1.0 Title Page

Statistical Analysis Plan

Study M12-919

A Multicenter, Single-Arm Study of the Effects of Atrasentan on Spermatogenesis and Testicular Function

Date: 08 Jun 2018

Version 1.0

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3.0 Introduction

Study M12-919 is a prospective, single-arm, open-label, multicenter, phase 2 study designed to evaluate the effect of Atrasentan (0.75 mg QD) on spermatogenesis and testicular function in men with diabetic nephropathy. This statistical analysis plan (SAP) describes the analysis to be performed by AbbVie clinical statisticians and programmers for the Study M12-919 study protocol Amendment 4.

The purpose of this document is to pre-specify all statistical analyses and data summaries of the primary and secondary safety endpoints to be included in the clinical study report (CSR).

Safety analyses will be performed using SAS Version 9.4 or higher (SAS Institute, Inc., Cary, NC 27513) under the UNIX operating system.

4.0 Study Background

4.1 Study Objective

The study objective is to evaluate the effect of Atrasentan on spermatogenesis and testicular function in men with diabetic nephropathy.

4.2 Study Design

This is a Phase-2, single-arm, open-label, multicenter study designed to evaluate the effect of Atrasentan (0.75 mg QD) on spermatogenesis and testicular function in men with diabetic nephropathy.

Subjects who provide consent will enter a Screening Period to assess eligibility. Eligible subjects will enter a 26-week Treatment Period (TP), followed by an Observational Period (OP) up to an additional 52 weeks if the subject qualifies.

In the Treatment Period, semen samples will be collected at two time-points over a 7-day period with each sample being separated by at least 2 days (48 hours) at Screening (baseline), T5 (Week 13) and T6/End of Treatment (EOT, Week 26).

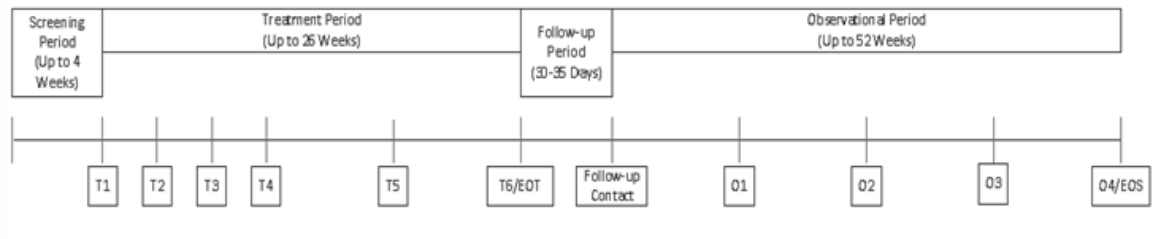
If at any time during the Treatment Period or at the T6/ EOT (Week 26) visit the subject's sperm concentration drops below 15×10^6 mL, the subject will be discontinued from study drug and enter into an Observational Period of up to an additional 52 weeks. If at the end of the 26-week Treatment Period there is a ≥ 50% reduction in sperm concentration from Screening (baseline), the subject will also enter into the Observational Period.

During the Observational Period, semen samples will be collected (at two time-points over a 7-day period with each sample being separated by at least 2 days [48 hours]) every 13 weeks until the subject's sperm concentration returns to within 15% of baseline or above, or until the end of the Observational Period.

General laboratory tests (including hematology, chemistry and urinalysis) will be collected for safety monitoring.

A schematic of the study design is shown below in Figure 1.

Figure 1. Study Schematic



4.3 Sample Size

Approximately 20 subjects (15 evaluable subjects) with diabetic nephropathy who are taking RAS inhibitors are planned to be enrolled in the study at approximately 20 sites.

The proportion of subjects with sperm concentration $< 15 \times 10^6$/mL in an unscreened population of healthy male subjects is reported to be approximately 10%. With 15 evaluable subjects, this study will have approximately 80% power to detect a 20% difference between the incidence rates in the Atrasentan group and the null hypothesis of 10% at 2-sided significance level of 0.2.

4.4 Interim Analysis

It is specified in the protocol that an interim analysis (IA) will be performed after all the subjects have completed or prematurely discontinued from the 26-week Treatment Period. The purpose of the IA was to include preliminary data to support registration in the EU.

In November 2017, AbbVie prematurely terminated the Phase 3 registration study (Study M11-352) with less than 25% of the planned number of primary endpoints achieved. Future development plans for atrasentan are unknown at this time. For study Study M12-919, it has been decided that the IA will not be performed. The decision has been documented in the Key Decision document (Appendix).

4.5 Multiplicity Testing Procedures for Type-I Error Control

There is no multiple testing in the study thus no adjustment is needed.

4.6 Missing Data Imputation

Missing data will not be imputed.

5.0 Definitions and Derivations

5.1 Definition of Study Dates

5.1.1 Date of First Dose of Atrasentan in TP

The date of first dose of atrasentan in TP is defined as the first date when a nonzero dose of atrasentan was taken as per "Atrasentan Dosing (Treatment Period)" electronic case report form (eCRF). This date is referred to as the Treatment 1 (T1) visit date (Day 1).

5.1.2 Date of Last Dose of Study Drug

The date of last dose of atrasentan in TP is defined as the last date when a nonzero dose of atrasentan was taken as per "Atrasentan Dosing (Treatment Period)" electronic case report form (eCRF).

5.1.3 Date of End of Study Visit

Subjects who do not meet the criteria to enter the Observational Period will be contacted by the Investigator (or designee) approximately 30 - 35 days after their date of last dose of study drug. This follow-up contact date will be the final contact date for these subjects.

For subjects who enter the Observational Period, the visit as which their sperm concentration returns to within ± 15% of the baseline or above will be the End of Study (EOS) visit date; otherwise the date of Observational Period Visit 4 (O4/Week 52) will be the date of EOS visit.

5.2 Definition of Study Time Points

For each subject, the ***study day*** of a specific study time point (date of interest on study) is defined as the number of days from the date for first dose of atrasentan (defined in Section 5.1.1). For dates after the first date of atrasentan, study day is calculated as:

Study day= Date of interest – first date of atrasentan + 1.

There is no Study Day 0.

5.3 Baseline and Final Observations in TP and OP

For Treatment Period, the baseline observation is defined as the last non-missing measurement collected on or before the date of first dose of study drug (T1/Day 1 Visit/Screening visit). The final observations in TP are defined as the last non-missing observations taken between the first dose and no more than 3 days after the last dose of study drug.

The final observation in Observational Period is defined as the last non-missing observations taken on or before the End of Study visit date.

6.0 Analysis of Data from the Treatment Period and Observational Period

6.1 General Statistical Methods

6.1.1 Methods for Categorical Endpoints

Categorical data (e.g., race, age categories) will be summarized using frequencies and percentages. Then number and percentage of subjects with missing information will also be summarized. Each subject will be counted only once in any category, for all variables other than the subject's race. Each subject has the option to identify himself as belonging to multiple races and hence the categories are not mutually exclusive. These summaries will be referred to as ***categorical summaries***.

6.1.2 Methods for Continuous Endpoints

Continuous data (e.g., age, sperm concentration) will be summarized using sample size, mean, standard deviation, median, 1st quartile, 3rd quartile, minimum and maximum among non-missing observations. The number and percentage of subjects with missing information will also be summarized. These summaries will be referred to as ***continuous summaries***.

6.2 Analysis Sets

Evaluable Set

The Evaluable Set (ES) includes subjects for whom either one of the following conditions is satisfied:

- The Overall Study Drug compliance status are ≥ 70%, and complete the 26-week treatment period and has all planned sperm samples collected; OR
- Receive at least one dose of study drug, and have a sperm concentration value less than 15×10^6/mL observed by the end of the Treatment Period or have a ≥ 50% reduction from baseline in sperm concentration at the end of the Treatment Period.

Safety Analysis Set

The Safety Analysis Set includes all subjects who receive at least one dose of atrasentan.

Sensitivity Analysis Set

The Sensitivity Analysis Set includes subjects who satisfy the following conditions:

- Achieve ≥ 70% overall study drug compliance; AND
- Complete the 26-week treatment period and have all planned sperm samples collected; or have a sperm concentration value < 15×10^6/mL observed by the end of the Treatment Period.

6.3 Demographics, Baseline Characteristics and Medical History

All demographic and baseline characteristics such as gender, race, age, weight, etc., will be summarized. Subject disposition, completion of study, or discontinuation from the study, will be summarized. The number and percentage of subjects who prematurely discontinue from the study will be summarized for the primary reason as well as for all reasons collected.

Concomitant medications reported by generic name assigned by the World Health Organization (WHO) dictionary will be summarized. For each concomitant medication, the number and percentage of subjects who take this medication will also be summarized.

Categorical summaries will be provided for race and ethnicity at baseline; and for assessment of peripheral edema (none, mild, moderate, severe), tobacco and alcohol use (unknown, never, current, former) at baseline. Categorical summaries will also be provided for subject medical history using body system and diagnosis/condition within body system using a lexicographic order.

Summaries of the demographic baseline characteristics and medical history will be based on the Safety Analysis Set.

6.4 Subject Disposition

For Treatment Period, accountability by investigator, completion of study drug, and discontinuation from the study drug will be summarized. The number and percentage of subjects who prematurely discontinued from the study drug will be summarized for the primary reason as well as for all reasons collected.

For Observational Period, the number of subjects entered Observational Period, reasons for entering the Observational Period, completion and discontinuation from the Observational Period will be summarized. The number and percentage of subjects who prematurely discontinued from the Study will be summarized for the primary reason and for all reasons collected.

6.5 Overall Study Drug Exposure and Compliance

Duration of treatment with study drug will be computed as follows:

> *Treatment duration in TP = Date of last dose of Atrasentan in* TP ─ *date of first dose of Atrasentan in* TP + *1.*

At each visit, compliance will be assessed as follows:

Percent (%) compliance for certain visit = # of pills taken / # of days for this visit × 100%

# of days for this visit = next visit start date ─ current visit start date.

Overall compliance will be calculated at the end of the Treatment Period as:

Percent (%) overall compliance = total # of pills taken / treatment duration in TP.

The number and percentage of subjects with at least 70% compliance with study drug at each visit during the Treatment Period will be summarized. The Overall Study Drug compliance for a subject (Yes or No) is defined as following: if the subject has at least 70% compliance with study drug at the end of the Treatment Period, then this subject is considered to be overall compliant to study drug; otherwise, the overall compliant status will be set to as No.

6.6 Concomitant Medications

A ***concomitant medication*** is defined as any medication other than the study drug that is taken from the first dose of atrasentan to the End of Treatment or End of Study visit. Concomitant medications reported by generic name assigned by the World Health Organization (WHO) dictionary will be summarized. Subjects who report taking more than one medication will be counted once in total number of subjects who are taking any concomitant medication. For each concomitant medication, the number and percentage of subjects who take this medication will also be summarized.

6.7 Efficacy Analysis

This is a safety study and no efficacy data will be collected.

6.8 Safety Analyses

6.8.1 Primary Safety Endpoint

The primary safety endpoint is the proportion of subjects in the Evaluable Set who have a sperm concentration $< 15 \times 10^6$/mL during the 26-week Treatment Period. Number and percentage of subjects with primary safety endpoint, along with the 2-sided 80% and 95% exact confidence interval will be calculated.

6.8.2 Secondary Safety Endpoints

The secondary safety endpoints are:

- The proportion of subjects who enter the Observational Period and do not return to within 15% of baseline or above during the 52-week Observational Period.
- Change from baseline to each visit in sperm concentration.
- Change from baseline to each visit in each of the components of the semen analysis (sperm motility, sperm morphology, sperm count, semen volume).
- Change from baseline to each visit in serum testosterone, estradiol, LH, FSH, and inhibin B.

Number and percentage of subjects who enter the Observational Period and do not return to within 15% of baseline or above during the 52-week Observational Period, along with the 2-sided 80% and 95% exact confidence interval will be calculated based on the Evaluable Set.

The other secondary safety endpoints will be analyzed based on the Safety Analysis Set. Continuous summaries will be provided for the changes from baseline to each visit; as well as the change from baseline to the last visit. Plots of mean sperm concentration with standard deviation at each visit will be provided.

6.9 Sensitivity Analyses

The same analysis for the primary safety endpoint and the first secondary safety endpoint will be performed using the Sensitivity Analysis Set.

7.0 Adverse Events Analyses

7.1 Analysis of Adverse Events (AEs)

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs, i.e., AEs that begin or worsen in severity after initiation of study drug throughout 30 days after the last dose of the study drug) will be summarized in descending order by MedDRA preferred term, as well as by system organ class (SOC) and MedDRA preferred term (PT).

The incidence rates of TEAEs will be summarized. Additionally, the TEAEs will also be summarized by the relationship to study drug and their maximum severity.

The adverse events reported as reasons for discontinuation will be summarized. Serious treatment-emergent adverse events will be evaluated in a similar manner.

Treatment-emergent adverse events (non-serious and serious) will be summarized as described below:

- An overview of the number and percentage of subjects with treatment-emergent adverse events.
- A summary of the number and percentage of subjects with treatment-emergent adverse events by primary MedDRA system organ class and preferred term.
- A summary of the number and percentage of subjects with treatment-emergent serious adverse events by primary MedDRA system organ class and preferred term.
- A summary of the number and percentage of subjects with treatment-emergent adverse events leading to discontinuation by primary MedDRA system organ class and preferred term.

- A summary of the number and percentage of subjects with possibly or probably drug-related treatment-emergent adverse events by primary MedDRA system organ class and preferred term.
- A summary of the number and percentage of subjects with treatment-emergent adverse events by primary MedDRA system organ class, preferred term and maximum relationship to study drug.
- A summary of the number and percentage of subjects with treatment-emergent adverse events by primary MedDRA system organ class, preferred term and maximum severity.
- A summary of subject numbers associated with treatment-emergent adverse events by primary MedDRA system organ class and preferred term.
- A summary of protocol-related adverse events in the Observational Period by primary MedDRA system organ class, preferred term and maximum severity.

For the Observational Period, the protocol-related adverse events will be summarized similarly from 30 days after the last dose of study drug through study completion.

7.2 Listing of TEAEs

The following additional listings will be prepared.

- List of all TEAEs by subject ID.
- Listing of all serious TEAEs by subject ID.
- Listing of all TEAEs that led to discontinuation of study drug by treatment arm and subject ID.
- Listing of subject numbers associated with each PT for all TEAEs.
- Listing of subject numbers associated with each PT for all TEAEs assessed by the investigator as having a reasonable possibility of being related to study drug.

7.3 Clinical Laboratory Data

Continuous summaries will be provided for laboratory assessments including semen sample analysis, hematology, chemistry and urianalysis at baseline and at each visit.

For each laboratory test, the mean change from baseline to each post-baseline visit will be summarized. For selected laboratory tests of interests, the number and percentage of subjects whose laboratory value has shifted from normal at baseline to abnormally high or low at final will be tabulated.

7.4 Vital Signs

Continuous summaries will be provided for age and height (collected at screening), weight, body mass index (BMI), blood pressure at baseline and at each treatment visit.

The mean change from baseline to each visit in vital signs, including sitting blood pressure, weight, will be summarized. Weight gain and edema will be assessed at every visit during the Treatment Period.

7.5 ECG Data

The number and percentage of subjects with shifts from baseline in the categories of normal, abnormal (not clinically significant/clinically significant) as indicated by the study site investigators will be summarized.

8.0 Appendix

Study M12-919/ABT-627 Interim Analysis Key Decision Document

Background	Endothelin receptor antagonists are well known to have preclinical findings of testicular toxicity, with atrasentan showing similar preclinical effects. Through a series of Scientific Advice interactions with the EMA, it was agreed that AbbVie would conduct a clinical study in patients with diabetes and kidney disease to evaluate the effect of atrasentan on spermatogenesis and testicular function. It was advised that "Preliminary data should already be provided at the time of MAA submission." Due to concerns regarding slow enrollment and potential planned timing of an MAA, a formal interim analysis once all subjects completed or discontinued dosing was incorporated as a mechanism to include preliminary data to support registration in the EU. In November 2017, AbbVie prematurely terminated the Phase 3 registration study (Study M11-352) with less than 25% of the planned number of primary endpoints achieved. Future development plans for atrasentan are unknown at this time.
Evaluation (include associated risk)	Data generated through the conduct of an interim analysis will not be used to support a MAA at this time. Thus no report is planned based on the interim analysis. A final analysis will be conducted after LSLV (which could occur anywhere in the time frame between July 2018 and May 2019) which would be available in time to support any future atrasentan development activities. There is no risk in this approach, since any potential registration plans would require discussion with regulatory agencies and generation of stability data, at which time, final results from Study M12-919 would be available. Additionally, all subjects globally have been permanently discontinued from atrasentan administration. Prior to their exposure, all subjects were consented regarding the potential risks to fertility.
Final Decision	Do not perform planned interim analysis for Study M12-919 study; do not amend protocol Study M12-919.
Justification	Data generated will not be used to support any current planned activities. Final analysis will be sufficient to support all planned activities.