Statistical Analysis Plan

Clinical trial protocol title:	A Phase 1, Single-Blind, Randomized, Placebo Controlled, Parallel-Group, Multiple-Dose Escalation Study to Investigate Safety, Tolerability, and Pharmacokinetics of Emodepside (BAY 44-4400) After Oral Dosing in Healthy Male Subjects
HMR code:	16-021
Sponsor code:	DNDI-EMO-02
EudraCT no:	2017-003020-75
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Issued:	29 August 2018
Version:	1
Based on:	Protocol version 5, 25 July 2018
Number of pages:	70
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1 List of abbreviations

λ_z	Terminal rate constant
ALT	Alanine Aminotransferase
AP	Alkaline Phosphatase
aPTT	Activated Partial Thromboplastin Time
AST	Serum Aspartate aminotransferase
AE	Adverse Event
AUC	Area under concentration-time curve
AUC_t	AUC from time zero to time t
AUC_t/Dose	AUC from time zero t to time t, corrected for dose
$AUC_{t,norm}$	AUC from time zero t to time t, corrected for dose and body weight
AUC_{last}	AUC from time zero to last measurable concentration
AUC_{last}/Dose	AUC from time zero to last measurable concentration, corrected for dose
$AUC_{last,norm}$	AUC from time zero to last measurable concentration, corrected for dose and body weight
BID	Twice daily dosing
BMI	Body Mass Index
BP	Blood Pressure
BQL	Below the limit of quantification
CI	Confidence Interval
CK	Creatine Kinase
CLss/F	Apparent Total body clearance at steady state
C_{max}	Maximum Plasma Concentration
C_{max}/Dose	C_{max} corrected by dose
$C_{max,norm}$	C_{max} corrected by dose and body weight
$C_{max,ss}$	Maximum plasma concentration at steady state
$C_{max,ss}$/Dose	C_{max} corrected by dose at steady state
$C_{max,ss,norm}$	C_{max} corrected by dose and body weight at steady state
C_{trough}	Trough Concentration
CRF	Case Report Form
CSR	Clinical StudyReport
ECG	Electrocardiogram
GLDH	Glutamate Dehydrogenase
GGT	Gamma-Glutamyl Transpeptidase
HbA1C	Glycated Haemoglobin
HMR	Hammersmith Medicines Research
HR	Heart Rate
ICH	International Conference on Harmonization
IMP	Investigational Medicine Product
LSF	Liquid Service Formulation
LDH	Lactate Dehydrogenase
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time
MRT_{inf}	Mean residence time from time zero to infinity
MRT_{last}	Mean residence time from time zero to last measurable concentration

N	Number of subjects
n	Number of observations used in analysis
OD	Once daily dosing
OGTT	Oral Glucose Tolerance Test
PCI	Potential clinical importance
PD	Pharmacodynamic(s)
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.
PT	Prothrombin Time
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
R	Accumulation Ratio
RBC	Red Blood Cells
$R_{ac}C_{max}$	Accumulation Ratio for C_{max}
$R_{ac}AUC$	Accumulation Ratio for AUC
RR	Portion of the ECG between consecutive R waves, representing the ventricular rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
$t_{1/2}$	Terminal elimination half-life
$t_{1/2, 0\text{-}t}$	Dominant half-life
TEAE	Treatment-Emergent Adverse Event
TSH	Thyroid-Stimulating Hormone
t_{max}	Time to maximum plasma concentration
Vz/F	Apparent Volume of Distribution
WBC	White Blood cell
WHO	World Health Organisation

2 Signatures

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

Helen Topping ***Senior Statistician, HMR***	Signature	30AUG2018 Date
Dr Jeremy Dennison ***Principal Investigator, HMR***	Signature	31 AUG 2018 Date
Jean-Yves Gillon ***Head of Translation, DNDi***	Signature	29 August 2018 Date
Frédéric Monnot ***Filarial Team Leader, DNDi***	Signature	29 August 2018 Date
Sabine Specht ***Head of Filarial Program, DNDi***	Signature BELOW PERTAINS	29 August 2018 Date

3 Introduction

This Statistical Analysis Plan (SAP) is based on the current trial protocol (version 5, 25 July 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(s)

- To investigate the safety and tolerability of emodepside (BAY44-4400) after multiple doses, administered as a LSF oral solution, in healthy male Caucasian subjects.

4.1.2 Secondary Objective(s)

- To investigate the pharmacokinetics (PK) of emodepside (BAY44-4400) after multiple doses, administered as an LSF oral solution.
- To investigate the time-matched profiles of selected pharmacodynamic (PD) markers in plasma, after multiple doses of emodepside (BAY44-4400),

administered as an LSF oral solution.

4.2 Study Endpoint(s)

4.2.1 Primary Endpoint(s)

- Adverse events (AEs)
- Physical examination findings
- Neurological examination findings (including assessments of tremor of the hands and fingers, coordination/cerebellar function (finger to finger, finger to nose, with eyes open and closed), pupil size and reaction to light)
- Vital signs: heart rate (HR), systolic and diastolic blood pressure (BP)
- 12-lead ECG (including heart rate (HR), PR, QRS, QTcB, QTcF)
- 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), glycated haemoglobin (HbA1C; at screening only);
    - Coagulation: activated partial thromboplastin time (aPTT), prothrombin time (PT);
    - Biochemistry: serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), glutamate dehydrogenase (GLDH), gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), creatine kinase (CK), amylase, lipase, free T3 and T4, thyroid-stimulating hormone (TSH), glucose, cholesterol (HDL, LDL, total), triglycerides, creatinine, urea, uric acid, bilirubin (total and conjugated), total protein, sodium, potassium, calcium, chloride, and magnesium;
    - At baseline (screening visit 1) and Day 9 additional hormones: leptin and prolactin levels
    - Urinalysis: by dipstick – glucose, ketone bodies, specific gravity, occult blood, pH, proteins, leucocytes, bilirubin, urobilinogen, nitrites.
- Ophthalmology assessments: including visual symptoms, past ocular history, best corrected distance visual acuity, colour vision assessment, Amsler grid assessment

4.2.2 Secondary Endpoint(s)

Pharmacokinetic Variables:

Emodepside plasma concentration–time data will be used to derive the following PK parameters of emodepside:

- After the first dose of emodepside (Day 0):

    - Main PK parameters:
    - Cohorts 1 & 2: AUC_{24}, AUC_{24}/D, C_{max}, C_{max}/D
    - Cohort 3: AUC_{12}, AUC_{12}/D, C_{max}, C_{max}/D
- After multiple doses of emodepside (Day 9):
    - Main PK parameters:
    - Cohorts 1 & 2: AUC_{∞}, AUC_{∞}/D, AUC_{24}, AUC_{24}/D, $C_{max,ss}$, $C_{max,ss}/D$
    - Cohort 3: AUC_{∞}, AUC_{∞}/D, AUC_{12}, AUC_{12}/D, $C_{max,ss}$, $C_{max,ss}/D$
- Accumulation ratios RA(C_{max}) and RA(AUC_{tau}) will be calculated
- C_{trough} will be derived from the concentration data (Days 1–9).

The above parameters may be calculated for the metabolites of emodepside, as appropriate.

Pharmacodynamic Variables:

- Time-matched profiles of glucose, glucagon, insulin, and cortisol
- Oral glucose tolerance test (OGTT)

Exploratory PK variables:

Emodepside plasma concentration–time data will be used to derive the following PK parameters of emodepside:

- After a single dose of emodepside (Day 0):
    - Cohorts 1 & 2: $AUC_{24,norm}$, $C_{max,norm}$, t_{max}, MRT_{last}, V_z/F
    - Cohorts 3: $AUC_{12,norm}$, $C_{max,norm}$, t_{max}, MRT_{last}, V_z/F
- After multiple doses of emodepside (Day 9):
    - $AUC_{\infty,norm}$, $AUC_{12,norm}$, $AUC_{24,norm}$, AUC_{last}, AUC_{last}/D, $AUC_{last,norm}$, $C_{max,ss,norm}$, $t_{1/2}$, λ_z, t_{max}, MRT_{∞}, V_z/F, CL_{ss}/F
    - Other optional parameters: AUC_{t-inf}, $\%AUC_{extra}$, points terminal

4.3 Statistical Hypotheses

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

5 Study Design

This will be a single-centre, single-blind, randomized, placebo-controlled, parallel-group, multiple-dose, dose-escalation study.

Each cohort will comprise 8 healthy Caucasian male subjects, 6 of whom will be randomised to receive emodepside, and 2 of whom will be randomised to receive placebo. 3 cohorts will be recruited, to test 3 multiple dose levels of emodepside LSF oral solution over 10 days.

6 Time and Events Table

Procedure	Screening		Day (s)												Follow-up (Day 30 ±2 Days)	Long-term follow-up visits (Days 60, 90, and 120 ±2 Days)[18]
	Day –28 to –3		–3	–2	–1	0	1	2–8	9	10–14	17 (±2)	20 (±2)	23 (±2)	27 (±2)		
	Visit 1	Visit 2														
Subject demographics and informed consent	X															
Inclusion/Exclusion Criteria	X					X										
Medical history	X															
Inpatient stay			←							→						X
Outpatient visit	X	X									X	X	X	X	X	X
Drugs of abuse screen and alcohol breath test[1]	X		X													X
Full physical examination[2]	X							X		X					X	
Short physical examination[2]					X	X	X	X	X	X	X	X	X	X		X
Full neurological examination[3]	X					X				X						
Short neurological examination[4]					X	X	X	X	X	X	X	X	X	X	X	X
Ophthalmological examination[5]	X	X								X						
Oral Glucose Tolerance Test (OGTT)[6]				X			X	X								X
Glucose, insulin, glucagon and cortisol[7]					X	X	X		X	X					X	
Administration of emodepside[8]						X	X	X	X							

Procedure	Screening		Day (s)												Follow-up (Day 30 ±2 Days)	Long-term follow-up visits (Days 60, 90, and 120 ±2 Days)[18]
	Day –28 to –3		–3	–2	–1	0	1	2–8	9	10–14	17 (±2)	20 (±2)	23 (±2)	27 (±2)		
	Visit 1	Visit 2														
12-lead safety ECGs[9]	X				X	X	X	X	X	X					X	
Vital signs[10]	X				X	X	X	X	X	X	X	X	X	X	X	X
AE monitoring[11]	←															→
PK of emodepside in plasma[12]						X	X	X	X	X	X	X	X	X	X	
PK of metabolites of emodepside in plasma[13]						X			X							
PK of emodepside and metabolites in urine[14]						X			X							
Laboratory safety tests[15]	X				X	X	X	X	X	X			X		X	X
Serology[16]	X															
Leptin and prolactin[7,17]	X								X							

1. Alcohol breath tests and drugs of abuse screen will be performed at Screening Visit 1 and Day–3. At long-term follow-up visits (Days 60, 90 and 120), only alcohol breath tests will be performed.
2. A full physical examination will be done at Screening Visit 1 and Follow-up and before the morning dose on Days 3–8 inclusive, and on Day 14. To include height at Screening Visit 1 and weight at Screening Visit 1 and on the morning of Day –1. Short physical examinations will be done at the following time points:
    - on Day –1: at –24, –23, –22, –20 and –12 h before the morning dose on Day 0
    - on Day 0: before and at 1, 2, 4, and 12 h after the morning dose
    - on Days 1 & 2: before the morning dose
    - on Day 9: before and at the following times after the morning dose: 0.5, 1, 2, 4, 12, 24 h (Day 10), 48 h (Day 11), 72 h (Day 12) and 96 h (Day 13)
    - at outpatients visits on Days 17, 20, 23, 27, and at long-term follow-up visits (Days 60, 90 and 120) (± 2 days)
3. A full neurological examination will be done at screening Visit 1, before the morning dose on Day 0 and on Day 14 after the morning dose (120 h).
4. A short neurological examination will be given at the following time points:
    - on Day –1: at –24, -23, -22, -20, and -12 h before the morning dose on Day 0
    - on Day 0: at 1, 2, 4, and 12 h after the morning dose
    - on Days 1–8: before the morning dose
    - on Day 9: before and at the following times after the morning dose: 1, 2, 4, 12, 24 (Day 10), 48 (Day 11), 72 (Day 12) and at 96 h (Day 13)
    - at outpatient visits on Days 17, 20, 23, 27 and at Follow-up (Day 30 ± 2 days), and long-term follow-up visits (Days 60, 90 and 120 ±2 days)

5. Ophthalmological examination will be performed at the second screening visit after all other eligibility criteria have been met, and on Day 10. If deemed necessary by the ophthalmologist, additional ophthalmology follow-up visit(s) may be scheduled for eye-related AEs. Subjects will be given the Ishihara test at screening visit 1.
6. Blood samples taken for glucose and insulin measurement will be used to complete an Oral Glucose Tolerance Test (OGTT). Samples taken will be:
    - on Day –2: at –48, –47, –46 and –44 h before the morning dose on Day 0
    - on Day 1: before and at 1, 2 and 4 h after the morning dose
    - on Day 8: before and at 1, 2 and 4 h after the morning dose
    - On day 120 at 0, 1, 2 and 4 h time points relative to dosing

    Subjects will fast until completion of the OGTT test; lunch will be provided immediately afterwards

7. Blood samples for measurement of glucose, insulin, glucagon and cortisol will be taken:
    - on Day –1: at –24, –23, –22, –20 and –12 h before the morning dose on Day 0
    - on Day 0: before and at 1, 2, 4 and 12 h after the morning dose
    - on Day 1: before the morning dose
    - on Day 9: before and at the following time points after the morning dose: 1, 2, 4, 12, 24 (Day 10), 48 (Day 11), 72 (Day 12), 96 (Day 13) and 120 h (Day 14); and at follow up (Day 30 (± 2 days)). Subjects will fast for the Day 11, 12, 13,14 and 30 time points.

    Leptin and prolactin will also be measured at Screening Visit 1 and Day 9, as part of the insulin blood sample.

8. Administration of the study medicine will be done in fasting conditions on Days 0–9 at approximatively the same time each morning (±15 mins):
    - in Cohorts 1 & 2, emodepside will be giving in the morning only
    - in Cohort 3, emodepside will be given in the morning and evening (at 12 h intervals). On the last day (day 9), emodepside will be given only in the morning
9. 12-lead ECGs will be recorded in triplicate (with 1 minute between recordings) at –24 h (Day –1) before the morning dose on Days 0 and 9; single recordings will be made at all other time points. ECGs will be recorded:
    - at Screening Visit 1 and at Follow-up (Day 30 ± 2 days)
    - on Day –1: at –24, –23.5, –23, –22.5, –22, –21, –20, –16 and –12 h before the morning dose on Day 0
    - on Day 0: before and at 0.5, 1, 1.5, 2, 3, 4, 8 and 12 h after the morning dose
    - on Days 1–8: before the morning dose
    - on Day 9: before and at the following times after the morning dose: 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24 (Day 10), 72 (Day 12) and 120 h (Day 14) after the Day 9 dose

    Subjects should rest in the supine position for 10 minutes before ECG measurements.

10. Vital signs will comprise blood pressure (BP) and heart rate (HR) at all time points, with oral temperature included at screening and –24 h before the morning dose on Day 0 (Day –1). Subjects should rest in the supine position for 10 minutes before single BP and HR measurements are taken. Vital signs will be measured:
    - at the first screening visit and at Follow-up (Day 30 ± 2 days)
    - on Day –1: at –24, –23.5, –23, –22.5, –22, –21, –20, –16 and –12 h before the morning dose on Day 0
    - on Day 0: before and at 0.5, 1, 1.5, 2, 3, 4, 8 and 12 h after the morning dose
    - on Days 1–8: before the morning dose

- on Day 9: before and at the following times after the morning dose: 0.5, 1, 1.5, 2, 3, 4, 8,12, 24, 36 (Day 10), 48 (Day 11), 72 (Day 12), 96 (Day 13) and 120 h (Day 14)
- at outpatients visits on Days 17, 20, 23 and 27 (± 2 days), and long-term follow-up visits (Days 60, 90 and 120 ±2 days)

11. Adverse event monitoring will be done throughout the study, but scheduled questioning will be done at the following time points:
    - at Screening Visit 1 and at Follow-up (Day 30 ± 2 days)
    - on Day –1, at -24, -23, -22, -21, -20, -18, -16, -12 h before the morning dose on Day 0
    - on Day 0: before and at 1, 2, 3, 4, 6, 8 and 12 h after the morning dose
    - on Days 1–8: before the morning dose
    - on Day 9: before and at the following times after the morning dose: 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36 (Day 10), 48 (Day 11), 72 (Day 12), 96 (Day 13) and 120 h (Day 14)
    - at outpatients visits on Days 17, 20, 23 and 27 (± 2 days), and long-term follow-up visits (Days 60, 90 and 120 ±2 days)
12. Blood samples for assay of emodepside in plasma will be taken:
    - on Day 0: before and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 15 h after the morning dose
    - on Days 1–8: before the morning dose
    - on Day 9: before and at the following times after the morning dose: 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 15, 24, 36 (Day 10), 48 (Day 11), 72 (Day 12), 96 (Day 13) and 120 h (Day 14)
    - at outpatients visits on Days 17, 20, 23 and 27 (± 2 days), and at Follow-up (Day 30 ± 2 days)

    Subjects should rest in the supine position for 10 minutes before blood is drawn (if possible).
13. Blood samples for assay of metabolites of emodepside in plasma will be taken:
    - on Day 0: before and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 15 h after the morning dose
    - on Day 9: before and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 15 h after the morning dose
14. Urine for assay of emodepside and its metabolites may be collected at the following time points:
    - On Day 0: from 0–4, 4–8, 8–12 and 12–24 h after the morning dose
    - On Day 9: from 0–4, 4–8, 8–12 and 12–24 h after the morning dose
15. Blood and urine samples for clinical laboratory safety tests (haematology, biochemistry, coagulation & urinalysis) will be taken: at Screening Visit 1; on Day –1 (–24 h before the morning dose on Day 0); before the morning dose on Day 0; before the morning dose on Days 1, 5 and 8; before, 24 h (Day 10) and 120 h after the morning dose on Day 9 (Day 14); at the Day 23 outpatient visit (± 2 days); at Follow-up (Day 30 ± 2 days); and at long-term follow-up (Days 60, 90 and 120 ± 2 days).

    Subjects should rest in the supine position for 10 minutes before blood is drawn (if possible).
16. Serology tests will comprise HIV 1 & 2, hepatitis B & C, and HbA1c
17. Blood samples for measurement of leptin and prolactin will be taken at Screening Visit 1 and before the morning dose on Day 9.
18. Subjects will be admitted to the ward on Day 119, before the Day 120 long-term follow-up visit.

7 Planned Analyses

7.1 Interim Analyses

Interim analyses will be performed. Blinded PK, safety and tolerability data will be reviewed after each cohort for dose selection. Details are given in the Interim Review Plan and in the safety Review Group Charter signed at the beginning of the study.

An additional interim analysis (including interim database lock) will be performed after Cohorts 1 and 2 have completed and unblinded, to evaluate the progression into later phase studies.

7.1.1 Persons responsible for analysis

Stephen Sah (HMR)	Statistician
Nick Jackson (HMR)	SAS Programmer

7.2 Final Analysis

This study will have one database, however Cohorts 1 and 2 will be analysed and reported separately from Cohort 3. Each cohort (Cohorts 1 and 2) and (Cohort 3) will be locked once all subjects have completed, data have been entered, all queries resolved and protocol deviations identified for that cohort of the study. Each cohort (Cohorts 1 and 2) and (Cohort 3) of the study will be unblinded following database lock. Final analyses will be carried out following database lock and unblinding for each cohort (Cohorts 1 and 2) and (Cohort 3) 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. 6 subjects per dose level (cohort) is considered sufficient to examine the safety and tolerability of emodepside, as well as the pharmacokinetics after single and multiple doses.

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 pharmacokinetic sample was analysed.
PK Parameter Population:	All subjects in the PK Concentration Population for whom pharmacokinetic parameters can be derived.

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

The primary endpoint will be analysed using the safety 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 active (emodepside) versus placebo.

11 General Considerations for Data Analyses

11.1 Data Display Treatment and Other Subgroup Descriptors

The sort order for treatment groups will be placebo, then study 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
Placebo [OD or BID]	PLA [OD or BID]
Emodepside xx mg [OD or BID]	xx mg [OD or BID]

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 or study drug will be included in the statistical analyses.

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

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

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

If time information (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 Day -2 if not recorded elsewhere etc.)

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 measurements will be taken at -24 h on Day -1, and at pre dose on Days 0 and 9. The mean of the three measurements taken on Day 0 pre dose for each subject will be used as their baseline value. Single measurements will be made at all other time points.

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 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 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.

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.
- Had their treatment assignment unblinded.

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 8.4 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 version September 2017 of the World Health Organisation (WHO) Drug Global dictionary.

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 21.0 or higher of the Medical Dictionary for Regulatory Activities (MedDRA).

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, clinical chemistry, coagulation 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, coagulation 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 at each planned assessment, and change in vital signs from baseline at each planned post-baseline assessment, will be summarised by 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 examination

Abnormal physical examination findings will be listed.

14.6.4 Neurological examination

Abnormal neurological examination findings will be listed.

14.6.5 Ophthalmology examination

Abnormal ophthalmology examination findings will be listed.

15 Pharmacokinetic Analyses

Analytical Services International Ltd will measure the plasma concentrations of emodepside. The pharmacokinetic analysis will be done by Statistics and Data Management Department at HMR. Pharmacokinetic parameters will be calculated using WinNonlin, version 7.0 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 * √ (exp(SD)^2 -1) with SD of log-transformed data*

15.1 Plasma PK

15.1.1 Pharmacokinetic Concentration Data

The plasma concentrations of emodepside and metabolites (if applicable) will be listed and summarised by treatment.

Using actual sample times, linear and semi-logarithmic concentration-time plots of each analyte for each subject will be prepared. For subjects receiving more than one dose of a treatment, profiles will be included for all doses 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. For clarity in presentation, individual profiles for different analytes will generally be separate.

Nominal blood sampling times will be used to calculate the geometric mean (geo SD) drug concentrations at each time point. Comparative linear and semi-logarithmic plots of the geometric mean (with geo standard deviation error bars) concentration-time data for each group will be prepared.

15.1.2 Pharmacokinetic Parameters

The pharmacokinetic parameters of emodepside and metabolites (if applicable) will be listed and summarised by treatment.

15.2 Urinary PK

If concentrations of emodespide and metabolites (if applicable) in urine are determined, the amount of emodepside excreted in the urine will be estimated and listed.

16 Pharmacodynamic Analyses

Summaries and listings will use the safety population.

Pharmacodynamic variables (glucose, insulin, glucagon, cortisol and oral glucose tolerance test) at each planned assessment, and change from baseline at each planned post-baseline assessment, will be summarised by treatment.

Individual PD subject profiles plotted against time will be presented for both absolute values and change from baseline.

17 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

18 ATTACHMENTS

18.1 Table of Contents for Data Display Specifications

For overall page layout refer to Appendix C.

Tables, figures and listings will be labelled A (for Cohorts 1 and 2) and B (for Cohort 3), e.g. 14.1A, 14.1B. Separate tables will be produced for Cohorts 1 and 2 and for Cohort 3.

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 18.2.1):

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			
14.2.1.1	Summary of emodepside plasma pharmacokinetic concentration-time data [units]	PK Concentration	16.2.6.1.1	T_PK1
14.2.1.2	Summary of derived emodepside plasma pharmacokinetic parameters	PK Parameter	16.2.6.1.2	T_PK3
14.2.1.3	Summary of log-transformed derived emodepside plasma pharmacokinetic parameter	PK Parameter	16.2.6.1.2	T_PK4
14.2.2.1	Summary of glucose	Safety	16.2.6.2.1	T_LB2
14.2.2.2	Summary of insulin	Safety	16.2.6.2.1	T_LB2
14.2.2.3	Summary of glucagon	Safety	16.2.6.2.1	T_LB2
14.2.2.4	Summary of cortisol	Safety	16.2.6.2.1	T_LB2
14.2.3.1	Summary of oral glucose tolerance test results	Safety	16.2.6.2.1	T_LB2
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
14.3.1.3	Summary of treatment-emergent adverse events by severity	Safety	16.2.7.1	T_AE3
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 laboratory values	Safety	16.4	T_LB2
14.3.5.4	Summary of urinalysis results	Safety	16.2.8.5	T_UR1

Table	Description	Population	Source Listing	Template (Shells below)
14.3.6.1	Summary of vital signs	Safety	16.4	T_VS1
14.3.7.1	Summary of ECG values	Safety	16.4	T_EG2
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)
14.2	PHARMACOKINETIC AND PHARMACODYNAMIC DATA			
14.2.1.1	Individual emodepside plasma concentration-time plots (linear and semi-log)	PK Concentration	16.2.6.1.1	F_PK1
14.2.1.2	Geometric mean (with geo SD error bars) emodepside plasma concentration-time plots (linear and semi-log)	PK Concentration	16.2.6.1.1	F_PK2
14.2.2.1	Individual glucose-time plots	Safety	16.4	F_SAF1
14.2.2.2	Individual insulin-time plots	Safety	16.4	F_SAF1
14.2.2.3	Individual glucagon-time plots	Safety	16.4	F_SAF1
14.2.2.4	Individual cortisol-time plots	Safety	16.4	F_SAF1
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 18.2.2):

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
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	
16.2.6.1.1	Listing of emodepside plasma pharmacokinetic concentration-time data	L_PK1_PG
16.2.6.1.2	Listing of derived emodepside plasma pharmacokinetic parameters	L_PK4_PG
16.2.6.1.3	Listing of emodepside plasma urine sample collections	L_PK2_PG
16.2.6.1.4	Individual emodepside plasma concentration-time plots for estimation of λz, with regression line	F_PK10
16.2.6.2.1	Listing of PD concentration-time data	L_PK1_PG
16.2.7	Adverse events	
16.2.7.1	Listing of all adverse events	L_AE1_PG
16.2.7.2	Listing of serious adverse events	L_AE1_PG
16.2.7.3	Listing of adverse events leading to withdrawal from study	L_AE1_PG
16.2.8	Laboratory values	
16.2.8.1	Listing of clinical chemistry abnormalities of potential clinical importance	L_LB1_PG
16.2.8.2	Listing of all clinical chemistry laboratory data for subjects with PCI	L_LB2_PG

Listing	Description	Template (Shells below)
	abnormalities*	
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 and physical 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
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
16.2.9.6	Listing of abnormal ophthalmology examination findings	L_PE1_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.

18.2 Data Display Specifications

18.2.1 Table Outlines

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 (%)
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*

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	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*					
(units/week)					

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

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 emodepside plasma pharmacokinetic parameters

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
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_AE3

Table 14.3.3.xx Summary of treatment-emergent adverse events by severity

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	Abdominal discomfort	x (xx.x)	x (xx.x)	
	Abdominal pain	x (xx.x)	x (xx.x)	
	↓			
Nervous system disorders	Dizziness			
	Headache			
	↓			
↓	↓			

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

Source: Listing 16.2.xx

Programming notes: *Each preferred term counted only once across all severities for each subject/treatment*
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 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 summarised as <5, 5-8, >8; specific gravity summarised as <=1.005, 1.006 - 1.010, 1.011 - 1.015, 1.016 - 1.020, 1.021 - 1.025, 1.026 - 1.029, >=1.030. Continued with all treatment groups and time points. The n's sum to N but the calculated percentages exclude Not Done.*

Template T_VS1

Table 14.3.6.xx Summary of vital signs

									Change from Baseline					
Variable (units)	Treatment	Planned Relative Time	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Systolic 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										
QTcF interval	Treatment 1	Time 1										
	(N=xx)	Time 2										
		Time 3										

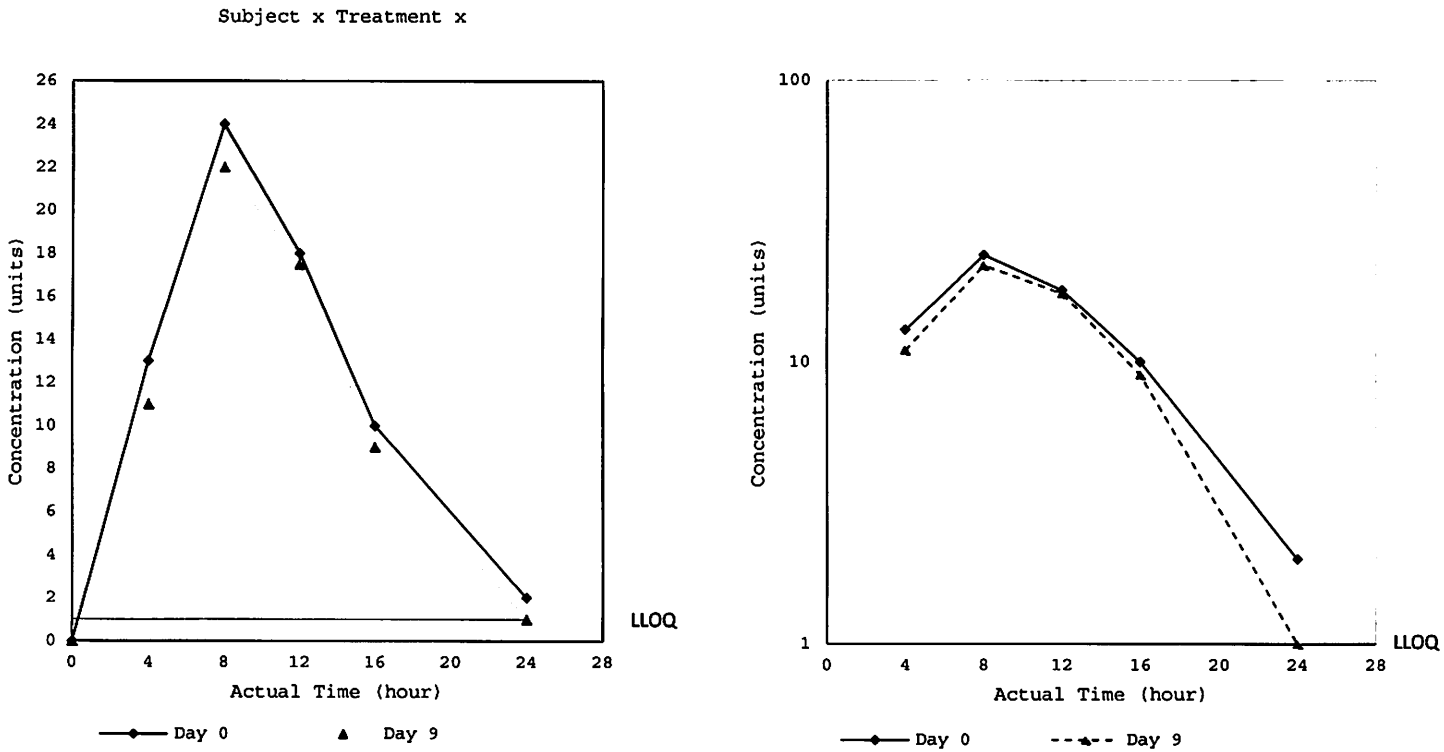
Source: Listing 16.2.xx

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

18.2.2 Figure Outlines

Template F_PK1

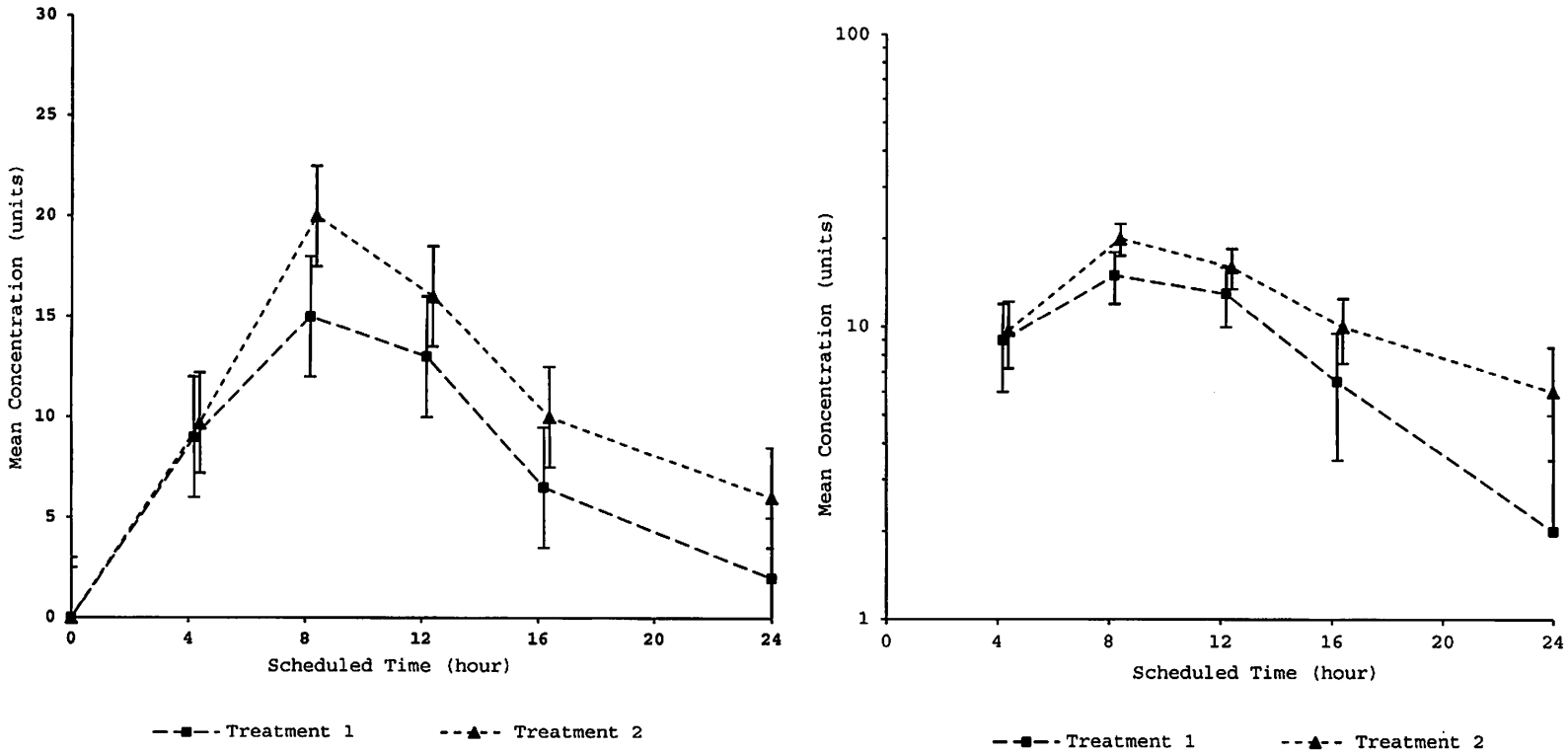
Figure 14.2.xx Individual emodepside plasma concentration-time plots (linear and semi-log)



Programming notes: *For parallel group studies with a multiple days, page by treatment and include one subject with both days on same page*

Template F_PK2

Figure 14.2.xx Geometric Mean (with Geo SD error bars) emodepside plasma concentration-time plots (linear and semi-log)

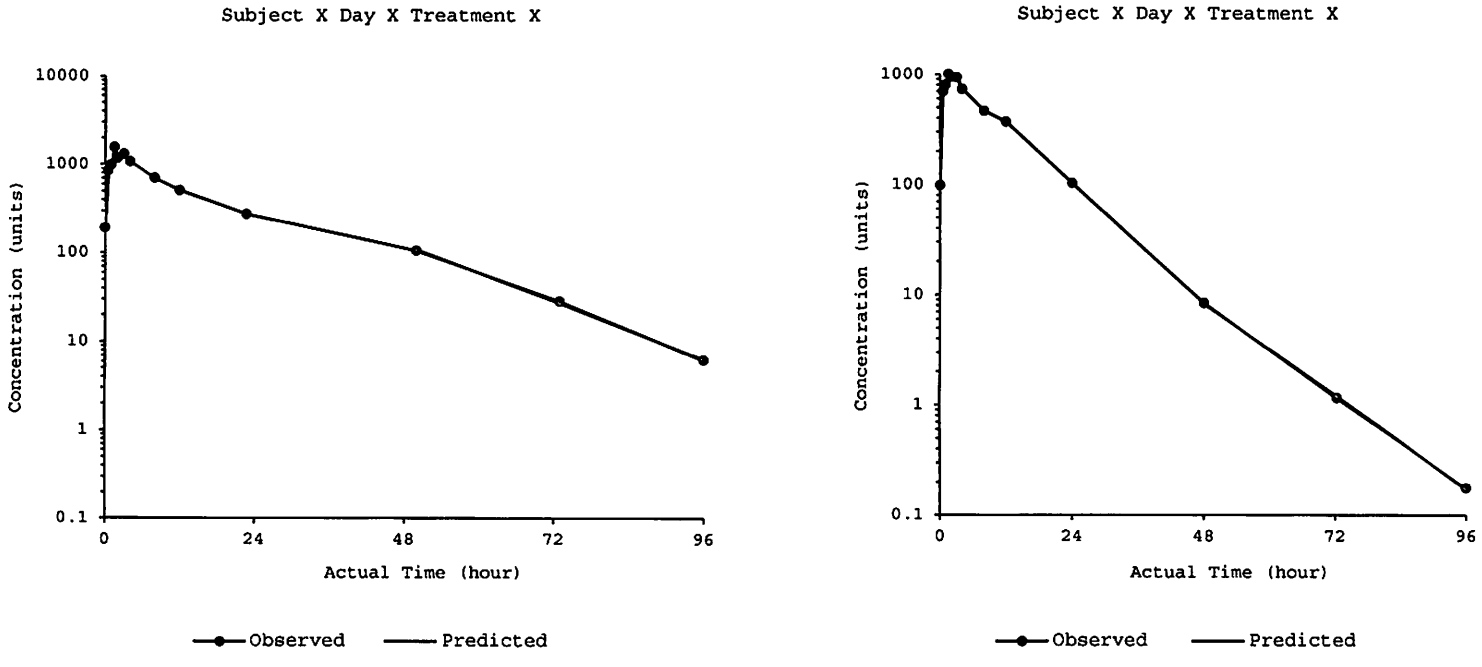


BLQ values observed post dose are imputed to half of the LLOQ. Pre dose values are imputed to zero

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

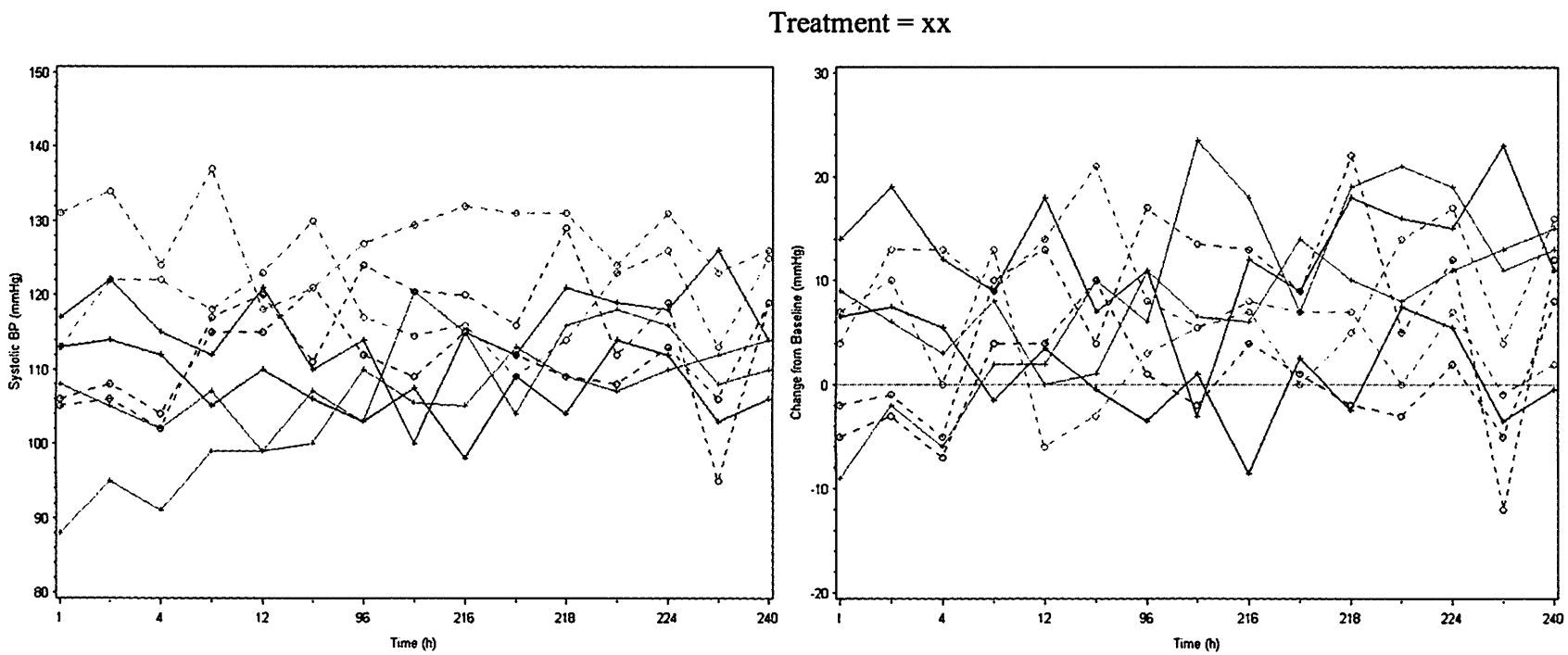
Template F_PK10

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



Template F_SAF1

Figure 14.3.1 Individual systolic blood pressure-time plots



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

18.2.3 Listing Outlines

Template L_SD1_PG

Listing 16.2.x.xx Listing of study dates

Treatment	Subject	Screening	First Dose	Final 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)	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

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 screening visit	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 screening visit

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	Duration (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 16.2.6.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 (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_PK2_PG

Listing 16.2.6.xx Listing of emodepside urine sample collections

								Cumulative amount excreted	
Treatment	Subject	{Add. time var.}	Study Day	Planned Relative Time	Start Date/ Start Time	Stop Date/ Stop Time	Conc. (units)/ Volume (units)	Amount excreted (units)	Absolute (units)	Relative to dose (%)
				Pre-dose			xxx.xx/ xxx.xx	xxx.xx		
				0-12 h			xxx.xx/ xxx.xx	xxx.xx	xxx.xx	x.xx
				12-24 h			xxx.xx/ xxx.xx	xxx.xx	xxx.xx	x.xx

Programming notes: *Planned relative time is in the form "0h to 12h" For spot samples (pre dose and follow up) only report urine concentrations and volumes.*

Template L_PK4_PG

Listing 16.2.xx Listing of derived emodepside plasma 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

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

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

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

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

Treatment	Subject	Planned Relative Time	Date/Time	Heart Rate (bpm)	PR Int. (msec)	QRS Dur. (msec)	QRS Axis (deg)	QT Int. (msec) Observed	QT Int. (msec) Change from Baseline	QTcB (msec) Observed	QTcB (msec) Change from Baseline	QTcF (msec) Observed	QTcF (msec) 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.
For ophthalmology listing replace column Site with Test.

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 v4)

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 v Planned Times

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

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

1.1.2 Missing and BQL Concentrations

No missing values will be imputed.

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

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

For urine concentrations reported as BQL it is not possible to impute a value. The amount excreted will be set to zero when concentration is BQL.

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.

$AUC_{(0-\infty)}$ values with <20% of this area extrapolated will be reported.

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.

For non-compartmental analysis uniform weighting will be applied.

If non-linear regression (i.e. compartmental) analysis is used then weighting by y^{-1} or y^{-2} should be investigated.

Justification for rule: The log transformation of the data in calculation of λ_z sufficiently deals with the heterogeneous variability of the concentration data and no further weighting is necessary.

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

A list of those parameters that will be log transformed will be given in the SAP.

In general, concentration and concentration-related quantities, rate constants and half-lives (e.g. C_{max}, AUC, $t_{1/2}$, CL/F, V_z/F and MRT) will be analysed after logarithmic transformation. Logarithmic transformations will use natural logarithms ($\log_e$).

If t_{max} is subjected to a statistical analysis, it will not be transformed and will be analysed using non-parametric methods (Cartwright et al.(1991)).

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 limit of quantification (LLOQ).

3 Parameter Definitions

3.1 Plasma Parameters

3.1.1 Single Dose

Emodepside parameters to be calculated on Day 0.

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 AUC 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	-	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}
Areas under the curve							
AUC_{12} *	Area under the plasma concentration-time curve from time zero to time 12 h	The area under the concentration-time curve from zero time (pre-dose) to time 12 h 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_{12}
AUC_{12}/Dose *	Dose-normalised AUC from time zero to 12 h	The dose-normalised AUC from time zero to 12h will be calculated as AUC_{12}/Dose Administered	(h*ng/mL)/mg	Y	-	AUCINTD	AUC_{12}/D
$AUC_{12,norm}$ *	Area under the concentration-time curve from time zero to 12h corrected by dose and body	The AUC from time zero to 12h normalised by dose and body weight will be calculated as AUC_{12}/(Dose administered*body weight)	(h*ng/mL)/(mg*kg)	Y	-	AUCINTWD	$AUC_{12,norm}$

Text Symbol	Definition	Calculation	Typical Units	Log Transform	WNL	CDISC Controlled Terminology	TFL Symbol
	weight						
AUC_{24} **	Area under the plasma concentration-time curve from time zero to time 24 h	The area under the concentration-time curve from zero time (pre-dose) to time 24 h 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_{24}
AUC_{24}/Dose **	Dose-normalised AUC from time zero to 24 h	The dose-normalised AUC from time zero to 24h will be calculated as AUC_{24}/Dose Administered	(h*ng/mL)/mg	Y	-	AUCINTD	AUC_{24}/D
$AUC_{24,norm}$ **	Area under the concentration-time curve from time zero to 24h corrected by dose and body weight	The AUC from time zero to 24h normalised by dose and body weight will be calculated as AUC_{24}/(Dose administered*body weight)	(h*ng/mL)/(mg*kg)	Y	-	AUCINTWD	$AUC_{24,norm}$
Clearance, volume of distribution and mean residence time							
V_z/F	Apparent volume of distribution during terminal phase after non-intravenous administration	Apparent volume of distribution will be calculated using the following formula: $V_z / F = \frac{Dose}{\lambda_z \bullet AUC_\infty}$	L	Y	Vz_pred (actually derives Vz_F_pred for oral dose)	VZFP	V_z/F
MRT_{last}	Mean Residence Time	The mean residence time will be calculated using: $MRT = \frac{AUMC}{AUC_\infty}$	h	Y	MRTLST_pred	MRTEVLST	MRT_{last}

* Calculated only for Cohort 3

**Calculated only for Cohorts 1 and 2

3.1.2 Multiple Dose

Emodepside parameters to be calculated on Day 9.

Text Symbol	Definition	Calculation	Typical Units	Log Transform	WNL	CDISC Controlled Terminology	TFL Symbol
Concentrations during and after multiple dosing							
C_{trough}	Trough plasma concentration	Trough plasma concentration (measured concentration at the end of a dosing interval at steady state [taken directly before next administration]) obtained directly from the concentration-time data.	ng/mL	Y	-	CTROUGH	C_{trough}
Concentrations and times (after final dose)							
$C_{max,ss}$	Maximum (peak) plasma concentration at steady state	The maximum (peak) plasma concentration will be obtained directly from the concentration-time data.	ng/mL	Y	Cmax	CMAX	$C_{max,ss}$
$C_{max,ss}$/Dose	Dose-normalised C_{max} at steady state	The dose-normalised C_{max} will be calculated as C_{max} /Dose administered	(ng/mL)/mg	Y	Cmax_D	CMAXD	$C_{max,ss}$/D
$C_{max,ss,norm}$	Observed maximum plasma concentration corrected by dose and body weight at steady state	The C_{max} normalised by dose and body weight will be calculated as C_{max}/(Dose administered*body weight)	(ng/mL)/(mg*kg)	Y	-	CMAXWD	$C_{max,ss,norm}$
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 (after final dose)							
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
$t_{½}$	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	$t_{1/2}$
$t_{½,dom}$	Dominant half-life	The dominant half-life calculated from the terminal slope of the log concentration-time (0-24h) curve, as follows:	h	Y	HL_Lambda_z	LAMZHLD	$t_{1/2,0-24}$

Text Symbol	Definition	Calculation	Typical Units	Log Transform	WNL	CDISC Controlled Terminology	TFL Symbol
		$t_{½}, dom = \frac{\log_e 2}{\lambda_z}$					
Areas under the curve (after final dose)							
AUC_{last}	Area under the plasma concentration-time curve from time zero to time of last measurable concentration	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
$AUC_{last,norm}$	Area under the concentration-time curve from time zero to time of last measurable concentration corrected by dose and body weight	The AUC from time zero to last measurable concentration normalised by dose and body weight will be calculated as AUC_{last}/(Dose administered*body weight)	(h*ng/mL)/(mg*kg)	Y	-	AUCLSTWD	$AUC_{last,norm}$
AUC_{12} *	Area under the plasma concentration-time curve from time zero to time 12 h	The area under the concentration-time curve from zero time (pre-dose) to time 12 h 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_{12}
AUC_{12}/Dose *	Dose-normalised AUC from time zero to 12 h	The dose-normalised AUC from time zero to 12h will be calculated as AUC_{12}/Dose Administered	(h*ng/mL)/mg	Y	-	AUCINTD	AUC_{12}/D
$AUC_{12,norm}$ *	Area under the concentration-time curve from time zero to 12h corrected by dose and body weight	The AUC from time zero to 12h normalised by dose and body weight will be calculated as AUC_{12}/(Dose administered*body weight)	(h*ng/mL)/(mg*kg)	Y	-	AUCINTWD	$AUC_{12,norm}$

Text Symbol	Definition	Calculation	Typical Units	Log Transform	WNL	CDISC Controlled Terminology	TFL Symbol
AUC_{24} **	Area under the plasma concentration-time curve from time zero to time 24 h	The area under the concentration-time curve from zero time (pre-dose) to time 24 h 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_{24}
AUC_{24}/Dose **	Dose-normalised AUC from time zero to 24 h	The dose-normalised AUC from time zero to 24h will be calculated as AUC_{24}/Dose Administered	(h*ng/mL)/mg	Y	-	AUCINTD	AUC_{24}/D
$AUC_{24,norm}$ **	Area under the concentration-time curve from time zero to 24h corrected by dose and body weight	The AUC from time zero to 24h normalised by dose and body weight will be calculated as AUC_{24}/(Dose administered*body weight)	(h*ng/mL)/(mg*kg)	Y	-	AUCINTWD	$AUC_{24,norm}$

Text Symbol	Definition	Calculation	Typical Units	Log Transform	WNL	CDISC Controlled Terminology	TFL Symbol
AUC_{∞}	Area under the plasma concentration-time curve from time zero to infinity	The area under the concentration-time curve will be 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: $AUC_{t-\infty} = \frac{\hat{C}_t}{\lambda_z}$ where $\hat{C}_t$ is the predicted value of the concentration at t_{last}.	h*ng/mL	Y	AUCINF_pred	AUCIFP	AUC_{inf}
AUC_{∞}/Dose	Dose-normalised AUC from time zero to infinity	The dose-normalised AUC from time zero to infinity will be calculated as AUC_{∞}/Dose Administered	(h*ng/mL)/mg	Y	-	AUCIFPD	AUC_{∞}/D
$AUC_{\infty,norm}$	Area under the concentration-time curve from time zero to infinity corrected by dose and body weight	The AUC from time zero to infinity normalised by dose and body weight will be calculated as AUC_{∞}/(Dose administered*body weight)	(h*ng/mL)/(mg*kg)	Y	-	AUCIFPWD	$AUC_{\infty,norm}$
$\%AUC_{extrap}$	Percentage of AUC_{∞} extrapolated from from t_{last} to infinity	$\%AUC_{extrap} = \frac{100 \times AUC_{t-\infty}}{AUC_{\infty}}$	%	N	AUC_%EXTRAP_pred	AUCPEP	$\%AUC_{extrap}$
Clearance, volume of distribution and mean residence time (after final dose)							
CL_{SS}/F	Apparent total clearance from plasma after oral administration	Apparent total clearance from plasma will be calculated using the following formula: $CL_{SS}/F = \frac{Dose}{AUC_{\tau}}$	L/h	Y	Clss_pred (actually derives Clss_F_pred for oral dose)	CLFTAU	CL_{SS}/F
V_z/F	Apparent volume of distribution after non-intravenous administration calculated at steady state	Apparent volume of distribution calculated at steady state will be calculated using the following formula: $V_z/F = \frac{Dose}{\lambda_z \bullet AUC_{\tau}}$	L	Y	Vz_pred (actually derives Vz_F_pred for oral dose)	VZFTAU	V_z/F

Text Symbol	Definition	Calculation	Typical Units	Log Transform	WNL	CDISC Controlled Terminology	TFL Symbol
MRT_{∞}	Mean Residence Time extrapolated to infinity	The mean residence time will be calculated using: $MRT = \frac{AUMC}{AUC_{\infty}}$	h	Y	MRTINF_pred	MRTEVIFP	MRT_{∞}
Accumulation and time invariance ratios							
$R_{ac(}AUC_{)}$	Accumulation ratio for AUC	Accumulation ratio will be calculated from AUC_{τ} at steady state and AUC_{τ} after single dose	-	N	-	ARAUC	$R_{ac(}AUC_{)}$
$R_{ac(}C_{max)}$	Accumulation ratio for C_{max}	Accumulation ratio will be calculated from C_{max} at steady state and C_{max} after single dose	-	N	-	ARCMAX	$R_{ac(}C_{max)}$

* Calculated only for Cohort 3

**Calculated only for Cohorts 1 and 2

Appendix C: Sample Page Layout

DNDi: DNDI-EMO-02 Cohorts 1 and 2 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: 16-021 Cohorts 1 and 2

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"