinetic Parameters

Treatment	Subject	{Add. time var.}	AUC_{inf} (units)	AUC_t (units)	C_{max} (units)	$t_{1/2}$ (units)	t_{max} (units)

Programming notes: *Continue with all parameters*

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	Time Since Last Dose	Severity/ Serious/ Withdrawal	Frequency/ Action Taken (1)/ Other Action Taken	Related to Study Drug/ Treatment Emergent?
Treatment 1	1001	Gastrointestinal Disorders / Intestinal Spasm / Entero-spasm	Resolved/ 24SEP2003 13:05/ 27OCT2003 7:50/ 34d 4h 5m	10d 7h 3m	Mild/ No/ Yes	Intermittent/ Dose not changed/ None	Possibly/ Yes

(1) Action Taken with Study Treatment

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 Abnormalities of Potential Clinical Importance

Treatment	Subject	Laboratory test (units)	Planned Relative Time	Date/Time	Study Day	Value	Reference Interval	RI	BL	Clinically Significant?
Treatment 1	1001	Alk Phos (U/L)	Time 1	01JAN2002 13:34	-1	64.00	32.0 - 92.0			
			Time 2	01APR2002 07:22	85	84.00	32.0 - 92.0			
		ALT (U/L)	Time 1	01JAN2002 18:56	-1	29.00	10.0 - 40.0			
			Time 2	01APR2002 09:22	85	70.00	10.0- 40.0	H	I	Y

RI for Reference Interval flag, BL for Change from Baseline flag;
H = Above reference interval, L = Below reference interval, I = Increase from baseline greater than pre-defined limit, D = Decrease from baseline greater than pre-defined limit

Programming notes: *Lists only double-flagged subjects*

Template L_LB2_PG

Listing 16.2.x.xx Listing of All Clinical Chemistry Laboratory Data for Subjects with PCI Abnormalities

				Alkaline Phosphatase (IU/L)			Alanine Amino Transferase (IU/L)			Aspartate Amino Transferase (IU/L)			Total Bilirubin (UMOL/L)		
Treatment	Subject	Planned Relative Time	Date/Time	Result	RI	BL	Result	RI	BL	Result	RI	BL	Result	RI	BL

				Chloride (MMOL/L)			Glucose (MMOL/L)			Potassium (MMOL/L)			Sodium (MMOL/L)		
Treatment	Subject	Planned Relative Time	Date/Time	Result	RI	BL	Result	RI	BL	Result	RI	BL	Result	RI	BL

				Calcium (MMOL/L)			Creatinine (UMOL/L)			Etc.		
Treatment	Subject	Planned Relative Time	Date/Time	Result	RI	BL	Result	RI	BL	Result	RI	BL

RI for Reference Interval flag, BL for Change from Baseline flag;
H = Above reference interval, L = Below reference interval, I = Increase from baseline greater than pre-defined limit, D = Decrease from baseline greater than pre-defined limit

Programming notes: *Lists only double-flagged subjects*
Include all parameters for the study following the order from the lab report (above is a guide only)

Template L_URI_PG

Listing 16.2.x.xx Listing of Urinalysis Data

		Planned Relative		Specific Gravity		pH		Protein		Glucose	
Treatment	Subject	Time	Date/Time	Result	RI	Result	RI	Result	RI	Result	RI

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

Programming notes: *Include all parameters for the study following the order from the lab report (above is a guide only)*

Template L_VS1_PG

Listing 16.2.x.xx Listing of Vital Signs of Potential Clinical Importance

Treatment	Subject	Planned Relative Time	Date/Time	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Etc (units)
		24 H	26SEP2012:09:57	63	148*	

* Value of potential clinical importance

Template L_EG1_PG

Listing 16.2.x.xx Listing of ECG Values of Potential Clinical Importance

								QT Int. (msec)		QTcB (msec)		QTcF (msec)	
Treatment	Subject	Planned Relative Time	Date/Time	Heart Rate (bpm)	PR Int. (msec)	QRS Dur. (msec)	QRS Axis (deg)	Observed	Change from Baseline	Observed	Change from Baseline	Observed	Change from Baseline
		24 H	26SEP2012:09:57	63	148	78	50	390	32.7 *	399	-27.7	396	-6.5

* Value of potential clinical importance

Programming notes: *Do not list RR*

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/Time	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_NE1_PG

Listing 16.2.x.xx Listing of Abnormal Neurological Examination Findings

Treatment	Subject	Planned Relative Time	Date/Time	Type	Assessment	Details

Programming Notes: *Type = (Mental Status, Cranial Nerves ,etc.)*
List only findings with an 'abnormal' result.
If subjects have multiple abnormal assessment at a given time, create a separate row for each assessment.

Appendix A: Laboratory Ranges

Pre-determined Changes for Laboratory Data (from FL140 v3)

Test	Test Code	Unit	Sex	Delta ranges	
				Acceptable decrease	Acceptable increase
Activated partial thromboplastin time	APTTT	sec	Both	− 8.0	+ 8.0
Alanine transferase	ALTN	IU/L	F	-	+ 30
Alanine transferase	ALTN	IU/L	M	-	+ 30
Albumin	ALB	g/L	Both	− 8	+ 8
Alkaline phosphatase	ALPN	IU/L	Both	− 30	+ 30
Amylase	AMY	U/L	Both	-	+ 150
Aspartate transferase	ASTN	IU/L	F	− 30	+ 30
Aspartate transferase	ASTN	IU/L	M	− 30	+ 30
Basophils	BASO	10^9/L	Both	-	+ 0.30
Bilirubin conjugated	DBIL	µmol/L	Both	-	+ 4.0
Bilirubin total	TBIL	µmol/L	F	− 20.0	+ 10.0
Bilirubin total	TBIL	µmol/L	M	− 20.0	+ 10.0
Bilirubin unconjugated	IBIL	µmol/L	Both	-	-
C-reactive protein	CRP	mg/L	Both	-	-
CK relative index	CKMBR	%	Both	-	-
Calcium	CA	mmol/L	Both	− 0.4	+ 0.4
Carbon dioxide	CO2	mmol/L	Both	− 8	+ 8
Chloride	CL	mmol/L	Both	− 10	+ 10
Cholesterol	CHOL	mmol/L	Both	-	+ 0.7
Creatine kinase	CK	IU/L	F	-	+ 400
Creatine kinase	CK	IU/L	M	-	+ 400
Creatinine	CREA	µmol/L	Both	-	+ 40
Creatinine (DOA urine)	CREDA-U	mmol/L	Both	-	-
Eosinophils	EOS	10^9/L	Both	-	+ 0.50
Erythrocyte sedimentation rate	ESR	mm/h	Both	-	-
Fibrinogen	FIB-C	g/L	Both	-	-
Free T3	FT3	pmol/L	Both	− 3.5	+ 3.5
Free T4	FT4	pmol/L	Both	− 15.0	+ 15.0
Gamma glutamyl transferase	GGT	IU/L	F	-	+ 40
Gamma glutamyl transferase	GGT	IU/L	M	-	+ 40
Globulin	GLOB	g/L	Both	− 8	-
Glucose	GLU	mmol/L	Both	− 1.5	+ 2.5
Haematocrit	HCT	L/L	Both	− 0.050	-
Haemoglobin	HB	g/L	Both	− 20	-
High density lipoprotein	HDL	mmol/L	Both	− 1.50	+ 1.50
International normalised ratio	INRR	ratio	Both	-	-
Lactate dehydrogenase	LDH	IU/L	Both	-	+ 150
Lymphocytes	LYMP	10^9/L	Both	− 1.50	+ 1.50
Magnesium	MG	mmol/L	Both	-	-
Mean cell haemoglobin	MCH	pg	Both	− 2.0	+ 2.0
Mean cell haemoglobin concentration	MCHC	g/L	Both	− 25	+ 25
Mean cell volume	MCV	fL	Both	− 10	+ 10

Test	Test Code	Unit	Sex	Delta ranges	
				Acceptable decrease	Acceptable increase
Monocytes	MONO	10^9/L	Both	− 0.50	+ 0.50
Neutrophils	NEUT	10^9/L	Both	− 2.00	+ 8.00
Phosphate	PHOS	mmol/L	Both	− 1.00	+ 1.00
Platelets	PLT	10^9/L	Both	− 100	+ 100
Platelets (citrate tube)	PLTC	10^9/L	Both	− 100	+ 100
Potassium	K	mmol/L	Both	− 0.8	+ 0.8
Prolactin	PROL	µg/L	Both	-	-
Prothrombin time	PTT	sec	Both	− 4.0	+ 4.0
Red blood cells	RBC	10^{12}/L	Both	− 1.0	-
Reticulocyte	RET	%	Both	-	-
Reticulocyte count	RETC	10^9/L	Both	-	-
Reticulocyte manual count	RETM	10^9/L	Both	-	-
Sodium	NA	mmol/L	Both	− 8	+ 8
Thrombin time	TT	sec	Both	-	-
Thyroid stimulating hormone	TSH	mIU/L	Both	− 3.00	+ 3.00
Total protein	TP	g/L	Both	− 15	-
Triglycerides	TG	mmol/L	Both	-	+ 1.5
Urea	UREA	mmol/L	Both	− 5.0	+ 2.0
Uric acid	UA	µmol/L	Both	− 100	+ 100
Urine pH	UPH	N/A	Both	− 4	+ 4
Urine red blood cells	URBC	10^6/L	Both	-	+ 10
Urine white blood cells	UWBC	10^6/L	Both	-	+ 100
White blood cells	WBC	10^9/L	Both	− 2.0	+ 8.0

Appendix B: Pharmacokinetic Analysis

1 Calculation Methods

1.1 Data Handling Conventions

1.1.1 Actual vs 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

Missing values will not be used in any way.

For calculation of all pharmacokinetic parameters and individual profile plots, plasma concentrations below the quantifiable limit (BQL) of the assay will not be used for the calculation of PK parameters (except BQL values observed at time points before the maximum concentration, which will be taken as zero).

BQL values observed post dose will be substituted by one half of the lower limit of quantification for calculation of plasma concentration summary statistics. Pre dose values will be taken as zero. The number of imputed values will be included in the summary table.

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

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.

For non-compartmental analysis uniform weighting will be applied.

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 General Considerations for Data Analysis

2.1 Derived and transformed data

In general, concentration and concentration-related quantities, rate constants and half-lives (e.g. C_{max}, AUC, $t_{1/2}$ and MRT) will be analysed after logarithmic transformation. Logarithmic transformations will use natural logarithms ($\log_e$). A list of those parameters that will be log transformed are given below.

2.2 Summary data

Means at any time will only be calculated if at least 2/3 of the individual data are measured and are above the lower of quantification (LLOQ).

3 Parameter Definitions

3.1 Plasma Parameters

3.1.1 Emodepside

Text Symbol	Definition	Calculation	Typical Units	Log Transform	WNL	CDISC Controlled Terminology	TFL Symbol
Concentrations and times							
C_{max}	Maximum (peak) plasma concentration	The maximum (peak) plasma concentration will be obtained directly from the concentration-time data.	ng/mL	Y	Cmax	CMAX	C_{max}
C_{max}/Dose	Dose-normalised C_{max} to infinity	The dose-normalised C_{max} will be calculated as C_{max} /Dose administered	(ng/mL)/mg	Y	Cmax_D	CMAXD	C_{max}/D
$C_{max,norm}$	Observed maximum plasma concentration corrected by dose and body weight	The C_{max} normalised by dose and body weight will be calculated as C_{max}/(Dose administered*body weight)	(ng/mL)/(mg*kg)	Y	N/A	CMAXWD	$C_{max,norm}$
t_{max}	Time to reach maximum (peak) plasma concentration	The first time of maximum (peak) plasma concentration will be obtained directly from the concentration-time data.	h	N	Tmax	TMAX	t_{max}
Half-life							
λ_z	Terminal rate constant	The apparent terminal phase rate-constant (λ_z) will be estimated by linear regression of logarithmically transformed concentration versus time data.	1/h	Y	Lambda_z	LAMZ	λ_z
Point terminal	Number of points for Lambda z	The number of time points used in calculating Lambda z	-	-	No_points_lambda_z	LAMZNPT	n_{pts}
$t_{½,0\text{-}7d}$	Terminal half-life	The 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	$t_{1/2,0\text{-}7d}$
$t_{½,0\text{-}24h}$	Dominant half-life	The half-life calculated from the terminal slope of the log concentration-time (0-24h) curve, as follows: $t_{½} = \frac{\log_e 2}{\lambda_z}$	h	Y	HL_Lambda_z	LAMZHLD	$t_{1/2,0\text{-}24}$

Text Symbol	Definition	Calculation	Typical Units	Log Transform	WNL	CDISC Controlled Terminology	TFL Symbol
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	AUC_last	AUCLST	AUC_{last}
AUC_{0-7d}	Area under the plasma concentration-time curve from time zero to 7 days	The area under the concentration-time curve from zero time (pre-dose) to 7 days will be calculated using the (specified) trapezoidal method. If λ_z is not estimable, a partial AUC is not calculated (when $t_{last}<t$).	h*ng/mL	Y	User specified area	AUCINT	AUC_{7d}
AUC_{0-7d}/Dose	Dose-normalised AUC from time zero to 7 days	The dose-normalised AUC from time zero to 7 days will be calculated as AUC_{0-7d}/Dose administered	(h*ng/mL)/mg	Y	N/A	AUCINTD	AUC_{7d}/D
$AUC_{0-7d,norm}$	Area under the concentration-time curve from time zero to 7 days corrected by dose and body weight	The AUC from time zero to 7 days normalised by dose and body weight will be calculated as AUC_{0-7d}/(Dose administered*body weight)	(h*ng/mL)/(mg*kg)	Y	N/A	AUCINTWD	$AUC_{7d,norm}$
Clearance, volume of distribution and mean residence time							
MRT_{last}	Mean Residence Time	The mean residence time will be calculated using: $$MRT = \frac{AUMC_{last}}{AUC_{last}}$$	h	Y	MRTlast	MRTEVLST	MRT_{last}

Appendix C: Sample Page Layout

DNDi : DNDI-EMO-03 Part 1 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 17-008 Part 1

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"