

STATISTICAL ANALYSIS PLAN

Study Title

Multicenter, open-label trial evaluating the efficacy and safety of perampanel added to monotherapy in patients with partial onset seizures with or without secondary generalized seizures

Protocol No./ Version

E2007-M065-412 / v2.1

Sponsor

Eisai Korea Inc.

Version No. (Version Date)

V1.0 (15-Jun-2018)

Written By

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C&R Research



Statistical Analysis Plan

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Version Information (Document revision history)

Version	Effective Date	Prepared by Name	Details
1.0	Sponsor's approval date	PPD	First version

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Abbreviation

Term	Definition
ADR	Adverse Drug Reaction
AE	Adverse Events
ATC code	Anatomical Therapeutic Chemical code
FAS	Full Analysis Set
MedDRA	Medical Dictionary for Regulatory Activities
PPS	Per-Protocol Set
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedure
WHODD	WHO Drug Dictionary

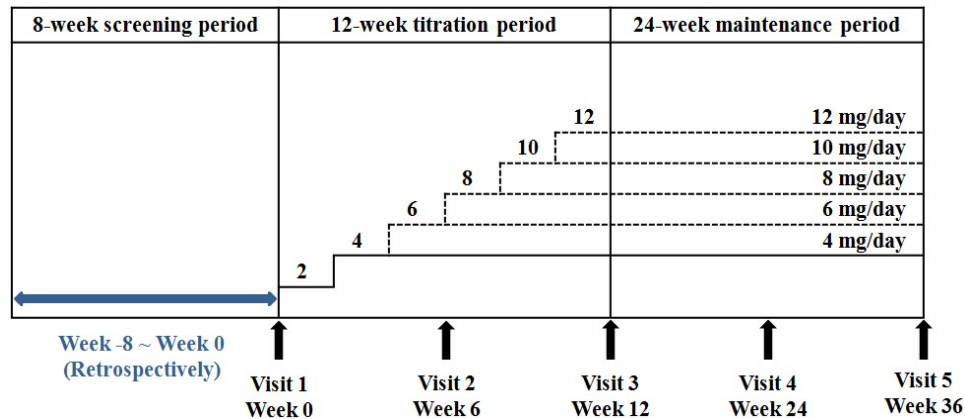
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1. Study Design

This is a multicenter, open label, single arm, for therapeutic use, study.



Prior to the study initiation, approval from IRB of each study site as well as written contract is required. Prior to the study participation, patients should receive sufficient explanation about the study and provide written consent regarding the access to and use of personal and medical information. After the consent process, subjects who meet all of the inclusion criteria and none of the exclusion criteria will receive the investigational product (Fycompa film-coated tablet). Information on baseline seizure count (frequency) will be collected retrospectively by the subject or guardian. This study consists of titration period (12 weeks) and maintenance period (24 weeks).

[Titration period (12 weeks)]

Subjects will initiate perampanel at 2 mg/day, which can be increased up to 12 mg by increments of 2 mg no more frequently than at 2-week interval according to the investigator's judgment. The dose can be maintained or reduced based on the subject's clinical response and tolerability according to the investigator's judgment. Subjects who cannot tolerate 4 mg/day will be withdrawn from the study. Subjects who are taking concomitant drugs that shorten the half-life of perampanel (phenytoin, carbamazepine, oxcarbazepine, etc.) will titrate the dose by increments of 2 mg/day no more frequently than at 1-week interval. Adjusting the type or dose of concomitant anti-epileptic drug is not allowed during this period.

[Maintenance period (24 weeks)]

Throughout the maintenance period, subjects will maintain the dose administered at the end of the titration period. However, the dose can be increased to maximum 12 mg/day or reduced to minimum 4 mg/day based on the subject's clinical response and tolerability according to the

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investigator's judgment. Subjects who reduce the dose during the maintenance period can increase the dose once tolerability is improved. Subjects who cannot tolerate 4 mg/day will be withdrawn from the study. Adjusting the type or dose of concomitant anti-epileptic drug is not allowed during this period.

In case of withdrawal, the dose will be tapered down and follow-up visit will take place 4 weeks after the last dose.

Subjects will visit the site for Visit 1 (Week 0), Visit 2 (Week 6), Visit 3 (Week 12), Visit 4 (Week 24) and Visit 5 (Week 36).

2. Study Objectives

2.1. Primary Objective

To evaluate the efficacy of perampanel added to monotherapy in patients with partial onset seizures with or without secondary generalization as measured by 50% responder rate

2.2. Secondary objectives

- 1) To evaluate the safety of perampanel added to monotherapy in patients with partial onset seizures with or without secondary generalization
- 2) To evaluate efficacy of perampanel added to monotherapy in patients with secondary generalized tonic clonic seizure

3. Justification of Sample Size

This study determines the efficacy and safety of perampanel as add-on therapy in patients with partial onset seizure. Primary efficacy endpoint is the 50% responder rate for partial onset seizure with or without secondary generalization. According to Bernhard J. Steinhoff et al.³⁴, the 50% responder rate was 35.3% in the test group and 19.3% in the control group. To ensure 90% power at two-sided significance level of 5%, 94 subjects are required. Considering 10% drop-out rate, a total of 105 subjects are required.

$$n = \frac{(Z_{\alpha/2} + Z_{\beta})^2 [p_T(1 - p_T)]}{(p_T - p_R)^2}$$

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$$= \frac{(1.96 + 1.282)^2 [0.353(1 - 0.353)]}{(0.353 - 0.193)^2}$$
$$= 93.77 \approx 94$$

$Z_{\alpha/2}$: Type I error (0.05/2)

Z_{β} : Type II error (0.1)

p_T : 50% responder rate in the test group

p_R : Reference value

4. Efficacy and Safety Endpoints

4.1 Efficacy Endpoints

4.1.1 Primary Efficacy Endpoint

50% responder rate for partial onset seizures with or without secondary generalization: the proportion of subjects achieving at least 50% reduction in the frequency of partial onset seizures with or without secondary generalization during the maintenance period compared to baseline

4.1.2 Secondary Efficacy Endpoints

- 1) 75% responder rate for partial onset seizures with or without secondary generalization
 - 2) 100% responder (seizure free) rate for partial onset seizures with or without secondary generalization
 - 3) Percent change from baseline in the frequency of partial onset seizures with or without secondary generalization during the titration period and maintenance period
 - 4) 50% responder rate for secondary generalized tonic-clonic seizure
 - 5) 75% responder rate for secondary generalized tonic-clonic seizure
 - 6) 100% responder (seizure free) rate for secondary generalized tonic-clonic seizure
 - 7) Percent change from baseline in the frequency of secondary generalized tonic-clonic seizure during the titration period and maintenance period
- * Secondary generalized tonic-clonic seizure is collected as 'complex partial onset seizure with secondary generalization'

4.2 Safety Endpoints

- 1) Adverse events
- 2) Laboratory tests
- 3) Vital signs
- 4) Physical measurements

5. Analysis Sets

5.1 Efficacy Analysis Set

Efficacy is analyzed primarily in the Full Analysis Set (FAS), and secondarily in the Per-Protocol Set (PPS). Safety is analyzed in the Safety Analysis Set.

- FAS: subjects who received at least one dose of investigational product and were assessed for primary efficacy at least once during the maintenance period (Week 12 - 5 days ~ Week 36 + 7 days).
- PPS: subjects in FAS who completed the study per protocol without major violation. Subjects who meet any of the following conditions are excluded from PPS.
 - 1) Deviation from selection criteria
 - 2) Use of prohibited concomitant medication or therapy
 - 3) Withdrawal
 - 4) Deviation from treatment compliance
 - 5) Other deviation considered as major protocol violation

5.2 Safety Analysis Set

Safety is analyzed in the Safety Analysis Set.

- Safety Analysis Set: subjects who received at least one dose of investigational product and were assessed for safety at least once.

6. Statistical Analysis Method

6.1 Analysis Program

Statistical analysis will use SAS® Version 9.4 (SAS Institute, Cary, NC, USA) or subsequent version.

6.2 General Principles of Result Analysis

All analyses will be descriptive. Continuous variables will be presented using descriptive statistics (number of subjects, mean, standard deviation, median, minimum and maximum), while categorical variables will be presented using frequency and percentage. In addition, with regard to efficacy, 95% confidence interval (t-distribution) for the mean will be presented for continuous variables, while 95% exact confidence interval will be presented for categorical variables. Values with a decimal point, such as mean, standard deviation, and percentage, will be rounded to two decimal places.

6.3 Handling of Withdrawal and Missing Data

All evaluation data will be analyzed as is without imputation for missing data.

In the analysis of duration of disease, missing month of the date of epilepsy diagnosis will be substituted with June and missing day will be substituted with 15. If the year is missing, the date of epilepsy diagnosis will be handled as missing data. If imputation results in negative duration of disease, the duration of disease will be 0.

6.4 Adjustment for covariate

Adjustment for covariate is not planned.

6.5 Multiple Comparison or Multiplicity of Testing

Multiple comparison or analysis of multiplicity of testing is not planned.

6.6 Interim Analysis

Interim analysis is not planned.

6.7 Sensitivity Analysis

Sensitivity analysis is not planned.

6.8 Study Participation

6.8.1 Subject Disposition

Subjects who completed the study and subjects who discontinued the study are presented using frequency and percentage. For those who discontinued the study, reason for discontinuation is presented using frequency and percentage.

6.8.2 Subject Disposition by Study Site

Subjects who completed the study and subjects who discontinued the study are presented by study site using frequency and percentage.

6.8.3 Protocol Deviation

For subjects with protocol deviation, excluding those who discontinued the study, reason for deviation is presented using frequency and percentage.

6.8.4 Analysis Sets

Number of subjects included in the Safety Analysis Set, FAS, and PPS is presented. Reason for exclusion from the data set is presented using frequency and percentage.

6.9 Demographic Information

Demographic and baseline disease characteristics, past/current disease, previous/concomitant medication, previous/concomitant medication (anti-epileptic drug), and concomitant non-pharmacological therapy at the time of enrollment are analyzed in the FAS.

- **Demographic characteristics**

Continuous data (age, height, body weight, BMI) is presented using descriptive statistics (number of subjects, mean, standard deviation, median (minimum, maximum)), and categorical data (age group (<65 years or ≥65 years), sex) is presented using frequency and percentage.

- $BMI (kg/m^2) = \text{body weight (kg)} / \text{height (m)}^2$

- **Baseline disease characteristics (epilepsy diagnosis: duration of disease, ILAE classification, cause, seizure type and frequency: partial-onset seizure with or without secondary generalization, simple partial seizure with motor involvement, complex partial seizure, complex partial seizure with secondary generalization, other seizures)**

Continuous data (duration of disease, partial-onset seizure with or without secondary generalization, simple partial seizure with motor involvement, complex partial seizure, complex partial seizure with secondary generalization, other seizures) is presented using descriptive statistics (number of subjects, mean, standard deviation, median (minimum, maximum)); for seizure type and frequency, 1st and 3rd quartiles are presented as well. Categorical data (ILAE classification, cause) is presented using frequency and percentage.

- Duration of disease (years) = (date of signing the consent form – date of initial diagnosis) / 365.25
- Seizure frequency = (number of seizures / (date of Visit 1 – date of 8 weeks prior to Visit 1)) x 28

▪ **Past and Current Medical History**

Diseases/procedures in past/current medical history are coded using SOC (System Organ Class) and PT (Preferred Term) of MedDRA (21.0 version). Represented codes are presented using frequency, percentage, and count.

Past medical history is defined as medical history 'not ongoing' at the time of visit, while current medical history is defined as medical history 'ongoing' at the time of visit.

▪ **Previous and Concomitant Medication**

Previous and concomitant medications are coded using 1st level (Anatomical main group) and 4th level (Chemical subgroup) of ATC classification system (2018 version). Represented codes are presented using frequency, percentage, and count.

Previous medications are defined as those taken before the study treatment, while concomitant medications are defined as those taken after the study treatment. Any medication for which the date of last dose is 'UK' (thus, it is not known whether the drug was administered before or after the study treatment) is included in both previous and concomitant medications.

▪ **Previous and Concomitant Medications (anti-epileptic drugs)**

Previous and concomitant medications (anti-epileptic drugs) are coded using 4th level (Chemical subgroup) and 5nd level (Chemical substance) of ATC classification system (2018 version).

Represented codes are presented using frequency, percentage, and count.

Previous medications are defined as those taken before the study treatment, while concomitant medications are defined as those taken after the study treatment. Any medication for which the date of last dose is 'UK' (thus, it is not known whether the drug was administered before or after the study treatment) is included in both previous and concomitant medications.

▪ Concomitant Non-Pharmacological Therapy

Concomitant non-pharmacological therapies are coded using SOC (System Organ Class) and PT (Preferred Term) of MedDRA (21.0 version). Represented codes are presented using frequency, percentage, and count.

6.10 Treatment Compliance

Treatment compliance during the study period is calculated as follows, and presented using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum).

$$\text{Treatment compliance (\%)} = \frac{\text{Actual number of administration days during the study period}}{\text{Expected number of administration days during the study period}} \times 100$$

6.11 Efficacy Analysis

In the efficacy analyses, seizure frequency is calculated as follows.

- Seizure frequency during the screening period = (number of seizure / (date of Visit 1 – date of 8 weeks prior to Visit 1)) x 28
- Seizure frequency during the titration period = (number of seizure / (date of end of Visit 3 or date of withdrawal during the titration period – date of start of Visit 2)) x 28
- Seizure frequency during the maintenance period = (number of seizure / (date of end of Visit 5 or date of withdrawal during the maintenance period – date of start of Visit 4)) x 28

6.11.1 Analysis of primary efficacy endpoint

50% responder rate for partial onset seizure with or without secondary generalization

Seizure frequency during the screening period and seizure frequency during the maintenance period in 50% responders, defined as subjects achieving at least 50% reduction in the frequency of partial onset seizures with or without secondary generalization during the maintenance period compared to baseline, are presented using descriptive statistics (number of subjects, mean, standard deviation, median (minimum, maximum), 1st quartile, and 3rd quartile), rate, and 95% CI. Seizure frequency is calculated as follows.

6.11.2 Analysis of secondary efficacy endpoints

1) 75% responder rate for partial onset seizure with or without secondary generalization

Seizure frequency during the screening period and seizure frequency during the maintenance period in 75% responders, defined as subjects achieving at least 75% reduction in the frequency of partial onset seizures with or without secondary generalization during the maintenance period compared to baseline, are presented using descriptive statistics (number of subjects, mean, standard deviation, median (minimum, maximum), 1st quartile, and 3rd quartile), rate, and 95% CI. Seizure frequency is calculated as follows.

2) 100% responder (seizure-free) rate for partial onset seizure with or without secondary generalization

Seizure frequency during the screening period and seizure frequency during the maintenance period in 100% responders (seizure-free subjects), defined as subjects achieving 100% reduction in the frequency of partial onset seizures with or without secondary generalization during the maintenance period compared to baseline, are presented using descriptive statistics (number of subjects, mean, standard deviation, median (minimum, maximum), 1st quartile, and 3rd quartile), rate, and 95% CI. Seizure frequency is calculated as follows.

3) Percent change from baseline in the frequency of partial onset seizure with or without secondary generalization during the titration period and maintenance period

Frequency of partial onset seizure with or without secondary generalization during the screening period, titration period, and maintenance period is presented using descriptive statistics (number of subjects, mean, standard deviation, median (minimum, maximum), 1st quartile, and 3rd quartile). Also, percent change in the frequency of partial onset seizure with or without secondary generalization during the titration period and maintenance period compared to the screening

period is calculated and presented using descriptive statistics (number of subjects, mean, standard deviation, median (minimum, maximum), 1st quartile, and 3rd quartile) along with corresponding 95% CI. Seizure frequency is calculated as follows.

4) 50% responder rate for secondary generalized tonic-clonic seizure

Seizure frequency during the screening period and seizure frequency during the maintenance period in 50% responders, defined as subjects achieving at least 50% reduction in the frequency of secondary generalized tonic-clonic seizure during the maintenance period compared to baseline, are presented using descriptive statistics (number of subjects, mean, standard deviation, median (minimum, maximum), 1st quartile, and 3rd quartile), rate, and 95% CI. Seizure frequency is calculated as follows.

5) 75% responder rate for secondary generalized tonic-clonic seizure

Seizure frequency during the screening period and seizure frequency during the maintenance period in 75% responders, defined as subjects achieving at least 75% reduction in the frequency of secondary generalized tonic-clonic seizure during the maintenance period compared to baseline, are presented using descriptive statistics (number of subjects, mean, standard deviation, median (minimum, maximum), 1st quartile, and 3rd quartile), rate, and 95% CI. Seizure frequency is calculated as follows.

6) 100% responder (seizure free) rate for secondary generalized tonic-clonic seizure

Seizure frequency during the screening period and seizure frequency during the maintenance period in 100% responders (seizure-free subjects), defined as subjects achieving 100% reduction in the frequency of secondary generalized tonic-clonic seizure during the maintenance period compared to baseline, are presented using descriptive statistics (number of subjects, mean, standard deviation, median (minimum, maximum), 1st quartile, and 3rd quartile), rate, and 95% CI. Seizure frequency is calculated as follows.

7) Percent change from baseline in the frequency of secondary generalized tonic-clonic seizure during the titration period and maintenance period

Frequency of secondary generalized tonic-clonic seizure during the screening period, titration period, and maintenance period is presented using descriptive statistics (number of subjects, mean, standard deviation, median (minimum, maximum), 1st quartile, and 3rd quartile). Also, percent change in the frequency of secondary generalized tonic-clonic seizure during the

titration period and maintenance period compared to the screening period is calculated and presented using descriptive statistics (number of subjects, mean, standard deviation, median (minimum, maximum), 1st quartile, and 3rd quartile) along with corresponding 95% CI. Seizure frequency is calculated as follows.

6.12 Safety Analysis

6.12.1 Extent of Exposure

With regard to extent of exposure during the study period, duration of treatment and total dose in the titration period and maintenance period are calculated as follows and presented using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum).

Duration of treatment in the titration period (days)

$$= \text{date of last dose} - \text{date of first dose} + 1$$

Duration of treatment in the maintenance period (days)

$$= \text{date of last dose} - \text{date of first dose} + 1$$

Total dose (mg) = sum of doses administered (daily dose x number of dosing days)

6.12.2 Adverse Events

Treatment-emergent adverse events (TEAEs) were analyzed (TEAEs refer to adverse events that were absent before study treatment and emerged after study treatment, or adverse events that were present before study treatment and worsened after study treatment). Subjects who experienced more than one TEAE are counted once.

ADRs are related adverse events considered as probably related or possibly related by the investigator, for which causal relationship to the investigational product cannot be ruled out. Those considered as not related by the investigator are defined as unrelated adverse events.

Incidence of TEAEs, ADRs, SAEs, and AEs leading to treatment discontinuation is presented using frequency and percentage along with 95% CI.

AEs, ADRs, SAEs, and AEs leading to treatment discontinuation are coded using SOC (System Organ Class) and PT (Preferred Term) of MedDRA and analyzed by causality and severity. Represented codes are presented using the number of subjects and incidence. Listing will be

provided for SAEs.

6.12.3 Laboratory Tests

For laboratory tests that are continuous variables, results at baseline, Week 36 (Visit 5), end-of-study visit, and follow-up as well as the change from baseline to the last dose of study treatment are presented using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum). Categorical variables are classified as 'Normal' or 'Abnormal' and the change from baseline to the last dose of study treatment is summarized using a shift table to present the frequency and percentage. Percentage is based on subjects who have results both at baseline and at subsequent timepoints.

In addition, laboratory test results will be classified into low (L), normal (N), or high (H) (LNH). To compare the laboratory parameters during the treatment period, 3 x 3 shift table presenting the LNH classification at baseline and LNH classification at each visit will be presented.

6.12.4 Vital Signs

Results at baseline (Visit 1), Week 6 (Visit 2), Week 12 (Visit 3), Week 24 (Visit 4), Week 36 (Visit 5), end-of-study visit, and follow-up as well as the change from baseline to each timepoint post-treatment are presented using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum).

6.12.5 Physical Measurement (Body Weight)

Results at baseline (Visit 1), Week 36 (Visit 5), end-of-study visit, and follow-up as well as the change from baseline to each timepoint post-treatment are presented using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum).

7. Plan for Revision of Analysis Method

Revision of analysis method is not planned.

8. TLF shell

List of Tables

Table	Table Description
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Statistical Analysis Plan

Number	
s1	14.1.1 Subject Disposition - All Enrolled Subject
s2	14.1.2 Subject Disposition by Study Site - All Enrolled Subject
s3	14.1.3 Major Protocol Deviations - All Enrolled Subject
s4	14.1.4 Analysis Sets - All Enrolled Subject
b1	14.1.5 Demographic Characteristics - Full Analysis Set
b2	14.1.6 Baseline Disease Characteristics - Full Analysis Set
b3	14.1.7 Past Medical History - Full Analysis Set
b4	14.1.8 Current Medical History - Full Analysis Set
b5	14.1.9 Previous Medications - Full Analysis Set
b6	14.1.10 Concomitant Medications - Full Analysis Set
b7	14.1.11 Previous Medications (anti-epileptic drugs) - Full Analysis Set
b8	14.1.12 Concomitant Medications (anti-epileptic drugs) - Full Analysis Set
b9	14.1.13 Concomitant Non-Pharmacological Therapy - Full Analysis Set
e1_1	14.2.2.1 50% Responder Rate for Partial Onset Seizures with or without Secondary Generalization - Full Analysis Set
e1_2	14.2.2.2 50% Responder Rate for Partial Onset Seizures with or without Secondary Generalization - Per Protocol Set
e2_1	14.2.3.1 75% Responder and 100% Responder (Seizure-Free) Rate for Partial Onset Seizures with or without Secondary Generalization - Full Analysis Set
e2_2	14.2.3.2 75% Responder and 100% Responder (Seizure-Free) Rate for Partial Onset Seizures with or without Secondary Generalization - Per Protocol Set
e3_1	14.2.4.1 Percent Change in the Frequency of Partial Onset Seizures with or without Secondary Generalization during the Titration Period and Maintenance Period compared to Screening Period - Full Analysis Set
e3_2	14.2.4.2 Percent Change in the Frequency of Partial Onset Seizures with or without Secondary Generalization during the Titration Period and Maintenance Period compared to Screening Period - Per Protocol Set
e4_1	14.2.5.1 - 50% Responder, 75% Responder, and 100% Responder (Seizure-Free) Rate for Secondary Generalized Tonic-Clonic Seizure - Full Analysis Set
e4_2	14.2.5.2 - 50% Responder, 75% Responder, and 100% Responder (Seizure-Free) Rate for Secondary Generalized Tonic-Clonic Seizure - Per Protocol Set

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e5_1	14.2.6.1 Percent Change in the Frequency of Secondary Generalized Tonic-Clonic Seizure during the Titration Period and Maintenance Period compared to Screening Period - Full Analysis Set
e5_2	14.2.6.2 Percent Change in the Frequency of Secondary Generalized Tonic-Clonic Seizure during the Titration Period and Maintenance Period compared to Screening Period - Per Protocol Set
ex1	14.3.1 Extent of Exposure - Safety Analysis Set
a1	14.3.2 Summary of Adverse Events - Safety Analysis Set
a2	14.3.3 Incidence of Treatment-Emergent Adverse Events by System Organ Class - Safety Analysis Set
a3	14.3.4 Incidence of Treatment-Emergent Adverse Drug Reactions by System Organ Class - Safety Analysis Set
a4	14.3.5 Incidence of Treatment-Emergent Serious Adverse Events by System Organ Class - Safety Analysis Set
a5	14.3.6 Incidence of Adverse Events Leading to Treatment Discontinuation by System Organ Class - Safety Analysis Set
a6	14.3.7 List of Treatment-Emergent Serious Adverse Events - Safety Analysis Set
a7	14.3.8 Incidence of Treatment-Emergent Adverse Events by System Organ Class and Severity - Safety Analysis Set
a8	14.3.9 Incidence of Treatment-Emergent Adverse Events by System Organ Class and Causality - Safety Analysis Set
l1	14.4.1.1 Hematology - Safety Analysis Set
l2	14.4.1.2 Blood Chemistry - Safety Analysis Set
l3	14.4.1.3 Urinalysis - Safety Analysis Set
l4	14.4.2 Urinalysis: Normal/Abnormal - Safety Analysis Set
l5	14.4.3.1 Hematology: LNH - Safety Analysis Set
l6	14.4.3.2 Blood Chemistry: LNH - Safety Analysis Set
l7	14.4.3.3 Urinalysis: LNH - Safety Analysis Set
v1	14.4.4 Vital Signs - Safety Analysis Set
pe1	14.4.5 Physical Measurement (Body Weight) - Safety Analysis Set



Statistical Analysis Plan

9. Roles and Responsibilities

Role	Name	Responsibility
Biostatistician	PPD	Statistical analysis
QC Biostatistician	PPD	Quality control for the statistical analysis process

10. Applied SOPs

SOP No.	SOP Version	SOP Name
0400	2.0_23-Oct-2017	Statistical Analysis Plan
0401	3.0_01-Jun-2017	Statistical Analysis Process

11. Applied SOP SDs

SD No.	SD Version	SD Title
SD 0400 A	2.0_03-May-2018	Statistical Analysis Plan
SD 0408 A	3.0_23-Oct-2017	STAT Master File Index

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