STATISTICAL ANALYSIS PLAN

Study Title:	ABS-LT: A Phase 3, Long-Term, Open Label, Multicenter Safety Study of Ambrisentan in Subjects with Pulmonary Hypertension
Name of Test Drug:	Ambrisentan
Study Number:	GS-US-300-0124
Protocol Version:	Version 2 Rest of World; Version 3 US
Protocol Date:	12 June 2013
Analysis Type:	End of Study
Analysis Plan Version:	Version 1.0
Analysis Plan Date:	13 July 2020
Analysis Plan Author:	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	adverse event
BMI	body mass index
BPM	beats per minute
CI	confidence interval
CRF	case report form
DMC	data monitoring committee
ECG	electrocardiogram
FAS	full analysis set
HLGT	high level group term
ICH	International Conference on Harmonisation
LLT	low level term
MedDRA	medical dictionary for regulatory activities
PAH	pulmonary arterial hypertension
PK	pharmacokinetics
PT	preferred term
Q1	first quartile
Q3	third quartile
ROW	Rest of World
SAP	statistical analysis plan
SOC	system organ class
TFLs	tables, figures, and listings
ULN	upper limit of normal
US	United States
WHO	World Health Organization

1. INTRODUCTION

1.1. Study Objectives

Primary Study Objectives	• The objective of this study is to monitor the long-term safety of ambrisentan in subjects with pulmonary hypertension (PH)
Secondary Study Objectives	N/A

1.2. Study Design

Design Configuration and Subject Population	This Phase 3, international, multicenter, open-label study will monitor the long-term safety of ambrisentan in subjects with PH. The target population is those men and women who are discontinuing a clinical study of ambrisentan in PH due to study closure by the Sponsor and for whom ambrisentan is not yet commercially available.
Treatment Groups	Available doses are 2.5 (Protocol Version 1 only), 5, or 10 mg once daily (qd). Investigators may adjust the ambrisentan dose as clinically indicated.
Key Eligibility Criteria	Men and women with PH who are discontinuing a clinical study of ambrisentan due to study closure by the Sponsor. Eligible subjects are those participating in countries where ambrisentan is not yet commercially available. Subjects participating in countries where ambrisentan is commercially available may be eligible if they do not qualify for treatment per the current prescribing information of that country. Subjects who have discontinued an ambrisentan clinical study for any other reason than Sponsor-initiated study closure are not eligible.
Study Periods/Phases	There is one study period: treatment. Treatment will continue until such time as the Investigator or subject chooses to stop ambrisentan treatment, ambrisentan becomes commercially available, or the Sponsor stops the study.

Schedule of Assessments

Week	Screening/Enrollment Visit 0	Laboratory Visits[a] Every 12 Weeks	Laboratory Visits[b] - Pregnancy Test Only Every 4 Weeks	Clinic Visits[c] Every 24 Weeks
Assessments				
Informed consent	X			
Medical history	X			
Vital signs/body weight	X			X
Clinical laboratory tests[d]	X[e]	X[d,f]		X[c]
Serum or urine pregnancy test[g]	X	X[d]	X[d]	X
CONMED assessment	X			X
Adverse events	X			X
Return unused ambrisentan	X			X
Dispense study drug[h]	X			X

a Laboratory Visits will be required every 12 weeks for United States (US) and every 4 weeks for Rest of World (ROW) and will be completed at a local phlebotomy lab or at the Investigator clinic.
b Laboratory Visits Pregnancy Test Only will be required every 4 weeks and will be completed at a local phlebotomy lab or at the Investigator clinic.
c Clinic Visits will be required every 24 weeks.
d Completion of the Laboratory Visit will be documented via telephone contact (within ± 2 days) if the Laboratory Visit occurs at a local phlebotomy lab.
e Clinical laboratory tests at the Screening/Enrollment Visit and Clinic Visits will include chemistry (including LFTs), hematology, and coagulation. Coagulation labs (PT, PTT, and INR) will only be completed for subjects who are receiving warfarin or any other warfarin like anticoagulants.
f Clinical laboratory tests at the Laboratory Visits will be limited to LFTs, specifically ALT, AST, alkaline phosphatase, GGT, and total bilirubin.
g Pregnancy testing required for women of childbearing potential.
h As necessary, a 3 month supply of study drug will be dispensed.

Randomization	This is an open-label study in up to 80 investigational sites worldwide. No randomization is planned.
Site and/or Stratum Enrollment Limits	NA
Study Duration	Subjects will receive treatment with ambrisentan until such time as the investigator or subject chooses to stop ambrisentan treatment, ambrisentan becomes commercially available, or the Sponsor stops the study.

1.3. Sample Size and Power

Planned Sample Size	Approximately 300 subjects will be eligible to enroll in this study at its inception
Power Statement	NA
Actual Enrollment and Impact on Power	NA

2. TYPE OF PLANNED ANALYSIS

The primary endpoint for this study is the incidence and severity of AEs associated with long-term exposure to ambrisentan in subjects with PH. When all subjects have completed the study, the database will be locked, the final analyses will be run, and data collected will be analyzed.

In addition, the data from this study will be reviewed on a regular basis by an internal Data Monitoring Committee (DMC) charged with protecting the safety of the study subjects. This committee will have the authority to recommend stopping the study early or modifying the study design for safety concerns. No adjustments for these interim summaries of safety data will be made to the final analysis.

This statistical analysis plan (SAP) covers the final analysis.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

3.1. Analysis Sets

Analysis sets define which subjects are included in an analysis. Because there are no efficacy analyses for this study, and because all subjects received at least one dose of study drug, only one analysis set will be defined.

3.1.1. Safety Analysis Set

The safety analysis set includes subjects who were enrolled into the study and received at least one dose of study drug and will be used for all analyses.

3.2. Subject Groups

Subjects were enrolled at 2.5 mg, 5 mg, and 10 mg ambrisentan, but adjustments to dose were allowed during the course of the study. Therefore, all subjects will be combined into one group: Ambrisentan.

3.3. Strata and Covariates

Analyses will not be stratified.

3.4. Examination of Subject Subsets

There are no planned analyses of subject subsets.

3.5. Multiple Comparisons

No adjustments for multiple comparisons will be performed.

3.6. Missing Data and Outliers

Missing Data

A missing data point for a given study visit may be due to any of the following reasons:

- A visit occurred in the window but data were not collected or were unusable
- A visit did not occur in the window
- A subject permanently discontinued from the study before reaching the window.

Values for missing data will not be imputed unless otherwise specified.

Outliers

No adjustments for outliers will be performed.

3.7. Data Handling Conventions and Transformations

Safety data will be used according to availability, with no imputation for missing data.

Some laboratory data will need to be transformed in order to utilize it. These transformations are presented in Section 7.3.

3.8. Visit Windows

3.8.1. Definition of Study Day 1

Study Day 1 (baseline) is defined as the day of first dose of study drug in this study.

3.8.2. Analysis Windows

Subject visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, selected observations will be assigned to visits based on the windows presented in Table 1. Day 1 is the day of first dose of study drug in this study and is expected to be the day after the Enrollment visit, however, the Enrollment visit and Day 1 may also be the same day.

Table 1. Visit Windows for Vital Signs

Visit	Target Day	Visit Window in Days	Comment
Baseline	N/A	N/A	Value at Enrollment visit will be used (expected to be the day prior to Day 1, but may be on Day 1)
Week 24	168	1-252	
Week 48	336	253-420	
Week X	X*7	[(X*7)-83] - [(X*7) + 84]	Week X is for 24-week periods through the end of study.

Depending on the statistical analysis method, single values may be required for each analysis window. If multiple valid, nonmissing measurements exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline, the value at the Enrollment visit will be selected. If there is not an Enrollment visit value, the last nonmissing value on or prior to the first dosing date of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, the baseline value will be the average of the measurements for continuous data, or the measurement with the lowest severity (e.g., normal will be selected over abnormal) for categorical data.

- For postbaseline values:

  The record closest to the nominal day for that visit will be selected.

  If there are 2 records that are equidistant from the nominal day, the later record will be selected.

  If there is more than 1 record on the selected day, the average will be taken for continuous data and the worse severity will be taken for categorical data, unless otherwise specified.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment

The number and percentage of subjects enrolled in each country and by each investigator within a country will be summarized. The denominator for this calculation will be the total number of enrolled subjects.

4.2. Disposition of Subjects

A summary of subject disposition will be provided. This summary will present the number of subjects enrolled, included in the safety analysis set, and the number and percentage of subjects who permanently discontinued study with reasons for permanent discontinuation.

The denominator for the percentages of subjects in each category will be the number of subjects in the safety analysis set.

No inferential statistics will be generated. A data listing of reasons for study discontinuation will be provided.

4.3. Extent of Exposure

4.3.1. Duration of Exposure to Study Drug

Duration of exposure to study drug will be defined as (last dose date first dose date + 1), regardless of temporary interruptions in study drug administration, and will be expressed in weeks (recorded to one decimal place, e.g., 4.5 weeks). Partial last dose dates with missing month and/or day will be estimated using the month and/or day of permanent discontinuation, or if that date is unavailable, the month and/or day of the last available visit date (including laboratory visits). Duration of exposure to study drug will be summarized using descriptive statistics (sample size, mean, standard deviation, median, first quartile (Q1), third quartile (Q3), minimum and maximum) and as the number and percentage of subjects exposed for specific periods (ie, through 12 weeks, through 24 weeks, etc).

The summary will be provided for subjects in the safety analysis set.

4.4. Protocol Deviations

A listing will be provided of subjects in the safety analysis set who violated at least one inclusion or exclusion criteria. The listing will include the criteria not met and related comments.

5. BASELINE DATA

5.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized for the safety analysis set using descriptive statistics (sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum) for continuous data and using the number and percent of subjects for categorical data.

Data to be included in this summary are gender, race, region, age, height, weight, body mass index (BMI), childbearing potential, PH etiology, years PH present, WHO functional class and previous ambrisentan study.

Years PH present will be calculated as the time from diagnosis date to first dose of study drug in this study. Partial dates will be estimated using “June 15” for missing month and day and “15” for missing day only.

5.2. Medical History

General medical history (i.e., conditions not specific to the disease being studied) data will be listed only. General medical history data will not be coded.

6. EFFICACY ANALYSES

No efficacy analyses will be performed.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

The safety analysis set will be the primary analysis set for evaluation of adverse events and deaths.

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System organ class (SOC), high level group term (HLGT), high level term (HLT), preferred term (PT), and lower level term (LLT) will be attached to the clinical database.

7.1.2. Adverse Event Severity

AEs are graded by the investigator as mild, moderate, or severe. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings, and will be considered the least severe for the purposes of sorting for data presentation.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator answers "Yes" to the question "Related to Ambrisentan?". Events for which the investigator did not record relationship to study drug will be considered related to study drug. Data listings will show relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) are those identified as serious in the clinical database. The clinical database will be reconciled with the SAE database from the Gilead Pharmacovigilance & Epidemiology Department before database finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent

Since all subjects received treatment with ambrisentan in a previous study, treatment-emergent AEs for this study are defined as all events that meet one of the following criteria:

- Began on or before the date of the last dose of study drug plus 30 days.
- Resulted in study drug discontinuation.

7.1.5.2. Incomplete Dates

If the date of onset is incomplete, then the month and year (or year alone if month is not recorded) of onset determine treatment emergent as follows. The event is treatment emergent if the month and year of onset (or year of onset) of the event meets the following criteria:

- The same as or before the month and year (or year) of the date of the last dose of study drug

7.1.6. Summaries of Adverse Events and Deaths

A brief summary of AEs will show the number and percentage of subjects who (1) had any treatment-emergent AE, (2) had any severe treatment-emergent AE, (3) had any moderate or severe AE, (4) had any treatment-emergent treatment-related AE, (5) had any severe treatment-emergent treatment-related AE, (6) had any moderate or severe treatment-emergent treatment-related AE, (7) had any treatment-emergent SAE, (8) had any treatment-emergent treatment-related SAE, (9) permanently discontinued from study drug or withdrew from the study due to an AE, and (10) died during study.

Summaries (number and percentage of subjects) of adverse events (by SOC and PT) will be provided using the safety analysis set as follows:

- All treatment-emergent AEs
- Treatment-emergent AEs by severity
- Treatment-emergent AEs related to study drug
- Treatment-emergent AEs related to study drug by severity
- All treatment-emergent AEs that caused permanent discontinuation from study drug
- All treatment-emergent AEs that caused study withdrawal
- All treatment-emergent AEs with an outcome of death
- All treatment-emergent SAEs
- Treatment-emergent SAEs by severity
- All treatment-emergent SAEs related to study drug

An additional summary will be provided for all treatment-emergent AEs by PT.

Multiple events will be counted once only per subject in each summary. For data presentation, SOC will be ordered alphabetically, with PT sorted by decreasing total frequency. For summaries by severity grade, the most severe event will be selected.

For each of the AE summaries, data will be summarized for all subjects combined, for all treatment-emergent AEs during the study.

In addition to the summaries, data listings will be provided for the following:

- All AEs (with a variable indicating whether the event is treatment-emergent)
- SAEs
- Deaths
- AEs leading to discontinuation of study drug or study withdrawal

7.1.7. Additional Analysis of Adverse Events

No additional analyses of adverse events are planned.

7.2. Laboratory Evaluations

7.2.1. Summaries of Numeric Laboratory Results

Laboratory tests were analyzed by local laboratories. Laboratory values that were not within the normal range limits of the local laboratory were captured on the CRF, along with the normal ranges. If the result was within the normal limits, the results and associated normal ranges were not captured and the CRF only captured the result of "Normal". Therefore, descriptive statistics will not be presented for laboratory measurements.

7.2.2. Shifts Relative to the Normal Range

The following summaries (number and percentage of subjects) relative to the respective laboratory test normal ranges will be provided.

- The number and percentage of subjects with ALT or AST within the following categories at any time during the study:

  >3xULN

  >5xULN

  >10xULN

  >20xULN

- The number and percentage of subjects with alkaline phosphatase >1.5xULN or total bilirubin >1xULN or >2xULN at any time during the study will be summarized

- Additionally, the number and percentage of subjects with ALT >3xULN or AST >3xULN, and total bilirubin >2xULN with or without alkaline phosphatase <2xULN simultaneously at any time during the study will be summarized

7.3. Transformation of Numeric Laboratory Data

Certain numeric laboratory data need to be transformed for the summary tables, although in the listings original inputted values will be presented. The following rules will be used for the data transformation.

- For values with a comma, treat the comma as a decimal. For example, treat "23,2" as 23.2.
- For values with units, remove the units. For example, treat "47 U/L" as 47.
- For values ending with symbol "`" or "%", remove the symbol. For example, treat "31`" as 31, and treat "14.7%" as 14.7.
- For values containing "NCS" or "ABNORMAL", remove the word and any associated punctuation. For example, treat "NCS 3.44" as 3.44 and "ABNORMAL, 11.2" as 11.2.
- For values starting with symbol "<", remove the symbol and subtract 0.01 from the number. For example, treat "<30" as 29.99.
- For postbaseline values reported as normal or values indicating the test was not performed, remove from summaries.

7.4. Body Weight and Vital Signs

Body weight and vital signs (systolic and diastolic blood pressure and heart rate) and change from baseline in body weight and vital signs will be summarized using descriptive statistics (sample size, mean, standard deviation, median, Q1, Q3, minimum and maximum) for each post-baseline clinic visit where 4 or more subjects have measurements. The target days and windows presented in Section 3.8.2 will be applied here to select the value at each visit.

7.5. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. The WHO preferred name and drug code will be attached to the clinical database. Prior and concomitant medications will be listed by subject.

7.6. Changes From Protocol-Specified Safety Analyses

The protocol specifies that safety data would be summarized by ambrisentan dose at enrollment and by maximum ambrisentan dose received at any time during the study. Instead, because most subjects were on 5 mg or 10 mg (approved doses) at some time during the study, safety data will be summarized using all ambrisentan doses combined as one group.

The protocol specifies that dose migrations will be summarized by a shift table. These data will be listed as part of the study drug administration listing instead due to multiple shifts per subject which cannot be appropriately characterized by a shift table.

The protocol specifies treatment-emergent AEs as those starting on or after the first dose of study drug up to the date of last dose of study drug. For the purposes of this SAP, treatment-emergent AEs are defined as those starting on or after the first dose of study drug up to the date of last dose of study drug plus 30 days.

The protocol specifies that safety data will be summarized for cumulative 24-week periods. This will not be done and only the cumulative study period will be summarized.

The protocol-specified shifts from baseline value (low, normal, or high) to postbaseline value (low, normal, or high) at each postbaseline clinical visit will not be provided for laboratory tests.

8. SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

9. SAP REVISION

Revision Date (dd month, yyyy)	Section	Summary of Revision	Reason for Revision

GS-US-300-0124-SAP

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Research eSigned	14-Jul-2020 19:57:46
PPD	Biostatistics eSigned	16-Jul-2020 22:54:13