STATISTICAL ANALYSIS PLAN

CiloMecT: Effect of Cilostazol as an Add-on Treatment to a Single Antiplatelet Agent (Acetylsalicylic Acid or Clopidogrel) on Platelet Function Testing and Bleeding Time in Healthy Volunteers

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Otsuka Pharmaceutical Co., Ltd.

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Statistical Analysis Plan
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Table of Contents

List of In-text Figures

List of Appendices

List of Abbreviations and Definition of Terms

Abbreviation	Definition
ADP	Adenosine diphosphate
AE	Adverse event
ALT	Alanine aminotransferase
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BT	(Skin) Bleeding time
BMI	Body mass index
CI	Confidence interval
CYP	Cytochrome P450
ECG	Electrocardiogram
EudraCT	European Clinical Trial Data Base
FAS	Full analysis set
IMP	Investigational medicinal product
IPA	Inhibition of platelet aggregation
MedDRA	Medical Dictionary for Regulatory Activities
OPC	Otsuka Pharmaceutical Co.
PE	Physical examination
PRP	Platelet rich plasma
SAP	Statistical analysis plan
TEAE	Treatment-emergent adverse event
VASP	Vasodilator-stimulated phosphoprotein
WHO-DD	World Health Organization Drug Dictionary

1 Introduction

This statistical analysis plan (SAP) documents the statistical analysis methodology and data analysis algorithms and conventions to be applied for a statistical analysis and reporting of pharmacodynamic and safety data of Trial 21-13-102. All amendments to the protocol are taken into consideration in developing the SAP.

2 Trial Objectives

The primary objective of this trial is to determine the effects of orally administered cilostazol 100 mg twice daily, Acetylsalicylic acid (ASA) 100 mg once daily or clopidogrel 75 mg once daily alone as well as in combination of cilostazol 100 mg twice daily/ clopidogrel 75 mg once daily or cilostazol 100 mg twice daily/ ASA 100 mg once daily on ex-vivo platelet function testing.

A key secondary objective is the effect of orally administered cilostazol 100 mg twice daily, ASA 100 mg once daily or clopidogrel 75 mg once daily alone as well as in combination of Cilostazol 100 mg twice daily/ clopidogrel 75 mg once daily or cilostazol 100 mg twice daily/ ASA 100 mg once daily on bleeding time in healthy subjects. While bleeding time is an important parameter in this regard it also does exhibit a higher level of intra- as well as interindividual variability and an additional tissue dependent variability. Therefore, bleeding time is evaluated as a key secondary parameter.

In addition, the effects of a combined administration of cilostazol 100 mg twice daily/ clopidogrel 75 mg once daily in subjects with a homozygous wildtype allele of *CYP2C19 (*1/*1)* showing normal *CYP2C19* activity will be compared with the effects of subjects carrying either the heterozygous *CYP2C19 (*1/*2)* isoform and with subjects carrying the homozygous *CYP2C19 (*2/*2)* isoforms, displaying a intermediate and poor *CYP2C19* activity, respectively.

A further secondary objective is to assess the safety variables after the orally administration of cilostazol 100 mg twice daily, ASA 100 mg once daily or clopidogrel 75 mg once daily alone as well as a combination of cilostazol 100 mg twice daily/ clopidogrel 75 mg once daily or cilostazol 100 mg twice daily/ ASA 100 mg once daily.

3 Trial Design

3.1 Type/Design of Trial

An open-label, single center, parallel group trial in healthy volunteers.

The trial will be conducted at one (1) investigational site in Germany.

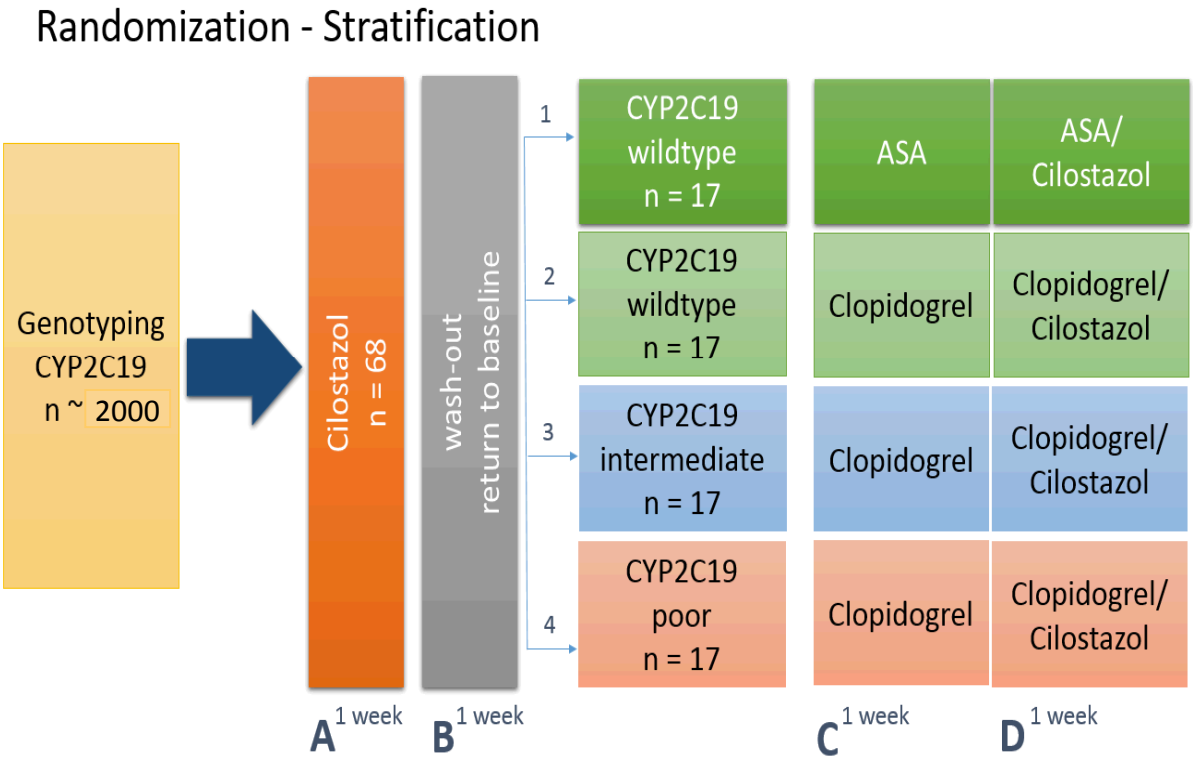

Figure 3.1-1 Trial Design Schematic

3.2 Trial Treatments

After signing screening informed consent, approximately 2000 subjects will be screened to evaluate inclusion/ exclusion criteria and to determine subjects *CYP2C19* genotype.

Screening will be performed until:

at least 38 (34+ 4 = replacements) subjects with *CYP2C19 wildtype allele (*1/*1)* (normal *CYP2C19* activity)

and

at least 19 (17+2 = replacements) subjects with *CYP2C19 heterozygous (*1/*2)* isoform (intermediate *CYP2C19* activity)

and

at least 19 (17+2 = replacements) subjects with *CYP2C19 homozygous (*2/*2)* isoform (poor *CYP2C19* activity) have been identified and screened.

For the purpose of statistical analyses 34 evaluable subjects with normal *CYP2C19* activity, 17 evaluable subjects with intermediate *CYP2C19* activity, and 17 evaluable subjects with low *CYP2C19* activity are required. Subjects who are considered not evaluable after the start of the trial (eg, due to early termination, or protocol violatin) will be replaced. Any replacement subjects must begin the trial at the start of the protocol.

The stated number of replacements for the individual study groups are estimates and may become higher in the case that data of unexpectedly high numbers of subjects are found to be of not evaluable in the course of the study.

All subjects suitable for enrolment/randomization are required to meet all inclusion criteria and no exclusion criterion.

The *CYP2C19* genotype will be determined by commercially-available technology. The Spartan RX® System will be used, allowing determination of the *CYP2C19* phenotype within 60 minutes in the patient's saliva. The assay allows to discriminate between the *CYP2C19 wildtype allele (*1/*1*, normal *CYP2C19* activity), *heterozygous (*1/*2*, low *CYP2C19* activity) and *homozygous* (*2/*2*, low *CYP2C19* activity) alleles.

The assay directly detects the *CYP2C19*2*, *3*, and *17* alleles. Besides the *1* allele these are the alleles with the highest frequency in Caucasian populations. The system

reports for each allele whether none, one or two copies of it are detected. Detection of one or two **2* alleles, for example, allows to determine whether the test subject has a *CYP2C19*1/*2* or *CYP2C19*2/*2* genotype. If no copy of the **2*, **3* or **17* alleles is detected it can be concluded that the test subject has a **1/*1* genotype.

The Spartan RX® *CYP2C19* system is certified in Europe and the testing will be performed by trained investigational site staff.

After signing treatment informed consent, 68 subjects will undergo further screening procedures in order to determine baseline characteristics. Subjects failing these procedures will be replaced by screened subjects matching the genotype (normal, intermediate or poor *CYP2C19* activity).

All 68 subjects will then be included in the treatment phase of the trial and will receive during the first week cilostazol 100 mg twice daily for 1 week (trial period A), followed by a 1 week wash-out period (trial period B, return to baseline). Subjects who fail to return to baseline with respect to platelet function testing and skin bleeding time will be re-tested within a further week.

Subjects will be stratified and randomized into 4 treatment groups according to their *CYP2C19* genotype (normal or low *CYP2C19* activity).

- Treatment group 1 will consist of subjects with CYP2C19 wildtype allele (*1/*1) and will receive standard doses of ASA 100 mg/day (Group 1, n=17) for 1 week (trial period C).
- Treatment group 2 will consist of subjects with CYP2C19 wildtype allele (*1/*1) and will receive standard doses of clopidogrel 75 mg/day (Group 2, n=17) for 1 week (trial period C).
- Treatment group 3 will consist of subjects with CYP2C19 heterozygous (*1/*2) isoform and will receive standard doses of clopidogrel 75 mg/day (Group 3, n=17) for 1 week (trial period C).
- Treatment group 4 will consist of subjects with CYP2C19 homozygous (*2/*2) isoform and will receive standard doses of clopidogrel 75 mg/day (Group 3, n=17) for 1 week (trial period C).

In the following week subjects in all treatment groups will receive cilostazol 100 mg twice daily for 1 week on top as an add-on therapy (trial period D).

Drug intake of ASA and clopidogrel will be in the morning hours, for cilostazol drug intake will be twice daily: once in the morning and once in the evening.

3.3 Trial Population

3.3.1 Number of Subjects and Description of Population

Approximately 2000 subjects will be screened and their *CYP2C19* genotype will be determined in order to identify at least 17 + 2 subjects with *CYP2C19 heterozygous (*1/*2)* isoform (Group 3) and 17 + 2 subjects with *CYP2C19 homozygous (*2/*2) isoforms* (Group 4) and at least 34 + 4 subjects with *CYP2C19 wildtype allele (*1/*1)* (Group 1+2).

This number of approximately 2000 subjects in screening is based on the published ~30% prevalence of *CYP2C19 heterozygous (*1/*2)* and 2% to 5% of *CYP2C19 homozygous (*2/*2)* isoforms in the Caucasian population and under consideration of the fact that the **2* isoform is closer to the lower end of probability in the German population.

A total of 68 healthy male volunteers, aged 18 to 45 years, will be dosed with trial medication and complete all trial procedures and periods. Trial participants who will early terminate their trial participation will be replaced. If the scheduled evaluation of the primary efficacy parameter (outlined in Section 6.1) cannot be performed (e.g. for technical reasons), additional subjects may be enrolled at the sponsor's discretion in agreement with the principal investigator. Any replacement subjects must begin the trial at the start of the protocol.

3.3.2 Subject Selection and Numbering

The investigational site will identify potential trial participants and perform screening procedures. Screened subjects will be assigned a unique identification number. The investigational site will maintain a confidential list identifying all subjects.

3.4 Trial Visit Window

Nominal visit will be used as analysis visit for analyses. The data from unscheduled visits will be not included in the summary tables.

4 Sample Size

The primary variable of the trial is ex-vivo inhibition of platelet aggregation. Comparisons of the inhibition of platelet aggregation are made between subjects during treatment of reference medication alone (Reference) and during the concomitant treatment of reference medication and cilostazol (Test). When assuming that the expected platelet aggregation treatment mean ratio is 1 with a standard deviation of 27% (Angiolillo *et al*, 2011) [1], for showing equivalence of a single parameter, a sample size of 17 patients per group would be required to provide a 90% power. That is, with the crossover design, 17 subjects yield a probability of 0.95 to reject the null hypotheses that the platelet aggregation with treatment of cilostazol along with reference medication versus reference medication along is below 0.70 or above 1.43, ie, the 95% confidence interval (CI) is contained within the equivalence limit [0.70,1.43].

Ex-vivo inhibition of platelet aggregation is the primary endpoint of the study and accordingly study hypothesis and sample size estimation has been based on the primary endpoint. Similar considerations apply to the assessment of bleeding time, for which the biological variation is considered to be greater than for platelet aggregation, as it is affected additionally by tissue- or organ-dependent differences in the physiology of the vascular bed. The hypothesis tested for bleeding time will be analogue to these tested for platelet aggregation, however, the statistical power of treatment effects estimated for platelet aggregation does not apply to bleeding time.

5 Statistical Analysis Sets

5.1 Efficacy Analysis Set

There are no efficacy analyses in this trial.

5.2 Safety Analysis Set

All subjects who receive at least one dose of trial medication are included in the safety and demographic and baseline characteristic analyses.

5.3 Pharmacokinetic Analysis Set

There are no pharmacokinetic analyses in this trial.

5.4 Pharmacodynamic Analysis Set

Pharmacodynamic analyses will be conducted using the full analysis set (FAS) defined in the clinical trial protocol. All subjects who complete both periods of treatment with reference medication alone and treatment with reference medication and cilostazol are included in the pharmacodynamic analyses and demographic and baseline characteristic analyses.

5.5 Handling of Missing Data

No data imputation will be performed for missing data in this trial.

6 Primary and Secondary Outcome Variables

6.1 Primary Outcome Variables

The primary analysis variable of the trial is ex-vivo inhibition of platelet aggregation (IPA).

- Ex-vivo platelet function: primary parameters to be determined in citrated platelet rich plasma (PRP) by
  - Light transmission aggregometry (5 μM ADP, residual aggregation at 5 minutes)
  - Light transmission aggregometry (Arachidonic acid 500 mg/L, residual aggregation at 5 minutes)

For individual subjects, IPA is defined as the percentage decrease of platelet aggregation of stimulated plasma before and after treatments with trial medications.

IPA (%) = 100 × (platelet aggregation at baseline − platelet aggregation after treatment) / platelet aggregation at baseline

6.2 Secondary Outcome Variables

- Skin bleeding time (BT): to be determined with Ivy method utilizing standardized bleeding with Surgicutt® device
- Ex-vivo platelet function as determined by
  - Light transmission aggregometry in PRP (20 μM ADP, collagen 1 mg/L and 2.5 mg/L, TRAP 25 μM residual aggregation at 5 minutes)
  - Multiple electrode impedance aggregometry in hirudine-anticoagulated blood (Multiplate®) (ASPI test, ADP test, ADP/PGE test, TRAP test)
  - VerifyNowTM (P2Y12 and Aspirin test)
  - Vasodilator-stimulated phosphoprotein (VASP) by flow cytometry

- P-Selectin expression by flow cytometry (ADP-stimulated, TRAP-stimulated, Unstimulated)

7 Disposition and Demographic Analysis

7.1 Subject Disposition

The number of subjects screened, treated, randomized to IMP, and completed the trial or withdrawn from the trial will be presented for screened subjects. The number and percentage of subjects withdrawn from the trial will be summarized by reason for withdrawal for treated subjects.

7.2 Demographic and Baseline Characteristics

The descriptive statistics (mean, standard deviation, minimum, median, maximum) of age, height, body weight (at screening), and body mass index (BMI) will be calculated for each treatment group. The number and percentage of subjects for sex, race, ethnicity, and country will be summarized for each treatment group.

7.3 Medical History

Medical history will be listed by subject.

7.4 Treatment Compliance

Treatment compliance (name of treatment, start/end date of treatment, dose, route) will be listed by subject.

7.5 Prior and Concomitant Medication

Concomitant medications will be summarized by World Health Organization Drug Dictionary (WHO-DD) (March 2015) anatomical therapeutic chemical (ATC) classification and preferred name for each treatment group.

7.6 Protocol Deviations

Not applicable

8 Efficacy Analyses

Not applicable

9 Safety Analyses

9.1 Extent of Exposure

The number and percentage of subjects will be summarized according to the duration of exposure (end date of each treatment − start date of each treatment + 1) to investigational medicinal product (IMP) for each treatment group.

9.2 Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as adverse events (AEs) that occurred after the start of IMP administration. TEAEs by treatment regimen are classified as below:

- TEAEs for cilostazol alone: TEAEs that occurred from the start of IMP administration in Period A until the start of IMP administration in Period C
- TEAEs for the reference medication alone: TEAEs that occurred from the start of IMP administration in Period C until the start of IMP administration in Period D
- TEAEs for the reference medication and cilostazol: TEAEs that occurred after the start of IMP administration in Period D

All adverse events will be coded by Medical Dictionary for Regulatory Activities (version 20.0) system organ class and preferred term. The incidence of the following events will be summarized by treatment group and by treatment regimen:

- Treatment-emergent AEs (TEAEs)
- TEAEs by severity
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuations of the IMP

TEAEs causally related to the IMP (“Related”, “Possibly related” or “Unlikely related”) will be summarized in the same manner. If multiple occurrences of the same event are observed in the same subject during the same treatment regimen, the occurrence with the highest severity will be used for all analyses.

9.3 Clinical Laboratory Data

For each clinical laboratory test items, the descriptive statistics for measured values at each timepoint and changes from baseline will be summarized for each treatment group. Shift tables will be produced for assessing changes from baseline in status (low/normal/high in accordance with the reference range) for each treatment group. For qualitative urinalysis, shift tables of changes from baseline will be produced for each treatment group.

The data on Visit 1 (Day −14 to 0) is defined as baseline for all treatment groups.

The potential Hy's Law Cases (any increase of aspartate aminotransferase [AST] or alanine aminotransferase [ALT] of ≥ 3 times the upper normal limit or screening value with an increase in total bilirubin of ≥ 2 times the upper normal limit or screening value) will be listed by subject.

9.4 Vital Sign Data

The descriptive statistics of measured values at each timepoint and changes from baseline will be summarized by treatment group.

The data on Visit 1 (Day −14 to 0) is defined as baseline for all treatment groups.

9.5 Physical Examination Data

Physical examination (PE) findings will be listed by subject. For body weight, the descriptive statistics of measured value at each timepoint and changes from baseline will be summarized by treatment group.

The data on Visit 1 (Day −14 to 0) is defined as baseline for all treatment groups.

9.6 Electrocardiogram Data

Shift table of abnormality in electrocardiogram (ECG) findings will be produced for each treatment group.

The data on Visit 1 (Day −14 to 0) is defined as baseline for all treatment groups.

10 Pharmacokinetic Analyses

There are no pharmacokinetic analyses in this trial.

11 Pharmacodynamic Analyses

11.1 Statistical Analyses of Primary Pharmacodynamic Endpoints

11.1.1 Inhibition of Platelet Aggregation

1) Equivalence will be indicated if the 95% confidence interval (CI) for the ratio (Test/Reference) of the IPA is contained within the equivalence limits of 0.70 to 1.43 for each parameter of platelet aggregation.

   Primary Analysis will be performed on the natural-log transformed IPA. The mixed-effect linear model for each parameter will include a term for treatment regimen as a fixed effect, and a term for subject as a random effect. From each analysis, the least squares treatment means and difference (T - R) and the 95% CI for the treatment difference will be obtained. Then, the antilogs of the difference and the confidence limits will provide the estimate and 95% CI for the ratio (T/R) of the geometric means of platelet aggregation parameters of the test and reference.

   This method will be used to compare drugs/combinations, ie, cilostazol/clopidogrel vs clopidogrel alone; cilostazol/ASA vs ASA alone, as well as the different genotype combinations.

   For the not log-transformed data, the same analyses will be conducted exploratory.
2) The IPA of each treatment regimen will be summarized using the descriptive statistics. The means for the treatment difference (T-R) and their 95 % CI will be calculated.

11.1.2 Platelet Aggregation

The descriptive statistics of measured values (ie, platelet aggregation) at each timepoint and changes from baseline will be summarized by treatment regimen. Box-plot diagrams will also be provided.

The data on Visit 1 (Day −14 to 0) is defined as baseline for all treatment groups.

11.2 Statistical Analyses of Secondary Pharmacodynamics Endpoints

11.2.1 Inhibition of Platelet Aggregation

IPA calculated from the light transmission aggregometry in PRP (20 µM ADP, residual aggregation at 5 minutes) will also be analysed using the methodology specified in Section 11.1.1.

11.2.2 Platelet Aggregation

For ex-vivo platelet function parameters, the descriptive statistics of measured values (ie, platelet aggregation) at each timepoint and changes from baseline will be summarized by treatment regimen. Box-plot diagrams will also be provided for the following parameters:

- Light transmission aggregometry in PRP (20µM ADP, residual aggregation at 5 minutes)
- Multiplate® (ASPI test, ADP test)
- VetifyNowTM (P2Y12 and Aspirin test)
- VASP by flow cytometry

The data on Visit 1 (Day −14 to 0) is defined as baseline for all treatment groups.

11.2.3 Skin Bleeding Time

Bleeding time at baseline, after monotherapy with cilostazol, aspirin or clopidogrel as well as concomitant treatment of cilostazol plus aspirin and cilostazol plus clopidogrel will also be analysed using the methodology specified in Section 11.1.1. Natural log-transformation will be applied to bleeding time to fit a mixed-effect linear model.

The descriptive statistics of measured values at each timepoint and changes from baseline will be summarized by treatment regimen.

The data on Visit 1 (Day −14 to 0) is defined as baseline for all treatment groups.

12 Pharmacogenomic Analyses

There are no pharmacogenomic analyses in this trial.

13 Interim Analysis

None.

14 Changes in Planned Analysis

The following modification from the statistical analysis specified in the protocol was made.

- A summary of descriptive statistics for ECG values specified in Section 7.3.4 of the protocol will be changed to a shift table of abnormality in ECG findings. ECG values were not collected in this trial.

- Sensitivity analysis described in Section 7.1.1 of the protocol will not be conducted. The number of subjects who dropped out of the analysis before finishing the third period was not substantial.

15 References

1 Angiolillo, D. J.; Piera Capranzano; Jose Luis Ferreiro; Masafumi Ueno; Davide Capodanno; Kodlipet Dharmashankar; Andrew Darlington; Sabrina Sumner; Bhaloo Desai; Ronald K. Charlton; Lyndon C. Box; Martin M. Zenni; Luis A. Guzman; Theodore A. Bass: Impact of adjunctive cilostazol therapy on platelet function profiles in patients with and without diabetes mellitus on aspirin and clopidogrel therapy. Thromb Haemost 2011; 106: 253–262

Appendix 1 List of Summary Tables

CT-1 Subject Disposition

CT-2 Reasons for Discontinuation

CT-3.1 Demographic and Baseline Characteristics - Safety Analysis Set

CT-3.2 Demographic and Baseline Characteristics - Pharmacodynamic Analysis Set

CT-4 Concomitant Medications

CT-5.1 Summary of Pharmacodynamic Parameters

CT-5.2 Summary of Pharmacodynamic Parameters by Genotype

CT-5.3 Descriptive Statistics for Inhibition of Platelet Aggregation

CT-5.4 Descriptive Statistics for Skin Bleeding Time

CT-5.5 Treatment Difference for Inhibition of Platelet Aggregation

CT-5.6 Treatment Difference for Inhibition of Platelet Aggregation by Genotype

CT-5.7 Descriptive Statistics for Platelet Aggregation

CT-6.1 Summary of Pharmacodynamic Parameters - Exploratory Analysis (not Log-transformed Data)

CT-6.2 Summary of Pharmacodynamic Parameters by Genotype - Exploratory Analysis (not Log-transformed Data)

CT-7 Extent of Exposure to Investigational Medicinal Product

CT-8.1 Summary of Adverse Events

CT-8.2.1 Incidence of All Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term for Each Treatment Group

CT-8.2.2 Incidence of All Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term for Each Treatment Regimen

CT-8.3.1 Incidence of Potentially Drug-related Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term for Each Treatment Group

CT-8.3.2 Incidence of Potentially Drug-related Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term for Each Treatment Regimen

CT-8.4.1 Incidence of Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term for Each Treatment Group

CT-8.4.2 Incidence of Serious Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term for Each Treatment Regimen

CT-8.5.1 Incidence of Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term for Each Treatment Group

CT-8.5.2 Incidence of Treatment-emergent Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term for Each Treatment Regimen

CT-8.6.1 Incidence of All Treatment-emergent Adverse Events According to Severity by MedDRA System Organ Class and Preferred Term for Each Treatment Group

CT-8.6.2 Incidence of All Treatment-emergent Adverse Events According to Severity by MedDRA System Organ Class and Preferred Term for Each Treatment Regimen

CT-9.1 Listing of Deaths

CT-9.2 Listing of Serious Adverse Events Other Than Deaths

CT-9.3 Listing of Adverse Events Leading to Discontinuation of Investigational Medicinal Product Administration

CT-10.1.1 Descriptive Statistics for Laboratory Test Results - Serum Chemistry

CT-10.1.2 Descriptive Statistics for Laboratory Test Results - Hematology and Coagulation

CT-10.1.3 Descriptive Statistics for Laboratory Test Results - Urinalysis

CT-10.2.1 Shift Table of Laboratory Test Results - Serum Chemistry

CT-10.2.2 Shift Table of Laboratory Test Results - Hematology and Coagulation

CT-10.2.3 Shift Table of Laboratory Test Results - Urinalysis

CT-10.3.1 Shift Table of Laboratory Test Results - Qualitative Urinalysis (1)

CT-10.3.2 Shift Table of Laboratory Test Results - Qualitative Urinalysis (2)

CT-10.4 Listing of Abnormal Laboratory Findings

CT-10.5 Listing of Potential Hy's Law Cases

CT-11.1 Descriptive Statistics for Vital Signs

CT-11.2 Descriptive Statistics for Body Weight

CT-12 Shift Table of Electrocardiogram Findings

Appendix 2 List of Summary Figures

Appendix 3 List of Subject Data Listings

DREAS-1 Discontinued Subjects and Reason for Discontinuation

SUBEX-1 Subjects Excluded From Analysis Set

DEMOG-1 Demographic Characteristics

SMED-1 Investigational Medicinal Product Compliance

AE-1 Adverse Events

LAB-1 Laboratory Test Results - Serum Chemistry

LAB-2 Laboratory Test Results - Hematology and Coagulation

LAB-3 Laboratory Test Results - Urinalysis

PDATA-1 Study Completion Status and Reason for Discontinuation

PDATA-2 Medical History and Current Symptoms

PDATA-3 Prior and Concomitant Medications

PDATA-4 Concomitant Therapy

PDATA-5 Vital Signs and Body Weight

PDATA-6 Electrocardiogram Results

PDATA-7 Platelet Aggregation - Primary Outcome Variables

PDATA-8 Platelet Aggregation - Secondary Outcome Variables

PDATA-9 Skin Bleeding Time

PDATA-10 Screen Failures

PDATA-11 Drug Screen, Alcohol Screen and Infectious Disease Test Results

PDATA-12 Physical Examination

PDATA-13 Drug Accountability