Statistical Analysis Plan H8H-CD-LAHH

A Phase 1 Study to Investigate the Absorption, Metabolism, and Excretion of [14C]-Lasmiditan Following Single Oral Dose Administration in Healthy Male and Female Subjects

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16.1.9 Documentation of Statistical Methods

STATISTICAL ANALYSIS PLAN

A Phase 1 Study to Investigate the Absorption, Metabolism, and Excretion of [^{14}C]-Lasmiditan Following Single Oral Dose Administration in Healthy Male and Female Subjects

Statistical Analysis Plan Status: Final
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Study Drug: [^{14}C]-Lasmiditan

Sponsor Reference Number: COL MIG-110
Covance Study Number: 8331469

Clinical Phase 1

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1 STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES

By signing this page when the Statistical Analysis Plan (SAP) is considered final, the signatories agree to the statistical and pharmacokinetic (PK) analyses to be performed for this study, and to the basic format of the tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the TFLs based upon this document can proceed. Any modifications to the SAP and TFLs made after signing may result in a work-scope change.

Covance approval:

PPD

PPD

07 June 2017
Date

PPD

09 June 2017
Date

Sponsor approval:

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Date

2 TABLE OF CONTENTS

3 ABBREVIATIONS

Abbreviations pertain to the SAP only (not the TFLs).

ADaM	analysis data model
AE	adverse event
CDISC	Clinical Data Interchange Standards Consortium
CRF	Case Report Form
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CV%	coefficient of variation
EC	Early Clinical
ECG	electrocardiogram
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
QTc	QT correction; QT interval corrected for heart rate
QTcF	QTc calculated using the Fridericia correction
SAP	Statistical Analysis Plan
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
$\%AUC_{extrap}$	percentage of AUC that is due to extrapolation from the time of the last quantifiable concentration to infinity
%FR	Percent of dose recovered in feces over a sampling interval
%UR	Percent of dose recovered in urine over a sampling interval
$AUC_{0-\infty}$	area under the concentration-time curve from time zero to infinity
$AUC_{0-tlast}$	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
A_{ef}	Amount excreted in feces over a sampling interval
A_{eu}	Amount excreted in urine over a sampling interval
BLQ	below the limit of quantification
BMI	body mass index

CL/F	apparent total clearance
C_{max}	maximum observed plasma concentration
CL_R	Renal clearance
LLOQ	lower limit of quantification
LS	least squares
PK	pharmacokinetic
PT	preferred term
R^2 -adjusted	adjusted coefficient of variation for goodness of fit
SD	standard deviation
SOC	system organ class
$t_{½}$	apparent terminal elimination half-life
t_{last}	Time of last quantifiable concentration
t_{max}	time of maximum observed concentration
TRA	total radioactivity
V_z/F	apparent volume of distribution during the terminal phase

4 INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final Version 1.0 dated 23 January 2017).

This SAP describes the planned analysis of the safety, tolerability, and PK data from this study. A detailed description of the planned TFLs to be presented in the Clinical Study Report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical analyses of PK data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement between CoLucid Pharmaceuticals, Inc. and Covance Early Clinical (EC) Biometrics. A limited amount of information concerning this study (eg, objectives, study design) is given to help the reader's interpretation. This SAP must be finalised prior to the lock of the clinical database for this study. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon between CoLucid Pharmaceuticals, Inc. and Covance EC Biometrics and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports."[1,2]

5 STUDY OBJECTIVES

The primary objectives of this study are:

- To assess the PK, metabolism, and routes and extent of elimination of a single oral dose of 200 mg (approximately 100 μCi) [^{14}C]-lasmiditan in healthy male and female subjects.

The secondary objectives of this study are:

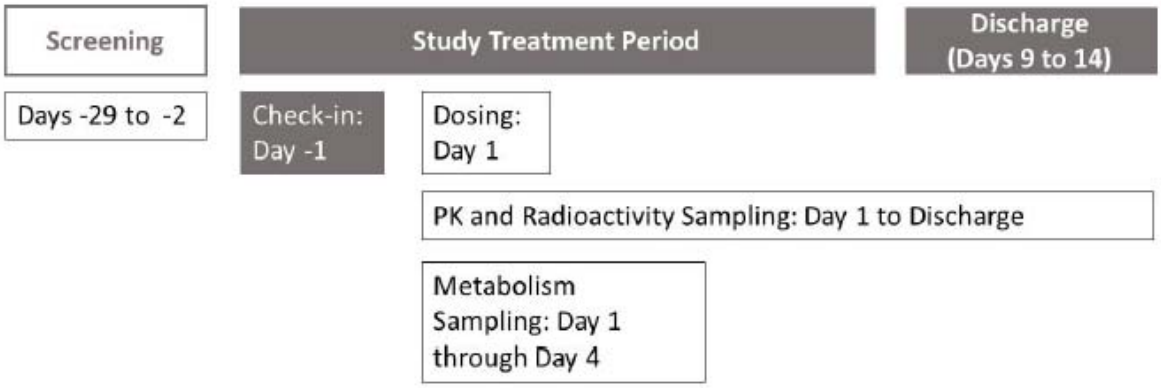
- To characterize and identify metabolites of lasmiditan in plasma, urine, and feces;
- To assess the safety and tolerability of lasmiditan.

6 STUDY DESIGN

This study will be an open-label, nonrandomized, AME study of [^{14}C]-lasmiditan administered as a 200-mg (approximately 100 µCi) oral solution to 8 healthy male and female subjects following at least a 10-hour fast from food (not including water).

A schematic of the study design is presented in Figure 1. The start of the study is defined as the date the first subject enrolled in the study signs an Informed Consent Form (ICF). A subject who completes all PK, radioactivity, and metabolism sampling prior to Discharge is considered to have completed the study. The end of the study is defined as the date the last subject completes the Follow-up Phone Call. The planned duration of study conduct is up to approximately 49 days from Screening through the Follow-up Phone Call.

Figure 1. Study Design Schematic



PK = pharmacokinetic.
Note: Single oral dose of [^{14}C]-lasmiditan at 200 mg (approximately 100 µCi) administered orally to subjects in a fasted state.

Subjects will be confined at the clinical site from the time of Check-in (Day -1) until Discharge (between Days 9 and 14, inclusive). After completing discharge procedures, subjects will be discharged from the clinical site on Day 14 or as early as Day 9, provided radioactivity has reached all of the following threshold values:

- plasma radioactivity levels below the limit of quantitation; AND
- ≥90% of the dose is recovered; AND
- urine total radioactivity ≤1% of the administered dose for 2 consecutive 24-hour intervals; AND
- fecal total radioactivity ≤1% of the administered dose for 2 consecutive 24-hour intervals.

Sample collection and confinement will continue until discharge criteria are met or the maximum stay (Day 14) is reached, unless otherwise agreed upon by the Sponsor and Investigator. A Follow-up Phone Call will be conducted 4 ± 2 days after Discharge.

Subjects experiencing emesis during the first 4 hours postdose may be discharged on the same day from the clinical site, provided there are no safety concerns, and after follow-up study procedures are performed. Subjects who are discharged from the study early will not be replaced.

Safety will be monitored with AE inquiries, clinical laboratory evaluations (Appendix A in the protocol), vital sign measurements (including orthostatic vital sign measurements), 12-lead electrocardiograms (ECGs), physical examination findings, and the Columbia Suicide Severity Rating Scale (C-SSRS) during the study. Pharmacokinetic and radioanalytical samples will be obtained through at least 192 hours (8 days) postdose and metabolism samples will be obtained through 96 hours (4 days) postdose. A study flow chart is presented in Table 6-1 in the protocol.

7 TREATMENT

The treatment administered will be a single dose of 200 mg (approximately 100 μCi) [^{14}C]-lasmiditan

8 SAMPLE SIZE JUSTIFICATION

The sample size chosen for this study was based on precedent set by other PK studies of similar nature and was not based on power calculations.

9 DEFINITION OF ANALYSIS POPULATIONS

The **Safety Population** will consist of all subjects who received at least 1 dose of study drug and have at least 1 postdose safety assessment.

The **PK Population** will consist of all subjects who received at least 1 dose of study drug and have evaluable PK data. A subject will be excluded from the PK summary statistics and statistical analysis if the subject has an adverse event (AE) of vomiting that occurs at or before 2 times median time to maximum concentration.

All protocol deviations that occur during the study will be considered prior to database lock for their severity/impact and will be taken into consideration when subjects are assigned to analysis populations. Details of subject assignment to the analysis populations will be listed.

The **All Subjects Population** will consist of any subjects who enrolled on to the study (signed informed consent) and had study assessments recorded on the database as per the protocol. The **All Subjects Population** will include the Safety Population.

10 STATISTICAL METHODOLOGY

10.1 General

Data listings will be provided for the All Subjects Population. Summary statistics and statistical analyses will be performed for subjects included in the relevant analysis populations (Safety/PK).

For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation, arithmetic coefficient of variation (CV%), median, minimum, maximum, and number. For log-normal data (eg, the PK parameters: areas under the concentration-time curve [AUCs] and maximum observed concentration [C_{max}]), the geometric mean and geometric CV% will also be presented. For categorical data, frequency counts and percentages will be presented. Data listings will be provided for all subjects up to the point of withdrawal, with any subjects excluded from the relevant population highlighted. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Missing values will not be imputed.

Data analysis will be performed using SAS® Version 9.3 or higher.

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1, and CDISC ADaM Implementation Guide Version 1.1. Pinnacle 21 Community Validator Version 2.2.0 will be utilised to ensure compliance with CDISC standards.

10.1.1 Definition of Baseline and Change from Baseline

Baseline for each parameter is defined as the last value measured prior to dosing, including repeat (vital signs or ECG) and unscheduled (clinical laboratory parameters) readings (see Section 10.1.2 for definitions of repeat and unscheduled readings).

Mean change from baseline is the mean of all individual subjects' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The individual subject's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

10.1.2 Repeat and Unscheduled Readings

Repeat readings occur when the original vital signs or ECG result requires confirmation. Repeat readings are labelled as 'Repeat' in the listings and replace the original readings in all summaries and changes from baseline presentations and calculations. Prior to dosing, all readings taken in addition to the original reading are defined as predose repeats. Postdose repeat readings are defined as readings collected within 15 minutes of the actual time of the original reading.

With the exception of predose results described above, unscheduled readings for vital signs or ECGs are defined as readings collected >15 minutes from the actual time of the original reading. Unscheduled readings are labelled as 'Unscheduled' in the listings. Because unscheduled postdose readings are not associated with any scheduled timepoint, they are excluded from all summaries (with the exception that they may be used as baseline, as stated in Section 10.1.1).

10.2 Demographics and Subject Disposition

The demographic variables age, sex, race, ethnicity, body weight, height, and body mass index will be summarised and listed. Subject disposition will be summarised and listed.

10.3 Pharmacokinetic Assessment

10.3.1 Pharmacokinetic Analysis

The following pharmacokinetic parameters will be determined, where possible, based on the plasma concentrations of lasmiditan, metabolites M3, M7, M8, and M18 and total radioactivity in whole blood and plasma, using non-compartmental methods performed using Phoenix WinNonlin (Certara United States, Inc.) version 6.4 or higher:

Parameter	Definition
$AUC_{0\text{-}tlast}$	Area under the concentration-time curve from time 0 to the time of last measurable concentration (t_{last}), calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations
$AUC_{0\text{-}\infty}$	Area under the concentration-time curve from time 0 extrapolated to infinity
$\%AUC_{(tlast\text{-}\infty)}$	Percentage of AUC that is due to extrapolation from the last measurable concentration to infinity
C_{max}	Maximum observed concentration
t_{max}	Time of maximum observed concentration
t_{last}	Time of last quantifiable concentration
$t_{1/2}$	Apparent terminal elimination half-life
λ_z	Apparent terminal elimination rate constant, where λ_z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase
CL/F	Apparent oral clearance (calculated for lasmitidan only)
V_z/F	Apparent volume of distribution during the terminal elimination phase (calculated for lasmitidan only)
AUC Ratio (Blood /Plasma)	$AUC_{0\text{-}\infty}$ of total radioactivity in whole blood/$AUC_{0\text{-}\infty}$ of total radioactivity in plasma
AUC Ratio (Lasmitidan/TRA)	$AUC_{0\text{-}\infty}$ of lasmitidan in plasma/$AUC_{0\text{-}\infty}$ of total radioactivity in plasma

AUC Ratio (Metabolite/TRA)	$AUC_{0-\infty}$ of metabolite in plasma/$AUC_{0-\infty}$ of total radioactivity in plasma (calculated for each metabolite)
M:P AUC Ratio	Metabolite to lasmitidan (parent) ratio calculated as: $AUC_{0-\infty}$ metabolite/$AUC_{0-\infty}$ lasmitidan

$AUC_{0-\infty}$, CL/F, and V_z/F will be calculated based on predicted Clast.

In addition, the following PK parameters will be calculated, whenever possible, for each subject based on the urine concentrations of lasmitidan, metabolites M3, M7, M8, M18 and total radioactivity. Parameters for lasmitidan and metabolites will be reported by the Covance Early Clinical Biometrics PK group; parameters for total radioactivity will be reported by the Covance Radioanalysis group.

Parameter	Definition
A_{eu}	Amount excreted in urine over a sampling interval, calculated as the sample weight (g) for the interval * concentration in urine. A specific gravity of 1 g/mL is assumed for urine.
Total A_{eu}	Cumulative amount excreted in urine, calculated as the sum of the A_{eu} for all sampling intervals
CL_R	Renal clearance, where CL_R = Total $A_{eu\ 0\text{-}x\ h}/AUC_{0\text{-}x\ h}$ (where x is the time of the last interval collected; calculated for lasmitidan only)
%UR	Percent of lasmitidan dose recovered in urine over a sampling interval, where %UR = 100 * (A_{eu} lasmitidan/lasmitidan dose) %UR for metabolites will be calculated as follows: %UR = 100 * (A_{eu} metabolite/(lasmitidan dose))
Total %UR	Cumulative percent of dose recovered in urine, calculated as the sum of %UR for all sampling intervals

The following PK parameters will be calculated, whenever possible, for each subject based on the fecal concentrations of total radioactivity. Parameters for total radioactivity will be reported by the Covance Radioanalysis group.

Parameter	Definition
A_{ef}	Amount excreted in feces over a sampling interval
Total A_{ef}	Cumulative amount excreted in feces, calculated as the sum of the A_{ef} for all sampling intervals
% FR	Percent of dose recovered in feces over a sampling interval, where %FR = 100 * (A_{ef}/dose)
Total % FR	Cumulative percent of dose recovered in feces, calculated as the sum of %FR for all sampling intervals

Additional pharmacokinetic parameters may be determined where appropriate.

Pharmacokinetic analysis will, where possible, be carried out using actual post dose times recorded in the raw data. If actual times are missing, nominal times may be used with sponsor approval.

Concentrations are used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters, with amount or concentration in the unit, will be presented as they are received from the analytical laboratory.

C_{max} and t_{max} will be obtained directly from the concentration-time profiles.

For multiple peaks, the highest post dose concentration will be reported as C_{max}. In the case that multiple peaks are of equal magnitude, the earliest t_{max} will be reported.

AUC_{0-t} or other common partial area may be used to determine ratios if $AUC_{0-\infty}$ cannot be calculated.

The amount excreted in urine (A_{eu}) for each urine collection interval will be calculated as the product of urine concentration and urine weight (assuming specific gravity is approximately 1); Total $Aeu_{0-x\ h}$ will be calculated by summing the A_{eu} values for each collection interval over the study collection period, where x is the end time of the last collection interval.

The percent of the dose excreted (%UR) will be calculated for each urine collection interval (i) according to the following formula:

$$\%UR(i) = \frac{A_{eu}(i)}{dose} \times 100$$

Total %UR will be calculated by summing the %UR values for each collection interval over the study collection period.

CL_R will be calculated over 0-x h according to the following formula:

$$CL_R = \frac{\text{Total Aeu}_{0\text{-x h}}}{AUC_{0\text{-x h}}}$$

10.3.1.1 Criteria for handling concentrations below the limit of quantification in Pharmacokinetic analysis

- Concentration values that are below the level of quantification (BLQ) will be set to zero, with defined exceptions as follows;
- Any embedded BLQ value (between 2 quantifiable concentrations) and BLQ values following the last quantifiable concentration in a profile will be set to missing for the purposes of PK analysis.
- If there are late positive concentration values following 2 BLQ concentration values in the apparent terminal phase, these values will be evaluated. If these values are considered to be anomalous, they will be set to missing.
- If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.
- If a predose concentration is missing, it may be set to zero with sponsor approval

10.3.1.2 Criteria for the Calculation of an Apparent Terminal Elimination Half-Life

- **Number of Data Points**

At least three data points will be included in the regression analysis and preferably should not include C_{max}.

- **Goodness of Fit**

When assessing terminal elimination phases, the R^2 adjusted (adjusted coefficient of variation for goodness of fit) value will be used as a measure of the goodness of fit of the data points to the determined line.

An elimination half-life will only be calculated if the R^2 adjusted value of the regression line is greater than or equal to 0.7.

- **Period of Estimation**

Time period used for the estimation of apparent terminal elimination half-lives, where possible, will be over at least two half-lives.

Where an elimination half-life is estimated over a time period of less than two half-lives, it will be flagged in the data listings at the discretion of the pharmacokineticist, and the robustness of the value should be discussed in the study report.

10.3.1.3 Calculation of AUC

- The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}.

- For any partial AUC determination (i.e. AUC0-x h), nominal time will generally be used for the end of the interval. Actual times for partial AUC intervals may be used at the discretion of the Pharmacokineticist.

- $AUC_{0-\infty}$ values where the percentage extrapolation is less than 20% will be reported. $AUC_{0-\infty}$ values where the percentage extrapolation is between 20 to 30% will be flagged and included in the descriptive statistics, whilst $AUC_{0-\infty}$ values where the percentage extrapolation is greater than 30% will be reported but excluded from descriptive statistics.

- If $AUC_{0-\infty}$ cannot be determined for all subjects, an alternative AUC measure, such as AUC to a fixed time point, may be used in the calculation of ratios.

10.3.1.4 Anomalous Values

If a value is considered to be anomalous due to being inconsistent with the expected pharmacokinetic profile, it may be appropriate to exclude this point from the pharmacokinetic analysis. However, the exclusion of data must have strong justification and will be documented in the raw data and study report.

Embedded BLQ values may be considered anomalous depending on the route of administration and the characteristics of the drug.

Positive predose value(s) greater than 5% of C_{max} may be excluded from the summary statistics of PK tables and statistical analysis at the discretion of the Pharmacokineticist.

10.3.2 Presentation of Pharmacokinetic Data

10.3.2.1 Presentation of Pharmacokinetic Plasma Drug Concentration Data

The following rules will be applied if there are values that are BLQ or if there are missing values (e.g., no result [NR]) in a concentration data series to be summarized.

- For the calculation of summary statistics, BLQ values will be set to zero.
- If an embedded BLQ value is considered anomalous within the concentration-time profile, this value will be excluded from the summary statistics.
- Where there is NR, these will be set to missing.
- If there are less than three values in the data series, only the min, max and N will be presented. The other summary statistics will be denoted as not calculated (NC). BLQ is considered a value.
- If all the values are BLQ, then the arithmetic mean, arithmetic SD, median, min and max will be presented as zero, and the geometric mean and geometric CV% will be denoted as NC.
- If the value of the arithmetic mean or median is below the lower limit of quantification, these values will be presented as zero and the geometric mean and geometric CV% will be denoted as NC.

10.3.2.2 Presentation of Pharmacokinetic Parameters

- For the calculation of summary statistics of PK parameters, all NR and NC values in a data series will be set to missing.
- The AUC values will be set to NC if they have been calculated using fewer than three concentrations, and/or three concentrations if the last is C_{max}.

10.4 Safety and Tolerability Assessments

10.4.1 Adverse Events

All AEs will be listed. The TEAEs will be summarised by treatment, severity, and relationship to the study drug. The frequency (the number of TEAEs, the number of subjects experiencing a TEAE, and the percentage of subjects experiencing a TEAE) of TEAEs will be summarised by treatment, and by Medical Dictionary for Regulatory Activities system organ class and preferred term. The summary and frequency TEAE tables will be presented for all causalities and for those TEAEs considered related to the study drug (those that have a relationship of reasonable

possibility). Any severe or serious AEs will be tabulated. For any AEs that change severity ratings the AE will be included only once under the maximum severity rating in the summaries.

10.4.2 Clinical Laboratory Parameters

Clinical chemistry, complete blood count (CBC) and urinalysis data will be listed. In addition, all clinical chemistry, CBC, and urinalysis data outside the clinical reference ranges will be listed by parameter and treatment.

Values for any clinical chemistry, CBC, and urinalysis values outside the clinical reference ranges will be flagged on the individual subject data listings.

10.4.3 Vital Signs

The vital signs data will be summarised by treatment, together with changes from baseline. .

Vital signs values outside the clinical reference ranges will be flagged on the individual subject data listings.

Orthostatic decreases of >20 mmHg for systolic blood pressure or >10 mmHg for diastolic blood pressure or an increase in heart rate of >30 bpm are considered to be of potential clinical concern and will also be highlighted on the individual data listings. Repeat and unscheduled readings will be handled as defined in Section 10.1.2. Orthostatic change is the standing value, minus the supine value taken prior to the standing value.

10.4.4 Electrocardiogram

The ECG data will be listed only.

10.4.5 Columbia Suicide Severity Rating Scale (C-SSRS)

Data from the C-SSRS questionnaire will be listed only.

10.4.6 Other Assessments

All other safety assessments not detailed in this section such as medical history etc. will be listed but not summarised or statistically analysed.

10.4.7 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

11 INTERIM ANALYSES

No interim statistical analyses are planned.

12 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol-specified statistical analyses.

13 DATA PRESENTATION

13.1 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of subjects or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, “No serious adverse events occurred for this study.”

14 REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.