STATISTICAL ANALYSIS PLAN

A PHASE 1 RANDOMIZED SINGLE ORAL DOSE CROSS-OVER STUDY INVESTIGATING DESMETRAMADOL DOSE PROPORTIONALITY AND FOOD EFFECT IN NORMAL HUMAN SUBJECTS

Protocol No: OMNI-PAIN-103
Final Protocol Date: 11 May 2020 Version 1.2
Compound Name: Desmetramadol

Celerion Project CA22121
Final Version 1.0
Date: 09 February 2021

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Compound Name: Desmetramadol

Protocol: OMNI-PAIN-103

Study Title: A Phase 1 Randomized Single Oral Dose Cross-Over Study Investigating Desmetramadol Dose Proportionality and Food Effect in Normal Human Subjects

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Compound Name: Desmetramadol

Protocol: OMNI-PAIN-103

Study Title: A Phase 1 Randomized Single Oral Dose Cross-Over Study Investigating Desmetramadol Dose Proportionality and Food Effect in Normal Human Subjects

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1. INTRODUCTION

The following statistical analysis plan (SAP) provides the framework for the summarization of the safety data from this unblinded study. The SAP may change due to unforeseen circumstances. Any changes made from the planned analysis within protocol, or after locking of the database will be documented in the clinical study report (CSR). The section referred to as Table Shells within this SAP describes the traceability of the tables, figures, and listings (TFLs) back to the data.

Any additional exploratory analyses not addressed within this SAP and/or driven by the data, or requested by the Syntrix Biosystems, will be considered out of scope and must be described in the CSR.

Celerion is only providing the SDTM/ADaM data associated with the safety analysis and the Sponsor will be incorporating the relevant pharmacokinetic (PK) domains to create a final submission ready package.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

The purpose of the study is to investigate in healthy human subjects desmetramadol dose-proportionality and food effect (desmetramadol is the M1 metabolite of tramadol). Dose proportionality will be assessed for 10, 20 and 30 mg single oral doses, and food effect will be assessed for the 30 mg single oral dose.

Primary Objectives:

To determine the dose proportionality of desmetramadol following oral single-dose administration of 10, 20 and 30 mg in fasted healthy subjects.

To determine the food effect on 30 mg desmetramadol in healthy subjects following oral single-dose administration.

To determine the safety and tolerability of desmetramadol following oral single-dose administration in fasted and fed healthy subjects.

Secondary Objectives:

Determine PK parameters for each M5 enantiomer in blood following oral single-dose administration of 10, 20 and 30 mg desmetramadol in fasted healthy subjects and of 30 mg desmetramadol administered with food.

Quantify total M1 and M5 excreted (unconjugated and de-conjungated) in the urine after the 30 mg fasted dosings and compute clearance of each and in relation to 24 hour creatinine clearance.

This SAP will only address the safety objective.

2.2 Endpoints

Safety endpoints are adverse events. Any abnormal laboratory values, abnormal vital signs, reported symptoms, or abnormal physical examination findings determined to be clinically significant by the Investigator/designee will be documented as adverse events. The safety assessments will be based on all reported adverse events, and changes in laboratory values from baseline. The severity and relationship to desmetramadol treatment will be recorded for all adverse events. Adverse events will be coded for summary and analysis using standardized preferred terms and system organ class.

Only safety objectives and endpoints will be addressed in this SAP.

3. STUDY DESIGN

An open-label, randomized, balanced, single-dose, four-treatment, four-period, four-sequence (using a Williams' square design) cross-over study with each dose separated by ≥ 3 days. Up to 32 subjects will be randomized to obtain a target sample of 24 subjects with PK responses at each of the four treatment periods.

Enrollment is estimated to take approximately 30 days. Subjects will be on study for 11 days. It will take approximately 6 weeks to complete the study after enrollment of the first subject.

Each subject will receive four treatments which will include the following four unblinded single-dose oral treatments:

- Treatment A: Desmetramadol 3 x 10 mg tablets following a high-fat, high-calorie breakfast served approximately 30 minutes before dosing and entirely consumed within 20 minutes;
- Treatment B: Desmetramadol 3 x 10 mg tablets;
- Treatment C: Desmetramadol 2 x 10 mg tablets;
- Treatment D: Desmetramadol 1 x 10 mg tablet.

Period			
I	II	III	IV
Treatment A	Treatment B	Treatment D	Treatment C
Treatment D	Treatment A	Treatment C	Treatment B
Treatment C	Treatment D	Treatment B	Treatment A
Treatment B	Treatment C	Treatment A	Treatment D

Before each oral dose, all subjects will be fasted overnight for at least 10 hours. In addition, subjects will fast for four hours after desmetramadol administration. Desmetramadol will be administered with approximately 240 ml of water. No water is allowed one hour before and one hour after each desmetramadol administration.

This will be an inpatient study. Subjects will be admitted to the clinical pharmacology unit on Day -1, and administered a single oral dose treatment on Day 1, Day 4, Day 7 and Day 10. After completing study procedures on Day 11 the subject will be discharged from the facility. As described in later sections, the data will be presented where each dose is in a different period on Day 1 (Protocol Day 1 is Period 1 Day 1, Protocol Day 4 is Period 2 Day 1, Protocol Day 7 is Period 3 Day 1, and Protocol Day 10 is Period 4 Day 1).

Blood and urine specimens will be collected for PK analysis.

4. ANALYSIS POPULATIONS

4.1 Analysis Populations

Only the safety and per-protocol population will be described or summarized in this SAP.

Safety Population

The safety population is defined as all subjects who receive at least one dose of study drug.

Per-Protocol Population

The per-protocol (PP) population is defined as subjects who meet the inclusion/exclusion criteria, complete Day 11, receive all four doses of study drug, and have provided for each study drug dose, at least 13 of the 15 PK blood samples.

4.2 Preliminary Data and Interim Analysis

Celerion Biometrics will not perform interim analyses.

5. TREATMENT DESCRIPTIONS

Treatment	Short Description	Long Description
Treatment A	30 mg Desmetramadol, fed	Desmetramadol 3 x 10 mg tablets, fed
Treatment B	30 mg Desmetramadol, fasted	Desmetramadol 3 x 10 mg tablets, fasted

Treatment	Short Description	Long Description
Treatment C	20 mg Desmetramadol, fasted	Desmetramadol 2 x 10 mg tablets, fasted
Treatment D	10 mg Desmetramadol, fasted	Desmetramadol 1 x 10 mg tablet, fasted

6. SAFETY

All relevant case report form (CRF) data will be listed by subject and chronologically by assessment time points. This will include rechecks, unscheduled assessments, and early termination. Note that SDTM.PC will not reside at Celerion and thus blood draw and urine collection data records will not be presented in the Celerion CSR/ appendix.

Applicable continuous variables will be summarized using n, arithmetic mean, SD, minimum, median, and maximum.

The level of precision will be presented as follows: minimum/maximum in the same precision as in the database, mean/median in one more precision level than minimum/maximum, SD in one more precision level than mean/median, and n will be presented as an integer. All percentages will be presented as an integer.

Where individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators.

6.1 Subject Disposition

Subjects will be summarized by number of subjects dosed, completed, and discontinued the study with discontinuation reasons by randomized treatment sequence and overall. This summary will also include the number of subjects in the per-protocol population and with criteria not met to be included in this population. The number of subjects with at least one protocol deviation will be summarized in this summary as well.

Note that number of subjects dosed is equivalent to number of subjects randomized.

A table will be provided that lists the subjects along with their individual dosing status. The number and percentage of subjects receiving each and all doses will be tabulated.

A table will be provided that lists the subjects along with their per-protocol population status and detail any applicable criteria that the subject didn’t qualify for this population.

6.2 Demographics

Descriptive statistics will be calculated for continuous variables (age, weight, height, and body mass index) by randomized treatment sequence and overall. Age will be derived from date of birth to date of first dosing.

Frequency counts will be provided for categorical variables (race, ethnicity, and sex) for each randomized treatment sequence and overall.

6.3 Adverse Events

All adverse events (AEs) occurring during this clinical trial will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), Version 23.1.

All AEs captured in the database will be listed in by-subject data listings including verbatim term, coded term, treatment, severity, relationship to study medication, and action; however, only treatment-emergent AEs (TEAEs) will be summarized.

A TEAE is defined as an AE that is starting or worsening at the time of or after study drug administration. Each TEAE will be attributed to a treatment based on the onset date and time of the AE. An AE that occurs during the washout period between drugs will be considered treatment-emergent to the last drug administered prior to onset of the AE.

If an AE increases in severity, that AE will be given a resolution date and time and a new record will be initiated with the new severity. If the severity of an AE remains the same or decreases, the AE will be kept open through to resolution.

TEAEs will be tabulated by System Organ Class (SOC) and Preferred Term. Summary tables will include number of subjects reporting the AE and as percent of number of subjects dosed by treatment. The number of AEs will be tabulated in a similar manner. Tables which tabulate the number of TEAEs by severity and relationship to study treatment will also be included.

Serious adverse events (SAEs), if present, will also be listed. Applicable narratives will be included in the CSR.

6.4 Clinical Laboratory Tests (Serum Chemistry, Hematology, Coagulation and Urinalysis)

Samples will be collected for hematology and serum chemistry at Screening and End of Study. Urinalysis and coagulation will only be collected at Screening.

Out-of-normal range flags will be recorded as follows: high (H) and low (L) for numerical results and did-not-match (*) for categorical results. Out-of-range values and corresponding recheck results will be listed.

For hematology and serum chemistry, descriptive statistics will be presented for each laboratory test by assessment time point and randomized treatment sequence. Change from Screening will be included in this summary. Screening is defined as the result closest and prior to dose which may include unscheduled or recheck results. Postdose unscheduled events or rechecks will not be included in summaries. Similarly early termination results will not be included in summaries.

For each laboratory test, a shift table will be developed to compare the frequency of the results at Screening (above normal, normal, or below normal) with the respective end of study results by randomized treatment sequence.

A tabulated summary of laboratory abnormalities by toxicity grade will also be provided.

6.5 Vital Signs

Vitals signs (systolic, diastolic, pulse, respiration rate, temperature) will be evaluated at the following study days: Screening, Day -1, End of Study as well as predose and 1 hour after the dose for each treatment. Screening will not be summarize.

For all vital signs, descriptive statistics (n, mean, SD, minimum, median, maximum) will be presented for each parameter by assessment time point and treatment. Change from baseline will be summarized in a similar manner. Baseline is defined as the result closest and prior to dose which may include unscheduled or recheck results. This will typically be the result collected prior and closest to the dose in each treatment. Postdose unscheduled events or rechecks will not be included in summaries. Similarly early termination results will not be included in summaries.

6.6 Electrocardiogram

ECG measurements (HR, PR, QRS, QT, QT corrected for heart rate using Fridericia's correction [QTcF] and RR) will be evaluated at Screening. Descriptive statistics (n, mean, SD, minimum, median, maximum) will be presented for each parameter by randomized treatment sequence.

Please note there is no ECG measured after treatment administered.

6.7 Concomitant Medications

All concomitant medications recorded during the study will be coded with the WHO Dictionary 01-SEP-2020 b2 and listed.

6.8 Physical Examination

Physical examinations will be performed at Screening and Day -1. Abnormal findings will be reported as medical history or adverse events. All data found in the CRF will be listed.

7. SUMMARY OF CHANGES FROM PROTOCOL-PLANNED ANALYSIS

The protocol outlined that clinical laboratory results would be summarized by treatment, however, this data was not collected by treatment and thus it's summarized by randomized treatment sequence. The protocol outlined that physical examinations would be summarized; however, this was documented as performed/not performed and thus is not summarized.

8. SUMMARY TABLES

Summary tables are numbered following the International Conference on Harmonization (ICH) structure but may be renumbered as appropriate during the compilation of the tables and figures for the CSR. Note that safety summary tables and figures will be generated using SAS® Version 9.4 or higher.

8.1 In-text Summary Tables and Figures

The following is a list of table and figure titles that will be included in the text of the CSR. Tables and figures will be numbered appropriately during compilation of the CSR.

Section 10:

Table 10-1	Subject Disposition Summary

Section 11:

Table 11-1	Demographic Summary by Randomized Treatment Sequence (Safety Population)

Section 12:

Table 12-1	Treatment-Emergent Adverse Event Frequency by Treatment - Number of Subjects Reporting the Event (% of Subjects Dosed)

8.2 Section 14 Summary Tables

The following is a list of table titles that will be included in Section 14 of the report. Table titles may be renumbered as appropriate during the compilation of the report.

14.1 Demographic Data Summary Tables

Table 14.1.1	Disposition Summary

Table 14.1.2	Subject Dosing Status and Study Disposition (Safety Population)
Table 14.1.3	Per-Protocol Population Status and Study Disposition (Safety Population)
Table 14.1.4	Demographic Summary (Safety Population)

14.3 Safety Data Summary Tables

14.3.1 Displays of Adverse Events

Table 14.3.1.1	Treatment-Emergent Adverse Event Frequency by Treatment – Number of Subjects Reporting the Event (% of Subject Dosed) (Safety Population)
Table 14.3.1.2	Treatment-Emergent Adverse Event Frequency by Treatment – Number of Adverse Events (% of Total Adverse Events) (Safety Population)
Table 14.3.1.3	Treatment-Emergent Adverse Event Frequency by Treatment, Severity, and Relationship to Drug – Number of Adverse Events (Safety Population)

14.3.2 Listings of Deaths, other Serious and Significant Adverse Events

Table 14.3.2.1	Serious Adverse Events (Safety Population) If no serious adverse event occurred, a statement 'No serious adverse event is reported'

14.3.3 Narratives of Deaths, other Serious and Certain other Significant Adverse Events

14.3.4 Abnormal Laboratory Value Listing (each patient)

Table 14.3.4.1	Out-of-Range Values and Recheck Results – Serum Chemistry (Safety Population)
Table 14.3.4.2	Out-of-Range Values and Recheck Results – Hematology (Safety Population)

14.3.5 Displays of Other Laboratory, Vital Signs, Electrocardiogram, Physical Examination, and Other Safety Data

Table 14.3.5.1	Clinical Laboratory Summary and Change From Baseline – Serum Chemistry (Safety Population)
Table 14.3.5.2	Clinical Laboratory Shift From Baseline – Serum Chemistry (Safety Population)
Table 14.3.5.3	Clinical Laboratory Summary and Change From Baseline – Hematology (Safety Population)
Table 14.3.5.4	Clinical Laboratory Shift From Baseline – Hematology (Safety Population)
Table 14.3.5.5	Abnormal Clinical Laboratory – Toxicity Grade - Serum Chemistry (Safety Population)
Table 14.3.5.6	Abnormal Clinical Laboratory – Toxicity Grade - Hematology (Safety Population)
Table 14.3.5.7	Vital Sign Summary (Safety Population)
Table 14.3.5.8	Vital Sign Change From Baseline (Safety Population)
Table 14.3.5.9	12-Lead Electrocardiogram Summary (Safety Population)

8.3 Section 16 Data Listings

Hepatitis and HIV results that are provided by the clinical laboratory will not be presented in subject data listings and will not be included in any database transfer.

Data listings are numbered following the ICH structure but may be renumbered as appropriate during the compilation of the TFLs for the CSR. The following is a list of appendix numbers and titles that will be included as data listings.

The protocol referred to a sequential day across the study which is contrast to the CRF which includes four unique periods where each of the dosing occurs on study Day 1. The data listing will use the period and day found in the CRF.

16.1 Study Information

Appendix 16.1.9	Statistical Methods
Appendix 16.1.10.1	Clinical Laboratory Reference Ranges

16.2 Subject Data Listings

16.2.1 Subject Disposition

Appendix 16.2.1	Subject Disposition (Safety Population)

16.2.2 Protocol Deviations

Appendix 16.2.2	Protocol Deviations

Note: Appendix 16.2.2 is generated in MS Word for inclusion in the study report.

16.2.4 Demographic Data

Appendix 16.2.4.1	Demographics (Safety Population)
Appendix 16.2.4.2	Physical Examination (Safety Population)
Appendix 16.2.4.3	Medical and Surgical History (Safety Population)
Appendix 16.2.4.4	Substance Use (Safety Population)

16.2.5 Compliance and/or Drug Concentration Data

Appendix 16.2.5.1	Subject Eligibility (Safety Population)
Appendix 16.2.5.2	Test Compound Description (Safety Population)
Appendix 16.2.5.3	Test Compound Administration Times (Safety Population)
Appendix 16.2.5.4	Meal Times (Safety Population)
Appendix 16.2.5.5	Concomitant Medications (Safety Population)

16.2.7 Adverse Events Listings

Appendix 16.2.7.1	Adverse Events (I of II) (Safety Population)
Appendix 16.2.7.2	Adverse Events (II of II) (Safety Population)
Appendix 16.2.7.3	Adverse Event Preferred Term Classification (Safety Population)

16.2.8 Listings of Individual Laboratory Measurements and Other Safety Observations

16.2.8.1	**Clinical Laboratory Data**
Appendix 16.2.8.1.1	Clinical Laboratory Report - Serum Chemistry (Safety Population)
Appendix 16.2.8.1.2	Clinical Laboratory Report - Hematology (Safety Population)
Appendix 16.2.8.1.3	Clinical Laboratory Report - Coagulation (Safety Population)
Appendix 16.2.8.1.4	Clinical Laboratory Report - Urinalysis (Safety Population)
Appendix 16.2.8.1.5	Clinical Laboratory Report - Urine Drug Screening (Safety Population)
Appendix 16.2.8.1.6	Clinical Laboratory Report - Other (Safety Population)
Appendix 16.2.8.2	Vital Signs (Safety Population)
Appendix 16.2.8.3	12-Lead Electrocardiogram (Safety Population)

9. TABLE SHELLS

9.1 In-text Summary Tables Shells

In-text Table 10-1 will be in the following format:

Table 10-1 Subject Disposition Summary

	Randomized Treatment Sequence				
Number (%) of Subjects	**ABDC**	**BCAD**	**CDBA**	**DACB**	**Overall**
Dosed	XX (XXX%)	XX (XXX%)	XX (XXX%)	XX (XXX%)	XX (XXX%)
Completed Study	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Discontinued Early	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Per-protocol Population	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
With Protocol Deviation(s)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)

Treatment A: Desmetramadol 3 x 10 mg tablets, fed
Treatment B: Desmetramadol 3 x 10 mg tablets, fasted
Treatment C: Desmetramadol 2 x 10 mg tablets, fasted
Treatment D: Desmetramadol 1 x 10 mg tablets, fasted

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In-text Table 11-1 will be in the following format:

Table 11-1 Demographic Summary by Randomized Treatment Sequence (Safety Population)

		Randomized Treatment Sequence				
Trait	**Category/Statistics**	**ABDC**	**BCAD**	**CDBA**	**DACB**	**Overall**
Sex	Male	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	Female	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Race	Asian	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	Black or African American	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	White	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Ethnicity	Not Hispanic or Latino	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Age (yrs)	n	X	X	X	X	X
	Mean	X.X	X.X	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX	XX	XX
	Median	X.X	X.X	X.X	X.X	X.X
	Maximum	XX	XX	XX	XX	XX
Weight (kg)	n	X	X	X	X	X
	Mean	X.X	X.X	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX	XX	XX
	Median	X.X	X.X	X.X	X.X	X.X
	Maximum	XX	XX	XX	XX	XX
Height (cm)	n	X	X	X	X	X
	Mean	X.X	X.X	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX	X.XX	X.XX

		Randomized Treatment Sequence				
Trait	**Category/Statistics**	**ABDC**	**BCAD**	**CDBA**	**DACB**	**Overall**
	Minimum	XX	XX	XX	XX	XX
	Median	X.X	X.X	X.X	X.X	X.X
	Maximum	XX	XX	XX	XX	XX
BMI (kg/m^2)	n	X	X	X	X	X
	Mean	X.X	X.X	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX	XX	XX
	Median	X.X	X.X	X.X	X.X	X.X
	Maximum	XX	XX	XX	XX	XX

Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

BMI = Body mass index
Age is at the time of first dose.

Source: Table 14.1.4

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In-text Table 12-1 will be in the following format:

Table 12-1 Treatment-Emergent Adverse Event Frequency by Treatment- Number of Subjects Reporting the Event (% of Subjects Dosed)

	Treatment				
Treatment-Emergent Adverse Events	**A**	**B**	**C**	**D**	**Overall**
Number of Subjects Dosed	XX (XXX%)	XX (XXX%)	XX (XXX%)	XX (XXX%)	XX (XXX%)
Number of Subjects With Treatment-Emergent Adverse Events	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Number of Subjects Without Treatment-Emergent Adverse Events	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
General disorders and administration site conditions	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Vessel puncture site pain	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Vessel puncture site reaction	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)

Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Adverse events are classified according to MedDRA® Version 23.1
Although a subject may have had 2 or more adverse events, the subject is counted only once within a category. The same subject may appear in different categories.

Source: Table 14.3.1.1

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9.2 Section 14 Summary Tables Shells

Table 14.1.1 Disposition Summary

	Randomized Treatment Sequence				
Number (%) of Subjects	ABDC	BCAD	CDBA	DACB	Overall
Dosed	XX (XXX%)	XX (XXX%)	XX (XXX%)	XX (XXX%)	XX (XXX%)
Completed Study	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Discontinued Early	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Personal reason	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Adverse Event	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Per-protocol Population	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Inc/exc violation	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Not completed on Day 11*	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Didn't achieve 13 PK samples^	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
With Protocol Deviation(s)#	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)

Treatment A: Desmetramadol 3 x 10 mg tablets, fed
Treatment B: Desmetramadol 3 x 10 mg tablets, fasted
Treatment C: Desmetramadol 2 x 10 mg tablets, fasted
Treatment D: Desmetramadol 1 x 10 mg tablets, fasted

Note: * Subject is not considered to complete Day 11 (Period 4 Day 2) if they discontinue the study early.
^ For each of the four treatments.
# Subjects who have at least one protocol deviation

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Table 14.1.2 Subject Dosing Status and Study Disposition (Safety Population)

Subject Number	Randomized Treatment Sequence	Dosed A	Dosed B	Dosed C	Dosed D	Dosed All doses	Study Completion Status	Date
X	ABDC	Yes	No	No	No	No	Terminated Study Prematurely	DDMONYYYY
X	BCAD	Yes	Yes	Yes	Yes	Yes	Completed Study	DDMONYYYY
X	CDBA	Yes	Yes	Yes	Yes	Yes	Completed Study	DDMONYYYY
X	DACB	Yes	Yes	Yes	Yes	Yes	Completed Study	DDMONYYYY
		XX(XX%)	XX(XX%)	XX(XX%)	XX(XX%)	XX(XX%)		

Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Programmer Notes: Please refer to Section 5 for the description of Treatments.

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Table 14.1.3 Per-Protocol Population Status and Study Disposition (Safety Population)

Subject Number	Randomized Treatment Sequence	Per-Protocol Population	Criteria that not qualified	Date
X	ABDC	No	Not completed on Day 11	DDMONYYYY
X	BCAD	Yes		DDMONYYYY
X	CDBA	No	Inc/exc violation	DDMONYYYY
X	DACB	Yes		DDMONYYYY

		XX(XX%)		

Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Programmer Notes: Please refer to Section 5 for the description of Treatments.

Program: /CAXXXXX/sas_prg/stsas/tab PROGRAMNAME.sas DDMMMYYYY HH:MM

Table 14.1.4 Demographic Summary (Safety Population)

Trait		Randomized Treatment Sequence ABDC	DACB	CDBA	BCAD	Overall
Sex	Male	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	Female	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Race	American Indian Or Alaska Native	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	Asian	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
	Black or African American	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Ethnicity	Not Hispanic or Latino	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)	X (XX.X%)
Age* (yrs)	n	X	X	X	X	X
	Mean	X.X	X.X	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX	XX	XX
	Median	X.X	X.X	X.X	X.X	X.X
	Maximum	XX	XX	XX	XX	XX
Weight (kg)	n	X	X	X	X	X
	Mean	X.X	X.X	X.X	X.X	X.X
	SD	X.XX	X.XX	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX	XX	XX
	Median	X.X	X.X	X.X	X.X	X.X
	Maximum	XX	XX	XX	XX	XX

Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Note: *Age is at the time of first dose.
Programmer notes: Please include BMI and height as well.

Program: /AAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Table 14.3.1.1 Treatment-Emergent Adverse Event Frequency by Treatment –
Number of Subjects Reporting the Event (% of Subjects Dosed) (Safety Population)

	Treatment				
Adverse Event	A	B	C	D	Overall
Number of Subjects Dosed	XX (XXX%)	XX (XXX%)	XX (XXX%)	XX (XXX%)	XX (XXX%)
Number of Subjects With TEAEs	X (X%)	X (X%)	X (XX%)	X (XX%)	X (XX%)
Number of Subjects Without TEAEs	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Eye disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Vision blurred	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Gastrointestinal disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Dyspepsia	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Nausea	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Musculoskeletal and connective tissue disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Back pain	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Muscle cramps	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Musculoskeletal pain	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Nervous system disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Headache NOS	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Reproductive system and breast disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Vaginal discharge	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Respiratory, thoracic and mediastinal disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Epistaxis	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Skin and subcutaneous tissue disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Sweating increased	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)

Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Note: Adverse events are classified according to MedDRA Version 23.1. TEAE = Treatment-emergent adverse events

Program: /AAXXXXX/ECR/sas_prg/stsas/tab progrname.sas DDMMMYYYY HH:MM

Table 14.3.1.2 Treatment-Emergent Adverse Event Frequency by Treatment – Number of Adverse Events (% of Total Adverse Events) (Safety Population)

	Treatment				
Adverse Event	A	B	C	D	Overall
Number of TEAEs	X (100%)	X (100%)	X (100%)	X (100%)	X (100%)
Eye disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Vision blurred	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Gastrointestinal disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Dyspepsia	X (XX%)	X (XX%)	X (XX%)	X (X%)	X (XX%)
Nausea	X (X%)	X (X%)	X (X%)	X (XX%)	X (X%)
Musculoskeletal and connective tissue disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Back pain	X (X%)	X (X%)	X (X%)	X (XX%)	X (X%)
Muscle cramps	X (XX%)	X (XX%)	X (XX%)	X (X%)	X (X%)
Musculoskeletal pain	X (X%)	X (X%)	X (X%)	X (XX%)	X (XX%)
Nervous system disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Headache NOS	X (X%)	X (X%)	X (X%)	X (XX%)	X (XX%)
Reproductive system and breast disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Vaginal discharge	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Respiratory, thoracic and mediastinal disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Epistaxis	X (X%)	X (X%)	X (X%)	X (XX%)	X (XX%)
Skin and subcutaneous tissue disorders	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)
Sweating increased	X (X%)	X (X%)	X (X%)	X (X%)	X (X%)

Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Note: Adverse events are classified according to MedDRA Version 23.1. TEAE = Treatment-emergent adverse events

Program: /AAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Table 14.3.1.3 Treatment-Emergent Adverse Event Frequency by Treatment, Severity, and Relationship to Drug – Number of Adverse Events (Safety Population)

		Number of Subjects With	Number of	Severity				Relationship to Study Product			
Adverse Event	Treatment	TEAEs	TEAEs	Mild	Moderate	Severe	Potentially Life-threatening	Definitely	Probably	Possibly	Not Related
Abdominal pain	A	X	X	X	X	X	X	X	X	X	X
Constipation	A	X	X	X	X	X	X	X	X	X	X
Dry throat	B	X	X	X	X	X	X	X	X	X	X
Dysmenorrhoea	B	X	X	X	X	X	X	X	X	X	X
Dyspepsia	D	X	X	X	X	X	X	X	X	X	X
Headache	A	X	X	X	X	X	X	X	X	X	X
Myalgia	C	X	X	X	X	X	X	X	X	X	X
Nasal congestion	B	X	X	X	X	X	X	X	X	X	X
Skin laceration	B	X	X	X	X	X	X	X	X	X	X
Treatment A		X	X	X	X	X	X	X	X	X	X
Treatment B		X	X	X	X	X	X	X	X	X	X
Treatment C		X	X	X	X	X	X	X	X	X	X
Treatment D		X	X	X	X	X	X	X	X	X	X
Overall		X	X	X	X	X	X	X	X	X	X

Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Note: Adverse events are classified according to MedDRA Version 23.1 TEAE = Treatment-emergent adverse events

Program: /AAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Table 14.3.2.1 Serious Adverse Events (Safety Population)

Will match 16.2.7

Or contain statement as follows:

"There were no serious adverse events recorded during the study."

Program: /AAXXXXX/ECR/sas_prg/stsas/programname.sas DDMMMYYYY HH:MM

Table 14.3.4.1 Out-of-Range Values and Recheck Results - Serum Chemistry (Safety Population)

Subject Number	Age/ Sex	Study Period	Day	Hour	Date	Time	Parameter1 <Range> (Unit)	Parameter2 <Range> (Unit)	Parameter3 <Range> (Unit)	Parameter4 <Range> (Unit)
X	XX/X	Screen	.	.	DDMMMYYYY	HH:MM:SS	XX H			XX H
		1	-X	-XX.XX	DDMMMYYYY	HH:MM:SS	XX L	XX L	XX L	

F = Female, M = Male
H = Above reference range, L = Below reference range

Programmer Notes: Replace Parameter1, 2 etc. with actual lab tests in the study. Sort unscheduled assessment and early termination chronologically with other scheduled assessments and rechecks. Recheck should be sorted with the scheduled time point the recheck is for.

Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Table 14.3.4.2 will resemble Table 14.3.4.1.

Table 14.3.5.1 Clinical Laboratory Summary and Change From Baseline – Serum Chemistry (Safety Population)

Laboratory Test (units)	Normal Range	Time Point	Statistic	Randomized Treatment Sequence ABDC	BCAD	CDBA	DACB
Testname (unit)	< - >#	Screening	n	X	X	X	X
			Mean	X.X*	X.X	X.X	X.X
			SD	X.XX	X.XX	X.XX	X.XX
			Minimum	XX	XX	XX	XX
			Median	X.X	X.X	X.X	X.X
			Maximum	XX	XX	XX	XX
Testname (unit)	< - >#	End of Study	n	X	X	X	X
			Mean	XX.XX	XX.XX	XX.XX^	XX.XX
			SD	X.XXX	X.XXX	X.XXX	X.XXX
			Minimum	XX.X	XX.X	XX.X	XX.X
			Median	XX.XX	XX.XX	XX.XX	XX.XX
			Maximum	XX.X	XX.X	XX.X	XX.X
Testname (unit)	< - >#	Change@	n	X	X	X	X
			Mean	XX.XX	XX.XX	XX.XX^	XX.XX
			SD	X.XXX	X.XXX	X.XXX	X.XXX
			Minimum	XX.X	XX.X	XX.X	XX.X
			Median	XX.XX	XX.XX	XX.XX	XX.XX
			Maximum	XX.X	XX.X	XX.X	XX.X

Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Note: # = Lowest of the lower ranges and highest of the higher ranges are used. Refer to Appendix 16.1.10.1 for the breakdown.
@ Change from baseline to end of study. Baseline is the screening measurement which is that collected closet and prior to first dose.

Programmer notes: Treatment means at specific time points will be flagged (with a *) if they are above or below the normal range. This only applies to the clinical laboratory treatment results (i.e., not the change from baseline or any other endpoints).

Program: /AAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Table 14.3.5.2 Clinical Laboratory Shift From Baseline - Serum Chemistry (Safety Population)

		Baseline L			Baseline N			Baseline H		
	Randomized Treatment	End of Study			End of Study			End of Study		
Laboratory Test (units)	Sequence	L	N	H	L	N	H	L	N	H
Testname (unit)	ABDC	X	XX	X	X	XX	X	X	XX	X
	BCAD	X	XX	X	X	XX	X	X	XX	X
	CDBA	X	XX	X	X	XX	X	X	XX	X
	DACB	X	XX	X	X	XX	X	X	XX	X

Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Note: N = Within Normal Range, L = Below Normal Range, H = Above Normal Range
Baseline is the screening measurement which is that collected closet and prior to first dose.

Program: /AAXXXXX/ECR/sas_prg/stsas/tab programame.sas DDMMMYYYY HH:MM

Table 14.3.5.3 will resemble Table 14.3.5.1
Table 14.3.5.4 will resemble Table 14.3.5.2

Table 14.3.5.5 Abnormal Clinical Laboratory – Toxicity Grade - Serum Chemistry (Safety Population)

Laboratory Test (units)	Time Point@	Grade	Randomized Treatment Sequence				
			ABDC N=XX n (%)	BCAD N=XX n (%)	CDBA N=XX n (%)	DACB N=XX n (%)	Overall n (%)
Testname (unit)	Screening	Grade 1	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
		Grade 2	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
	End of Study	Grade 2	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
	All*		<similar to above>				

Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Note: @Includes post-baseline measurements.
*All = The number of subjects who met this criteria at least once during the treatment category.

Programmer notes: Only rows with at least one subject will be present.

Program: /AAXXXXX/ECR/sas_prg/stsas/tab programe.sas DDMMMYYYY HH:MM

Table 14.3.5.6 will resemble Table 14.3.5.5

Table 14.3.5.7 Vital Sign Summary (Safety Population)

			Treatment			
Vital Sign (units)	Time Point	Statistic	A	B	C	D
Testname (unit)	Baseline	n	X	X	X	X
		Mean	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX
		Median	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX
Testname (unit)	Hour 1	n	X	X	X	X
		Mean	XX.XX	XX.XX	XX.XX	XX.XX
		SD	X.XXX	X.XXX	X.XXX	X.XXX
		Minimum	XX.X	XX.X	XX.X	XX.X
		Median	XX.XX	XX.XX	XX.XX	XX.XX
		Maximum	XX.X	XX.X	XX.X	XX.X
	End of Study	n	X	X	X	X
		Mean	XX.XX	XX.XX	XX.XX	XX.XX
		SD	X.XXX	X.XXX	X.XXX	X.XXX
		Minimum	XX.X	XX.X	XX.X	XX.X
		Median	XX.XX	XX.XX	XX.XX	XX.XX
		Maximum	XX.X	XX.X	XX.X	XX.X

Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Note: Baseline is the screening measurement which is that collected closet and prior to first dose.

Program: /AAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Table 14.3.5.8 Vital Sign Change From Baseline (Safety Population)

			Treatment			
Vital Sign (units)	Time Point	Statistic	A	B	C	D
Testname (unit)	Change from Baseline to Hour 1	n	X	X	X	X
		Mean	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX
		Median	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX
	Change from Baseline to End of Study	n	X	X	X	X
		Mean	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX
		Median	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX

Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Note: Baseline is the screening measurement which is that collected closet and prior to first dose.

Program: /AAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

Table 14.3.5.9 12-Lead Electrocardiogram Summary (Safety Population)

			Randomized Treatment Sequence			
Measurement (units)	Time Point	Statistic	ABDC	BCAD	CDBA	DACB
Testname (unit)	Screening	n	X	X	X	X
		Mean	X.X	X.X	X.X	X.X
		SD	X.XX	X.XX	X.XX	X.XX
		Minimum	XX	XX	XX	XX
		Median	X.X	X.X	X.X	X.X
		Maximum	XX	XX	XX	XX

Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Program: /AAXXXXX/ECR/sas_prg/stsas/tab programname.sas DDMMMYYYY HH:MM

10. LISTING SHELLS

Appendix 16.1.10.1 Clinical Laboratory Reference Ranges

Laboratory Group	Test Name	Sex	Age Category	Reference Range	Unit	
Serum Chemistry	Testname1	MALE	0-25	XX - XXX	mEq/L	
	Testname2	MALE	26-99	XX - XXX	U/L	
				XX - XXX	U/L	
	<similar for all other tests note that age will only be presented when different normal range exists>					
Hematology	<similar to serum chemistry>					
Urinalysis	Testname	MALE		NEGATIVE	Urine Drug Screening	
	Amphetamines	MALE		NOT DETECTED		

Program: /CAXXXXX/sas_prg/stsas/standardlis/cdash_lis_lno.sas 27NOV2015 18:34

Appendix 16.2.1 Subject Disposition (Safety Population)

Subject Number	Randomization Sequence	Actual Sequence	Study Period	Date	Completed Study?	Primary Discontinuation Reason	If Discontinuation Reason is Other, Specify
1	ABDC	ABDC	Post	DDMONYYYY	YES		
2	CDBA	CDBA	Post	DDMONYYYY	YES		
3	BCAD	B_	Post	DDMONYYYY	NO	Adverse Event	

Treatment A: Desmetramadol 3 x 10 mg tablets, fed
Treatment B: Desmetramadol 3 x 10 mg tablets, fasted
Treatment C: Desmetramadol 2 x 10 mg tablets, fasted
Treatment D: Desmetramadol 1 x 10 mg tablets, fasted

Programmer Notes: If the discontinuation reason is "Other", please specify.

Program: /CAXXXXX/sas_prg/stsas/standardlis/cdash_lis_dis.sas 27NOV2015 18:35

Appendix 16.2.4.1 Demographics (Safety Population)

Subject Number	Year Of Birth	Age* (yrs)	Sex	Race	Ethnicity	Height (cm)	Weight (kg)	Body Mass Index (kg/m²)	Informed Consent Date
1	YYYY	47	Male	< >	Not Hispanic or Latino	XXX	XX.X	XX.XX	DDMMMYYYY
2	<similar to above.>								

Note: *Age is at the time of first dose.

Program: /CAXXXXX/sas_prg/stsas/standardlis/cdash_lis_dem.sas 27NOV2015 18:35

Appendix 16.2.4.2 Physical Examination (Safety Population)

Subject Number	Study Period	Day	Hour	Date	Question	Result
1	Screen			DDMONYYYY	Was PE performed? (Yes/No)	YES
	1	-1	-17.0	DDMONYYYY	Was PE performed? (Yes/No)	NO
2	Screen			DDMONYYYY	Was PE performed? (Yes/No)	YES
	1	-1	-17.0	DDMONYYYY	Was PE performed? (Yes/No)	NO

Program: /CAXXXXX/sas_prg/stsas/standardlis/cdash_lis_phy_best_practice.sas 27NOV2015 18:35

Appendix 16.2.4.3 Medical and Surgical History (Safety Population)

Subject Number	Any History?	Date Start	Date End	Ongoing?	Condition or Event
1	No				
2	Yes	YYYY		YES	< >

<note date can be YYYY, MONYYYY, or DDMONYYYY based on individual subject data>

Program: /CAXXXXX/sas_prg/stsas/standardlis/cdash_lis_mh.sas 27NOV2015 18:35

Appendix 16.2.4.4 Substance Use (Safety Population)

Subject Number	Substance	Description of Use	Start Date	End Date
1	Tobacco Use	NON-SMOKER	03DEC1967	06OCT2016
		0-4 CIGARETTES WEEK	06OCT2016	
2	Tobacco Use	NON-SMOKER	DDMONYYYY	

Program: /CAXXXXX/sas_prg/stsas/standardlis/cdash_lis_su.sas 27NOV2015 18:35

Appendix 16.2.5.1 Subject Eligibility (Safety Population)

Subject Number	Study Period	Did subject meet all eligibility criteria?	Specify
1	Screen	YES	
2	Screen	NO	<This column is only presented if data are present.>

Program: /CAXXXXX/sas_prg/stsas/standardlis/cdash_lis_ie.sas 27NOV2015 18:35

Appendix 16.2.5.2 Test Compound Description

Compound	Form	Route
< >	SOLUTION	ORAL

Program: /CAXXXXX/sas_prg/stsas/standardlis/cdash_lis_med.sas 27NOV2015 18:35

Appendix 16.2.5.3 Test Compound Administration Times (Safety Population)

Subject Number	Study Period	Treatment	Day	Hour	Actual Date	Actual Time	Compound	Planned Dosage	Comments
1	1	A	1	0.0	DDMONYYYY	HH:MM:SS	< >	500 NCI	<This column prints only if data is present>

Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Program: /CAXXXXX/sas_prg/stsas/standardlis/cdash_lis_med2.sas 27NOV2015 18:35

Appendix 16.2.5.4 Meal Times (Safety Population)

Subject Number	Study Period	Treatment	Day	Timed Hour	Timed Interval#	Event	Start Date	Start Time	Stop Time
1	1	A	-1	-15.0		DINNER	DDMONYYYY	HH:MM:SS	HH:MM:SS
				-11.0		SNACK	DDMONYYYY	HH:MM:SS	HH:MM:SS
			1	4.1		LUNCH	DDMONYYYY	HH:MM:SS	HH:MM:SS

Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Note: #Start HR to Stop HR

Program: /CAXXXXX/sas_prg/stsas/standardlis/cdash_lis_mel.sas 27NOV2015 18:35

Appendix 16.2.5.5 Concomitant Medications (Safety Population)

Subject Number	Any Medications?	Treat-ment	Medication (WHO DD*)	Dosage	Route	Start Date	Start Time	Stop Date	Stop Time	Frequency	Indication	Ongoing
1	NO		None									
2	NO		None									
3	YES	B	CETIRIZINE (CETIRIZINE)	X MG	BY MOUTH	DDMONYYYY	UNK	DDMONYYYY	HH:MM	XXXXXXX	XXXXXXX	NO
			PARACETAMOL (PARACETAMOL)	X MG	XXXXXXXXX	DDMONYYYY	HH:MM	XXXXXXXX	HH:MM	XXXXXXXX	XXXXXXXX	XX

Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Note: *Concomitant medications are coded with WHO Dictionary Version 01-SEP-2020 b2.
UNK = Unknown, WHO DD = World Health Organization Drug Dictionary

Program: /CAXXXXX/sas_prg/stsas/standardlis/cdash_lis_con.sas 27NOV2015 18:35

Appendix 16.2.7.1.1 Adverse Events (I of II) (Safety Population)

Subject Number	Treatment	TE?^	Adverse Event	Preferred Term*	Time From Last Dose (DD:HH:MM)	Start Date	Start Time	End Date	End Time	Duration (DD:HH:MM)
1			None							
2			None							
3		No	XXXXXXXXXXXXX XXXXXXXXXXXXXXXXX	XXXXXXXXXXXXXXXXX XXXXXXXXXXXX	XX:XX:XX	DDMONYYYY	HH:MM	DDMONYYYY	HH:MM	DD:HH:MM
	B	Yes	XXXXXXXXXXXXXXXXX	XXXXXXXXXXXXXXXXXXXXXX	<similar to above>					

Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Note: *Adverse events are classified according to MedDRA Version 23.1.
^ = Abbreviation for treatment-emergent.

Program: /CAXXXXX/sas_prg/stsas/standardlis/cdash_lis_ae.sas 27NOV2015 18:35

Appendix 16.2.7.1.2 Adverse Events (II of II) (Safety Population)

Subject Number	Treatment	Adverse Event	Onset Date	Onset Time	Freq^	Severity	Ser*	Outcome	Relationship to Study Product	Action
1		None								
2		None								
3		XXXXXXXXXXXXXXXXXXXX	DDMONYYYY	XX:XX	Cont.	Mild	NS	Resolved	Unrelated	None
	B	XXXXXXXXXXXXXXXXXXXX	DDMONYYYY	XX:XX	<similar to above>					

Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Note: Ser* represents Serious: NS = Not Serious
Freq^ represents Frequency: SE = Single Episode, Inter. = Intermittent, Cont. = Continuous

Programmer Notes: When there is a serious event, create another listing that provides details.

Program: /CAXXXXX/sas_prg/stsas/standardlis/cdash_lis_ae2.sas 27NOV2015 18:35

Appendix 16.2.7.3 Adverse Event Preferred Term Classification (Safety Population)

Subject Number	Treatment	Adverse Event	Preferred Term*	System Organ Class	Onset Date	Onset Time
1		None				
2		None				
3		XXXXXXXXXXXXXXXX	XXXXXXXXXXXXXXXXXXXXX	XXXXXXXXXXXXXXXXXXXX	DDMONYYYY	HH:MM
	B	XXXXXXXXXXXXXXXXXXXXXXX	XXXXXXXXXXXXXXXXXXXXX	XXXXXXXXXXXXXXXXXXXXXXXX	DDMONYYYY	HH:MM

Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Note: * Adverse events are classified according to MedDRA Version 23.1.

Program: /CAXXXXX/sas_prg/stsas/standardlis/cdash_lis_ae4.sas 27NOV2015 18:35

Appendix 16.2.8.1.1 Clinical Laboratory Report - Serum Chemistry (Safety Population)

Subject Number	Age#/ Sex	Study Period	Treat-ment	Day	Hour	Date	Chloride M: 97-105 (mEq/L)	Potassium M: 3.7-5.2 (mEq/L)	Phosphorus M: 2.4-4.4 (mg/dL)	Sodium M: 135-143 (mEq/L)
1	XX/M	Screen			.	DDMONYYYY	XXX	X.X	X.X	XXX H
1		1	A	1	X	DDMONYYYY	XXX H	X.X	X.X	XXX H
					Recheck	DDMONYYYY	XXX	X.X	X.X	XXX

<similar to above for all subjects/time points>

Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Note: # Age is at time of first dose. F = Female, M = Male
H = Above Normal Range

Program: /CAXXXXX/sas_prg/stsas/standardlis/cdash_lis_lab.sas 27NOV2015 18:44

Appendices 16.2.8.1.2 and 16.2.8.1.3 will resemble Appendix 16.2.8.1.1

Appendix 16.2.8.1.4 Clinical Laboratory Report - Urinalysis (Safety Population)

Subject Number	Age#/ Sex	Study Period	Date	Testname1	Testname2	Testname3	Testname4
1	XX/M	Screen	DDMONYYYY	XXX	X.X L	X.X	XXX H
<similar to above for all subjects>							

Note: # Age is at time of first dose. F = Female, M = Male
H = Above Normal Range
L = Below Normal Range

Program: /CAXXXXX/sas_prg/stsas/standardlis/cdash_lis_lab.sas 27NOV2015 18:44

Appendix 16.2.8.1.5 Clinical Laboratory Report – Urine Drug Screening (Safety Population)

Subject Number	Age#/ Sex	Study Period	Day	Date	Drugname1	Drugname2	Drugname3	Drugname4
1	XX/M	Screen		DDMONYYYY	Not Detected	Not Detected	Not Detected	Not Detected
			-1	DDMONYYYY	Not Detected	Not Detected	Not Detected	Not Detected

<similar to above for all subjects>

Note: # Age is at time of first dose. F = Female, M = Male
H = Above Normal Range
L = Below Normal Range

Program: /CAXXXXX/sas_prg/stsas/standardlis/cdash_lis_lab.sas 27NOV2015 18:44

Appendix 16.2.8.1.6 Clinical Laboratory Report - Other (Safety Population)

Subject Number	Age#/ Sex	Study Period	Date	Testname1	Testname2	Testname3	Testname4
1	XX/M	Screen	DDMONYYYY	XXX	X.X L	X.X	XXX H
<similar to above for all subjects>							

Note: # Age is at time of first dose. F = Female, M = Male
H = Above Normal Range
L = Below Normal Range

Program: /CAXXXXX/sas_prg/stsas/standardlis/cdash_lis_lab.sas 27NOV2015 18:44

Appendix 16.2.8.2 Vital Signs (Safety Population)

Subject Number	Study Period	Treatment	Day	Hour	Date	Time	Blood Pressure (mm Hg) Test	Blood Pressure (mm Hg) Sys/Dia	Pulse (bpm)	Respiration (brpm)	Temperature (°C)	Weight (kg)
1	Screen				DDMONYYYY	HH:MM:SS						XX.X
							SIT1	XXX/ XX	XX	XX	XX.X	
					R	HH:MM:SS	SIT1	XXX/ XX				
					R	HH:MM:SS	SIT1	XXX/ XX				
1		A	-1	-17.0	DDMONYYYY	HH:MM:SS	SIT1	XXX/ XX				

Treatment A: < >
Treatment B: < >
Treatment C: < >
Treatment D: < >

Note: SIT1 = 1-minute sitting, R = Recheck Value, brpm = breaths/min

Program: /CAXXXXX/sas_prg/stsas/standardlis/cdash_lis_vit.sas 27NOV2015 18:35

Appendix 16.2.8.3 12-Lead Electrocardiogram (Safety Population)

Subject Number	Study Period	Date	Time	Recheck	Result	Heart Rate (bpm)	PR (msec)	QRS (msec)	QT (msec)	QTcF* (msec)	RR (msec)	Specify/Comments
1	Screen	DDMONYYYY	X:XX:XX		ANCS	XX	XXX	XX	XXX	XXX	XXX	EARLY REPOLARIZATION; LEFT AXIS DEVIATION
2	Screen	DDMONYYYY	X:XX:XX	R		XX	XXX	XX	XXX	XXX	XXX	

Note: ANCS = Abnormal, Not Clinically Significant
QTcF* = QT corrected for heart rate using Fridericia's correction.

Program: /CAXXXXX/sas_prg/stsas/standardlis/cdash_lis_ecg.sas 27NOV2015 18:35