Statistical Analysis Plan

Clinical trial protocol title:	A phase 1, blinded, randomised, placebo-controlled, parallel-group, single-dose, dose-escalation study to investigate safety, tolerability, and pharmacokinetics of Emodepside (BAY 44-4400) after oral dosing in healthy male subjects
HMR code:	15-020 Part 2
Sponsor code:	DNDI-EMO-001 Part 2
EudraCT no:	2015-003592-29
CRO details:	Hammersmith Medicines Research Cumberland Avenue London NW10 7EW
Sponsor details:	DND*i*, Chemin Louis Dunant 15, 1202 Geneva Switzerland
Issued:	10 March 2017
Version:	1
Based on:	Protocol version 5, Final, 18 January 2017
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1 List of abbreviations

λ_z	Terminal rate constant
AE	Adverse Event
ANOVA	Analysis of variance
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under concentration-time curve
$AUC_{(0-24)}$	Area under the plasma concentration-time curve from time zero to 24h
$AUC_{(0-24)/D}$	Dose-normalised AUC from time zero to 24h
$AUC_{(0-24),norm}$	Area under the concentration-time curve from time zero to 24h corrected by dose and body weight
AUC_t	AUC from time zero to time t
$AUC_{t-\infty}$	AUC from time t to infinity
$AUC_{t,\ norm}$	AUC from time zero (pre-dose) to the time of last quantifiable concentration corrected by dose and body weight
AUC_∞	Area under the plasma drug concentration vs. time from zero to infinity
AUC_∞/D	The area under the plasma drug concentration *vs*. time curve from time zero to infinity, corrected for dose.
$AUC_{\infty,\ norm}$	The area under the concentration-time curve from time zero to infinity corrected by dose and body weight
BMI	Body Mass Index
BP	Blood pressure
BQL	Below the limit of quantification
CI	Confidence Interval
CK	Creatine kinase
CL/F	Apparent Total body clearance
C_{max}	Maximum Plasma Concentration
C_{max}/D	C_{max} corrected by dose
$C_{max,norm}$	C_{max} corrected by dose and body weight
CRF	Case Report Form
CTR	Clinical Trial Report
CV	Coefficient of Variation
CVb	Between subject CV
ECG	Electrocardiogram
GLDH	Glutamate dehydrogenase
GGT	Gamma-glutamyl transpeptidase
HbA1C	Glycated haemoglobin
HDL	High-density lipoprotein
HMR	Hammersmith Medicines Research
HR	Heart Rate
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IR	Immediate release
LDH	Lactate dehydrogemnase
LDL	Low-density lipoprotein
LSF	Liquid Service Formulation

MCH	Hemoglobin amount per red blood cell
MCHC	The amount of hemoglobin relative to the size of the cell (hemoglobin concentration) per red blood cell
MCV	Average red blood cell size
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time
N	Number of subjects
n	Number of observations used in analysis
PC	Personal Computer
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
RBC	Red blood cells
RR	Portion of the ECG between consecutive R waves, representing the ventricular rate
SAP	Statistical Analysis Plan
SD	Standard deviation
$t_{1/2}$	Terminal elimination half-life
$t_{1/2,dom}$	Dominant half-life
TEAE	Treatment-Emergent Adverse Event
T_{max}	Time to maximum plasma concentration
TSH	Thyroid-stimulating hormone
Vz/F	Apparent volume of distribution
WBC	White blood cells
WHO	World Health Organisation

2 Signatures

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

Stephen Sah
Statistician, HMR

Signature

21 Mar 2017
Date

Malcom Boyce
Principal Investigator, HMR

Signature

21 MAR 2017
Date

p/o Jean-Yves GILLON
Head Translational Sciences DNDi

Karen Dequatre Cheeseman
Clinical Project Manager
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16 March 2017
Date

Robert Don
Head of Filarial Diseases Program
DNDi

Signature

17 March 2017
Date

3 Introduction

This Statistical Analysis Plan (SAP) is based on the current trial protocol (version 5, Final 18 January 2017). Where statistical methods differ substantially between this SAP and the protocol, the differences will be identified in the SAP.

This SAP describes the datasets and the statistical methods to be used for the reporting and analysis of all data collected in Part 2 (cohorts 9 and 10), except for the 12-lead ECG continuous monitoring data which will be analysed by iCardiac Ltd (or an alternative provider), if applicable.

The randomisation code will not be broken before this SAP is finalised and signed. 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 trial report (CTR). Any deviations from this SAP will be documented in the CTR.

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 v6.3 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 (BAY 44-4400) after single oral doses administered as solution or immediate release (IR) tablets in healthy male subjects.

4.1.2 Secondary Objective(s)

- To investigate the pharmacokinetics (PK) of emodepside (BAY 44-4400), after administration as oral solution, and IR tablet (optional)
- To conduct an exploratory investigation of the relative bioavailability of the 5 mg and 20 mg IR tablet formulation using data generated in this study (optional)
- Possibility to determine the effect of food on the bioavailability of emodepside (BAY 44-4400) after single oral doses administered as solution or IR tablets.

4.2 Study Endpoint(s)

4.2.1 Safety and Tolerability Variables:

- Adverse Events (AEs).
- Physical and Neurological examination findings (including assessments of alertness, speech, language, and comprehension; cranial nerves; motor exam; coordination/cerebellar function; tremor of the hands, legs and head (postural, kinetic and rest tremor); sensation; and gait and postural stability (Pull test); mood; and sleepiness.).
- Vital signs: heart rate (HR), systolic and diastolic blood pressure (BP) in supine and sitting position (Cohort 10 only in supine), weight, body mass index (BMI; height at screening only), oral temperature.
- 12-lead ECG (HR, PR, QRS, QTcF), and for selected cohorts 12-lead ECG continuous recording (for emodepside exposure response analysis - HR, PR, QRS and QTcF).
- Clinical laboratory parameters:
  Hematology: hemoglobin, hematocrit, MCV, MCH, MCHC, platelets, reticulocytes, white blood cells (WBC) differential, red blood cells (RBC), glycated haemoglobin (HbA1C) (at screening);
  Coagulation: activated partial thromboplastin time (aPTT), prothrombin time (PT);
- Biochemistry: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), glutamate dehydrogenase (GLDH), gamma-glutamyl transpeptidase (GGT), LDH, CK, amylase, lipase, free T4 and T3, thyroid-stimulating hormone (TSH), glucose, cholesterol (high-density lipoprotein [HDL], and low-density lipoprotein [LDL], total), triglycerides, creatinine, urea, uric acid, bilirubin (total and conjugated), total protein, sodium, potassium, calcium, chloride and magnesium in serum;

- Urinalysis: by dipstick - glucose, ketone bodies, specific gravity, occult blood, pH, proteins, leucocytes, bilirubin, urobilinogen, nitrites.

- Ophthalmological assessments (Cohort 10 only)

4.2.2 Pharmacokinetic Variables:

Based on the plasma concentration time data , the following PK parameters of emodepside will be calculated.

- Main PK parameters: AUC_{∞}, AUC_{∞}/D, C_{max}, C_{max}/D, of emodepside (BAY 44-4400)
- Exploratory PK parameters: $C_{max,norm}$, T_{max}, $t_{½}$, MRT, CL/F, $AUC_{\infty,norm}$, AUC_t, $AUC_{t,norm}$, V_z/F of emodepside (BAY 44-4400)
- Other parameters: λ_z, $AUC_{t-\infty}$, points terminal

The following PK parameters of metabolites of emodepside may be calculated:
AUC_{∞}, AUC_{∞}/D, C_{max}, C_{max}/D, $C_{max,norm}$, T_{max}, $T_{½}$, $AUC_{\infty,norm}$, AUC_t, $AUC_{t,norm}$

In urine, the amount and concentration of emodepside and possibly its metabolites will be measured. The appropriate specific PK parameters to be calculated will be decided according to the concentration.

4.2.3 Pharmacodynamic Variables:

- Profiles of glucose and insulin, glucagon and cortisol (Cohort 9 only), only on Pre-Day (Day -1), Profile Day (Day 0), and Day 1.
- Single samples of prolactin and leptin, only on Pre-Day (Day -1), Profile Day (Day 0), and Day 1(Cohort 9 only).

4.3 Statistical Hypotheses

No formal statistical testing will be done.

5 Study Design

This is a single-center, blinded, randomised, placebo-controlled, parallel-group, single-dose, 2-cohort, dose-escalation, comparison study investigating safety, tolerability, and PK of

emodepside, after administration as an oral liquid service formulation (LSF) solution in healthy male subjects. Within each cohort, subjects will be randomised to receive either emodepside or placebo (n=8 per cohort; 6 assigned to emodepside and 2 assigned to placebo).

Subjects in Cohort 9 will receive 10mg solution of emodepside or matching placebo in a fed state and subjects in Cohort 10 will receive 40mg solution of emodepside in fasted state.

Table 1: Time and Events Table (Part 2, Cohort 9)

Study Procedure	Screen		In-Patient Phase[a]																										See Table [b]				Follow-Up
	Visit		Pre-Day										Profile-Day												Evaluation										
Day ± allowable deviation	-28 to -2	-2	-1										0												1	2	3	4	5	6	7					7 +3
Subject information and Informed Consent	X																																		
Medical history (including demographics and previous / concomitant medications)	X																																		
Physical examination[c]	X																																		X
Neurological examination[d]	X																																		X
Ward Admission (approx.16h)		X																																	
Urine drugs of abuse and alcohol breath test	X	X																																	
Hours [a] (pre/post drug)		**-36**	**-24***	**-23.5**	**-23**	**-22.5**	**-22**	**-21**	**-20**	**-18**	**-16**	**-12**	**0***	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**4**	**5**	**6**	**8**	**12**	**24**	**36**	**48**	**72**	**96**	**120**	**144**	**168**					
Glucose, Insulin, Glucagon, and Cortisol profiles			X		X		X		X			X	X		X		X			X				X	X										
Samples for Prolactin & Leptin			X										X												X										
Administration of emodepside[e]													X																						
12-lead safety ECG[f]	X		X[f]	X	X	X	X	X	X		X	X	X[f]	X	X	X	X		X	X			X	X	X		X	X	X	X	X	X			X
ECGs extracted from continuous recordings[g]													X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]		X[g]	X[g]	X[g]	X[g]										
Vital signs[h]	X		X[h]	X	X	X	X[h]	X	X[h]	X	X	X[h]	X[h]	X	X	X	X[h]		X	X[h]		X	X	X[h]	X[h]	X	X	X	X	X	X	X				X
Adverse event monitoring[i]	X	X	X				X		X			X	X		X		X		X	X		X	X	X	X	X	X	X	X	X	X				X
PK and metabolites[j] in plasma													X[j]	X	X[j]	X	X[j]	X	X	X[j]		X	X[j]	X[j]	X[j]	X	X[j]	X	X	X	X	X				X
PK in urine[k]													0–4[k]							4–8[k]			8–12[k]	12–24[k]										
Laboratory Safety[l,m]	X[m]		X										X												X		X	X	X	X	X	X			X
Neurological[d] examination and short physical examination[c]			X[c]				X		X			X	X				X			X				X	X	X	X								

*: In fasted subjects, all assessments at Hour –24 on Day –1 and Hour 0 on Day 0 are immediately before the administration of study drug (emodepside). In fed subjects, all assessments at Hour –24 on Day –1 and at Hour 0 on Day 0 are before the FDA breakfast. The only exception is the 12-lead ECG continuous recording (see footnote g).

[a]: Including a 10-minute supine phase before supine BP, HR, body temperature, ECG; and for 5 minutes after each nominal timepoint for ECGs extracted from continuous recording (see footnote); and also recommended before drawing blood samples. Before sitting BP assessments minimum 3-minute sitting period.

[b]: If mean half-life of emodepside in any cohort is longer than predicted, there are options to extend in-house period, or out-patient ambulatory visits up to Day 14 if necessary, from Cohort 5 onwards and in subsequent cohorts. Refer to Option 1, Option 2, and Option 3 as outlined in Table .

[c]: Height at screening only, for calculation of BMI. Weight at screening for calculation of BMI, also at -24h (Day -1) for PK calculations.

[d]: Neurological examination designed for the study, see Protocol Section 8.19.4 and Study Procedures Manual

[e]: Administration of study drug while fasting or after a high-calorie, high-fat breakfast

[f]: To include 3 repeat ECGs at these timepoints, with a time difference of about 1 minute, and single recordings at other timepoints

[g]: For selected cohorts in Part 1 (see Protocol Section 8.19.2 continuous 12-lead ECG recording will be started 1 hour before dosing and continue for 24 hours post-dosing. ECGs will be extracted at predose, at three timepoints (-60, -45, and -30 minutes for fasted subjects or -90, -75, and -60 minutes for fed subjects) and at the timepoints at which PK blood samples are drawn. Subjects will be supine for 10 minutes prior to and 5 minutes after each nominal timepoint. When ECG extraction coincide with safety ECGs, vital signs and blood draws, procedures will be performed in said order.

[h]: Vital signs to include BP (supine; plus sitting BP at the indicated timepoints[h]) and HR. Oral temperature only at screening and -24h.

[i]: Adverse Event (AE) monitoring will be throughout the study (spontaneous and solicited) to include questioning for tolerability and safety, however at these indicated timepoints will be specific questioning about AEs.

[j]: In addition to the PK sample, metabolite samples are collected only for the indicated time points [j]. As an option, at the sponsor's discretion, an additional sample of no more than 1mL may be taken at each PK timepoint from all subjects in up to 2 cohorts.

[k]: Start and end of urine collection for each bottle are indicated as hours post drug..

[l]: Hematology, Coagulation, Chemistry; Urinalysis by dip stick.

[m]: At Screening only: HIV 1, 2, Hepatitis B, C, HbA1C, in additional to hematology, coagulation, urinalysis, and chemistry.

Table 2. Follow-Up after Day 7 – Schedule Options 1, 2, or 3 Depending on Emodepside Plasma Concentrations at Day 7 in Previous Cohort(s) (from Cohort 5 onwards), Respectively.

For Screening and Days -2 through Day 8 see Table 1

OPTION 1	**Out-Patient Phase**					
Day						**Follow-Up Visit at 3 weeks (+3 days) post-dose**
	Discharge on Day 7					
Physical Examination						(see Table 1)
Neurological Examination						(see Table 1)
12-lead ECG						(see Table 1)
Vital signs[n]						(see Table 1)
Adverse event monitoring[l]						(see Table 1)
PK in plasma						(see Table 1)
Laboratory Safety[l,m]						(see Table 1)
OPTION 2	**Out-Patient Phase**					
Day	**Up to 4 visits during the period from Day 8–21 inclusive (as needed)**					**Follow-Up Visit at 3 weeks (+3 days) post-dose**
	Ambulatory Evaluation Visits, Scheduled As Needed					
Physical Examination						(see Table 1)
Neurological Examination						(see Table 1)
12-lead ECG						(see Table 1)
Vital signs[n]						(see Table 1)
Adverse event monitoring[l]	X		X	X	X	(see Table 1)
PK in plasma	X		X	X	X	(see Table 1)
Laboratory Safety[l,m]	X		X	X	X	(see Table 1)
OPTION 3	**Discharge from Ward on Day X**					
Day	**8 (±1)** (as needed)		**10 (±1)** (as needed)	**12 (±2)** (as needed)	**14 (±2)** (max.)	**Follow-Up Visit at 3 weeks (+3 days) post-dose**
	Prolonged In-House Evaluation Phase with Discharge from Ward on Day X (8-14)					
Physical Examination						(see Table 1)
Neurological Examination						(see Table 1)
12-lead ECG						(see Table 1)
Vital signs[n]						(see Table 1)
Adverse event monitoring[l]	X		X	X	X	(see Table 1)
PK in plasma	X		X	X	X	(see Table 1)
Laboratory Safety[l,m]	X		X	X	X	(see Table 1)

Table 3. Schedule of Events (Part 2, Cohort 10)

Study Procedure	Screening Visits			In-Patient Phase[a]																												Out-patient phase			Follow-Up
	1	2		Pre-Day										Profile-Day											Evaluation										
Day ± allowable deviation	-28 to -2	-7 to –1	-2	-1										0											1		2	3	4	5	6	7	10 ±1	14 ±2	18 ±2	21 +3
Subject information and Informed Consent	X																																		
Medical history (including demographics, previous/concomitant medications)	X																																		
Physical examination[b]	X																																		X
Neurological examination[c]	X																																		X
Colour blindness test[d]	X																																		
Ophthalmology exam[e]		X																																	
Ward Admission (approx.16h)			X																																
Urine drugs of abuse and alcohol breath test	X		X																																
Hours[a] (pre/post drug)			**-36**	**-24***	**-23.5**	**-23**	**-22.5**	**-22**	**-21**	**-20**	**-18**	**-16**	**-12**	**0***	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**4**	**5**	**6**	**8**	**12**	**24**	**36**	**48**	**72**	**96**	**120**	**144**	**168**				
Glucose and Insulin profiles				X		X							X	X		X									X	X									
Administration of emodepside[f]														X																					
12-lead safety ECG	X			X[g]		X							X	X[g]		X									X	X		X	X	X	X	X	X			X
Vital signs[h]	X			X	X	X						X	X	X	X	X								X	X	X	X	X	X	X	X	X	X			X
Adverse event monitoring[i]	X		X	X				X		X			X	X		X		X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK in plasma[j]														X	X	X				(X)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Safety[k,l]	X[l]			X										X												X		X	X	X	X	X	X	X	X	X	X
Neurological[c] examination and short physical examination[b]				X[b]		X							X	X		X									X	X	X	X								
Travel and stay at ophthalmology clinic																	X	X	X	X	X	X														
Ophthalmology exam[m]																			X																	

* All assessments at Hour 0 on Day 0 are immediately before the administration of study drug (emodepside), and assessments at Hour –24 on Day –1 will be time-matched to Profile Day

(dosing Day)

[a] Including a 10-minute supine phase before supine BP, HR, body temperature, ECG; and also recommended before drawing blood samples.

[b] Height at screening only, for calculation of BMI. Weight at screening for calculation of BMI, also at -24h (Day -1) for PK calculations.

[c] Neurological examination designed for the study, see Protocol Section 8.19.4 and Study Procedures Manual.

[d] Colour blindness to be determined at Screening visit 1.

[e] If subjects are eligible for study entry based on Screening visit 1 assessments, they will be asked to undergo an ophthalmology exam (Screening visit 2) within a week before Profile Day or on Pre−Day at the latest. All assessments for Screening Visit 1 will be performed prior to Screening Visit 2, but visits can be combined if necessary.

[f] Administration of study drug is in the fasted-state only.

[g] To include 3 repeat ECGs at these timepoints, with a time difference of about 1 minute, and single recordings at other timepoints.

[h] Vital signs to include supine BP and HR. Oral temperature only at screening and -24h.

[i] Adverse Event (AE) monitoring will be throughout the study (spontaneous and solicited) to include questioning for tolerability and safety, however at these indicated timepoints will be specific questioning about AEs.

[j] Timepoint shown as (X) indicates sample will be taken off-site whilst at the ophthalmology clinic. As an option, at the sponsor's discretion, an additional sample of no more than 1 mL may be taken at each PK timepoint from all subjects in up to 3 cohorts.

[k] Hematology, Coagulation, Chemistry; Urinalysis by dip stick.

[l] At Screening only: HIV 1, 2, Hepatitis B, C, HbA1C, in additional to hematology, coagulation, urinalysis, and chemistry.

[m] Ophthalmology exams will be performed on Profile-Day (Day 0) approximately 2-2.5 h post-dose. If deemed necessary by the ophthalmologist additional ophthalmology follow-up visit(s) may be scheduled for eye-related AEs.

6 Planned Analyses

6.1 Interim Analyses

No interim analyses are planned. However, the blinded safety and PK data will be reviewed after Cohort 9.

6.1.1 Persons responsible for analysis

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

6.2 Final Analysis

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

6.2.1 Persons responsible for analysis

Stephen Sah (HMR)	Statistician
Nick Jackson (HMR)	SAS Programmer
Bhavini Ladwa (HMR)	Data Manager

7 Sample Size Considerations

7.1 Sample Size Assumptions

No formal sample size calculations have been performed as this is an exploratory study. A sample size of 8 per cohort will be considered sufficient to examine the safety and tolerability of emodepside as well as the PK after single oral administration of the investigational drug. For evaluation, a minimum number of 6 evaluable subjects per cohort is required.

8 Analysis Populations

The following population sets 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 has been 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 received, regardless of the treatment to which they were randomised.

The primary endpoint will be analysed using the safety population.

8.1 Analysis Datasets

All analysis datasets will be based on observed data, except as outlined in Section 10.2.

9 Treatment Comparisons

The treatment comparison of interest is active (emodepside) versus placebo.

9.1 Data Display Treatment and Other Subgroup Descriptors

The sort order for treatment groups will be placebo, then study treatment in ascending dose order.
Listings of data will be sorted and displayed by treatment group, subject number, and also by date and time if applicable.

All subjects in cohorts 9 and 10 receiving the same formulation of placebo will be combined to form a pooled placebo group.

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

Treatment Groups	Short Description
Placebo [solution](Fed)	PLA [sol](Fed)
Placebo [solution](Fasted)	PLA [sol](Fasted)
Emodepside (xx mg) [solution](Fed)	xx mg [sol](Fed)
Emodepside (xx mg) [solution](Fasted)	xx mg [sol](Fasting)

9.1.1 Conventions for Summary Statistics and Data Displays

The minimum set of summary statistics for numeric variables will be: n, mean, standard deviation (or standard error), 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). 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.

Placebo subjects will be pooled across cohorts 9 and 10 taking into account formulation and fed/fasted status.

10 Data Handling Conventions

10.1 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 10.2.

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.

10.2 Derived and Transformed Data

For ECGs, vital signs, glucose, insulin, glucagon, cortisol and neurological examinations recorded on Day -1 the baseline will be the -24 h value and for Day 0 the baseline will be the pre-dose value on Day 0. The AUC_{0-24} for change from baseline in glucose, insulin, glucagon and cortisol will be calculated on Day -1 and Day 0, using the linear-linear trapezoidal method. For prolactin and leptin the baseline will be pre-dose on Day 0.

Laboratory data will be reported in standard units. The baseline will be the latest value recorded pre-dosing on Day 0. Out-of-range laboratory tests may be repeated. If a test is out-of-range at a baseline timepoint 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 made at some timepoints on Day -1 and Day 0, the mean of the three measurements for each subject will be used at each timepoint.

The pharmacokinetic parameters to be derived are given in Appendix B

10.3 Assessment Windows

No assessment windows are defined for this report.

10.4 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) 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	40–100 beats/min
Respiration rate	8–20 per min
Oral temperature	35.5–37.8°C

QTcB or QTcF > 450 msec and increases in QTcB or QTcF from baseline of > 30 msec will be considered to be potentially clinically important.

11 Study Population

11.1 Disposition of Subjects

The disposition of all subjects in the safety population will be summarised including: number of subjects randomised; number completing the study (i.e. not withdrawn), by treatment; and number discontinued (withdrawn) from the study. The number of subjects in each analysis population will be summarised 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.

11.2 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 and time.

- Had their treatment assignment unblinded.

In addition, subjects with minor time deviations (measurements taken outside the allowable windows given in the protocol) will be identified.

11.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics (e.g. physical examination, neurological 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 2016 of the WHO Drug dictionary.

11.4 Treatment Compliance

Dates and times of dosing will be listed.

12 Safety Analyses

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

12.1 Extent of Exposure

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

12.2 Adverse Events

Adverse events will be coded using the version of the Medical Dictionary for Regulatory Activities (MedDRA) (version 20.0).

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 and preferred term. 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 subjects with adverse events will be summarised by actual treatment:

- TEAEs by system organ class and preferred term
- Drug-related ("related" as recorded by the Investigator) TEAEs by system organ class and preferred term

Subjects with more than one TEAE will be counted only once, at the greatest severity or causal relationship, for each 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.

12.3 Deaths and Serious Adverse Events

Adverse events leading to deaths and serious adverse events will be listed separately (fatal events will be listed separately from non-fatal events).

12.4 Adverse Events Leading to Withdrawal from the Study

Adverse events leading to withdrawal will be listed separately.

12.5 Clinical Laboratory Evaluations

Haematology, clinical chemistry and urinalysis evaluation at each planned assessment, and change from baseline at each planned post-baseline assessment, will be summarised by actual 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.

12.6 Other Safety Measures

12.6.1 Vital signs

Vital signs evaluation at each planned assessment, and change in vital signs baseline at each planned post-baseline assessment, will be summarised by actual treatment. Individual subject profiles will be plotted for each vital sign parameter (Blood Pressure and Heart Rate).

Vital signs data of potential clinical importance will be listed separately.

12.6.2 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 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.

12.6.3 Neurological examination

Neurological examination results will be summarised and normal and abnormal neurological examination findings will be listed in detail according to the CRF. Total scores from neurological questionnaires at each planned assessment, and change from baseline at each planned post-baseline assessment, will be summarised by actual treatment.
Total scores from neurological questionnaires will also be listed.

12.6.4 Physical examination

Physical examination results will be summarised and abnormal physical examination findings will be listed.

12.6.5 Ophthalmology assessments

Ophthalmology assessments results will be summarised and listed by time point.

13 Pharmacokinetic Analyses

Analytical Services International Ltd, London, U.K. will measure the plasma and urine 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 6.3.

In addition, the plasma and urine concentration of emodepside metabolite(s) may be measured. If and when these data become available a SAP amendment will be written to specify their reporting (if applicable).

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 transformed parameters, the primary measure of central tendency will be the geometric mean[4]; for untransformed 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

13.1 Plasma PK

13.1.1 Pharmacokinetic Concentration Data

The plasma concentrations of emodepside and metabolites (if applicable) will be listed and summarised by treatment. Means at any time will only be calculated if at least 2/3rds of the individual data points are above the lower limit of quantification.

Individual and mean plasma concentration–time profiles will be presented graphically.

13.1.2 Pharmacokinetic Parameters

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

To assess the effect of food, analysis of variance (ANOVA) models will be fitted to the fed (Part 2, Cohort 9) solution and relevant fasted (Part 1, Cohort 5) solution data with the logarithm of the pharmacokinetic parameters AUC_{0-24} as the dependent variable, and formulation as a fixed effect. The estimated least square means and residual variance from the model will be used to construct 90% CIs for the difference in means on the log scale for the comparison of fed versus fasted solutions.

13.2 Urinary PK

If concentrations of emodespide in urine are determined, the amount of emodespide excreted in the urine will be estimated. The data will be listed and summarised by treatment.

14 Pharmacodynamic Analyses

Summaries and listings will use the safety population.
Pharmacodynamic variables (glucose, insulin, glucagon, cortisol, prolactin and leptin) at each planned assessment, and change from baseline at each planned post-baseline assessment, will be summarised by actual treatment.
In addition, for glucose and insulin (Cohorts 9 and 10), glucagon and cortisol (Cohort 9):

- Individual subject profiles will be plotted
- The difference between change from baseline on Day 0 and Day -1 will be summarised at each planned post-baseline assessment by actual treatment
- The AUC_{0-24} of change from baseline will be summarised for each day and treatment

Individual Insulin and PK Concentration Plots, including Related Significantly Important AE Durations will be produced.

For calculation of pharmacodynamics parameters, summary statistics and individual profile plots, values below the quantifiable limit of the assay will be substituted by one half of the lower limit of quantification.

15 Changes from the Protocol Specified Statistical Analysis

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

1) The definition of treatment-emergent adverse event has been updated from "an AE will be considered as treatment emergent if it appeared after the first dosing, or if appeared before dosing and worsened after dosing" to:

   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].

2) The AUC_{0-24} of change from baseline for glucose, insulin, glucagon and cortisol will be summarised for each day and treatment

3) The following emodepside parameters have been added to those mentioned in the protocol:

   Main PK parameters: AUC_{0-24} and AUC_{0-24}/D

   Exploratory PK parameters: $AUC_{0-24,norm}$,$t_{1/2,dom}$

4) The following analyses have been added for glucose, insulin, glucagon and cortisol:

   The difference between change from baseline on Day 0 and Day -1 will be summarised at each planned post-baseline assessment by actual treatment

   The AUC_{0-24} of change from baseline will be summarised for each day and treatment

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.

5. FL140 HMR Laboratory alert and delta ranges ver 3 (HMR Lab form).

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 B for Part 2, e.g., 14.1B

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

The following tables and figures will be produced (templates provided in Sections 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			
14.2.1.1	Summary of Emodepside Plasma Pharmacokinetic Concentration-Time Data (ng/mL)	PK	16.2.6.1.1	T_PK1
14.2.1.2	Summary of Derived Emodepside Plasma Pharmacokinetic Parameters	PK	16.2.6.1.2	T_PK3
14.2.1.3	Summary of Log-Transformed Derived Emodepside Plasma Pharmacokinetic Parameters	PK	16.2.6.1.2	T_PK4
14.2.1.4	Assessment of the Effect of Food on the PK of Emodepside	PK	16.2.6.1.2	T_PK7
14.2.2	Summary of Derived Emodepside Urine Pharmacokinetic Parameters	PK	16.2.6.2	T_PK3
14.2.3.1	Summary of Glucose	Safety	16.2.6.3	T_PD1
14.2.3.2	Summary of Difference Between Day -1 and Day 0 in Glucose	Safety	16.2.6.3	T_PD2
14.2.3.3	Summary of AUC_{0-24} for Change from Baseline in Glucose	Safety	16.2.6.4	T_PD3
14.2.4.1	Summary of Insulin	Safety	16.2.6.3	T_PD1
14.2.4.2	Summary of Difference Between Day -1 and Day 0 in Insulin	Safety	16.2.6.3	T_PD2
14.2.4.3	Summary of AUC_{0-24} for Change from Baseline in Insulin	Safety	16.2.6.3	T_PD3
14.2.5.1	Summary of Glucagon	Safety	16.2.6.3	T_PD1
14.2.5.2	Summary of Difference Between Day -1 and Day 0 in Glucagon	Safety	16.2.6.3	T_PD2
14.2.5.3	Summary of AUC_{0-24} for Change from Baseline in Glucagon	Safety	16.2.6.3	T_PD3

Table	Description	Population	Source Listing	Template (Shells below)
14.2.6.1	Summary of Cortisol	Safety	16.2.6.3	T_PD1
14.2.6.2	Summary of Difference Between Day -1 and Day 0 in Cortisol	Safety	16.2.6.3	T_PD2
14.2.6.3	Summary of AUC_{0-24} for Change from Baseline in Cortisol	Safety	16.2.6.3	T_PD3
14.2.7	Summary of Prolactin	Safety	16.2.6.3	T_PD1
14.2.8	Summary of Leptin	Safety	16.2.6.3	T_PD1
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 Grade	Safety	16.2.7.1	T_AE1
14.3.1.4	Summary of Drug Related Treatment-Emergent Adverse Events by Severity Grade	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 Urinalysis Dipstick Results	Safety	16.2.8.5	T_UR1
14.3.6.1	Summary of Vital Signs	Safety	16.4	T_VS1
14.3.6.2	Summary of AUC0-24 for Change from Baseline in Supine Diastolic Blood Pressure (h*mmHg)	Safety	16.4	T_VS2
14.3.6.3	Summary of AUC0-24 for Change from Baseline in Supine Systolic Blood Pressure (h*mmHg)	Safety	16.4	T_VS2
14.3.6.4	Summary of AUC0-24 for Change from Baseline in Supine	Safety	16.4	T_VS2

Table	Description	Population	Source Listing	Template (Shells below)
	Heart Rate (h*beats/min)			
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	16.4	T_EG3
14.3.8.1	Summary of Neurological Examination Data	Safety	16.2.9.5	T_NE1
14.3.8.2	Summary of Neurological Examination Questionnaire Data	Safety	16.2.9.6	T_LB2
14.3.9	Summary of Physical Examination Data	Safety	16.2.9.4	T_PE1
14.3.10	Summary of Ophthalmological Examination Data	Safety	16.2.9.7	T_NE1

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	16.2.6.1.1	F_PK1
14.2.1.2	Geometric mean (+/- SD) Emodepside Plasma Concentration-Time Plots (Linear and Semi-log)	PK	16.2.6.1.1	F_PK2
14.2.2.1	Individual Glucose-Time Plots	PD	16.2.6.3	F_PD1
14.2.2.2	Individual Glucose and PK Concentration Plots - Including Related Significantly Important AE Durations	PD	16.2.6.3, 16.2.6.1.1, 16.2.7.1	F_PD2
14.2.3.1	Individual Insulin-Time Plots	PD	16.2.6.3	F_PD1
14.2.3.2	Individual Insulin-Time Plots 0-12h	PD	16.2.6.3	F_PD1
14.2.3.3	Individual Insulin and PK Concentration Plots - Including Related Significantly Important AE Durations	PD	16.2.6.3, 16.2.6.1.1, 16.2.7.1	F_PD2
14.2.4	Individual Glucagon-Time Plots	PD	16.2.6.3	F_PD1
14.2.5	Individual Cortisol-Time Plots	PD	16.2.6.3	F_PD1
14.3	SAFETY DATA			
14.3.1.1	Individual Systolic Blood Pressure-Time Plots	Safety	16.2.9.1	F_PD1
14.3.1.2	Individual Diastolic Blood Pressure-Time Plots	Safety	16.2.9.1	F_PD1
14.3.2	Individual Heart Rate-Time Plots	Safety	16.2.9.1	F_PD1

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

Listing	Description	Template (Shells below)
16.2.1	Study dates & disposition of subjects	
16.2.1.1	Listing of Study Dates	L_SD1_PG
16.2.1.2	Listing of Reasons for Withdrawal	L_SD2_PG
16.2.2	Protocol deviations	
16.2.2.1	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	L_DV1_PG
16.2.2.2	Listing of Subjects with Time Deviations	L_TD1_PG
16.2.2.3	Listing of Subjects with Other Protocol Deviations	L_DV2_PG
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	Individual Emodepside Plasma Concentration-Time Plots (log scale) for Estimation of λz, with Regression Line	F_PK10
16.2.6.2	Listing of Emodepside Urine Excretion Rate Data	L_PK3_PG
16.2.6.3	Listing of PD concentration-Time Data	L_PK1_PG
16.2.6.4	Listing of Derived AUC0-24 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 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
16.2.9	Vital signs, ECG variables, neurological, physical findings and Ophthalmological Assessment	
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 Neurological Examination Findings	L_NE1_PG
16.2.9.6	Listing of Neurological Questionnaire Findings	L_NE2_PG
16.2.9.7	Listing of Ophthalmological Examination Data	L_NE1_PG

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	Treatment 2	Etc	All Subjects
Safety Population	Randomised					
	Completed					
	Withdrawn					
		Death				
		Adverse Events				
		Withdrawal by subject				
		Physician decision				
		Protocol violation				
		Study terminated by Sponsor				
		Lost to follow-up				
		Other				
PK Concentration	Included					
PK Parameter	Included					

Source: Listing 16.2.xx

Programming notes: Continued with all treatment groups and column for "All emodepside"
This table will contain one column for placebo, each dose/formulation, all active and all subjects.

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				
	Min				
	Median				
	Max				
Sex	N				
	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				
	Min				
	Median				
	Max				
Weight (kg)	n				
	Mean				
	SD				

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

*includes only those subjects who drink alcohol or smoke

Source: Listing 16.2.xx

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

Template T_AE1

Table 14.3.3.xx Summary of Treatment-Emergent Adverse Events

		Treatment 1 (N=xx)		Treatment 2 (N=xx)		Etc
System Organ Class	Preferred Term	n	%	n	%	
Number of subjects with AEs						
Gastrointestinal disorders	Total number of subjects					
	Abdominal discomfort					
	Abdominal pain					
	↓					
Nervous system disorders	Total number of subjects					
	Dizziness					
	Headache					
	↓					
↓	↓					

*Subjects with ≥1 adverse event are counted only once per system organ class and preferred term.

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.
For tables by severity a sub-heading will be added to each table page

Template T_LB1

Table 14.3.4.xx Summary of Laboratory Values of Potential Clinical Importance

Lab Test	Treatment	Planned Relative Time	n	Double Flags HI	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*

Template T_LB2

Table 14.3.3.2 Summary of Chemistry Laboratory Values

											Change from Baseline					
Laboratory Test (units)	Treatment	Planned Relative Time	n	Mean	95% CI	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
	Treatment 1 (N=xx)	-20h													

Source: Listing 16.2.xx

Note: Baseline on Day -1 is -24h value, baseline on Day 0 is Day 0, pre-dose

Programming notes: *Continued with all treatments and time points.*
For the summary of neurological questionnaires the first column will be headed "Questionnaire (Total Score)" and the footnote will be removed

Template T_UR1

Table 14.3.3.4 Summary of Urinalysis Dipstick Results

Planned Relative Time	Result	Treatment 1 (N=xx) n	%	Treatment 2 (N=xx) n	%
Time 1	Positive				
	Negative				
	No Result				
	Not Done				
Time 2	Positive				
	Negative				
	No Result				
	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

Template T_VS1

Table 14.3.4 Summary of Vital Signs

									Change from Baseline					
	Treatment	Planned Relative Time	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Systolic BP (mmHg)	Treatment 1 (N=xx)	-20h												

Source: Listing 16.2.xx

Note: Baseline on Day -1 is -24h value, baseline on Day 0 is Day 0, pre-dose

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

Template T_VS2

Table 14.3.4 Summary of AUC0-24 for Change from Baseline in Supine Diastolic Blood Pressure (h*mmHg)

	Day -1					Day 0					Day 0 - Day -1			
Treatment	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max	N	Mean	SD	95% CI (Lower, Upper)
Treatment 1 (N=xx)														

Source: Listing 16.2.xx

Difference is change from mean baseline

Programming notes: *Continued with all treatments*

Template T_EG2

Table 14.3.5.1 Summary of ECG Values

									Change from Baseline					
Variable	Treatment	Planned Relative Time	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Heart Rate (bpm)	Treatment 1 (N=xx)	-20h												
		-21h												
		-23h												
	Treatment 2 (N=xx)	-20h												
		-21h												
		-23h												
PR Interval (msec)	Treatment 1 (N=xx)	-20h												
		-21h												
		-23h												
	Treatment 2 (N=xx)	-20h												
		-21h												
		-23h												

Source: Listing 16.2.xx

Note: Baseline on Day -1 is -24h value, baseline on Day 0 is Day 0, pre-dose

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 n	%	481, – 500 msec n	n	> 500 msec n	%	31-60 msec Increase n	%	>60 msec Increase n	%
QT interval	Treatment 1	1h										
	(N=xx)	2h										
		3h										
	Treatment 2	1h										
	(N=xx)	2h										
		3h										
QTcB interval	Treatment 1	1h										
	(N=xx)	2h										
		3h										
	Treatment 2	1h										
	(N=xx)	2h										
		3h										

Source: Listing 16.2.xx

Note: Baseline on Day -1 is -24h value, baseline on Day 0 is Day 0, pre-dose

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

Template T_PE1

Table 14.3.8.xx Summary of Physical Examination Data

Body System	Planned Relative Time	Result	Treatment 1 (N=xx)	Treatment 2 (N=xx)
General Appearance	Time 1	Normal	n (%)	
		Abnormal NCS	x (xx)	
		Abnormal CS		
	Time 2	Normal		
		Abnormal NCS		
		Abnormal CS		
HEENT	Time 1	Normal		
		Abnormal NCS		
		Abnormal CS		
	Time 2	Normal		
		Abnormal NCS		
		Abnormal CS		

Source: Listing 16.2.xx

Programming notes: *Continued with all body system, treatments and time points. Include rows for each outcome in CRF*
If results are missing "missing" row will be added. Percentages calculated using the number of available results as denominator.

Template T_NE1

Table 14.3.8.xx Summary of Neurological Examination Data

Mental Status

Body System	Planned Relative Time	Result	Treatment 1 (N=xx) n (%)	Treatment 2 (N=xx) n (%)
Alertness	Time 1	Normal	x (xx)	
		Abnormal NCS	x (xx)	
		Abnormal CS		
	Time 2	Normal		
		Abnormal NCS		
		Abnormal CS		
Speech	Time 1	Normal		
		Abnormal NCS		
		Abnormal CS		
	Time 2	Normal		
		Abnormal NCS		
		Abnormal CS		

Source: Listing 16.2.xx

Programming notes: *Continued with all examinations/test, treatments and time points. Include rows for each outcome in CRF*
For Ophthalmological assessment, replace body system with Test
If results are missing "missing" row will be added. Percentages calculated using the number of available results as denominator.
Use PESCAT as subheading (not for Ophthalmological Assessment).

Template T_PK1

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

Treatment	N	Planned Relative Time	n	No. Imputed	Mean	95% CI	SD	%CV	Median	Min	Max
Dose 1		1h									
Dose 2											

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	n	Mean	95% CI	SD	%CV	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	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_PK7

Table 14.2.xx Assessment of the Effects of Food on the PK of Emodepside

		LS Means			
Parameter	Treatment	Fed	Fasted	Ratio (Fed/Fasted)	90% CI
Cmax (Units)		xxxx.xx	xxxx.xx	xxxx.xx	(xxxx.xx, xxxx.xx)

Source: Listing 16.2.xx

Programming notes: *Continued with* AUC_{inf}

Template T_PD1

Table 14…xx Summary of Glucose

									Change from Baseline					
Treatment	Planned Relative Time	n	Mean	95% CI	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Treatment 1 (N=xx)	-24h	x	x	x	x	x	x	x						
	-20h	x	x	x	x	x	x	x	x	x	x	x	x	x

Note: Baseline on Day -1 is -24h value, baseline on Day 0 is Day 0, pre-dose

Programming notes: *Continued with all PD parameters, treatments and timepoints*
Change from baseline calculated from "pre-dose" on each day

Template T_PD2

Table 14…xx Summary of Difference Between Day -1 and Day 0 in Glucose

	Planned Relative Time	Day -1 – Day 0			
Treatment		n	Mean	SD	95% CI
Treatment 1 (N=xx)					

Note: Difference is change from baseline

Programming notes: *Continued with time points and treatments*

Template T_PD3

Table 14…xx Summary of AUC_{0-24} for change from baseline in Glucose (units)

	Day -1					Day 0					Day -1 – Day 0			
Treatment	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max	n	Mean	SD	95% CI
Treatment 1 (N=xx)														

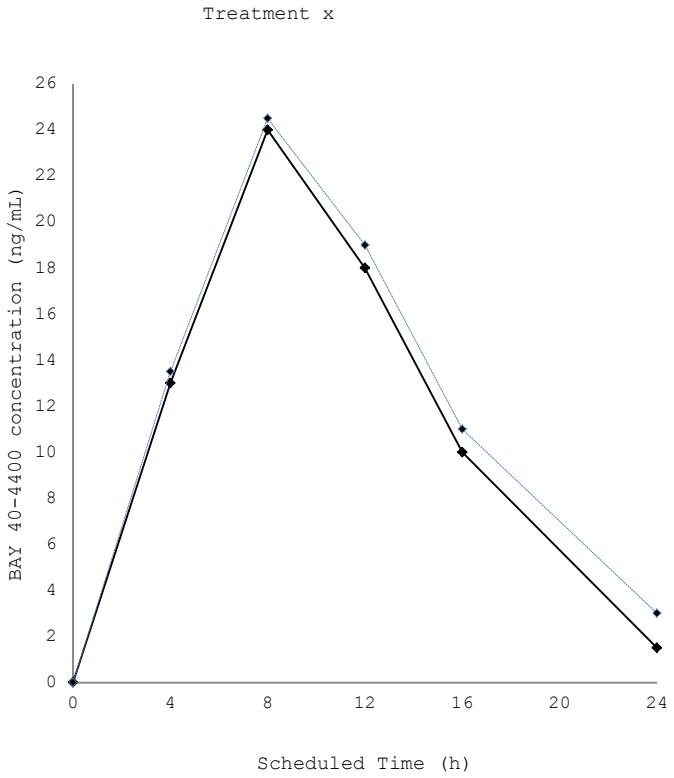
Note: Difference is change from baseline

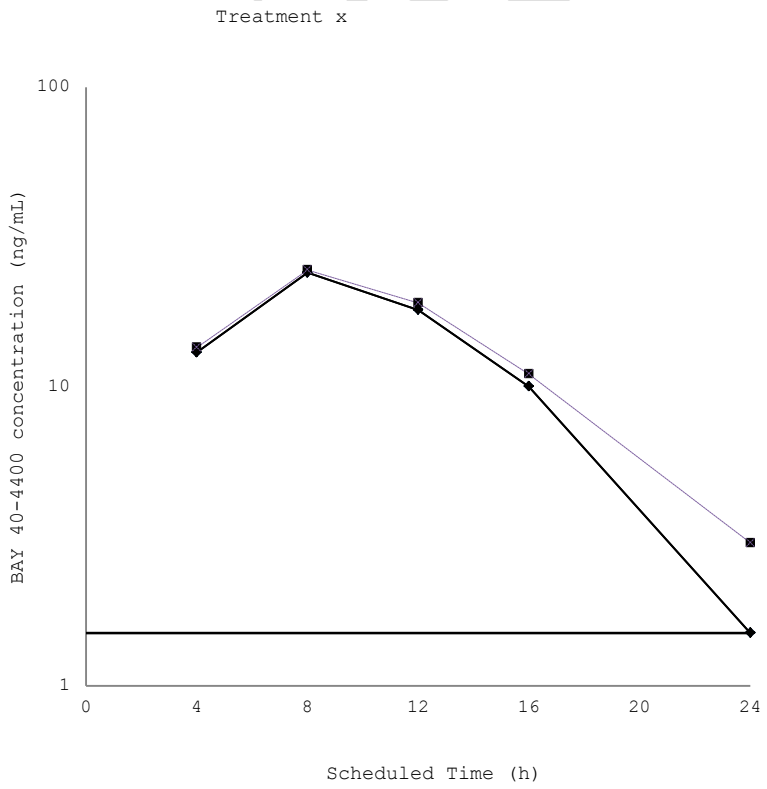
Programming notes: Continued with all treatments

17.2.2 Figure Outlines

Template F_PK1

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

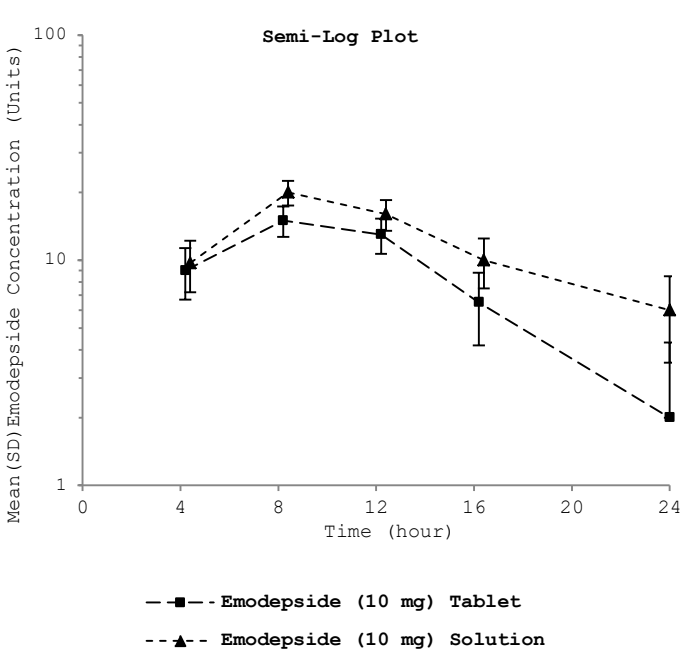


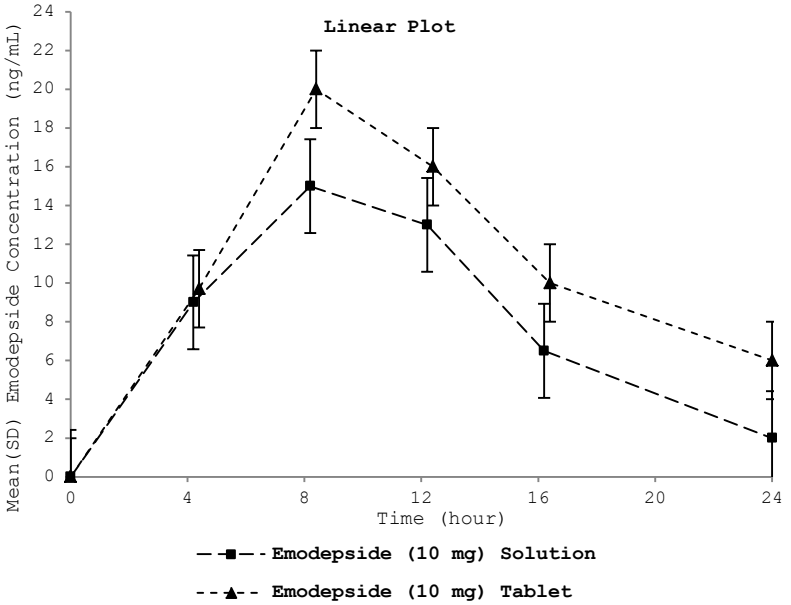


Programming note: Plot will include all subjects for a given treatment group

Template F_PK2

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

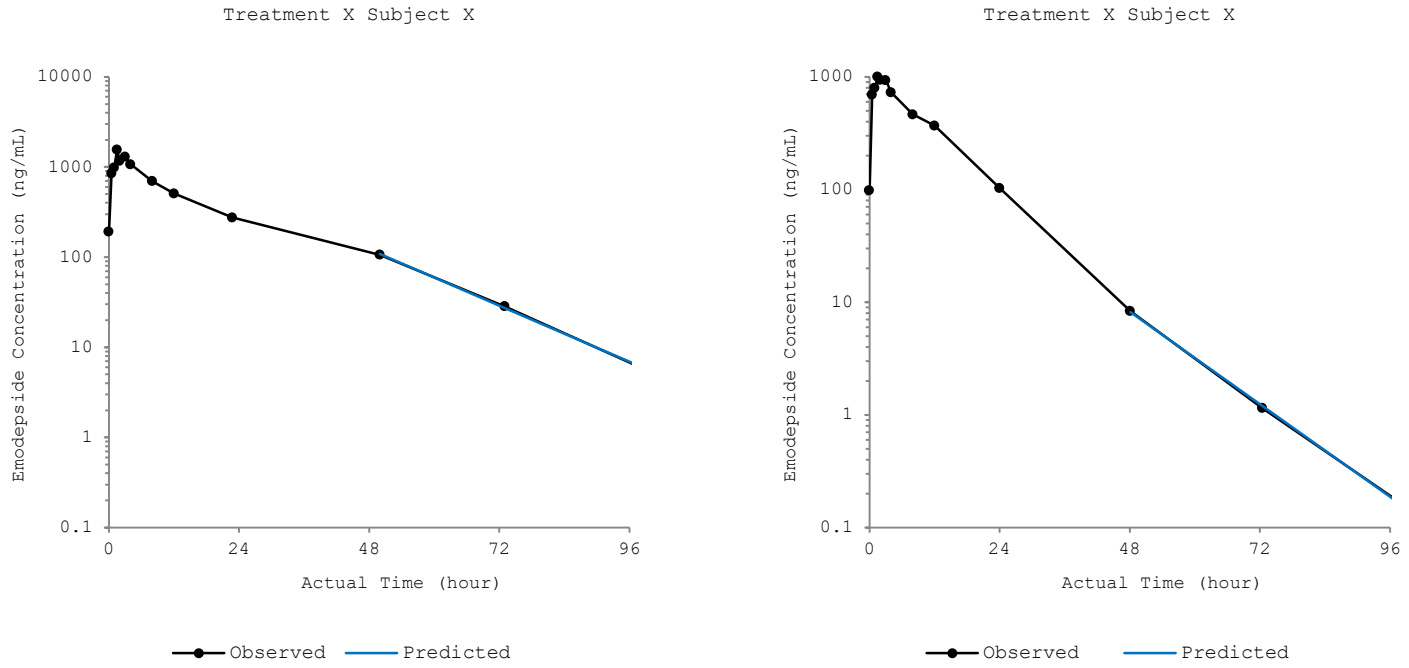




Programming note: The SD is the geometric standard deviations

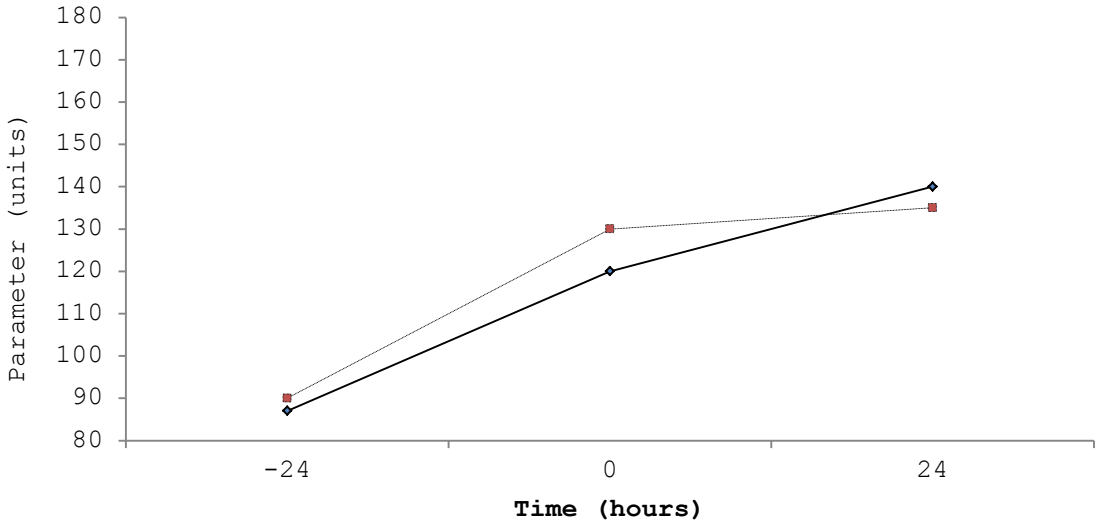
Template F_PK10

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



Template F_PD1

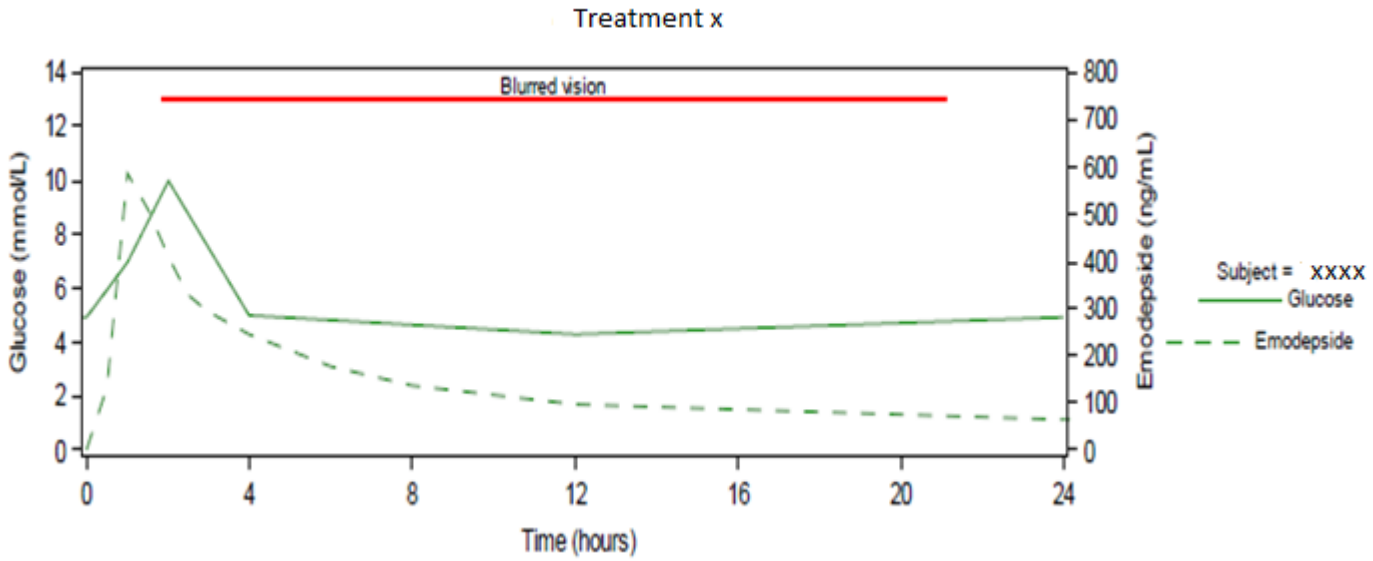
Figure **16.2.**xx Individual Glucose-Time Plots



Programming note: Continue with Insulin, Glucagon and Cortisol land normal rages as reference lines.
For Blood pressure and Heart Rate, include PCI limits as reference lines.
Plot will include all subjects for a given treatment group
4 plots per page

Template F_PD2

Figure **16.2.**xx Individual Glucose and PK Concentration Plots - Including Related Significantly Important AE Durations



Cohorts with at least 1 related significant AE displayed

Programming note: Continue with Insulin
2 plots per page

17.2.3 Listing Outlines

Template L_SD1_PG

Listing 16.2.x.xx Listing of Study Dates

Treatment	Subject	Screening	Day -1	Day 0	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

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	Timepoint	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 16.2.2.3 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	PK concentration

Programming notes: *continue for all populations*

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	Ethnicity	Height (cm)	Weight (kg)	BMI (kg/m2)	Alcohol Consumption (units/week)	Cigarettes (daily)
Treatment 1 ↓												

Template L_CM1_PG

Listing 16.2.x.xx Listing of Concomitant Medications

Treatment	Subject	Drug Name/ Indication	Dose/ Units/ Freq/ Route	Date/time Started/ Date Stopped	Time Since Last Dose	Pre-Started Trial?	Ongoing Medication?

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_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

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	Normal Range	NR	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

NR for Normal Range 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) Result	NR	BL	Alanine Amino Transferase (IU/L) Result	NR	BL	Aspartate Amino Transferase (IU/L) Result	NR	BL	Total Bilirubin (UMOL/L) Result	NR	BL

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

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

NR for Normal Range 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

Listing 16.2.x.xx Listing of Urinalysis Data

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

NR for Reference interval flag, H = Above reference interval, L = Below reference interval

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
		Pre-dose (1)	26SEP2012:09:57	63	148	78	50		390	32.7 *	399	-27.7	419	-11
		Pre-dose (2)												
		Pre-dose (3)												
		Mean Pre-dose												
		24 H												

* 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 NCS' or 'Abnormal CS' 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 Neurological Examination Findings

Treatment	Subject	Planned Relative Time	Date/Time	Type	Assessment	Details

Programming Notes: *Type = (Mental Status, Mood, Cranial Nerves etc.*
List all findings
If subjects have multiple abnormal assessment at a given time, create a separate row for each assessment.
For Ophthalmological assessment, the columns will be Treatment, Subject, Planned relative Time, Date/Time, Test and Details

Template L_NE2_PG

Listing 16.2.x.xx Listing of Neurological Questionnaire Findings

Mental Status

Treatment	Subject	Planned Relative Time	Date/Time	Hamilton Depression Rating Scale	Total Score Epworth Sleepiness Score	BDI-II

Template L_PK1_PG

Listing 16.2.4.xx Listing of Emodepside Plasma Pharmacokinetic Con centration-Time Data

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

BLQ = Below Limit of Quantification

Programming notes: *Values below LLOQ are shown as* BLQ
For PD: BLQ values are imputed to half LLOQ
For the listings of derived AUC0-24 PD concentrations, the columns will be Treatment, Subject, Planned Relative Time, Concentrations (units)

Template L_PK3_PG

Listing 16.2.4 xx Listing of Emodepside Urine Excretion Rate Data

Treatment	Subject	Planned Relative Time	Start Date/Time	Stop Date/Time	Urine Conc. (units)	Total Sample Volume (mL)	Amount excreted (units)

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*

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	− 7.5	+ 7.5
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	-	+ 0.3
Bilirubin conjugated	DBIL	µmol/L	Both	-	+ 4.0
Bilirubin total	TBIL	µmol/L	F	− 20	+ 10.0
Bilirubin total	TBIL	µmol/L	M	− 20	+ 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	-	+ 0.5
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	+ 15
Gamma glutamyl transferase	GGT	IU/L	F	-	+ 40
Gamma glutamyl transferase	GGT	IU/L	M	-	+ 40
Globulin	GLOB	g/L	Both	− 7.5	-
Glucose	GLU	mmol/L	Both	− 1.5	+ 2.5
Haematocrit	HCT	L/L	Both	− 0.05	-
Haemoglobin	HB	g/L	Both	− 20	-
High density lipoprotein	HDL	mmol/L	Both	− 1.5	+ 1.5
International normalised ratio	INRR	ratio	Both	-	-
Lactate dehydrogenase	LDH	IU/L	Both	-	+ 150
Lymphocytes	LYMP	10^9/L	Both	− 1.5	+ 1.5
Magnesium	MG	mmol/L	Both	-	-
Mean cell haemoglobin	MCH	pg	Both	− 2	+ 2
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	+ 0.5
Neutrophils	NEUT	10^9/L	Both	− 2	+ 8
Phosphate	PHOS	mmol/L	Both	− 1	+ 1
Platelets	PLT	10^9/L	Both	− 100	+ 100
Platelets (citrate tube)	PLTC	10^9/L	Both	− 100	+ 100
Potassium	K	mmol/L	Both	− 0.75	+ 0.75
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	+ 3
Total protein	TP	g/L	Both	− 15	-
Triglycerides	TG	mmol/L	Both	-	+ 1.5
Urea	UREA	mmol/L	Both	− 5	+ 2
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	+ 8

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

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 will be substituted by one half of the lower limit of quantification for calculation of plasma concentration summary statistics . The number of imputed values will be included in the summary table.

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.

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, $t_{1/2}$, CL/F, V_z/F 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}/D	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}
$t_{½}$	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	$t_{1/2}$
$t_{½,0\text{-}24}$	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	TBC	$t_{1/2,0\text{-}24}$

Text Symbol	Definition	Calculation	Typical Units	Log Transform	WNL	CDISC Controlled Terminology	TFL Symbol
Areas under the curve							
AUC_t	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}
$AUC_{t,norm}$	Area under the concentration-time curve from time zero (pre-dose) to the time of last quantifiable concentration corrected by dose and body weight	The AUC normalised by dose and body weight will be calculated as AUC_t/(Dose administered*body weight)	(h*ng/mL)/(mg*kg)	Y	N/A	AUCLSTWD	$AUC_{last,norm}$
$AUC_{t-\infty}$	Area under the exponential curve from t_{last} to infinity	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	N/A	N/A	AUCIFO	AUC_{t-inf}
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 $AUC_{t-\infty}$.	h*ng/mL	Y	AUCINF_pred	AUCIFP	AUC_{inf}
AUC_{∞}/Dose	Dose-normalised AUC to infinity	The dose-normalised AUC to infinity will be calculated as AUC_{∞}/Dose administered	(h*ng/mL)/mg	Y	AUCINF_D_pred	AUCIFPD	AUC_{inf}/D
$AUC_{\infty,norm}$	Area under the concentration-time curve from time zero to infinity corrected by dose and body weight	The AUC normalised by dose and body weight will be calculated as AUC_{∞}/(Dose administered*body weight)	(h*ng/mL)/(mg*kg)	Y	N/A	AUCIFPWD	$AUC_{inf,norm}$
$\%AUC_{extrap}$	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	$\%AUC_{extrap}$

Text Symbol	Definition	Calculation	Typical Units	Log Transform	WNL	CDISC Controlled Terminology	TFL Symbol
AUC_{0-24}	Area under the plasma concentration-time curve from time zero to 24h	The area under the concentration-time curve from zero time (pre-dose) to 24h 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_{0-24}/D	Dose-normalised AUC from time zero to 24h	The dose-normalised AUC from time zero to 24h will be calculated as AUC_{0-24}/Dose administered	(h*ng/mL)/mg	Y	N/A	AUCINTD	AUC_{24}/D
$AUC_{0-24,norm}$	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_{0-24}/(Dose administered*body weight)	(h*ng/mL)/(mg*kg)	Y	N/A	AUCINTWD	$AUC_{last,norm}$
Clearance, volume of distribution and mean residence time							
CL/F	Apparent total clearance from plasma after oral administration	Apparent total clearance from plasma will be calculated using the following formula: $CL/F = \frac{Dose}{AUC_{\infty}}$	L/h	Y	Cl_pred (actually derives Cl_F_pred for oral dose)	CLFP	CL/F
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	Mean Residence Time	The mean residence time will be calculated using: $MRT = \frac{AUMC}{AUC_{\infty}}$	h	Y	MRTINF_pred	MRTIFP	MRT
AUMC	Area under the first moment of the plasma concentration-time curve from time zero to infinity	The area under the first moment of the concentration-time curve from zero time (pre-dose) extrapolated to infinite time will using the (specified) trapezoidal method, as for AUC.	h^2*ng/mL	-	AUMCINF_pred	AUMCIFP	AUMC

Appendix C: Sample Page Layout

DND*i* : DNDI-EMO-001 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 15-020 Part 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"

Table of contents

1 List of abbreviations

λ_z	Terminal rate constant
AE	Adverse Event
ANOVA	Analysis of variance
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under concentration-time curve
$AUC_{(0-24)}$	Area under the plasma concentration-time curve from time zero to 24h
$AUC_{(0-24)/D}$	Dose-normalised AUC from time zero to 24h
$AUC_{(0-24),norm}$	Area under the concentration-time curve from time zero to 24h corrected by dose and body weight
AUC_t	AUC from time zero to time t
$AUC_{t-\infty}$	AUC from time t to infinity
$AUC_{t,\ norm}$	AUC from time zero (pre-dose) to the time of last quantifiable concentration corrected by dose and body weight
AUC_∞	Area under the plasma drug concentration vs. time from zero to infinity
AUC_∞/D	The area under the plasma drug concentration *vs*. time curve from time zero to infinity, corrected for dose.
$AUC_{\infty,\ norm}$	The area under the concentration-time curve from time zero to infinity corrected by dose and body weight
BMI	Body Mass Index
BP	Blood pressure
BQL	Below the limit of quantification
CI	Confidence Interval
CK	Creatine kinase
CL/F	Apparent Total body clearance
C_{max}	Maximum Plasma Concentration
C_{max}/D	C_{max} corrected by dose
$C_{max,norm}$	C_{max} corrected by dose and body weight
CRF	Case Report Form
CTR	Clinical Trial Report
CV	Coefficient of Variation
CVb	Between subject CV
ECG	Electrocardiogram
GLDH	Glutamate dehydrogenase
GGT	Gamma-glutamyl transpeptidase
HbA1C	Glycated haemoglobin
HDL	High-density lipoprotein
HMR	Hammersmith Medicines Research
HR	Heart Rate
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IR	Immediate release
LDH	Lactate dehydrogemnase
LDL	Low-density lipoprotein
LSF	Liquid Service Formulation

MCH	Hemoglobin amount per red blood cell
MCHC	The amount of hemoglobin relative to the size of the cell (hemoglobin concentration) per red blood cell
MCV	Average red blood cell size
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time
N	Number of subjects
n	Number of observations used in analysis
PC	Personal Computer
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
RBC	Red blood cells
RR	Portion of the ECG between consecutive R waves, representing the ventricular rate
SAP	Statistical Analysis Plan
SD	Standard deviation
$t_{1/2}$	Terminal elimination half-life
$t_{1/2,dom}$	Dominant half-life
TEAE	Treatment-Emergent Adverse Event
T_{max}	Time to maximum plasma concentration
TSH	Thyroid-stimulating hormone
Vz/F	Apparent volume of distribution
WBC	White blood cells
WHO	World Health Organisation

3 Introduction

This Statistical Analysis Plan (SAP) is based on the current trial protocol (version 5, Final 18 January 2017). Where statistical methods differ substantially between this SAP and the protocol, the differences will be identified in the SAP.

This SAP describes the datasets and the statistical methods to be used for the reporting and analysis of all data collected in Part 2 (cohorts 9 and 10), except for the 12-lead ECG continuous monitoring data which will be analysed by iCardiac Ltd (or an alternative provider), if applicable.

The randomisation code will not be broken before this SAP is finalised and signed. 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 trial report (CTR). Any deviations from this SAP will be documented in the CTR.

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 v6.3 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 (BAY 44-4400) after single oral doses administered as solution or immediate release (IR) tablets in healthy male subjects.

4.1.2 Secondary Objective(s)

- To investigate the pharmacokinetics (PK) of emodepside (BAY 44-4400), after administration as oral solution, and IR tablet (optional)
- To conduct an exploratory investigation of the relative bioavailability of the 5 mg and 20 mg IR tablet formulation using data generated in this study (optional)
- Possibility to determine the effect of food on the bioavailability of emodepside (BAY 44-4400) after single oral doses administered as solution or IR tablets.

4.2 Study Endpoint(s)

4.2.1 Safety and Tolerability Variables:

- Adverse Events (AEs).
- Physical and Neurological examination findings (including assessments of alertness, speech, language, and comprehension; cranial nerves; motor exam; coordination/cerebellar function; tremor of the hands, legs and head (postural, kinetic and rest tremor); sensation; and gait and postural stability (Pull test); mood; and sleepiness.).
- Vital signs: heart rate (HR), systolic and diastolic blood pressure (BP) in supine and sitting position (Cohort 10 only in supine), weight, body mass index (BMI; height at screening only), oral temperature.
- 12-lead ECG (HR, PR, QRS, QTcF), and for selected cohorts 12-lead ECG continuous recording (for emodepside exposure response analysis - HR, PR, QRS and QTcF).
- Clinical laboratory parameters:
  Hematology: hemoglobin, hematocrit, MCV, MCH, MCHC, platelets, reticulocytes, white blood cells (WBC) differential, red blood cells (RBC), glycated haemoglobin (HbA1C) (at screening);
  Coagulation: activated partial thromboplastin time (aPTT), prothrombin time (PT);
- Biochemistry: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), glutamate dehydrogenase (GLDH), gamma-glutamyl transpeptidase (GGT), LDH, CK, amylase, lipase, free T4 and T3, thyroid-stimulating hormone (TSH), glucose, cholesterol (high-density lipoprotein [HDL], and low-density lipoprotein [LDL], total), triglycerides, creatinine, urea, uric acid, bilirubin (total and conjugated), total protein, sodium, potassium, calcium, chloride and magnesium in serum;

- Urinalysis: by dipstick - glucose, ketone bodies, specific gravity, occult blood, pH, proteins, leucocytes, bilirubin, urobilinogen, nitrites.

- Ophthalmological assessments (Cohort 10 only)

4.2.2 Pharmacokinetic Variables:

Based on the plasma concentration time data , the following PK parameters of emodepside will be calculated.

- Main PK parameters: AUC_{∞}, AUC_{∞}/D, C_{max}, C_{max}/D, of emodepside (BAY 44-4400)
- Exploratory PK parameters: $C_{max,norm}$, T_{max}, $t_{½}$, MRT, CL/F, $AUC_{\infty,norm}$, AUC_t, $AUC_{t,norm}$, V_z/F of emodepside (BAY 44-4400)
- Other parameters: λ_z, $AUC_{t-\infty}$, points terminal

The following PK parameters of metabolites of emodepside may be calculated:
AUC_{∞}, AUC_{∞}/D, C_{max}, C_{max}/D, $C_{max,norm}$, T_{max}, $T_{½}$, $AUC_{\infty,norm}$, AUC_t, $AUC_{t,norm}$

In urine, the amount and concentration of emodepside and possibly its metabolites will be measured. The appropriate specific PK parameters to be calculated will be decided according to the concentration.

4.2.3 Pharmacodynamic Variables:

- Profiles of glucose and insulin, glucagon and cortisol (Cohort 9 only), only on Pre-Day (Day -1), Profile Day (Day 0), and Day 1.
- Single samples of prolactin and leptin, only on Pre-Day (Day -1), Profile Day (Day 0), and Day 1(Cohort 9 only).

4.3 Statistical Hypotheses

No formal statistical testing will be done.

5 Study Design

This is a single-center, blinded, randomised, placebo-controlled, parallel-group, single-dose, 2-cohort, dose-escalation, comparison study investigating safety, tolerability, and PK of

emodepside, after administration as an oral liquid service formulation (LSF) solution in healthy male subjects. Within each cohort, subjects will be randomised to receive either emodepside or placebo (n=8 per cohort; 6 assigned to emodepside and 2 assigned to placebo).

Subjects in Cohort 9 will receive 10mg solution of emodepside or matching placebo in a fed state and subjects in Cohort 10 will receive 40mg solution of emodepside in fasted state.

Table 1: Time and Events Table (Part 2, Cohort 9)

Study Procedure	Screen		In-Patient Phase[a]																										See Table [b]				Follow-Up
	Visit		Pre-Day										Profile-Day												Evaluation										
Day ± allowable deviation	-28 to -2	-2	-1										0												1	2	3	4	5	6	7					7 +3
Subject information and Informed Consent	X																																		
Medical history (including demographics and previous / concomitant medications)	X																																		
Physical examination[c]	X																																		X
Neurological examination[d]	X																																		X
Ward Admission (approx.16h)		X																																	
Urine drugs of abuse and alcohol breath test	X	X																																	
Hours [a] (pre/post drug)		**-36**	**-24***	**-23.5**	**-23**	**-22.5**	**-22**	**-21**	**-20**	**-18**	**-16**	**-12**	**0***	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**4**	**5**	**6**	**8**	**12**	**24**	**36**	**48**	**72**	**96**	**120**	**144**	**168**					
Glucose, Insulin, Glucagon, and Cortisol profiles			X		X		X		X			X	X		X		X			X				X	X										
Samples for Prolactin & Leptin			X										X												X										
Administration of emodepside[e]													X																						
12-lead safety ECG[f]	X		X[f]	X	X	X	X	X	X		X	X	X[f]	X	X	X	X		X	X			X	X	X		X	X	X	X	X	X			X
ECGs extracted from continuous recordings[g]													X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]		X[g]	X[g]	X[g]	X[g]										
Vital signs[h]	X		X[h]	X	X	X	X[h]	X	X[h]	X	X	X[h]	X[h]	X	X	X	X[h]		X	X[h]		X	X	X[h]	X[h]	X	X	X	X	X	X	X				X
Adverse event monitoring[i]	X	X	X				X		X			X	X		X		X		X	X		X	X	X	X	X	X	X	X	X	X				X
PK and metabolites[j] in plasma													X[j]	X	X[j]	X	X[j]	X	X	X[j]		X	X[j]	X[j]	X[j]	X	X[j]	X	X	X	X	X				X
PK in urine[k]													0–4[k]							4–8[k]			8–12[k]	12–24[k]										
Laboratory Safety[l,m]	X[m]		X										X												X		X	X	X	X	X	X			X
Neurological[d] examination and short physical examination[c]			X[c]				X		X			X	X				X			X				X	X	X	X								

*: In fasted subjects, all assessments at Hour –24 on Day –1 and Hour 0 on Day 0 are immediately before the administration of study drug (emodepside). In fed subjects, all assessments at Hour –24 on Day –1 and at Hour 0 on Day 0 are before the FDA breakfast. The only exception is the 12-lead ECG continuous recording (see footnote g).

[a]: Including a 10-minute supine phase before supine BP, HR, body temperature, ECG; and for 5 minutes after each nominal timepoint for ECGs extracted from continuous recording (see footnote); and also recommended before drawing blood samples. Before sitting BP assessments minimum 3-minute sitting period.

[b]: If mean half-life of emodepside in any cohort is longer than predicted, there are options to extend in-house period, or out-patient ambulatory visits up to Day 14 if necessary, from Cohort 5 onwards and in subsequent cohorts. Refer to Option 1, Option 2, and Option 3 as outlined in Table .

[c]: Height at screening only, for calculation of BMI. Weight at screening for calculation of BMI, also at -24h (Day -1) for PK calculations.

[d]: Neurological examination designed for the study, see Protocol Section 8.19.4 and Study Procedures Manual

[e]: Administration of study drug while fasting or after a high-calorie, high-fat breakfast

[f]: To include 3 repeat ECGs at these timepoints, with a time difference of about 1 minute, and single recordings at other timepoints

[g]: For selected cohorts in Part 1 (see Protocol Section 8.19.2 continuous 12-lead ECG recording will be started 1 hour before dosing and continue for 24 hours post-dosing. ECGs will be extracted at predose, at three timepoints (-60, -45, and -30 minutes for fasted subjects or -90, -75, and -60 minutes for fed subjects) and at the timepoints at which PK blood samples are drawn. Subjects will be supine for 10 minutes prior to and 5 minutes after each nominal timepoint. When ECG extraction coincide with safety ECGs, vital signs and blood draws, procedures will be performed in said order.

[h]: Vital signs to include BP (supine; plus sitting BP at the indicated timepoints[h]) and HR. Oral temperature only at screening and -24h.

[i]: Adverse Event (AE) monitoring will be throughout the study (spontaneous and solicited) to include questioning for tolerability and safety, however at these indicated timepoints will be specific questioning about AEs.

[j]: In addition to the PK sample, metabolite samples are collected only for the indicated time points [j]. As an option, at the sponsor's discretion, an additional sample of no more than 1mL may be taken at each PK timepoint from all subjects in up to 2 cohorts.

[k]: Start and end of urine collection for each bottle are indicated as hours post drug..

[l]: Hematology, Coagulation, Chemistry; Urinalysis by dip stick.

[m]: At Screening only: HIV 1, 2, Hepatitis B, C, HbA1C, in additional to hematology, coagulation, urinalysis, and chemistry.

Table 2. Follow-Up after Day 7 – Schedule Options 1, 2, or 3 Depending on Emodepside Plasma Concentrations at Day 7 in Previous Cohort(s) (from Cohort 5 onwards), Respectively.

For Screening and Days -2 through Day 8 see Table 1

OPTION 1	**Out-Patient Phase**					
Day						**Follow-Up Visit at 3 weeks (+3 days) post-dose**
	Discharge on Day 7					
Physical Examination						(see Table 1)
Neurological Examination						(see Table 1)
12-lead ECG						(see Table 1)
Vital signs[n]						(see Table 1)
Adverse event monitoring[l]						(see Table 1)
PK in plasma						(see Table 1)
Laboratory Safety[l,m]						(see Table 1)
OPTION 2	**Out-Patient Phase**					
Day	**Up to 4 visits during the period from Day 8–21 inclusive (as needed)**					**Follow-Up Visit at 3 weeks (+3 days) post-dose**
	Ambulatory Evaluation Visits, Scheduled As Needed					
Physical Examination						(see Table 1)
Neurological Examination						(see Table 1)
12-lead ECG						(see Table 1)
Vital signs[n]						(see Table 1)
Adverse event monitoring[l]	X		X	X	X	(see Table 1)
PK in plasma	X		X	X	X	(see Table 1)
Laboratory Safety[l,m]	X		X	X	X	(see Table 1)
OPTION 3	**Discharge from Ward on Day X**					
Day	**8 (±1)** (as needed)		**10 (±1)** (as needed)	**12 (±2)** (as needed)	**14 (±2)** (max.)	**Follow-Up Visit at 3 weeks (+3 days) post-dose**
	Prolonged In-House Evaluation Phase with Discharge from Ward on Day X (8-14)					
Physical Examination						(see Table 1)
Neurological Examination						(see Table 1)
12-lead ECG						(see Table 1)
Vital signs[n]						(see Table 1)
Adverse event monitoring[l]	X		X	X	X	(see Table 1)
PK in plasma	X		X	X	X	(see Table 1)
Laboratory Safety[l,m]	X		X	X	X	(see Table 1)

Table 3. Schedule of Events (Part 2, Cohort 10)

Study Procedure	Screening Visits			In-Patient Phase[a]																												Out-patient phase			Follow-Up
	1	2		Pre-Day										Profile-Day											Evaluation										
Day ± allowable deviation	-28 to -2	-7 to –1	-2	-1										0											1		2	3	4	5	6	7	10 ±1	14 ±2	18 ±2	21 +3
Subject information and Informed Consent	X																																		
Medical history (including demographics, previous/concomitant medications)	X																																		
Physical examination[b]	X																																		X
Neurological examination[c]	X																																		X
Colour blindness test[d]	X																																		
Ophthalmology exam[e]		X																																	
Ward Admission (approx.16h)			X																																
Urine drugs of abuse and alcohol breath test	X		X																																
Hours[a] (pre/post drug)			**-36**	**-24***	**-23.5**	**-23**	**-22.5**	**-22**	**-21**	**-20**	**-18**	**-16**	**-12**	**0***	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**4**	**5**	**6**	**8**	**12**	**24**	**36**	**48**	**72**	**96**	**120**	**144**	**168**				
Glucose and Insulin profiles				X		X							X	X		X									X	X									
Administration of emodepside[f]														X																					
12-lead safety ECG	X			X[g]		X							X	X[g]		X									X	X		X	X	X	X	X	X			X
Vital signs[h]	X			X	X	X						X	X	X	X	X								X	X	X	X	X	X	X	X	X	X			X
Adverse event monitoring[i]	X		X	X				X		X			X	X		X		X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK in plasma[j]														X	X	X				(X)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Safety[k,l]	X[l]			X										X												X		X	X	X	X	X	X	X	X	X	X
Neurological[c] examination and short physical examination[b]				X[b]		X							X	X		X									X	X	X	X								
Travel and stay at ophthalmology clinic																	X	X	X	X	X	X														
Ophthalmology exam[m]																			X																	

* All assessments at Hour 0 on Day 0 are immediately before the administration of study drug (emodepside), and assessments at Hour –24 on Day –1 will be time-matched to Profile Day

(dosing Day)

[a] Including a 10-minute supine phase before supine BP, HR, body temperature, ECG; and also recommended before drawing blood samples.

[b] Height at screening only, for calculation of BMI. Weight at screening for calculation of BMI, also at -24h (Day -1) for PK calculations.

[c] Neurological examination designed for the study, see Protocol Section 8.19.4 and Study Procedures Manual.

[d] Colour blindness to be determined at Screening visit 1.

[e] If subjects are eligible for study entry based on Screening visit 1 assessments, they will be asked to undergo an ophthalmology exam (Screening visit 2) within a week before Profile Day or on Pre−Day at the latest. All assessments for Screening Visit 1 will be performed prior to Screening Visit 2, but visits can be combined if necessary.

[f] Administration of study drug is in the fasted-state only.

[g] To include 3 repeat ECGs at these timepoints, with a time difference of about 1 minute, and single recordings at other timepoints.

[h] Vital signs to include supine BP and HR. Oral temperature only at screening and -24h.

[i] Adverse Event (AE) monitoring will be throughout the study (spontaneous and solicited) to include questioning for tolerability and safety, however at these indicated timepoints will be specific questioning about AEs.

[j] Timepoint shown as (X) indicates sample will be taken off-site whilst at the ophthalmology clinic. As an option, at the sponsor's discretion, an additional sample of no more than 1 mL may be taken at each PK timepoint from all subjects in up to 3 cohorts.

[k] Hematology, Coagulation, Chemistry; Urinalysis by dip stick.

[l] At Screening only: HIV 1, 2, Hepatitis B, C, HbA1C, in additional to hematology, coagulation, urinalysis, and chemistry.

[m] Ophthalmology exams will be performed on Profile-Day (Day 0) approximately 2-2.5 h post-dose. If deemed necessary by the ophthalmologist additional ophthalmology follow-up visit(s) may be scheduled for eye-related AEs.

6 Planned Analyses

6.1 Interim Analyses

No interim analyses are planned. However, the blinded safety and PK data will be reviewed after Cohort 9.

6.1.1 Persons responsible for analysis

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

6.2 Final Analysis

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

6.2.1 Persons responsible for analysis

Stephen Sah (HMR)	Statistician
Nick Jackson (HMR)	SAS Programmer
Bhavini Ladwa (HMR)	Data Manager

7 Sample Size Considerations

7.1 Sample Size Assumptions

No formal sample size calculations have been performed as this is an exploratory study. A sample size of 8 per cohort will be considered sufficient to examine the safety and tolerability of emodepside as well as the PK after single oral administration of the investigational drug. For evaluation, a minimum number of 6 evaluable subjects per cohort is required.

8 Analysis Populations

The following population sets 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 has been 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 received, regardless of the treatment to which they were randomised.

The primary endpoint will be analysed using the safety population.

8.1 Analysis Datasets

All analysis datasets will be based on observed data, except as outlined in Section 10.2.

9 Treatment Comparisons

The treatment comparison of interest is active (emodepside) versus placebo.

9.1 Data Display Treatment and Other Subgroup Descriptors

The sort order for treatment groups will be placebo, then study treatment in ascending dose order.
Listings of data will be sorted and displayed by treatment group, subject number, and also by date and time if applicable.

All subjects in cohorts 9 and 10 receiving the same formulation of placebo will be combined to form a pooled placebo group.

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

Treatment Groups	Short Description
Placebo [solution](Fed)	PLA [sol](Fed)
Placebo [solution](Fasted)	PLA [sol](Fasted)
Emodepside (xx mg) [solution](Fed)	xx mg [sol](Fed)
Emodepside (xx mg) [solution](Fasted)	xx mg [sol](Fasting)

9.1.1 Conventions for Summary Statistics and Data Displays

The minimum set of summary statistics for numeric variables will be: n, mean, standard deviation (or standard error), 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). 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.

Placebo subjects will be pooled across cohorts 9 and 10 taking into account formulation and fed/fasted status.

10 Data Handling Conventions

10.1 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 10.2.

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.

10.2 Derived and Transformed Data

For ECGs, vital signs, glucose, insulin, glucagon, cortisol and neurological examinations recorded on Day -1 the baseline will be the -24 h value and for Day 0 the baseline will be the pre-dose value on Day 0. The AUC_{0-24} for change from baseline in glucose, insulin, glucagon and cortisol will be calculated on Day -1 and Day 0, using the linear-linear trapezoidal method. For prolactin and leptin the baseline will be pre-dose on Day 0.

Laboratory data will be reported in standard units. The baseline will be the latest value recorded pre-dosing on Day 0. Out-of-range laboratory tests may be repeated. If a test is out-of-range at a baseline timepoint 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 made at some timepoints on Day -1 and Day 0, the mean of the three measurements for each subject will be used at each timepoint.

The pharmacokinetic parameters to be derived are given in Appendix B

10.3 Assessment Windows

No assessment windows are defined for this report.

10.4 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) 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	40–100 beats/min
Respiration rate	8–20 per min
Oral temperature	35.5–37.8°C

QTcB or QTcF > 450 msec and increases in QTcB or QTcF from baseline of > 30 msec will be considered to be potentially clinically important.

11 Study Population

11.1 Disposition of Subjects

The disposition of all subjects in the safety population will be summarised including: number of subjects randomised; number completing the study (i.e. not withdrawn), by treatment; and number discontinued (withdrawn) from the study. The number of subjects in each analysis population will be summarised 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.

11.2 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 and time.

- Had their treatment assignment unblinded.

In addition, subjects with minor time deviations (measurements taken outside the allowable windows given in the protocol) will be identified.

11.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics (e.g. physical examination, neurological 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 2016 of the WHO Drug dictionary.

11.4 Treatment Compliance

Dates and times of dosing will be listed.

12 Safety Analyses

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

12.1 Extent of Exposure

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

12.2 Adverse Events

Adverse events will be coded using the version of the Medical Dictionary for Regulatory Activities (MedDRA) (version 20.0).

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 and preferred term. 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 subjects with adverse events will be summarised by actual treatment:

- TEAEs by system organ class and preferred term
- Drug-related ("related" as recorded by the Investigator) TEAEs by system organ class and preferred term

Subjects with more than one TEAE will be counted only once, at the greatest severity or causal relationship, for each 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.

12.3 Deaths and Serious Adverse Events

Adverse events leading to deaths and serious adverse events will be listed separately (fatal events will be listed separately from non-fatal events).

12.4 Adverse Events Leading to Withdrawal from the Study

Adverse events leading to withdrawal will be listed separately.

12.5 Clinical Laboratory Evaluations

Haematology, clinical chemistry and urinalysis evaluation at each planned assessment, and change from baseline at each planned post-baseline assessment, will be summarised by actual 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.

12.6 Other Safety Measures

12.6.1 Vital signs

Vital signs evaluation at each planned assessment, and change in vital signs baseline at each planned post-baseline assessment, will be summarised by actual treatment. Individual subject profiles will be plotted for each vital sign parameter (Blood Pressure and Heart Rate).

Vital signs data of potential clinical importance will be listed separately.

12.6.2 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 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.

12.6.3 Neurological examination

Neurological examination results will be summarised and normal and abnormal neurological examination findings will be listed in detail according to the CRF. Total scores from neurological questionnaires at each planned assessment, and change from baseline at each planned post-baseline assessment, will be summarised by actual treatment.
Total scores from neurological questionnaires will also be listed.

12.6.4 Physical examination

Physical examination results will be summarised and abnormal physical examination findings will be listed.

12.6.5 Ophthalmology assessments

Ophthalmology assessments results will be summarised and listed by time point.

13 Pharmacokinetic Analyses

Analytical Services International Ltd, London, U.K. will measure the plasma and urine 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 6.3.

In addition, the plasma and urine concentration of emodepside metabolite(s) may be measured. If and when these data become available a SAP amendment will be written to specify their reporting (if applicable).

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 transformed parameters, the primary measure of central tendency will be the geometric mean[4]; for untransformed 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

13.1 Plasma PK

13.1.1 Pharmacokinetic Concentration Data

The plasma concentrations of emodepside and metabolites (if applicable) will be listed and summarised by treatment. Means at any time will only be calculated if at least 2/3rds of the individual data points are above the lower limit of quantification.

Individual and mean plasma concentration–time profiles will be presented graphically.

13.1.2 Pharmacokinetic Parameters

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

To assess the effect of food, analysis of variance (ANOVA) models will be fitted to the fed (Part 2, Cohort 9) solution and relevant fasted (Part 1, Cohort 5) solution data with the logarithm of the pharmacokinetic parameters AUC_{0-24} as the dependent variable, and formulation as a fixed effect. The estimated least square means and residual variance from the model will be used to construct 90% CIs for the difference in means on the log scale for the comparison of fed versus fasted solutions.

13.2 Urinary PK

If concentrations of emodespide in urine are determined, the amount of emodespide excreted in the urine will be estimated. The data will be listed and summarised by treatment.

14 Pharmacodynamic Analyses

Summaries and listings will use the safety population.
Pharmacodynamic variables (glucose, insulin, glucagon, cortisol, prolactin and leptin) at each planned assessment, and change from baseline at each planned post-baseline assessment, will be summarised by actual treatment.
In addition, for glucose and insulin (Cohorts 9 and 10), glucagon and cortisol (Cohort 9):

- Individual subject profiles will be plotted
- The difference between change from baseline on Day 0 and Day -1 will be summarised at each planned post-baseline assessment by actual treatment
- The AUC_{0-24} of change from baseline will be summarised for each day and treatment

Individual Insulin and PK Concentration Plots, including Related Significantly Important AE Durations will be produced.

For calculation of pharmacodynamics parameters, summary statistics and individual profile plots, values below the quantifiable limit of the assay will be substituted by one half of the lower limit of quantification.

15 Changes from the Protocol Specified Statistical Analysis

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

1) The definition of treatment-emergent adverse event has been updated from "an AE will be considered as treatment emergent if it appeared after the first dosing, or if appeared before dosing and worsened after dosing" to:

   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].

2) The AUC_{0-24} of change from baseline for glucose, insulin, glucagon and cortisol will be summarised for each day and treatment

3) The following emodepside parameters have been added to those mentioned in the protocol:

   Main PK parameters: AUC_{0-24} and AUC_{0-24}/D

   Exploratory PK parameters: $AUC_{0-24,norm}$,$t_{1/2,dom}$

4) The following analyses have been added for glucose, insulin, glucagon and cortisol:

   The difference between change from baseline on Day 0 and Day -1 will be summarised at each planned post-baseline assessment by actual treatment

   The AUC_{0-24} of change from baseline will be summarised for each day and treatment

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.

5. FL140 HMR Laboratory alert and delta ranges ver 3 (HMR Lab form).

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 B for Part 2, e.g., 14.1B

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

The following tables and figures will be produced (templates provided in Sections 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			
14.2.1.1	Summary of Emodepside Plasma Pharmacokinetic Concentration-Time Data (ng/mL)	PK	16.2.6.1.1	T_PK1
14.2.1.2	Summary of Derived Emodepside Plasma Pharmacokinetic Parameters	PK	16.2.6.1.2	T_PK3
14.2.1.3	Summary of Log-Transformed Derived Emodepside Plasma Pharmacokinetic Parameters	PK	16.2.6.1.2	T_PK4
14.2.1.4	Assessment of the Effect of Food on the PK of Emodepside	PK	16.2.6.1.2	T_PK7
14.2.2	Summary of Derived Emodepside Urine Pharmacokinetic Parameters	PK	16.2.6.2	T_PK3
14.2.3.1	Summary of Glucose	Safety	16.2.6.3	T_PD1
14.2.3.2	Summary of Difference Between Day -1 and Day 0 in Glucose	Safety	16.2.6.3	T_PD2
14.2.3.3	Summary of AUC_{0-24} for Change from Baseline in Glucose	Safety	16.2.6.4	T_PD3
14.2.4.1	Summary of Insulin	Safety	16.2.6.3	T_PD1
14.2.4.2	Summary of Difference Between Day -1 and Day 0 in Insulin	Safety	16.2.6.3	T_PD2
14.2.4.3	Summary of AUC_{0-24} for Change from Baseline in Insulin	Safety	16.2.6.3	T_PD3
14.2.5.1	Summary of Glucagon	Safety	16.2.6.3	T_PD1
14.2.5.2	Summary of Difference Between Day -1 and Day 0 in Glucagon	Safety	16.2.6.3	T_PD2
14.2.5.3	Summary of AUC_{0-24} for Change from Baseline in Glucagon	Safety	16.2.6.3	T_PD3

Table	Description	Population	Source Listing	Template (Shells below)
14.2.6.1	Summary of Cortisol	Safety	16.2.6.3	T_PD1
14.2.6.2	Summary of Difference Between Day -1 and Day 0 in Cortisol	Safety	16.2.6.3	T_PD2
14.2.6.3	Summary of AUC_{0-24} for Change from Baseline in Cortisol	Safety	16.2.6.3	T_PD3
14.2.7	Summary of Prolactin	Safety	16.2.6.3	T_PD1
14.2.8	Summary of Leptin	Safety	16.2.6.3	T_PD1
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 Grade	Safety	16.2.7.1	T_AE1
14.3.1.4	Summary of Drug Related Treatment-Emergent Adverse Events by Severity Grade	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 Urinalysis Dipstick Results	Safety	16.2.8.5	T_UR1
14.3.6.1	Summary of Vital Signs	Safety	16.4	T_VS1
14.3.6.2	Summary of AUC0-24 for Change from Baseline in Supine Diastolic Blood Pressure (h*mmHg)	Safety	16.4	T_VS2
14.3.6.3	Summary of AUC0-24 for Change from Baseline in Supine Systolic Blood Pressure (h*mmHg)	Safety	16.4	T_VS2
14.3.6.4	Summary of AUC0-24 for Change from Baseline in Supine	Safety	16.4	T_VS2

Table	Description	Population	Source Listing	Template (Shells below)
	Heart Rate (h*beats/min)			
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	16.4	T_EG3
14.3.8.1	Summary of Neurological Examination Data	Safety	16.2.9.5	T_NE1
14.3.8.2	Summary of Neurological Examination Questionnaire Data	Safety	16.2.9.6	T_LB2
14.3.9	Summary of Physical Examination Data	Safety	16.2.9.4	T_PE1
14.3.10	Summary of Ophthalmological Examination Data	Safety	16.2.9.7	T_NE1

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	16.2.6.1.1	F_PK1
14.2.1.2	Geometric mean (+/- SD) Emodepside Plasma Concentration-Time Plots (Linear and Semi-log)	PK	16.2.6.1.1	F_PK2
14.2.2.1	Individual Glucose-Time Plots	PD	16.2.6.3	F_PD1
14.2.2.2	Individual Glucose and PK Concentration Plots - Including Related Significantly Important AE Durations	PD	16.2.6.3, 16.2.6.1.1, 16.2.7.1	F_PD2
14.2.3.1	Individual Insulin-Time Plots	PD	16.2.6.3	F_PD1
14.2.3.2	Individual Insulin-Time Plots 0-12h	PD	16.2.6.3	F_PD1
14.2.3.3	Individual Insulin and PK Concentration Plots - Including Related Significantly Important AE Durations	PD	16.2.6.3, 16.2.6.1.1, 16.2.7.1	F_PD2
14.2.4	Individual Glucagon-Time Plots	PD	16.2.6.3	F_PD1
14.2.5	Individual Cortisol-Time Plots	PD	16.2.6.3	F_PD1
14.3	SAFETY DATA			
14.3.1.1	Individual Systolic Blood Pressure-Time Plots	Safety	16.2.9.1	F_PD1
14.3.1.2	Individual Diastolic Blood Pressure-Time Plots	Safety	16.2.9.1	F_PD1
14.3.2	Individual Heart Rate-Time Plots	Safety	16.2.9.1	F_PD1

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

Listing	Description	Template (Shells below)
16.2.1	Study dates & disposition of subjects	
16.2.1.1	Listing of Study Dates	L_SD1_PG
16.2.1.2	Listing of Reasons for Withdrawal	L_SD2_PG
16.2.2	Protocol deviations	
16.2.2.1	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	L_DV1_PG
16.2.2.2	Listing of Subjects with Time Deviations	L_TD1_PG
16.2.2.3	Listing of Subjects with Other Protocol Deviations	L_DV2_PG
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	Individual Emodepside Plasma Concentration-Time Plots (log scale) for Estimation of λz, with Regression Line	F_PK10
16.2.6.2	Listing of Emodepside Urine Excretion Rate Data	L_PK3_PG
16.2.6.3	Listing of PD concentration-Time Data	L_PK1_PG
16.2.6.4	Listing of Derived AUC0-24 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 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
16.2.9	Vital signs, ECG variables, neurological, physical findings and Ophthalmological Assessment	
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 Neurological Examination Findings	L_NE1_PG
16.2.9.6	Listing of Neurological Questionnaire Findings	L_NE2_PG
16.2.9.7	Listing of Ophthalmological Examination Data	L_NE1_PG

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	Treatment 2	Etc	All Subjects
Safety Population	Randomised					
	Completed					
	Withdrawn					
		Death				
		Adverse Events				
		Withdrawal by subject				
		Physician decision				
		Protocol violation				
		Study terminated by Sponsor				
		Lost to follow-up				
		Other				
PK Concentration	Included					
PK Parameter	Included					

Source: Listing 16.2.xx

Programming notes: *Continued with all treatment groups and column for "All emodepside"*
This table will contain one column for placebo, each dose/formulation, all active and all subjects.

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				
	Min				
	Median				
	Max				
Sex	N				
	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				
	Min				
	Median				
	Max				
Weight (kg)	n				
	Mean				
	SD				

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

*includes only those subjects who drink alcohol or smoke

Source: Listing 16.2.xx

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

Template T_AE1

Table 14.3.3.xx Summary of Treatment-Emergent Adverse Events

		Treatment 1 (N=xx)		Treatment 2 (N=xx)		Etc
System Organ Class	Preferred Term	n	%	n	%	
Number of subjects with AEs						
Gastrointestinal disorders	Total number of subjects					
	Abdominal discomfort					
	Abdominal pain					
	↓					
Nervous system disorders	Total number of subjects					
	Dizziness					
	Headache					
	↓					
↓	↓					

*Subjects with ≥1 adverse event are counted only once per system organ class and preferred term.

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.
For tables by severity a sub-heading will be added to each table page

Template T_LB1

Table 14.3.4.xx Summary of Laboratory Values of Potential Clinical Importance

Lab Test	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*

Template T_LB2

Table 14.3.3.2 Summary of Chemistry Laboratory Values

											Change from Baseline					
Laboratory Test (units)	Treatment	Planned Relative Time	n	Mean	95% CI	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
	Treatment 1 (N=xx)	-20h													

Source: Listing 16.2.xx

Note: Baseline on Day -1 is -24h value, baseline on Day 0 is Day 0, pre-dose

Programming notes: *Continued with all treatments and time points.*
For the summary of neurological questionnaires the first column will be headed "Questionnaire (Total Score)" and the footnote will be removed

Template T_UR1

Table 14.3.3.4 Summary of Urinalysis Dipstick Results

Planned Relative Time	Result	Treatment 1 (N=xx) n	%	Treatment 2 (N=xx) n	%
Time 1	Positive				
	Negative				
	No Result				
	Not Done				
Time 2	Positive				
	Negative				
	No Result				
	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

Template T_VS1

Table 14.3.4 Summary of Vital Signs

									Change from Baseline					
	Treatment	Planned Relative Time	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Systolic BP (mmHg)	Treatment 1 (N=xx)	-20h												

Source: Listing 16.2.xx

Note: Baseline on Day -1 is -24h value, baseline on Day 0 is Day 0, pre-dose

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

Template T_VS2

Table 14.3.4 Summary of AUC0-24 for Change from Baseline in Supine Diastolic Blood Pressure (h*mmHg)

	Day -1					Day 0					Day 0 - Day -1			
Treatment	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max	N	Mean	SD	95% CI (Lower, Upper)
Treatment 1 (N=xx)														

Source: Listing 16.2.xx

Difference is change from mean baseline

Programming notes: *Continued with all treatments*

Template T_EG2

Table 14.3.5.1 Summary of ECG Values

									Change from Baseline					
Variable	Treatment	Planned Relative Time	n	Mean	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Heart Rate (bpm)	Treatment 1 (N=xx)	-20h												
		-21h												
		-23h												
	Treatment 2 (N=xx)	-20h												
		-21h												
		-23h												
PR Interval (msec)	Treatment 1 (N=xx)	-20h												
		-21h												
		-23h												
	Treatment 2 (N=xx)	-20h												
		-21h												
		-23h												

Source: Listing 16.2.xx

Note: Baseline on Day -1 is -24h value, baseline on Day 0 is Day 0, pre-dose

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 n	%	481, – 500 msec n	n	> 500 msec n	%	31-60 msec Increase n	%	>60 msec Increase n	%
QT interval	Treatment 1	1h										
	(N=xx)	2h										
		3h										
	Treatment 2	1h										
	(N=xx)	2h										
		3h										
QTcB interval	Treatment 1	1h										
	(N=xx)	2h										
		3h										
	Treatment 2	1h										
	(N=xx)	2h										
		3h										

Source: Listing 16.2.xx

Note: Baseline on Day -1 is -24h value, baseline on Day 0 is Day 0, pre-dose

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

Template T_PE1

Table 14.3.8.xx Summary of Physical Examination Data

Body System	Planned Relative Time	Result	Treatment 1 (N=xx)	Treatment 2 (N=xx)
General Appearance	Time 1	Normal	n (%)	
		Abnormal NCS	x (xx)	
		Abnormal CS		
	Time 2	Normal		
		Abnormal NCS		
		Abnormal CS		
HEENT	Time 1	Normal		
		Abnormal NCS		
		Abnormal CS		
	Time 2	Normal		
		Abnormal NCS		
		Abnormal CS		

Source: Listing 16.2.xx

Programming notes: *Continued with all body system, treatments and time points. Include rows for each outcome in CRF*
If results are missing "missing" row will be added. Percentages calculated using the number of available results as denominator.

Template T_NE1

Table 14.3.8.xx Summary of Neurological Examination Data

Mental Status

Body System	Planned Relative Time	Result	Treatment 1 (N=xx) n (%)	Treatment 2 (N=xx) n (%)
Alertness	Time 1	Normal	x (xx)	
		Abnormal NCS	x (xx)	
		Abnormal CS		
	Time 2	Normal		
		Abnormal NCS		
		Abnormal CS		
Speech	Time 1	Normal		
		Abnormal NCS		
		Abnormal CS		
	Time 2	Normal		
		Abnormal NCS		
		Abnormal CS		

Source: Listing 16.2.xx

Programming notes: *Continued with all examinations/test, treatments and time points. Include rows for each outcome in CRF*
For Ophthalmological assessment, replace body system with Test
If results are missing "missing" row will be added. Percentages calculated using the number of available results as denominator.
Use PESCAT as subheading (not for Ophthalmological Assessment).

Template T_PK1

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

Treatment	N	Planned Relative Time	n	No. Imputed	Mean	95% CI	SD	%CV	Median	Min	Max
Dose 1		1h									
Dose 2											

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	n	Mean	95% CI	SD	%CV	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	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_PK7

Table 14.2.xx Assessment of the Effects of Food on the PK of Emodepside

		LS Means			
Parameter	Treatment	Fed	Fasted	Ratio (Fed/Fasted)	90% CI
Cmax (Units)		xxxx.xx	xxxx.xx	xxxx.xx	(xxxx.xx, xxxx.xx)

Source: Listing 16.2.xx

Programming notes: *Continued with* AUC_{inf}

Template T_PD1

Table 14…xx Summary of Glucose

									Change from Baseline					
Treatment	Planned Relative Time	n	Mean	95% CI	SD	Median	Min	Max	n	Mean	SD	Median	Min	Max
Treatment 1 (N=xx)	-24h	x	x	x	x	x	x	x						
	-20h	x	x	x	x	x	x	x	x	x	x	x	x	x

Note: Baseline on Day -1 is -24h value, baseline on Day 0 is Day 0, pre-dose

Programming notes: *Continued with all PD parameters, treatments and timepoints*
Change from baseline calculated from "pre-dose" on each day

Template T_PD2

Table 14…xx Summary of Difference Between Day -1 and Day 0 in Glucose

	Planned Relative Time	Day -1 – Day 0			
Treatment		n	Mean	SD	95% CI
Treatment 1 (N=xx)					

Note: Difference is change from baseline

Programming notes: *Continued with time points and treatments*

Template T_PD3

Table 14…xx Summary of AUC_{0-24} for change from baseline in Glucose (units)

	Day -1					Day 0					Day -1 – Day 0			
Treatment	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max	n	Mean	SD	95% CI
Treatment 1 (N=xx)														

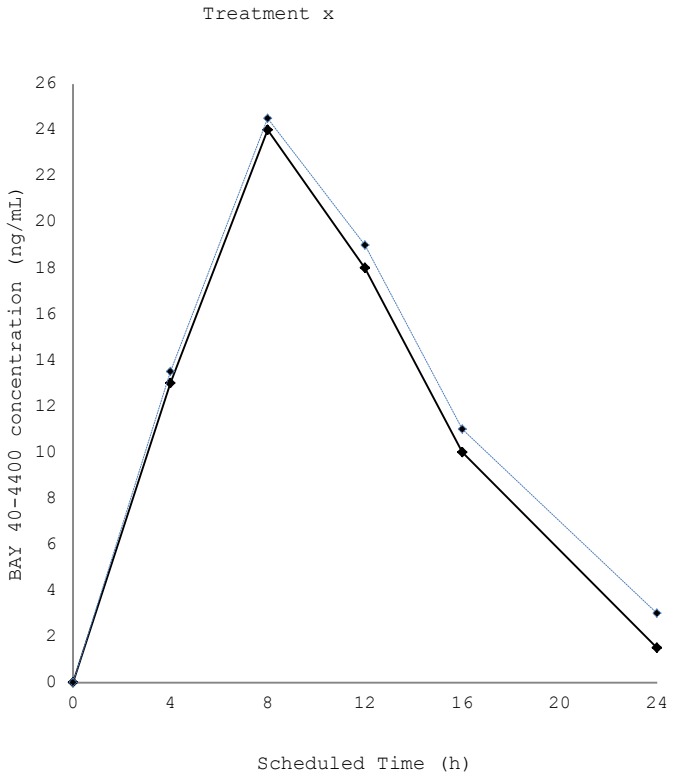
Note: Difference is change from baseline

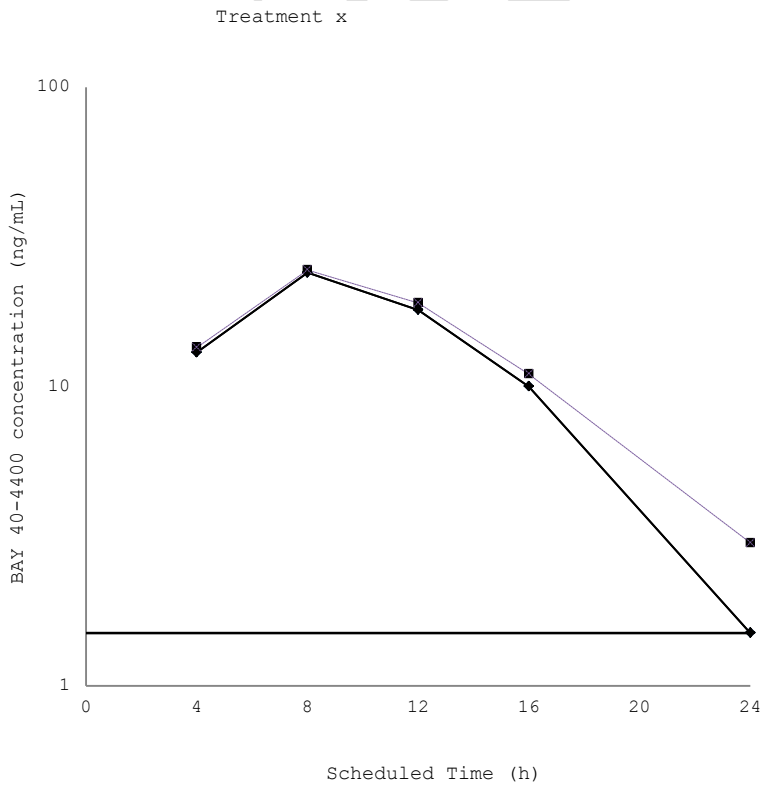
Programming notes: Continued with all treatments

17.2.2 Figure Outlines

Template F_PK1

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

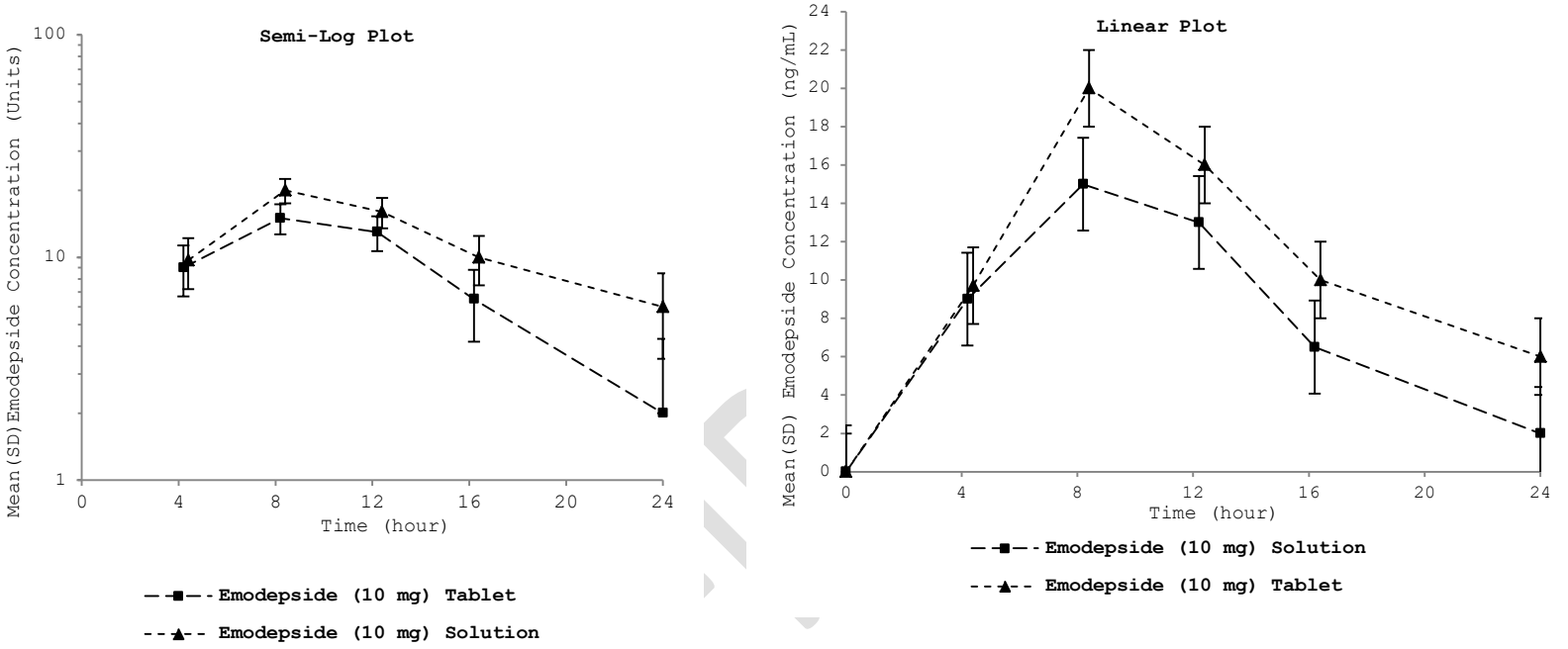




Programming note: Plot will include all subjects for a given treatment group

Template F_PK2

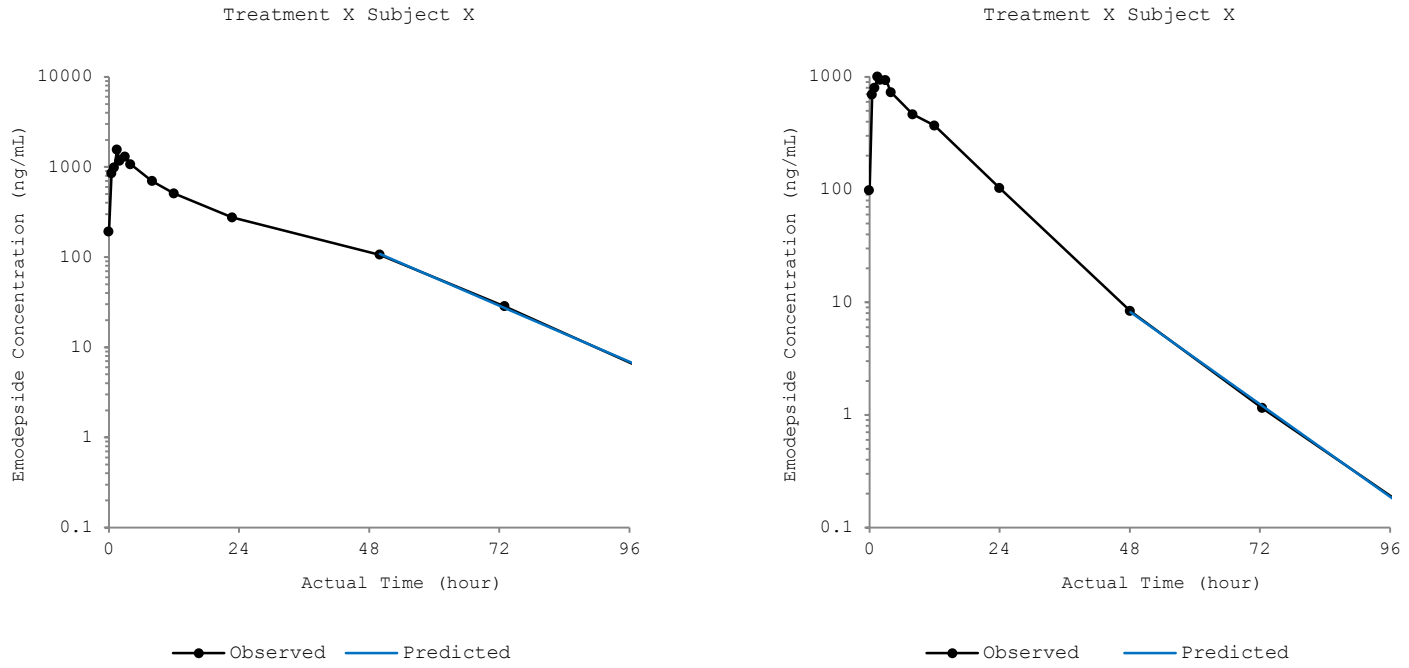
Figure 16.2.4.xx Geometric mean (+ SD) of Emodepside Plasma Concentration-Time Plots (Linear and Semi-log)



Programming note: The SD is the geometric standard deviations

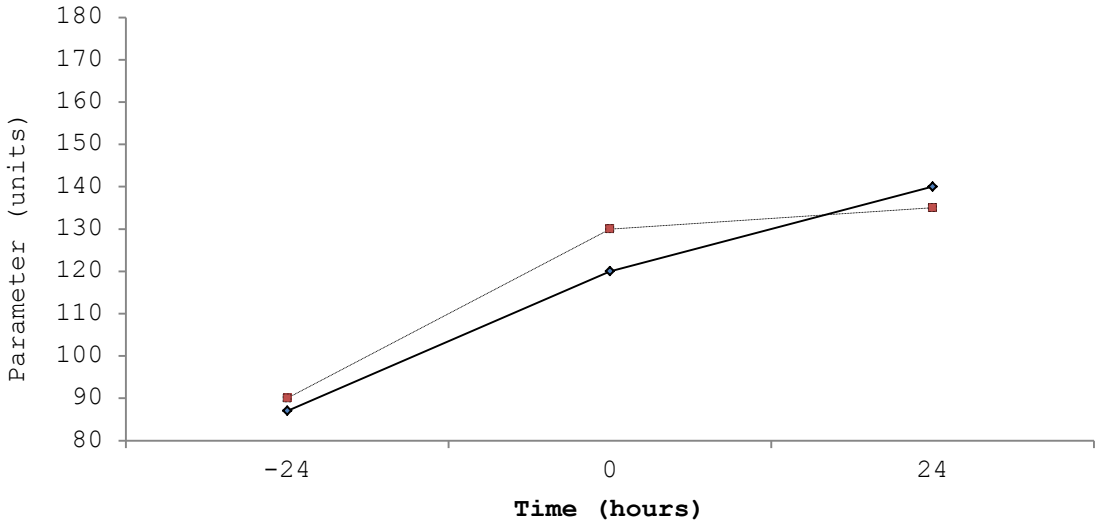
Template F_PK10

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



Template F_PD1

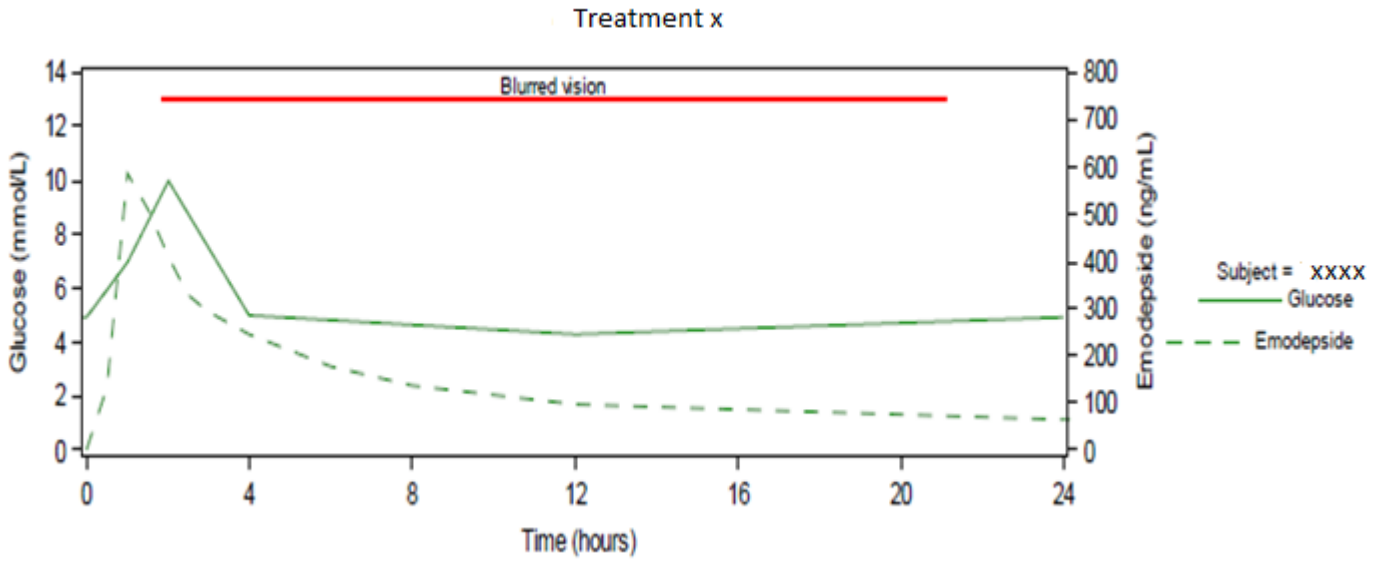
Figure **16.2.**xx Individual Glucose-Time Plots



Programming note: Continue with Insulin, Glucagon and Cortisol land normal rages as reference lines.
For Blood pressure and Heart Rate, include PCI limits as reference lines.
Plot will include all subjects for a given treatment group
4 plots per page

Template F_PD2

Figure **16.2.**xx Individual Glucose and PK Concentration Plots - Including Related Significantly Important AE Durations



Cohorts with at least 1 related significant AE displayed

Programming note: Continue with Insulin
2 plots per page

17.2.3 Listing Outlines

Template L_SD1_PG

Listing 16.2.x.xx Listing of Study Dates

Treatment	Subject	Screening	Day -1	Day 0	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

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	Timepoint	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 16.2.2.3 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	PK concentration

Programming notes: *continue for all populations*

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	Ethnicity	Height (cm)	Weight (kg)	BMI (kg/m2)	Alcohol Consumption (units/week)	Cigarettes (daily)
Treatment 1 ↓												

Template L_CM1_PG

Listing 16.2.x.xx Listing of Concomitant Medications

Treatment	Subject	Drug Name/ Indication	Dose/ Units/ Freq/ Route	Date/time Started/ Date Stopped	Time Since Last Dose	Pre-Started Trial?	Ongoing Medication?

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_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

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	Normal Range	NR	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

NR for Normal Range 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) Result	NR	BL	Alanine Amino Transferase (IU/L) Result	NR	BL	Aspartate Amino Transferase (IU/L) Result	NR	BL	Total Bilirubin (UMOL/L) Result	NR	BL

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

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

NR for Normal Range 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

Listing 16.2.x.xx Listing of Urinalysis Data

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

NR for Reference interval flag, H = Above reference interval, L = Below reference interval

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
		Pre-dose (1)	26SEP2012:09:57	63	148	78	50		390	32.7 *	399	-27.7	419	-11
		Pre-dose (2)												
		Pre-dose (3)												
		Mean Pre-dose												
		24 H												

* 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 NCS' or 'Abnormal CS' 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 Neurological Examination Findings

Treatment	Subject	Planned Relative Time	Date/Time	Type	Assessment	Details

Programming Notes: *Type = (Mental Status, Mood, Cranial Nerves etc.*
List all findings
If subjects have multiple abnormal assessment at a given time, create a separate row for each assessment.
For Ophthalmological assessment, the columns will be Treatment, Subject, Planned relative Time, Date/Time, Test and Details

Template L_NE2_PG

Listing 16.2.x.xx Listing of Neurological Questionnaire Findings

Mental Status

Treatment	Subject	Planned Relative Time	Date/Time	Hamilton Depression Rating Scale	Total Score Epworth Sleepiness Score	BDI-II

Template L_PK1_PG

Listing 16.2.4.xx Listing of Emodepside Plasma Pharmacokinetic Con centration-Time Data

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

BLQ = Below Limit of Quantification

Programming notes: *Values below LLOQ are shown as* BLQ
For PD: BLQ values are imputed to half LLOQ
For the listings of derived AUC0-24 PD concentrations, the columns will be Treatment, Subject, Planned Relative Time, Concentrations (units)

Template L_PK3_PG

Listing 16.2.4 xx Listing of Emodepside Urine Excretion Rate Data

Treatment	Subject	Planned Relative Time	Start Date/Time	Stop Date/Time	Urine Conc. (units)	Total Sample Volume (mL)	Amount excreted (units)

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*

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	− 7.5	+ 7.5
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	-	+ 0.3
Bilirubin conjugated	DBIL	µmol/L	Both	-	+ 4.0
Bilirubin total	TBIL	µmol/L	F	− 20	+ 10.0
Bilirubin total	TBIL	µmol/L	M	− 20	+ 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	-	+ 0.5
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	+ 15
Gamma glutamyl transferase	GGT	IU/L	F	-	+ 40
Gamma glutamyl transferase	GGT	IU/L	M	-	+ 40
Globulin	GLOB	g/L	Both	− 7.5	-
Glucose	GLU	mmol/L	Both	− 1.5	+ 2.5
Haematocrit	HCT	L/L	Both	− 0.05	-
Haemoglobin	HB	g/L	Both	− 20	-
High density lipoprotein	HDL	mmol/L	Both	− 1.5	+ 1.5
International normalised ratio	INRR	ratio	Both	-	-
Lactate dehydrogenase	LDH	IU/L	Both	-	+ 150
Lymphocytes	LYMP	10^9/L	Both	− 1.5	+ 1.5
Magnesium	MG	mmol/L	Both	-	-
Mean cell haemoglobin	MCH	pg	Both	− 2	+ 2
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	+ 0.5
Neutrophils	NEUT	10^9/L	Both	− 2	+ 8
Phosphate	PHOS	mmol/L	Both	− 1	+ 1
Platelets	PLT	10^9/L	Both	− 100	+ 100
Platelets (citrate tube)	PLTC	10^9/L	Both	− 100	+ 100
Potassium	K	mmol/L	Both	− 0.75	+ 0.75
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	+ 3
Total protein	TP	g/L	Both	− 15	-
Triglycerides	TG	mmol/L	Both	-	+ 1.5
Urea	UREA	mmol/L	Both	− 5	+ 2
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	+ 8

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

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 will be substituted by one half of the lower limit of quantification for calculation of plasma concentration summary statistics . The number of imputed values will be included in the summary table.

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.

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, $t_{1/2}$, CL/F, V_z/F 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}/D	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}
$t_{½}$	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	$t_{1/2}$
$t_{½,0\text{-}24}$	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	TBC	$t_{1/2,0\text{-}24}$

Text Symbol	Definition	Calculation	Typical Units	Log Transform	WNL	CDISC Controlled Terminology	TFL Symbol
Areas under the curve							
AUC_t	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}
$AUC_{t,norm}$	Area under the concentration-time curve from time zero (pre-dose) to the time of last quantifiable concentration corrected by dose and body weight	The AUC normalised by dose and body weight will be calculated as AUC_t/(Dose administered*body weight)	(h*ng/mL)/(mg*kg)	Y	N/A	AUCLSTWD	$AUC_{last,norm}$
$AUC_{t-\infty}$	Area under the exponential curve from t_{last} to infinity	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	N/A	N/A	AUCIFO	AUC_{t-inf}
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 $AUC_{t-\infty}$.	h*ng/mL	Y	AUCINF_pred	AUCIFP	AUC_{inf}
AUC_{∞}/Dose	Dose-normalised AUC to infinity	The dose-normalised AUC to infinity will be calculated as AUC_{∞}/Dose administered	(h*ng/mL)/mg	Y	AUCINF_D_pred	AUCIFPD	AUC_{inf}/D
$AUC_{\infty,norm}$	Area under the concentration-time curve from time zero to infinity corrected by dose and body weight	The AUC normalised by dose and body weight will be calculated as AUC_{∞}/(Dose administered*body weight)	(h*ng/mL)/(mg*kg)	Y	N/A	AUCIFPWD	$AUC_{inf,norm}$
$\%AUC_{extrap}$	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	$\%AUC_{extrap}$

Text Symbol	Definition	Calculation	Typical Units	Log Transform	WNL	CDISC Controlled Terminology	TFL Symbol
AUC_{0-24}	Area under the plasma concentration-time curve from time zero to 24h	The area under the concentration-time curve from zero time (pre-dose) to 24h 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_{0-24}/D	Dose-normalised AUC from time zero to 24h	The dose-normalised AUC from time zero to 24h will be calculated as AUC_{0-24}/Dose administered	(h*ng/mL)/mg	Y	N/A	AUCINTD	AUC_{24}/D
$AUC_{0-24,norm}$	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_{0-24}/(Dose administered*body weight)	(h*ng/mL)/(mg*kg)	Y	N/A	AUCINTWD	$AUC_{last,norm}$
Clearance, volume of distribution and mean residence time							
CL/F	Apparent total clearance from plasma after oral administration	Apparent total clearance from plasma will be calculated using the following formula: $CL/F = \frac{Dose}{AUC_{\infty}}$	L/h	Y	Cl_pred (actually derives Cl_F_pred for oral dose)	CLFP	CL/F
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	Mean Residence Time	The mean residence time will be calculated using: $MRT = \frac{AUMC}{AUC_{\infty}}$	h	Y	MRTINF_pred	MRTIFP	MRT
AUMC	Area under the first moment of the plasma concentration-time curve from time zero to infinity	The area under the first moment of the concentration-time curve from zero time (pre-dose) extrapolated to infinite time will using the (specified) trapezoidal method, as for AUC.	h^2*ng/mL	-	AUMCINF_pred	AUMCIFP	AUMC

Appendix C: Sample Page Layout

DND*i* : DNDI-EMO-001 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 15-020 Part 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"