## 1.0 Title Page

# Clinical Study Protocol M12-919

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

# Incorporating Administrative Change 1 and Amendments 1, 2, 3 and 4

| | |
|---|---|
| AbbVie Investigational Product: | Atrasentan (ABT-627) |
| Date: | 08 April 2016 |
| Development Phase: | 2 |
| Study Design: | Phase 2, single-arm, multicenter study. |
| EudraCT Number: | 2016-000722-19 |
| Investigators: | Multicenter (Investigator information is on file at AbbVie). |
| Sponsor: | AbbVie* |
| Sponsor/Emergency Contact: | [redacted] |

*The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

## 1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

| Protocol | Date |
|---|---|
| Original | 14 February 2014 |
| Amendment 1 | 25 April 2014 |
| Amendment 2 | 15 October 2014 |
| Amendment 3 | 06 May 2015 |

The purpose of this amendment is to:

- Revise, clarify and describe in more detail the overall study design and plan.

  ***Rationale:*** *With more safety data available on Atrasentan and considering the study objectives, it was determined the selection criteria can be amended to enhance participation in the trial while maintaining subject's safety.*

The changes are as follows:

Study Design Changes:

- Broaden the duration of the screening period to up to 4 weeks

  ***Rationale:*** *Allow time for repeat testing and potential subject schedule*
- Redefine visit windows.

  ***Rationale:*** *Enhance subject compliance to the visit schedule.*
- Remove collection of duplicate semen samples at T4/Week 6 visit

  ***Rationale:*** *Align semen sample collection with the spermatogenesis cycle to every 13 weeks.*
- Remove collection of duplicate semen samples at T6/EOT visit if subjects prematurely discontinues study drug as a result of entering the Observational Period

  ***Rationale:*** *it is determined collection of semen samples from these subjects is not necessary as these subjects would be providing two sets of semen samples within 2 weeks*

- Remove Week 6 visit from the Observational Period

  ***Rationale:*** *Align semen sample collection to spermatogenesis cycle every 13 weeks.*
- Replace the O5/EOS visit with a phone contact for subjects who return to within 15% of baseline or above

  ***Rationale:*** *Safety can be adequately monitored via a telephone contact.*
- Update the following study procedures
  - Move Physical Examination to the T1/Day 1 visit from Screening.
  - Add measurement of hormone levels to the T1/Day 1 visit
  - Remove lipid profile assessments
  - Update the requirement for two FMV urine collections to one FMV urine collection during the Screening Period
  - Update the requirement for limited chemistry to completed chemistry at each visit during the Observational Period
  - Move Hb A1c and urinalysis to the O1/Week 13 visit from the EOS/Week 52 visit

  ***Rationale:*** *Ensure appropriate timing of baseline physical examination (immediately before first dose administration) and eliminate laboratory tests that have been deemed not necessary based on study objectives.*
- Study Design Clarifications:
  - Individual tests may be repeated within the screening window instead of a full rescreening of all procedures.
  - Provide clear direction on when a subject enters the Observational Period
  - Provide clear definition of when the follow-up contact is performed

Selection Criteria Changes:

- Inclusion Criterion 3: remove requirement for being on a stable dose of ACE or ARB prior to the Screening Period.

  ***Rationale:*** *Align with scientific objectives of the study while maintaining the target study population*

- Inclusion Criterion 4: lowered eGFR criterion to ≥ 35 mL/min/1.73 $m^2$

  ***Rationale:*** *To expand the study population to subjects that are more closely aligned with the target atrasentan population.*

- Inclusion Criterion 6: increase the upper limit of SBP to 180 mmHg

  ***Rationale:*** *To accept expected fluctuations in blood pressure and align with blood pressure targets across atrasentan studies.*

- Inclusion Criterion 7: increase the serum potassium upper limit to 6.0 mEq/L

  ***Rationale:*** *To accept expected fluctuations in serum chemistry*

- Inclusion Criterion 10: streamline description for male contraception requirements

  ***Rationale:*** *details are provided in Section 5.2.4 of the protocol*

- Inclusion Criterion 15: redefine acceptable testosterone levels

  ***Rationale:*** *subjects with kidney disease have lower levels of testosterone that may not correlate with baseline sperm concentration*

- Inclusion Criterion 16: lessen required duration for being on alpha-blockers to at least 2 weeks prior to the initial screening visit.

  ***Rationale:*** *Two weeks of alpha-blockers is considered stable treatment for the purposes of excluding effect on spermatogenesis*

- Inclusion Criterion 17: lessen required duration for being on 5 alpha reductase inhibitors to at least 3 months prior to the initial screening visit.

  ***Rationale:*** *Three months of 5 alpha reductase inhibitors is considered stable treatment for the purposes of excluding effect on spermatogenesis*

- Exclusion Criterion 5: only exclude subjects currently symptomatic and on treatment.

  ***Rationale:*** *History of resolved infection is not confounding to the inclusion of the target patient population*

- Exclusion Criterion 8: lessen duration of drug, alcohol or substance abuse to 3 months prior to the initial screening.

  ***Rationale:*** *Three months of lack of abuse is a reasonable timeframe to determine subject's potential compliance with study requirements.*

- Exclusion Criterion 11: only exclude subjects who are currently receiving or have received hormone replacement therapy within the 6 months prior to the initial screening visit.

  ***Rationale:*** *Past hormone therapy use is not confounding to the study objective; only subjects with current or recent use need to be excluded.*
- Exclusion Criterion 15: remove moderate edema and pulmonary edema and to revise the required time frame to 4 weeks prior to the initial screening visit

  ***Rationale:*** *A subject with a history of pulmonary edema, which would be identified as part of the diagnosis of heart failure, would not be allowed into the study per Exclusion Criterion 17. Adequate medical management of peripheral or facial edema within the 4 weeks prior to screening is an acceptable length of time for assessment of subject eligibility at the initial screening visit.*
- Selection Criteria Clarifications:
  - Inclusion Criterion 5: the BNP upper limit should be less or equal than 200 pg/L
  - Exclusion Criterion 2: only exclude subjects unable to provide semen samples
  - Exclusion Criterion 3: only exclude subjects with azoospermia.
  - Exclusion Criterion 16: all subjects with pulmonary hypertension are excluded and not only those who are receiving oxygen
  - Exclusion Criterion 25: allergies should be known to both thiazide and loop diuretics
  - Additional updates to the selection criteria have been made to provide definitive time frames for some criteria.
- Selection Criteria that have been deleted:
  - Inclusion Criterion 12: HbA1c

    ***Rationale:*** *It is acceptable to allow all patients with diabetes into this study, regardless of glucose control, as subjects will receive close medical oversight on the management of diabetes.*
  - Inclusion Criterion 13: Follicle Stimulating Hormone (FSH)

***Rationale:*** *To align with the scientific objectives of the study without excluding potentially eligible subjects.*

- Inclusion Criterion 14: Luteinizing Hormone (LH)

  ***Rationale:*** *To align with the scientific objectives of the study without excluding potentially eligible subjects*

- Exclusion Criterion 4: Prior history of radiation to the testes

  ***Rationale:*** *To align with the scientific objectives of the study without excluding potentially eligible subjects.*

- Exclusion Criterion 6: History of male infertility

  ***Rationale:*** *The subject's fertility history is not confounding to the study objective, provided the subject meets the inclusion criteria for sperm concentration and semen sample provision.*

- Exclusion Criterion 7: Prior history of occupational exposure to environmental toxins

  ***Rationale:*** *The subject's toxin exposure history is not confounding to the study objective, provided the subject meets the inclusion criteria for sperm concentration and semen sample provision.*

- Exclusion Criterion 10: BMI

  ***Rationale:*** *To align with the target population of atrasentan across clinical trials*

- Exclusion Criterion 12: Evidence or history of hypogonadism

  ***Rationale:*** *Diagnosis of hypogonadism is not confounding to the study objective, provided the subject meets inclusion criteria for sperm concentration and semen sample provision.*

- Exclusion Criterion 13: Current use of hot tub/Jacuzzi/sauna or within the previous 12 weeks

  ***Rationale:*** *use of hot tub/Jacuzzi/sauna is not confounding to the study objective, provided the subject meets inclusion criteria for sperm concentration and semen sample provision.*

Other Changes:

- Remove "Single Country" from study title

  ***Rationale:*** *Allow for conducting the study in multiple countries*
- Revise Section 5.2.3, Prior and Concomitant Therapy
  - Addition of Prior Therapy Section (now known as Section 5.2.3.1)

    ***Rationale:*** *Consistency with revised inclusion and exclusion criteria*
  - Addition of Concomitant Therapy Section (now known as Section 5.2.3.2)

    ***Rationale:*** *administrative; separate from prior therapy and prohibited therapy text*
  - Change to numbering for Prohibited Therapy Section (now known as Section 5.2.3.3)

    ***Rationale:*** *administrative*
  - Addition of Guidance for Managing Edema or Weight Gain Section (now known as Section 5.2.3.4)

    ***Rationale:*** *administrative*
- Addition of Section 5.2.4, Contraception Recommendations

  ***Rationale:*** *revision per AbbVie policies to provide clear and full description on contraception requirements*
- Revise criteria for discontinuation of subjects
  - Subjects will not be discontinued at the T4/Week 6 visit if the subject has a weight gain of > 3 kg from baseline and a BNP > 300 ng/L.
  - Subjects will not be discontinued at the T4/Week 6 visit if subject has an increase in serum creatinine > 0.5 mg/dL (> 48 umol/L) and > 20% increase from baseline

    ***Rationale:*** *To allow for continued participation of subjects in the study with continued medical oversight by the principal investigator.*

Other Clarifications:

- Section 5.3.1.1, Study Procedures, weight gain and assessment of edema will be assessed during the Treatment Period

- Section 5.3.2.6, Handling/Processing of Samples, provide direction for local lab handling and name/contact information for central morphology laboratory
- Section 5.5.2.2, Storage and Disposition of Study Drugs, provide specific details for the storage of study drug on site and management of study drug exposed to temperatures outside the allowed range and allow for local destruction of study drug.
- Section 5.5.6, Treatment Compliance, removed directions for calculation, as information is not being collected
- Complete Section 5.6, Discussion and Justification of Study Design
- Section 6.4, Adverse Event Collection Period, clarify the collection period and reporting of adverse events
- Section 6.6, Pregnancy, add statement regarding the requirement for obtaining written informed consent from the subject's pregnant partner prior to releasing medical information
- Section 9.3, Subject Information and Consent:
  - Clarify that information regarding incentives and compensation can be found in the informed consent form
  - Clarify the use of samples collected and stored in the event a subject withdraws consent.
- First secondary variable/endpoint: clarify that subjects whose sperm concentration returns to levels above 15% of their baseline are included.

Administrative changes are made throughout the protocol to remove duplicative information and reordering of information to provide clearer understanding of the procedures, to include, but not limited to the following:

- Streamline the synopsis by including only the main selection criteria,
- Reorganize text throughout,
- Clarify required procedures,
- Add standard international units to eligibility lab values,
- Update Table 1, Study Activities, to align with study design changes,
- Streamline footnotes,

- Update Abbreviations and Definition of Terms subsections (Section 1.3),
- Update contact information (Section 7.0),
- Update and re-organize Section 15.0, Reference List
- Update signatory.

  ***Rationale:*** *Administrative/clarification*

An itemized list of changes made to this amendment can be found in Appendix C.

## 1.2 Synopsis

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|---|---|
| **AbbVie** | **Protocol Number:** M12-919 |
| **Name of Study Drug:** Atrasentan | **Phase of Development:** 2 |
| **Name of Active Ingredient:** Atrasentan | **Date of Protocol Synopsis:** 08 April 2016 |
| **Protocol Title:** A Multicenter, Single-Arm Study of the Effects of Atrasentan on Spermatogenesis and Testicular Function | |
| **Objectives:** The study objective is to evaluate the effect of Atrasentan on spermatogenesis and testicular function in men with diabetic nephropathy. | |
| **Investigators:** Multicenter | |
| **Study Sites:** Approximately 20 sites. | |
| **Study Population:** Subjects with type 1 or 2 diabetes and nephropathy (e-GFR ≥ 35 ml/min/1.73 $m^2$ and a urinary albumin to creatinine ratio (UACR) ≥ 30 mg/g creatinine and < 5,000 mg/g (≥ 3.4 mg/mmol and < 565 mg/mmol)). | |
| **Number of Subjects to be Enrolled:** Approximately 20 subjects will be enrolled to complete 15 evaluable subjects. | |
| **Methodology:**<br>This is a prospective, open-label, multicenter, single-arm study. Eligible subjects will be treated with Atrasentan 0.75 mg once daily (QD) for 26 weeks while remaining on their RAS inhibitors. Semen samples will be collected at Screening (baseline), Week 13 and Week 26/End of Treatment (EOT) visits. 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) for each scheduled collection period. The average of the 2 semen samples will be used as the value for that collection period. If at any time during the Treatment Period or at the Week 26/EOT visit, the subjects' sperm concentration drops below 15 million/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 baseline, the subject will 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. Subjects who do not meet the criteria to enter the Observational Period will have a follow-up contact from the Investigator (or designee) 30 to 35 days after the last dose of study drug. Subjects, whose sperm concentration returns to within 15% of baseline or above during the Observational Period, will have a follow-up contact from the Investigator (or designee) within 14 days of the collection of the second semen sample. | |
| **Diagnosis and Main Criteria for Inclusion/Exclusion:**<br>**Main Inclusion:**<br>• Male subject 30 to 75 years of age, inclusive at the time of Screening.<br>• Subject has type 1 or 2 diabetes and is receiving treatment with at least one anti-hyperglycemic medication and ACEi or ARB (RAS inhibitor). | |

**Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):**

**Main Inclusion (Continued):**

- Subject has an eGFR ≥ 35 mL/min/1.73 m2 with the CKD-EPI formula and UACR ≥ 30 to < 5,000 mg/g creatinine (≥ 3.4 mg/mmol and < 565 mg/mmol).
- Subject is able to provide a semen specimen at the required intervals.
- Subject has a baseline sperm concentration ≥ 30 million per mL at Screening.

**Main Exclusion:**

- Subject has had treatment with hormone suppressive agents, including androgens, estrogens, anabolic steroids, glucocorticoids, ketoconazole, cyclosporine, or cancer chemotherapy within the 6 months prior to the initial screening visit or planned during the study.
- Subject is currently receiving or has received hormone replacement therapy within the last 6 months prior to the Screening Period.
- Subject has a history of severe peripheral edema or facial edema unrelated to trauma or a history of myxedema in the prior 4 weeks to the initial screening visit.
- Subject has a history of pulmonary hypertension, pulmonary fibrosis or any lung disease requiring either oxygen therapy (e.g., chronic obstructive pulmonary disease, emphysema).
- Subject has a documented diagnosis of heart failure, previous hospitalization for heart failure or current or constellation of symptoms (dyspnea on exertion, pedal edema, orthopnea, paroxysmal nocturnal dyspnea) felt to be compatible with heart failure, that was not explained by other causes, and for which there was a change in medication or other management directed at heart failure.

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| **Investigational Product:** | Atrasentan |
| **Dose:** | 0.75 mg QD |
| **Mode of Administration:** | Oral |
| **Reference Therapy:** | Not applicable |
| **Dose:** | Not applicable |
| **Mode of Administration:** | Not applicable |

**Duration of Treatment:** 26 weeks

**Criteria for Evaluation:**

**Safety:**

**Primary Safety Endpoint:**

The proportion of subjects who have a sperm concentration < $15 \times 10^6$/mL during the 26-week Treatment Period.

**Criteria for Evaluation (Continued):**

**Safety (Continued):**

**Secondary Safety Measures up to the End of Study:**

- 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.

**Pharmacokinetic:**

Atrasentan apparent oral clearance (CL/F) and volume of distribution (V/F) may be estimated using population pharmacokinetic techniques.

**Statistical Methods:**

**Analysis Datasets:**

The following datasets will be used for the analysis of safety endpoints:

- The Evaluable Set will consist of all subjects who achieve the following: 1) ≥ 70% overall study drug compliance; and 2) having completed the 26-week treatment period and having all planned sperm samples collected; or having a sperm concentration value < $15 \times 10^6$/mL observed by the end of the Treatment Period.
- The Safety Analysis Set includes all subjects who receive at least one dose of Atrasentan.

**Sample Size Justification:**

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 open label, single-arm 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.

**Safety:**

**Primary Safety Analysis:**

The primary safety analysis will be conducted on the evaluable set for the primary safety endpoint. The simple percentage of subjects and a 2-sided 80% exact confidence interval will be calculated. When 15 evaluable subjects are available, if 4 or more subjects have a sperm concentration < $15 \times 10^6$/mL, the trial will claim that Atrasentan has a statistically significant effect on the primary endpoint.

**Secondary Safety Analysis:**

The secondary analysis on 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 will be performed on the evaluable set. The other secondary safety analyses will be conducted on the Safety population. For proportion endpoints, the simple percentage of subjects and a 2-sided exact 80% confidence interval will be calculated.

The continuous variable of the secondary endpoints will be summarized by sample size (N), mean, standard deviation, minimum and maximum.

**Statistical Methods (Continued):**

**Adverse Events (AEs) Analysis:**

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs (i.e., AEs that begin or worsen in severity after initiation of study drug) throughout the 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. The incidence rates of treatment-emergent AEs will be summarized. Additionally, the treatment-emergent AEs 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 adverse events will be evaluated in a similar manner.

For the Observational Period, the protocol related AEs will be summarized similarly from 30 days after the last dose of study drug through study completion. The number and percentage of subjects who report protocol-related adverse events in the Observational Period will also be summarized.

**Laboratory Data:**

For each laboratory test, the mean change from baseline to the minimum, maximum, and to each visit will be summarized. Additionally for selected laboratory tests of particular 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. The mean change from baseline to each visit in vital signs, including weight, will be summarized.

**Interim Analysis:**

An interim analysis will be performed after all the subjects have completed or prematurely discontinued from the 26-week Treatment Period. The database will be formally locked and versioned. The primary, applicable secondary and other safety analyses will be performed on this version of the clinical database. There is no need to adjust significance level since the only comparison is in the primary analysis which will be conducted using data from the 26-week Treatment Period.

## 1.3 List of Abbreviations and Definition of Terms

**Abbreviations**

| | |
|---|---|
| ACEi | Angiotensin-converting enzyme inhibitor |
| AE | Adverse event |
| ALT | Serum alanine aminotransaminase |
| AST | Serum aspartate aminotransaminase |
| ARB | Angiotensin II receptor blocker |
| BNP | Brain natriuretic peptide |
| BP | Blood pressure |
| BUN | Blood urea nitrogen |
| CAD | Coronary artery disease |
| CFR | Code of federal regulations |
| CHF | Congestive heart failure |
| CKD | Chronic kidney disease |
| CL/F | Oral clearance |
| CRA | Clinical Research Associate |
| CRF | Case report form |
| CV | Cardiovascular |
| CVD | Cerebrovascular disease |
| DBP | Diastolic blood pressure |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| EDTA | Edetic acid (ethylenediaminetetraacetic acid) |
| eGFR | Estimated glomerular filtration rate |
| EPI | Epidemiology collaboration |
| EOS | End of Study |
| EOT | End of Treatment |
| ESRD | End stage renal disease |
| ET | Endothelins |
| $ET_A$ | Endothelin-A |
| $ET_B$ | Endothelin-B |
| FMV | First morning void |

| | |
|---|---|
| FSH | Follicle stimulating hormone |
| GCP | Good Clinical Practice |
| GI | Gastrointestinal |
| $HBA_{1c}$ | Glucosylated hemoglobin $A_{1c}$ |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IMP | Investigational medicinal product |
| IND | Investigational new drug |
| IRB | Institutional Review Board |
| IUD | Intrauterine device |
| IWRS | Interactive voice response/Interactive Web Response System |
| IVRS | Interactive voice response system |
| LH | Luteinizing hormone |
| MI | Myocardial infarction |
| MTLDD | Maximum tolerated labeled daily dose |
| OLE | Open-label extension |
| PD | Premature discontinuation |
| PK | Pharmacokinetic |
| QD | Once daily |
| MedDRA | Medical dictionary for regulatory activities |
| RAS | Renin angiotensin system |
| RBC | Red blood cell |
| SAE | Serious adverse event |
| SBP | Systolic blood pressure |
| SGPT | Serum glutamic pyruvic transaminase |
| SGOT | Serum glutamic oxaloacetic transaminase |
| SI | Standard International Units |
| SOP | Standard operating procedure |
| SUSAR | Suspected unexpected serious adverse reactions |
| T | Testosterone |
| TGF-β | Transforming growth factor beta |
| UACR | Urinary albumin to creatinine ratio |
| ULN | Upper limit of normal |
| US | United States |

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|---|---|
| V/F | Volume of distribution |
| WBC | White blood cell |

## Definition of Terms

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|---|---|
| First morning void urine | The first void of the morning collected after 5:00 am or upon raising for the day. |
| Stable dose | Same type and regimen of medication. |
| Duplicate semen samples | Set of two semen samples collected over a 7-day period with each sample being separated by at least 2 days (48 hours) for a scheduled collection period. Each collection period lasts up to 14 days and is associated with a specific study visit. |

## 2.0 Table of Contents

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## 3.0 Introduction

The endothelins (ET), first identified in 1988, are a family of three paracrine/autocrine peptide factors (ET-1, ET-2 and ET-3) produced in a variety of tissues.[1] ET-1, the main isoform in mammalian tissues and fluids, is produced primarily in endothelial cells, but also in vascular smooth muscle cells. ET-2 is produced predominantly in the kidney and intestine, and ET-3 has been found in high concentrations in the brain.[2,3] Endothelins act as modulators of vasomotor tone, nociception, cell proliferation, and hormone production.[2-4] Two types of endothelin receptors have thus far been identified, $ET_A$ and $ET_B$. $ET_A$ receptors have a high affinity for ET-1 and ET-2, whereas $ET_B$ receptors have equal affinity for all ET-related peptides.[4,5] ETA receptors are primarily responsible for ET-1 mediated vasoconstriction, cell proliferation, and promotion of vascular remodeling.[6] $ET_B$ receptors are thought to provide a mechanism for the removal of excessive endothelins; they may also modulate arterial tone, however, when ET-1 concentrations are elevated.[7]

The roles for $ET_A$ and $ET_B$ receptor subtypes in renal and cardiovascular (CV) disease are under investigation. Animal and human data suggest that $ET_B$ receptor blockade could be harmful to the kidney, whereas $ET_A$ receptor blockade may improve glomerular function by attenuating the vasoconstrictive action of ET-1.[8,9] Endothelins may play a significant role in the pathophysiologic changes that occur at the vascular level in diabetes mellitus and lead to complications of retinopathy, neuropathy, and renal failure.[10] Glucose is a strong stimulator of endothelin receptor expression in cultured endothelial and vascular smooth muscle cells[11] and recent evidence suggests a relationship between the duration of type I diabetes mellitus and the elevation of plasma ET-1. ET-1 levels are higher in subjects with both diabetes and hypertension[12] and they correlate with long-term control of the disease in type 1 diabetes. Additionally, endothelins may play a role in volume homeostasis by inducing renal vasoconstriction and sodium retention, as has been demonstrated in humans.[13]

The drug substance ABT-627 [2R-(4-methoxyphenyl)-4S-(1,3-benzodioxol-5-yl)-1-(N,N-di-(N-butyl)-aminocarbonyl-methyl)-pyrrolidine-3R-carboxylic acid] is an orally bioavailable, potent endothelin receptor antagonist with a high selectivity for the $ET_A$ receptor.[14] Preclinical studies have demonstrated that ABT-627 (Atrasentan) inhibits mitogen and vascular biological responses induced by ET-1 challenge.[15]

ET-1 has also been shown to play a role in the pathogenesis of proteinuria and glomerular injury in a rat model of proliferative nephritis.[16] Administration of a selective $ET_A$ receptor antagonist to rats with experimental glomerulonephritis showed reduction in mesangial cell proliferation, supporting the hypothesis that ET-1 is a potent mitogen for mesangial cells.[17] In a rat model of diabetic nephropathy, Atrasentan treatment attenuated albuminuria and glomerulosclerosis in association with reductions in glomerular permeability (and urine TGFb).[17,18] In a double-blind, placebo-controlled, Phase 2 crossover study in 11 subjects with type 1 diabetes and proteinuria who were not receiving renin-angiotensin system (RAS) inhibitors, (Study M96-499) Atrasentan 5 mg per day for 42 days resulted in a 65% reduction in urinary albumin excretion. Mean arterial blood pressure (BP) was also reduced; however, there was only a weak correlation between change in BP and albuminuria reduction. The most commonly experienced treatment-emergent adverse events in the Atrasentan group were peripheral edema (64%), rhinitis (36%) and headache (18%), whereas in the placebo group the rates were: peripheral edema (0%), rhinitis (11%) and headache (56%).

In subsequent Study M10-815, a double-blind, randomized, placebo-controlled study of 89 subjects with type 2 diabetes and albuminuria who were on stable doses of RAS inhibitors, treatment with Atrasentan 0.75 or 1.75 mg per day for 8 weeks resulted in significant reductions in the mean urinary albumin to creatinine ratio (UACR) from baseline for subjects taking 0.75 mg per day (42% reduction, 1-sided $P = 0.023$) and 1.75 mg per day (35% reduction, 1-sided $P = 0.073$) compared to placebo (11% reduction), whereas subjects receiving 0.25 mg per day had a non-significant mean UACR reduction of 21% ($P = 0.291$). The most commonly experienced treatment-emergent adverse events were peripheral edema in 9% of placebo, 14% in

0.25 mg Atrasentan, 18% in 0.75 mg Atrasentan and 46% in the 1.75 mg Atrasentan dose groups, most of which were mild to moderate in severity and did not result in discontinuation from the study. There was no statistical significant difference in serum concentration of ET-1 of those subjects receiving Atrasentan as compared to placebo.

In a series of Phase 2b, dose-ranging studies involving 255 subjects who were taking the maximum tolerated labeled daily dose (MTLDD) of RAS inhibitors (Studies M11-350, M12-812 and M12-830), the UACR lowering effect of Atrasentan was confirmed. In Study M11-350 (RADAR), 153 subjects from the US, Canada and Taiwan, were randomized to placebo, 0.75 mg or 1.25 mg daily of Atrasentan for 12 weeks. UACR reductions of 37.7% and 40.6% were observed with the respective doses (0.75 and 1.25 mg per day), compared to placebo ($P < 0.01$). In Study M12-812, of 54 Japanese subjects, doses of 0.75 and 1.25 mg daily resulted in 31.4% and 53.7% UACR reduction, respectively, compared to placebo. In Study M12-830, of 48 subjects, doses of 0.5 and 1.25 mg daily resulted in 27.6% and 37.4% UACR reduction, respectively. The most common adverse event was peripheral edema, which was not different among the treatment groups in all three studies. There were three serious adverse events of congestive heart failure (1 [1.5%] in placebo, 1 [1.2%] in 0.75 mg and 1 [1.0%] in 1.25 mg groups).

The Phase 3 study (Study M11-352) is ongoing to characterize the safety and efficacy of Atrasentan in delaying renal disease progression in subjects with type 2 diabetes and nephropathy who have residual albuminuria while receiving MTLDD of RAS inhibitors. The primary endpoint will be the time to doubling of serum creatinine or end stage renal disease (ESRD).

**Effect of Atrasentan on Testicular Function in Clinical Studies**

Because of the nonclinical findings affecting male fertility, a Phase 2a clinical study, Study M10-815, included assessment of the neurohormonal axis in a subset of male subjects. These assessments evaluated FSH and inhibin B, which were measured at baseline and after 8 weeks of treatment or early termination and again at 30 days after the

last dose of study drug. In this study, the mean changes from baseline to final value in both FSH and inhibin B were not statistically significantly different between placebo and Atrasentan, nor were they clinically relevant.

At 30 days after the last dose of study drug, mean FSH decreased in all groups during the 30-day follow-up period, with greater decreases in all Atrasentan groups compared with placebo; the difference between placebo (least squares mean change of –0.03 mIU/mL) and the 0.75 mg Atrasentan group (–1.75 mIU/mL) was statistically significant ($P = 0.002$). Mean inhibin B increased in all groups during the 30-day follow-up period, with smaller increases in all Atrasentan groups compared with placebo and with no statistically significant differences between groups.

One Phase 2b study, Study M12-812, also included evaluation of testosterone for all male subjects. Mean testosterone levels measured at baseline were at the higher range of normal in all treatment groups (470 ng/dL in the Atrasentan 0.75 mg group, 513 ng/dL in the placebo group, and 584 ng/dL in the Atrasentan 1.25 mg group). By Week 8, there was a decline in testosterone observed in both Atrasentan groups; however, a statistically significant decrease in testosterone from baseline was observed only in the Atrasentan 1.25 mg group (–83 ng/dL, $P = 0.020$ for difference from baseline) with a further statistically significant decline (–120 ng/dL from baseline) at post treatment follow-up visit compared with baseline visit observed only in this treatment group. Despite the observed decreases in testosterone in the Atrasentan 1.25 mg group toward the end of treatment and at the follow-up visit, the mean values for all treatment groups remained within the normal range.

A Phase 2 study from the original prostate cancer clinical development program also included evaluation of testosterone levels. Study M01-366 was a randomized, double-blind, placebo-controlled study of 10 mg Atrasentan QD versus placebo QD in men with hormone-naïve prostate cancer who had undergone a radical prostatectomy, but had not begun hormonal therapy and who were exhibiting signs of biochemical failure defined as both prostate-specific antigen (PSA) between 0.4 ng/mL and 5 ng/mL and a PSA doubling time ≤ 12 months. Testosterone levels were measured at baseline, during

Weeks 2, 6, 12, and 24 and every 12 weeks thereafter. One hundred ninety-nine men with a mean age of 65 years were enrolled. Mean testosterone at baseline was within normal range and was similar between the treatment groups (approximately 354 ng/dL in the placebo group [n = 107] and approximately 372 ng/dL in the Atrasentan group [n = 111]). The mean exposure to Atrasentan was 442 days. Among all randomized subjects, the testosterone levels with Atrasentan were significantly increased relative to placebo at Week 12, Week 24, and Final Visit. A subset of subjects enrolled into an open-label extension (OLE) study, during which all subjects received Atrasentan 10 mg, including those originally randomized to receive placebo. Among those who entered the open-label extension study, in an analysis that compared groups according to their original randomization, at the Final Visit, there was a mean decrease in testosterone levels for the 72 subjects originally randomized to Atrasentan (–54 ng/dL) that was statistically significantly different ($P = 0.008$) from a small mean increase for the 75 subjects originally randomized to placebo (19.6 ng/dL). Among all subjects who enrolled into the open-label extension, a mean increase in testosterone was observed at Week 12 (original treatment groups analyzed as one), but testosterone declined compared with baseline at Week 96 and Week 108 in the small number of subjects still on study. Of note, subjects enrolled in the OLE were permitted to start hormone ablative treatment at the discretion of the PI. Thus average testosterone values during the OLE will be confounded by these androgen reducing therapies.

In a clinical study evaluating the effect of bosentan, a dual endothelin antagonist, on spermatogenesis, 25% of male subjects experienced a ≥ 50% decrease in sperm count, yet their counts remained within the normal range after 6 months of treatment without changes in sperm morphology, motility, or serum hormone levels. One subject developed marked oligospermia after 3 months of therapy, which was reversible following discontinuation of bosentan. These results are noted in the US prescribing information for both bosentan and ambrisentan.[19,20] In ARIES-E, a clinical study with chronic ambrisentan administration, there was no clear evidence of a detrimental effect on sperm count; however, a decrease in plasma inhibin B and an increase in plasma FSH not associated with a change in testosterone were observed.[21]

The purpose of this study (Study M12-919) is to evaluate the effect of prolonged administration of Atrasentan on spermatogenesis and testicular function (Section 4.0).

## 3.1 Differences Statement

This study is designed to evaluate the effect of Atrasentan (0.75 mg once daily [QD]) on spermatogenesis and testicular function in men with diabetic nephropathy. Prior studies in this population have not evaluated the effect of Atrasentan on spermatogenesis and testicular function.

## 3.2 Benefits and Risks

Atrasentan is a highly potent and selective endothelin-A ($ET_A$) receptor antagonist being developed for the treatment of patients with diabetic nephropathy. This study will provide safety information of Atrasentan administration for 26 weeks on spermatogenesis and testicular function.

Atrasentan has been evaluated in 5 studies in patients with diabetic nephropathy: one Phase 2a study in subjects with type 1 diabetic nephropathy who were not receiving renin-angiotensin-aldosterone system (RAS) inhibitors (Study M96-499), one Phase 2a study in subjects with type 2 diabetic nephropathy who were receiving stable doses of RAS inhibitors (Study M10-815) and three Phase 2b studies (Studies M11-350, M12-830, and M12-812) in patients with type 2 diabetes and nephropathy who were receiving MTLDD of RAS inhibitors.

All studies showed that Atrasentan effectively reduced urinary albumin excretion with minimal fluid retention for up to 12 weeks of treatment.

The primary toxicities of Atrasentan in animals are effects on the reproductive system of both males and females and teratogenic effects on the fetus. The effects of Atrasentan on male fertility are similar to those seen with other drugs in this class; seminiferous tubule atrophy as well as reduced male fertility are considered to be class effects of ET antagonists. Effects observed in animals with Atrasentan are similar to those reported

for the –entans bosentan and ambrisentan. As indicated above, testicular toxicity leading to impaired male fertility is a common feature of this class.

# 4.0 Study Objective

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

# 5.0 Investigational Plan

## 5.1 Overall Study Design and Plan: Description

This is a Phase 2, prospective, open-label, multicenter, single-arm study designed to evaluate the effect of Atrasentan on spermatogenesis and testicular function in men with diabetic nephropathy. Approximately 20 subjects (to complete 15 evaluable subjects) with diabetic nephropathy who are taking RAS inhibitors are planned to be enrolled in the study at approximately 20 sites.

Subjects who provide consent, will enter a Screening Period to assess eligibility. Eligible subjects will enter a 26-week Treatment Period, followed by an Observational Period if the subject qualifies. General laboratory tests (including hematology, chemistry and urinalysis) will be collected for safety monitoring and semen samples will be collected throughout the subject's study participation.

If at any time during the Treatment Period or at the T6/End of Treatment (EOT) (Week 26) visit the subject's sperm concentration drops below 15 million/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 $\geq$ 50% reduction in sperm concentration from baseline the subject will also enter into the Observational Period.

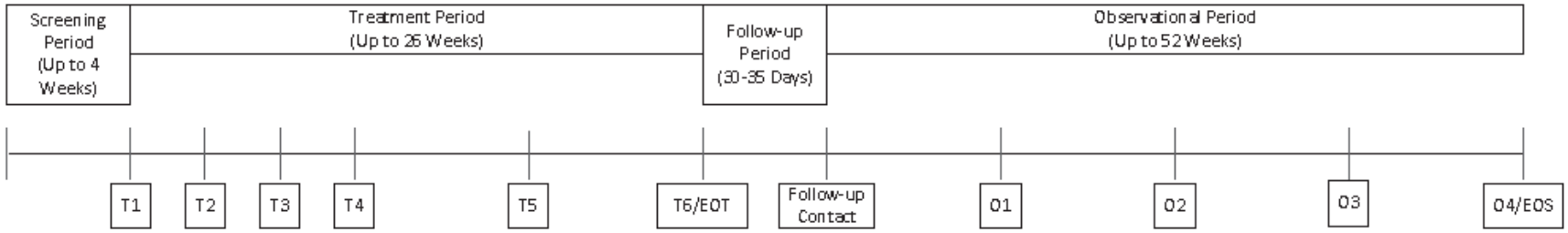
During the Observational Period, laboratory tests and semen samples will be collected.

Subjects who do not meet the criteria for entering the Observational Period will have a contact from the Investigator (or designee) 30 to 35 days after their last dose of study drug.

The study was designed to enroll approximately 20 subjects to obtain 15 evaluable subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled.

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

**Figure 1. Study Schematic**



**Screening Period**

The Screening Period will last up to 4 weeks. Procedures to be performed during the Screening Period are outlined in the Study Activities Table (Table 1). Subjects will be given supplies and instructions for obtaining the first morning void urine sample and scheduled to return to the site within the 4-week Screening Period to return the first morning void urine sample. In addition, the subject will provide the semen samples according to the specific windows for semen collection (Section 5.3.2.1) within the 4-week Screening Period. Tests for eligibility may be repeated within the subject's 4-week Screening Period. Subjects who fail to meet eligibility criteria will be allowed to re-screen at the investigator's discretion.

**Treatment Period**

Eligible subjects will return for the T1 visit (Day 1) no more than 4 weeks from the initial screening visit. The procedures to be performed at the T1 visit are outlined in the Study Activities Table (Table 1), including initial administration of open-label study drug (Atrasentan).

The Treatment Period consists of five additional site visits over a 26 week period.

- The T2 (Week 2) visit will take place 2 weeks (± 7 days) after the T1 visit.
- The T3 (Week 4) visit will take place 2 weeks (± 7 days) after the T2 visit.
- The T4 (Week 6) visit will take place 2 weeks (± 7 days) after the T3 visit.
- The T5 (Week 13) visit will take place 7 weeks (± 7 days) after the T4 visit. At this visit, subjects will be provided with supplies and instructions for the collection of the duplicate semen samples and will be scheduled for the collection of the semen samples according to the specific windows for semen collection (Section 5.3.2.1). Supplies and instructions for obtaining the first morning void urine sample within 1 day of the T6 visit will also be given to the subjects. The site will also call into IVRS/IWRS at this visit and dispense study drug to the subject.

If the average of the two semen samples is < 15 million/mL, the subject will discontinue from study drug and return to the End of Treatment Visit (EOT) 5 days (± 3 days) of the last dose of study drug. For this subject, semen samples will not be collected at the EOT visit.

The T6/EOT (Week 26) visit will take place 13 weeks (± 7 days) after the T5 visit. Subjects will be provided with supplies and instructions for the collection of the duplicate semen samples, and will be scheduled for the collection of the semen samples according to the specific windows for semen collection (Section 5.3.2.1). If the average of the two semen samples is < 15 million/mL or there is a ≥ 50% reduction in sperm concentration from Screening at T6/EOT (Week 26) visit, the subject will enter the Observational Period.

The procedures to be performed at each visit are outlined in the Study Activities Table (Table 1).

**Follow-Up Contact**

Only those subjects who do not meet criteria to enter the Observational Period will be contacted by the Investigator (or designee) approximately 30 to 35 days after their last dose of study drug to solicit changes to concomitant medications and AEs and SAEs. This follow-up contact will be the final contact for these subjects.

**Observational Period**

Only those subjects with a sperm concentration below 15 million/mL at any time during the Treatment Period or with a ≥ 50% reduction from Screening (baseline) at the end of the 26-week Treatment Period will enter the Observational Period.

The Observational Period will consist of up to 4 study visits and last up to 52 weeks.

- The O1 (Week 13) visit will take place 13 weeks (± 7 days) after the subject's EOT visit.

- The O2 (Week 26) visit will take place 13 weeks (± 7 days) after the O1 visit with the remaining visits (O3 [Week 39] and O4 /End of Study [EOS; Week 52]) following every 13 weeks (± 7 days) thereafter.

The procedures to be performed at these visits are outlined in the Study Activities Table (Table 1).

During the Observational Period duplicate semen samples will be collected until the subject's sperm concentration returns to within 15% of baseline or above, or until the end of the Observational Period. At each visit, subjects will be provided with supplies and instructions for the collection of the semen samples, and will be scheduled for the collection of the semen samples according to the specific windows for semen collection (Section 5.3.2.1). If at any time during the Observational Period the sperm concentration returns to within 15% of baseline or above, subjects will have completed their participation in the Observational Period. The visit at which their sperm concentration returned to within 15% of baseline or above will be considered their End of Study visit. These subjects will also be contacted by the Principal Investigator (or designee) within 14 days of the collection of the second semen sample. This contact will be the final contact for these subjects.

All other subjects will continue study visits until the End of Study visit.

## 5.2 Selection of Study Population

Subjects will be males who meet all of the inclusion criteria and none of the exclusion criteria.

### 5.2.1 Inclusion Criteria

1. Male subject 30 to 75 years of age, inclusive at the time of Screening.
2. Subject has voluntarily signed and dated an Informed Consent Form, approved by an Institutional Review Board (IRB)/Independent Ethics (IEC), after the nature of the study has been explained and the subject has had the opportunity to ask

questions. The informed consent must be signed before any study-specific procedures are performed.

3. Subject has type 1or 2 diabetes and is receiving treatment with at least one anti-hyperglycemic medication and ACEi or ARB (RAS inhibitor).
4. Subject has an eGFR ≥ 35 mL/min/1.73 $m^2$ with the CKD-EPI formula and UACR ≥ 30 to < 5,000 mg/g creatinine (≥ 3.4 mg/mmol and < 565 mg/mmol).
5. Subject has a serum BNP ≤ 200 pg/L (200 ng/mL).
6. Subject has systolic blood pressure ≥ 110 and ≤ 180 mmHg at Screening.
7. Subject has a serum potassium ≥ 3.5 (3.5 mmol/L) and ≤ 6.0 mEq/L (6.0 mmol/L).
8. Subject is able to provide a semen specimen at the required intervals.
9. Subject has a baseline sperm concentration ≥ 30 million per mL at Screening.
10. If the subject is sexually active with female partner(s) of childbearing potential, he must agree, from initial study drug administration through 90 days after the last dose of study, to practice the protocol specified contraception (Section 5.2.4).
11. Subject must agree not to donate sperm from initial study drug administration through 90 days after the last dose of study drug.
12. (intentionally left blank; criterion deleted)
13. (intentionally left blank; criterion deleted)
14. (intentionally left blank; criterion deleted)
15. Subject has a total Testosterone > 150 ng/dL (5.20 nmol/L).
16. Subjects currently using alpha blockers must be on a stable dose for at least 2 weeks prior to the initial screening visit and expected to remain on a stable dose during the study.
17. Subject currently using 5 alpha reductase inhibitors must be on a stable dose for at least 3 months prior to the initial screening visit and expected to remain on a stable dose during the study.

**Rationale for the Inclusion Criteria**

(1, 3 – 7) To select the appropriate subject population with diabetes-related kidney disease.

(2) In accordance with harmonized GCP.

(8, 9, 15 – 17) To select a patient population with an acceptable sperm concentration for the evaluation.

(10, 11) The impact of Atrasentan on pregnancies is unknown.

### 5.2.2 Exclusion Criteria

1. Prior history of prostate cancer with or without treatment.
2. Untreated retrograde ejaculation or anejaculation; history of prostatectomy with aspermia. Subjects with treated retrograde ejaculation will be allowed with approval of the Study Designated Physician.
3. Prior history of vasectomy unless subject has undergone reversed vasectomy.
4. (intentionally left blank; criterion deleted)
5. Currently symptomatic and receiving treatment for sexually transmitted disease (STD), prostatitis, orchitis or epididymitis.
6. (intentionally left blank; criterion deleted)
7. (intentionally left blank; criterion deleted)
8. Drug, alcohol or substance abuse within the 3 months prior to the initial screening visit.
9. Subject has had treatment with hormone suppressive agents, including androgens, estrogens, anabolic steroids, glucocorticoids, ketoconazole, cyclosporine, or cancer chemotherapy within the 6 months prior to the initial screening visit or planned during the study.

10. (intentionally left blank; criterion deleted)
11. Subject is currently receiving or has received hormone replacement therapy within the 6 months prior to the initial screening visit.
12. (intentionally left blank; criterion deleted)
13. (intentionally left blank; criterion deleted)
14. Renal transplant.
15. Subject has a history of severe peripheral edema or facial edema unrelated to trauma or a history of myxedema in the prior 4 weeks prior to the initial screening visit.
16. Subject has a history of pulmonary hypertension, pulmonary fibrosis or any lung diseases requiring oxygen therapy (e.g., chronic obstructive pulmonary disease, emphysema).
17. Subject has a documented diagnosis of heart failure, previous hospitalization for heart failure or current or constellation of symptoms (dyspnea on exertion, pedal edema, orthopnea, paroxysmal nocturnal dyspnea) felt to be compatible with heart failure, that was not explained by other causes, and for which there was a change in medication or other management directed at heart failure.
18. Subject has elevated liver enzymes (serum alanine aminotransaminase [ALT] and/or serum aspartate aminotransaminase [AST]) > 3 × the upper limit of normal (ULN) during the Screening Period.
19. Subject has a hemoglobin < 9 g/dL during the Screening Period.
20. Subject has a history of an allergic reaction or significant sensitivity to Atrasentan (or its excipients) or similar compounds.
21. Subject has significant comorbidities (e.g., advanced malignancy, advanced liver disease) with a life expectancy of less than 1 year.

22. Subject has clinically significant cerebrovascular disease (CVD) or coronary artery disease (CAD) within 3 months prior to the initial screening visit, defined as one of the following:
    - Hospitalization for Myocardial Infarction or unstable angina; or
    - New onset angina with positive functional study or coronary angiogram revealing stenosis; or
    - Coronary revascularization procedure; or
    - Transient ischemic attack (TIA) or stroke.
23. Subject has received any investigational drug within 3 months prior to the initial screening visit.
24. Subject is currently receiving rosiglitazone, moxonidine, aldosterone blockers, aliskiren or a combination of ACEi and ARB.
25. Subjects with known allergy to both thiazide and loop diuretics.
26. The subject is considered by the Investigator unsuitable to participate in the trial for any other reason, for instance due to a significant serious underlying condition.

**Rationale for the Exclusion Criteria**

(1 – 3, 5, 8, 26) To exclude an inappropriate subject population.

(9, 11) To avoid bias for the evaluation of safety by concomitant use of other medications.

(14 – 25) To ensure the safety of subjects throughout the study.

### 5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of Screening, or receives during the study, must be recorded along with the reason for use, date(s) of

administration including start and end dates, and dosage information including dose, route and frequency.

The AbbVie study designated physician (listed in Section 6.5) should be contacted if there are any questions regarding concomitant or prior therapy(ies).

#### 5.2.3.1 Prior Therapy

Subjects currently using alpha blockers should have been on a stable dose for at least 2 weeks prior to the initial screening visit and must be on a stable dose during the study.

Subjects currently using 5-alpha reductase inhibitors should have been on a stable dose for at least 3 months prior to the initial screening visit and must be on a stable dose during the study.

#### 5.2.3.2 Concomitant Therapy

If medically necessary, changes to or interruption of ACEi or ARB doses during the Treatment or Observational Periods of the study will be allowed. Plasma levels of Atrasentan may be affected by concomitant use of CYP3A or OATP inhibitors (e.g., protease inhibitors, clarithromycin, ketoconazole, gemfibrozil, ciclosporin). Potent P-gp inhibitors may potentially increase the plasma exposure of Atrasentan. In addition, plasma levels of sensitive P-gp substrates (e.g., dabigatran) may be affected by concomitant use of Atrasentan. Caution should be used in patients taking any of these medications during the trial.

#### 5.2.3.3 Prohibited Therapy

Subjects should not enter into the study if they are currently receiving or have received testosterone or hormone replacement therapy within 6 months of the initial screening visit. In addition, subjects should not receive hormone replacement therapy while enrolled in the study.

Treatment with hormone suppressive agents, including androgens, estrogens, anabolic steroids, glucocorticoids, ketoconazole, cyclosporine, or cancer chemotherapy during the study is prohibited.

Combinations of ACEi/ARB medications and/or concomitant use of aldosterone blockers or aliskiren are not allowed.

Use of hot tub/Jacuzzi/sauna are prohibited during the study.

#### 5.2.3.4 Guidance for Managing Edema or Weight Gain

Weight will be measured at each visit during the Treatment Period of the study, preferably using the same device and under the same circumstances (i.e., same time of the day, no shoes or coats during measurement). Results will be compared with the previous visit. If there is an increase of ≥ 2 kg during the Treatment Period, it is recommended to implement the following activities:

- Rule out measurement errors or obvious reasons for the increase (i.e., diet transgression, different clothing than previously).

Evaluate for the presence of edema. This may be indicative of fluid retention as the cause for weight gain.

Ascertain whether the subject has exceeded the recommended daily dietary salt intake (≤ 5 grams of sodium chloride).

If the subject is receiving a diuretic and has edema, increase the dose of the diuretic as necessary. Re-assess the subject's tolerability within 1 week as well their blood pressure, edema, weight, eGFR, hemoglobin, sodium and potassium.

If the subject is not receiving a diuretic, it is suggested to start a diuretic according to eGFR stratum and titrate the dose according to the response to the initial dose (see below):

| | eGFR < 45 mL/min | eGFR 45 – 60 mL/min | eGFR > 60 |
|---|---|---|---|
| **Recommended Diuretic and Dose** | Loop diuretic<br>20 – 40 mg per day of furosemide or equivalent<br>OR<br>Chlorthalidone<br>25 mg per day or equivalent | Loop diuretic<br>20 mg per day of furosemide or equivalent<br>OR<br>Chlorthalidone<br>12.5 – 25 mg per day or equivalent | Chlorthalidone<br>12.5 mg per day or equivalent |
| **Re-Check for BP, Weight, Edema, eGFR and Hb** | 1 week SBP target 110 – 140 | | |

In both of the above noted scenarios (numbers 4 and 5), adjust the dose of diuretic accordingly after 1 week or sooner if the subject is short of breath. Changes in the type of diuretic can be made at the discretion of the Investigator. There is no upper diuretic dose limit during the Treatment Period.

If weight continues to increase (i.e., > 3 kg in 6 weeks or the previous visit during the Treatment Period) despite the modification in the doses of diuretics, contact the study designated physician.

Discontinuation of an existing diuretic may be allowed under the following conditions or at the discretion of the investigator:

- Orthostatic Hypotension: by the presence of a supine-to-standing BP decrease ≥ 20 mmHg systolic or ≥ 10 mmHg diastolic within 3 minutes of standing.
- SBP equal to or below 110 mmHg at any visit.
- Hypokalemia (< 3.5 mEq/L) unresponsive to replacement therapy.

The AbbVie study designated physician should be contacted if there are any questions.

### 5.2.4 Contraception Recommendations

If the male subject has a female partner who is postmenopausal or permanently sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy), no contraception is required.

If the subject is sexually active with female partner(s) of childbearing potential, he must agree from initial study drug administration through 90 days after the last dose of study drug to practice contraception with:

- Condom use and female partner(s) using at least one of the following contraceptive measures
  - Intrauterine device (IUD);
  - hormonal contraceptives (oral, vaginal, parenteral or transdermal);
  - Barrier method (contraceptive sponge, diaphragm, or vaginal ring with spermicidal jellies or creams).
- True abstinence: refraining from sexual intercourse when this is line with the preferred and usual lifestyle of the subject. (Note: Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

Additionally, subject agrees not to donate sperm from initial study drug administration through 90 days after the last dose of study drug.

## 5.3 Efficacy and Safety Assessments/Variables

### 5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures described in this protocol are summarized in Table 1.

## Table 1. Study Activities

| Activity | Screening Period (Up to 4 Weeks)[a] | Treatment Period[b] | | | | | | Observational Period[b,c] | | | FU Contact[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | T1[e] (Day 1) | T2 (Week 2) | T3 (Week 4) | T4 (Week 6) | T5 (Week 13) | T6/EOT (Week 26)[f] | O1 (Week 13) | O2, O3 (Weeks 26, 39) | O4/End of Study (Week 52) | |
| Informed Consent[g] | X | | | | | | | | | | |
| Medical History | X | X[h] | | | | | | | | | |
| Concomitant Medications | X | X | X | X | X | X | X | X | X | X | X |
| Complete Physical Exam | | X | | | | | X | | | | |
| Vital Signs[i] | X | X | X | X | X | X | X | X | X | X | |
| Semen Sample Collection[j] | X | | | | | X | X | X | X | X | |
| Assess Peripheral Edema | X | X | X | X | X | X | X | | | | |
| 12-Lead ECG | | X | | | | | X | | | | |
| Hematology | X | X | | X | X | X | X | X | X | X | |
| Limited Chemistry | | | | X | X | | | | | | |
| Complete Chemistry | X | X | | | | X | X | X | X | X | |
| BNP | X | | | | X | | X | | | | |
| $HbA1_c$ | X | | | | | | X | X | | | |
| Urinalysis | X | | | | | | X | X | | | |
| FMV Urine Collection for UACR[k] | X | | | | | | X | | | | |
| Serum total T, estradiol, LH, FSH, inhibin B[l] | X | X | | X | X | X | X | X | X | X | |
| IVRS Call | X | X | | | | X | X | | | | |

## Table 1. Study Activities (Continued)

| Activity | Screening Period (Up to 4 Weeks)[a] | Treatment Period[b] | | | | | | Observational Period[b,c] | | | FU Contact[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | T1[e] (Day 1) | T2 (Week 2) | T3 (Week 4) | T4 (Week 6) | T5 (Week 13) | T6/EOT (Week 26)[f] | O1 (Week 13) | O2, O3 (Weeks 26, 39) | O4/End of Study (Week 52) | |
| Monitor AEs and SAEs[m] | X | X | X | X | X | X | X | X | X | X | X |
| PK Analysis[n] | | | | X | X | X | | | | | |
| Dispense Study Drug | | X | | | | X | | | | | |
| Drug Accountability/Compliance Assessment | | | X | X | X | X | X | | | | |

a. Screening procedures and laboratory tests may be repeated during the Screening Period, per the Investigator's discretion. Semen samples may be repeated per Section 5.3.2.5.

b. All Treatment and Observational Period visits must be completed within ± 7 days of the expected visit date.

c. If at any time during the Observational Period, the sperm concentration returns to within 15% of baseline or above, subjects will have completed their participation in the Observational Period. The visit at which their sperm concentration returned to within 15% of baseline or above will be considered their End of Study visit.

d. Subjects not entering the Observational Period should be contacted by the Principal Investigator (or designee) 30 – 35 days after the last dose of study drug. Subjects who have returned to within 15% of their baseline sperm concentration or above during the Observational Period should be contacted by the Principal Investigator (or designee) within 14 days of the collection of the second semen sample.

e. The T1/Day 1 visit should be completed within 4 weeks from the initial screening visit.

f. Subjects completing the End of Treatment Visit because their sperm concentration has dropped below 15 million/mL during the Treatment Period will not provide duplicate semen samples at the T6/EOT visit.

g. Informed consent can be collected up to 30 days prior to conduct of initial study procedures.

h. Updates only.

i. Vital signs include BP, weight, temperature and pulse rate will be collected at every visit. Height will be collected at initial Screening visit only. Weight gain will be assessed at each visit during the Treatment Period.

j. Subjects will be scheduled for the collection of the duplicate semen samples according to the specific windows for semen collection noted in Section 5.3.2.5.

## Table 1. Study Activities (Continued)

k. For Screening, subjects will be given supplies and instructions for the FMV urine collection, which should be collected and returned to the study site within the 4-week Screening Period. For the T6/EOT visit, the first morning void (FMV) urine collection will be collected within 1 day before the visit.

l. Total testosterone sample should be collected at approximately the same time of day at each visit.

m. Protocol-related non-serious and serious adverse events (SAEs) will be collected from the time the subject signs the study-specific informed consent. All adverse events (serious and nonserious) will be captured from the time of study drug administration through 30 days after the last dose of study drug. For subjects entering the Observational Period, protocol-related non-serious and serious adverse events will be collected beginning 30 days after the last dose of study drug through the post-therapy Observational Period.

n. Blood samples only to be collected for atrasentan PK analysis and possible metabolites of atrasentan at the following visits: T3/Week 4 (immediately before dose and 15 minutes, 30 minutes, 1 hour post dose), T4/Week 6 (immediately before dosing) and T5/Week 13 (immediately before dosing).

#### 5.3.1.1 Study Procedures

**Informed Consent**

A signed informed consent will be obtained from the patient before any study procedures are undertaken at the initial screening visit. Informed consent can be collected up to 30 days prior to Screening. Details about how informed consent will be obtained and documented are provided in Section 9.3.

**Medical History**

A complete medical history, including history of tobacco and alcohol use and colonoscopy history, will be obtained from each patient during the initial Screening visit and updated during the Screening Period and at the T1/Day 1 visit, as necessary. Alcohol and tobacco use definitions are as follows:

| | |
|---|---|
| **Tobacco:** | Cigarettes, pipes, cigars, chewing tobacco |
| **Alcohol Use:** | Non-drinker: consumes less than 3 drinks per year<br>Drinker: consumes at least 3 drinks per year<br>Light: less than 2 drinks per day<br>Moderate: 2 to 4 drinks per day<br>Heavy: more than 4 drinks per day |

For the purposes of the study, it is the clinical discretion of the investigator to define what constitutes alcohol abuse.

**Physical Examination**

A complete physical examination will be performed at the T1/Day 1 visit (baseline) and the T6/EOT visit.

Any clinically significant changes will be documented as adverse events.

**Vital Signs**

Vital sign determination of sitting BP, weight, temperature and pulse rate will be obtained at all on-site visits. Vital signs performed at the T1/Day 1 Visit will serve as the baseline. Weight gain will be assessed at every visit during the Treatment Period. Careful consideration should be used to ensure that the appropriate cuff size is used for all sitting BP determinations. Resting BP will be measured two times in the non-dominant arm using the appropriate cuff size at least 2 minutes apart. All BP readings should be collected by trained and qualified personnel with standard equipment. BP should be measured consistently by the same method for all visits. Height will be collected at the initial Screening visit only.

**Assessment of Edema**

Assessment of edema will be performed at Screening and at every Treatment Visit. The assessment of edema should be performed by the same site personnel at approximately the same time (if possible) at each visit and the time of assessment will be recorded. The severities of edema for each subject will be defined by the following categories:

- None: edema is not present on examination;
- Mild: edema is present on examination, but asymptomatic and the subject is willing to continue study medication;
- Moderate: edema is present on examination, but symptomatic and the subject is willing to continue study medication;
- Severe: edema is present on examination, but symptomatic and the subject is unwilling to continue study medication, or subject has an adverse event of pulmonary edema or congestive heart failure (CHF).

New onset or worsening edema, as deemed by the Investigator, will be captured as adverse events. The date of edema resolution will also be captured.

**12-Lead Electrocardiogram (ECG)**

A 12-lead resting ECG will be obtained at the T1/Day 1 visit prior to initial dose of study drug and at the T6/EOT visit. The ECG measurements at the T1/Day 1 visit will serve as the baseline measurements for clinical assessment.

**First Morning Void (FMV) Urine Sample Collection**

One first morning void urine collection will be obtained during the Screening Period, and prior to the T6/EOT visit. The first morning void is defined as the subject's first void after 5:00 AM or upon rising for the day. The central laboratory will provide specific instructions for collection and storage of specimens. The UACR values will be reported to the Investigator by the central laboratory on the laboratory reports.

If a subject did not collect the required FMV sample(s), re-dispense supplies and instructions for collection of the FMV sample. Once the FMV sample is collected by the subject, he/she will return to the site to return the sample for the respective visit.

**Laboratory Tests**

A central laboratory will be utilized for the clinical laboratory tests. Samples will be obtained for the laboratory tests listed in Table 2 at the visits specified in Table 1. Blood draws should be performed after vital sign determinations have been completed for each visit.

The Investigator will review all laboratory test results in a timely manner. All laboratory test results that are considered clinically significant by the Investigator will be followed to a satisfactory resolution.

Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory chosen for this study.

**Table 2. Clinical Laboratory Tests**

| Hematology | Clinical Chemistry | Urinalysis |
|---|---|---|
| Hematocrit<br>Hemoglobin<br>Red Blood Cells (RBC)<br>White Blood Cells (WBC)<br>Neutrophils<br>Bands<br>Lymphocytes<br>Monocytes<br>Basophils<br>Eosinophils<br>Platelet count (estimate not acceptable) | Albumin<br>Alkaline phosphatase<br>ALT (SGPT)<br>AST (SGOT)<br>Bicarbonate<br>Blood Urea Nitrogen (BUN)<br>Calcium<br>Potassium<br>Chloride<br>Cholesterol<br>Creatinine<br>Direct Bilirubin<br>Glucose<br>LDH<br>Phosphorus<br>Sodium<br>Total bilirubin<br>Total protein<br>Triglycerides<br>Uric acid | Blood<br>Glucose<br>Ketones<br>pH<br>Protein<br>Specific gravity |
| **Limited Chemistry** | | **Urine Tests** |
| Sodium<br>Albumin<br>Potassium<br>Bicarbonate<br>Creatinine<br>Chloride<br>BUN | | First morning void urine:<br>UACR |
| | | **Additional Tests** |
| | | BNP<br>Pharmacokinetic measurement<br>$HbA_{1c}$<br>Serum total T*<br>Estradiol<br>LH<br>FSH<br>Inhibin B |

* The testosterone sample should be collected at approximately the same time of the day at each visit.

The CKD-EPI formula will be used to calculate eGFR at the Screening visit to determine eligibility for the study. The central laboratory will also calculate the eGFR on the laboratory profile report at each visit during the Treatment and Observational Periods.

### 5.3.2 Drug Concentration Measurements

#### 5.3.2.1 Collection of Samples for Pharmacokinetic Analysis

For all subjects, blood samples for assay of Atrasentan and possible metabolites of Atrasentan will be collected by venipuncture into a 4 mL evacuated K2 EDTA containing collection tube at the T3 (Week 4) visit at immediately prior to dose and 15 minutes,

30 minutes and 1 hour post dose and at the T4 (Week 6) visit immediately before dosing and the T5 (Week 13) immediately before dosing.

A total of 6 blood samples per subject are planned to be collected for pharmacokinetic (PK) analysis. A sufficient amount of blood will be collected to provide approximately 2 mL plasma from each sample. Immediately after collection, the blood samples will be inverted several times to ensure good mixing of the blood and anticoagulant, and will be placed in an ice bath. The date and time of collection of each blood sample will be noted and the date and time of the two previous doses of study drug will be recorded to the nearest minute on the appropriate eCRF.

Arrangements will be made with the central laboratory for the shipment of samples to AbbVie:

AbbVie Sample Receiving
[redacted]
c/o Delivery Services
1150 S. Northpoint Blvd.
Waukegan, IL 60085

Phone: [redacted]
Fax:
Email:

#### 5.3.2.2 Handling/Processing of Samples

The blood samples for pharmacokinetic analysis will be centrifuged (1100 – 1600 × G for approximately 10 minutes) within 1 hour of collection using a centrifuge to separate the plasma. The plasma samples will be transferred using plastic pipettes into screw-capped polypropylene tubes labeled with the drug name, type of sample (plasma), the protocol number, the subject number and study visit. The plasma samples will be frozen at –20°C or colder within 2 hours after collection and will remain frozen until shipped to the central laboratory.

#### 5.3.2.3 Disposition of PK Samples

The frozen plasma samples for pharmacokinetic analysis will be packed in dry ice sufficient to last during transport (3 days) and shipped from the study site to the central laboratory. An inventory of the samples included in the shipment will accompany the package. The central laboratory will provide instructions regarding the collection, processing and shipping of these samples.

#### 5.3.2.4 Measurement Methods

Plasma concentrations of Atrasentan and possible metabolites will be measured under the supervision of the Drug Analysis Department at AbbVie.

#### 5.3.2.5 Collection of Semen Samples for Analysis

Semen samples will be obtained for the tests listed in Table 3 during the scheduled collection period for the visits specified in Table 1. Semen samples should be collected at 2 time-points over a 7-day period with each sample being separated by at least 2 days. If for any reason one of the duplicate samples is inadequate or not obtained, then a replacement sample will be collected to ensure that two samples are available for each scheduled collection period. If clinically relevant confounding symptoms, illness or conditions are suspected, replacement sample/samples may be obtained at the investigator's discretion. All semen samples for a scheduled collection period must be collected within 14 days of the collection of the first semen sample. Subjects must abstain from ejaculation for at least 2 days but not more than 7 days prior to semen sample collection. The average of the 2 semen samples will be used as the value for that collection period. If the semen sample is collected at the scheduled study visit, the sample should be obtained after all study procedures have been completed.

The semen sample will be sent for processing as soon as possible after collection. Semen motility analysis should be started with 1 hour of sample collection. The full ejaculate must be captured at each semen collection. Subjects should be evaluated, per the site's standard procedure, for retrograde ejaculation if the full ejaculate is < 1.0 mL. The Study

Designated Physician should be consulted if retrograde ejaculation is identified or diagnosed at any time during the study. If the full ejaculate is not captured in the collection container, then a replacement specimen should be collected.

**Table 3. Semen Analysis Tests**

| |
|---|
| Semen Volume |
| Sperm Concentration |
| Sperm Motility |
| Sperm Morphology |

### 5.3.2.6 Handling/Processing of Samples

Detailed instructions regarding collection and preparation of the semen samples will be provided by the local laboratory processing the semen specimen. The specimen container should be kept at ambient temperature, between 30° and 37°C, to avoid temperature changes that may affect the spermatozoa.

The local laboratory processing the semen specimens will analyze the samples for volume, concentration and motility following their standard operating procedures, and will prepare 4 slides for morphology analysis to be conducted by the central morphology laboratory (Tulane Andrology Laboratory). Written instructions on preparation and fixing of sperm morphology slides and shipment to the central morphology laboratory will be provided to the site semen analysis laboratory. Slides must be labeled, per the instructions provided by the morphology laboratory, with the subject's initials, subject number, study visit, sample identifier, and the date and time of collection.

Morphology slides will be sent for morphology analysis to:

Tulane Andrology Laboratory
1430 Tulane Ave., SL-42; [redacted]
New Orleans, LA 70112-2699
United States

### 5.3.3 Efficacy Variables

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

### 5.3.4 Safety Variables

#### 5.3.4.1 Primary Safety Variable

The primary safety variable is the proportion of subjects who have a sperm concentration $< 15 \times 10^6$/mL during the 26-week Treatment Period.

#### 5.3.4.2 Secondary Safety Variables

- 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.

Safety data will be analyzed for the data collected throughout Treatment Period and up to 35 days post-treatment. The following safety endpoints will be collected:

- The incidence of adverse events and the proportion of subjects who are discontinued from the study due to adverse events.
- The change from baseline to each visit in chemistry, hematology, and urine measurements.
- The change from baseline to each visit in vital signs.

### 5.3.5 Pharmacokinetic Variables

Plasma concentrations of Atrasentan and its possible metabolites will be obtained at the times indicated in Section 5.3.2.1. Population pharmacokinetic modeling techniques may

be used to estimate population central values for apparent oral clearance (CL/F) and volume of distribution (V/F) and conditional estimate values of these parameters for the individual subjects may also be determined.

Additional pharmacokinetic variables may be calculated if useful in the interpretation of the data.

## 5.4 Removal of Subjects from Therapy or Assessment

### 5.4.1 Discontinuation of Individual Subjects

Subjects will be discontinued from study drug immediately if any of the following events occur:

- Clinically significant deterioration of the subject's medical status that is thought to possibly or probably be related to study drug by the Investigator.
- The subject requests withdrawal from the study.
- Investigator request (for any reason).
- Achievement of the primary study endpoint (sperm concentration $< 15 \times 10^6$/mL).
- Chronic dialysis or renal transplant.
- Subject is lost to follow-up.

If the subject is permanently discontinued from study drug and does not meet the criteria to enter the Observational Period, the procedures outlined for the T6/End of Treatment visit must be completed 5 days (± 3 days) of the last dose of study drug. Additionally, the subject will be contacted by the Investigator (or designee) approximately 30 to 35 days after their last dose of study drug.

If the subject meets the criteria to enter the Observational Period during the Treatment Period, the subject will permanently discontinue from study drug and the procedures outlined for the T6/End of Treatment visit should be completed 5 days (± 3 days) of the last dose of study drug. Following discontinuation of the study drug, the subject will

continue to be monitored during the Observational Period until sperm concentration returns to within 15% of baseline or above, or through the O4/EOS visit, whichever occurs first unless the subject withdraws consent.

Subjects who prematurely discontinue from the Treatment Period for other reasons than achievement of the primary study endpoint, will not be replaced unless the discontinuation rate exceeds 25% in the Treatment Period. Subjects may be added to ensure that 15 evaluable subjects are assessed.

If the subject is permanently discontinued from the Observational Period for other reasons than returning to within 15% of their baseline sperm concentration or above, the procedures outlined for the O4/End of Study visit must be completed 5 days (± 3 days) of the discontinuation.

The date and reason for premature discontinuation in either period will be recorded in the subject's source documents and on the appropriate eCRF.

### 5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The Investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the Investigator by telephone and subsequently provide written instructions for study termination.

## 5.5 Treatments

### 5.5.1 Treatments Administered

Each subject will receive 0.75 mg Atrasentan once daily for up to 26 weeks.

### 5.5.2 Identity of Investigational Products

The individual study drug information is presented in Table 4.

**Table 4. Identity of Investigational Products**

| Study Drug | Dosage Strength | Formulation | Manufacturer |
|---|---|---|---|
| Atrasentan | 0.75 mg | Film-coated tablet | AbbVie |

#### 5.5.2.1 Packaging and Labeling

Study drug in tablet form will be packaged in bottles containing 32 tablets and a desiccant canister. Each bottle will be labeled as per country requirements.

Each label must remain affixed to the bottle. All blank spaces on the label will be completed by site staff prior to dispensing.

Subjects will receive open-label Atrasentan 0.75 mg. Subjects will be instructed to take 1 tablet daily.

Each bottle will have a unique kit number. This kit number is assigned to a subject via IVRS/IWRS and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Each kit number will be captured in the eCRF system. Study drug product is not to be re-dispensed among subjects.

#### 5.5.2.2 Storage and Disposition of Study Drugs

The study drug must be stored between (15° to 25°C/59° to 77°F), in the supplied bottle which contains a desiccant. Desiccant canister should be returned to the bottle directly after each tablet removal. Each clinical site should have a temperature recording device in the drug storage area. A temperature log is to be maintained to document proper storage conditions. The temperature must be recorded every business day. If the storage temperature falls outside the allowed range, the excursion must be reported immediately, either by contacting AbbVie directly, or through the ATEMS module of the IVRS/IWRS system. In the event of a temperature excursion, affected study drug should be

quarantined and should not be dispensed until notification of the final assessment and disposition is received.

The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use, destroyed at the site according to local regulations and instructions from AbbVie or returned to AbbVie or a local depot for destruction.

### 5.5.3 Method of Assigning Subjects to Treatment Groups

This is a single arm study. Subjects meeting entry criteria will be centrally registered using an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS/IWRS will be provided to each site. Study drug will be dispensed at the study visits summarized in Table 1. Returned study drug should not be re-dispensed to the subject.

### 5.5.4 Selection and Timing of Dose for Each Subject

Each subject will receive Atrasentan 0.75 mg. Subjects will be instructed to take study drug once per day at approximately the same time each day (preferably in the morning).

### 5.5.5 Blinding

#### 5.5.5.1 Blinding of Investigational Product

This is an open-label study.

### 5.5.6 Treatment Compliance

The Investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

In order to document compliance with the treatment regimen, subjects will be instructed to return all bottles (even if empty) to the study site personnel at each treatment visit. The study site personnel will document compliance by recording the total number of doses dispensed and returned (brought back) per bottle during each visit during the Treatment Period in IVRS/IWRS and on the appropriate eCRF page.

Subjects will be encouraged to take study drug as prescribed. At each visit, compliance will be assessed and counseled if the subject has taken more study drug than expected or if subject's non-compliant rate is < 100% compliant. Overall compliance will be calculated at the end of the Treatment Period.

### 5.5.7 Drug Accountability

The Investigator or representative will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating the Proof of Receipt or similar document or via direct recording in the IVRS/IWRS. An accurate (running) inventory of study drug will be kept in IVRS/IWRS, and will include the lot number, Proof of Receipt number(s), the number of tablets dispensed, subject number, initials of person who dispensed the drug and the date study drug was dispensed for each subject. An overall accountability of the study drug will be performed and verified by the Monitor throughout the study and at the site close-out visit. All study drug unit doses must be inventoried, accounted for, and returned to AbbVie per instructions from AbbVie and according to local regulations.

The Investigator and/or subinvestigator(s) agree not to supply study medication to any persons not enrolled in the study.

## 5.6 Discussion and Justification of Study Design

### 5.6.1 Discussion of Study Design and Choice of Control Groups

This study is designed to assess the effects of Atrasentan on spermatogenesis and testicular function during treatment period and up to 52 weeks follow-up. The open-label

design is chosen for this study because no change in spermatogenesis or testicular function is expected without treatment in healthy volunteers.

### 5.6.2 Appropriateness of Measurements

All safety measurements in this study are standard and validated. All clinical and laboratory procedures in this study are standard and generally accepted.

### 5.6.3 Suitability of Subject Population

The purpose of this study is to assess the effects of Atrasentan on spermatogenesis and testicular function by assessing sperm concentration in subjects with Type 1 or 2 diabetes and nephropathy who are also being treated with a RAS inhibitor.

Therefore, subjects who have been treated with a RAS inhibitor (ACEi or ARBs), who have an estimated GFR $\geq$ 35 mL/min/1.73 $m^2$ with the CKD-EPI formula and UACR $\geq$ 30 to < 5,000 mg/g creatinine ($\geq$ 3.4 mg/mmol and < 565 mg/mmol) with sperm and testosterone levels within normal ranges have been selected as the target population. Subjects who have underlying diseases/conditions and/or on medications affecting spermatogenesis or testicular function, history of allergic reaction or significant sensitivity to atrasentan or drugs similar to the study drug will be excluded to avoid confounding factors related to the effects being studied.

### 5.6.4 Selection of Doses in the Study

The dose of 0.75 mg was selected following analysis of the results of the Phase 2b trials. The rationale for selecting a single dose of Atrasentan is based on the narrow therapeutic index of this drug and the need to balance the efficacy in reducing albuminuria with the safety and blood pressure change parameters. Subjects that enroll in the study will receive 0.75 mg QD of Atrasentan for up to 26 weeks during theTreatment Period.

Dose selection for the Phase 2b studies was based on the exposure-response analyses and clinical results from Study M10-815. Statistically significant exposure-response relationships for both the efficacy (UACR reduction) and the incidence of edema were

then quantified from all Phase 2 studies. The simulations showed that a proportion of subjects achieving a 40% reduction in UACR increase with increasing dose from 0.25 mg per day approximately reaching a nadir in the range of 0.75 to 1.25 mg per day dose. The simulations, however, also showed that the probability of edema increases with increasing atrasentan exposure with predicted incidences of 32% and 38% at a dose of 1.25 mg and 1.5 mg per day. Although a slightly higher efficacy is predicted at doses greater than 1.25 mg per day, the predicted rate of edema is higher at these doses.

# 6.0 Adverse Events

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide an Other cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

## 6.1 Definitions

### 6.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

### 6.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) within 24 hours of the site being made aware of the serious adverse event.

| | |
|---|---|
| **Death of Subject** | An event that results in the death of a subject. |
| **Life-Threatening** | An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form. |
| **Hospitalization or Prolongation of Hospitalization** | An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility. |
| **Congenital Anomaly** | An anomaly detected at or after birth, or any anomaly that results in fetal loss. |

| | |
|---|---|
| **Persistent or Significant Disability/Incapacity** | An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle). |
| **Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome** | An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. |

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

## 6.2 Adverse Event Severity

The investigator will use the following definitions to rate the severity of each adverse event:

| | |
|---|---|
| **Mild** | The adverse event is transient and easily tolerated by the subject. |
| **Moderate** | The adverse event causes the subject discomfort and interrupts the subject's usual activities. |
| **Severe** | The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening. |

## 6.3 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

| | |
|---|---|
| **Reasonable Possibility** | An adverse event where there is evidence to suggest a causal relationship between the study drug and the adverse event. |
| **No Reasonable Possibility** | An adverse event where there is no evidence to suggest a causal relationship between the study drug and the adverse event. |

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

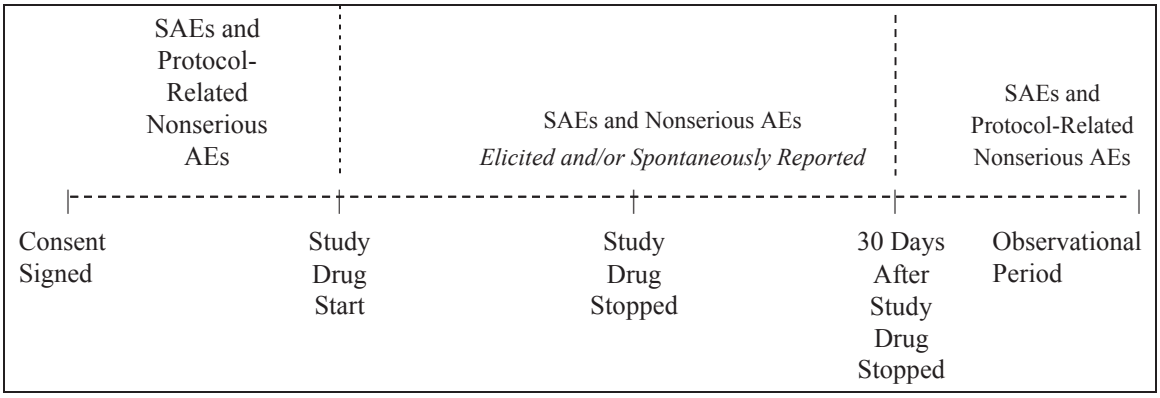
If an investigator's opinion of no reasonable possibility of being related to study drug is given, an Other cause of event must be provided by the investigator for the serious adverse event.

## 6.4 Adverse Event Collection Period

All adverse events reported from the time of study drug administration until 30 days following discontinuation of study drug administration have elapsed will be collected, whether solicited or spontaneously reported by the subject. In addition, protocol-related nonserious and serious adverse events will be collected from the time the subject signed the study-specific informed consent through the post-therapy Observational Period.

Adverse event information will be collected as shown in Figure 2.

**Figure 2. Adverse Event Collection**




## 6.5 Adverse Event Reporting

In the event of a serious adverse event, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the electronic data capture (EDC) system. Serious adverse events that occur prior to the site having access to the RAVE® system or if RAVE is not operable, should be documented on the SAE Non CRF paper forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of being made aware of the serious adverse event.

| | |
|---|---|
| **Email:** | [redacted] |
| **FAX to:** | [redacted] |

For safety concerns, contact the Renal Safety Team at:

Renal Safety Management Team
[redacted]
AbbVie Inc.
1 North Waukegan Road
North Chicago, IL 60064

Office: [redacted]
Email:

For any subject safety concerns, please contact the physician listed below:

Primary Study Designated Physician:

[redacted]

In emergency situations involving study subjects when the Study Designated Physician is unavailable, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated back-up AbbVie Renal Medical Director.

**Phone:** [redacted]

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with

Directive 2001/20/EC. The reference document used for SUSAR reporting in the EU countries will be the most current version of the Investigator's Brochure.

### 6.6 Pregnancy

Pregnancy in a study subject partner must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy.

In the event of pregnancy occurring in the partner of an enrolled subject, written informed consent for release of medical information from the partner must be obtained prior to the collection of any pregnancy-specific information and the pregnancy will be followed to outcome.

Pregnancy in a study subject partner is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

## 7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), the following AbbVie Clinical Monitor(s):

| Primary Contact: | Alternate Contact: |
|---|---|
| [redacted] | |

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

# 8.0 Statistical Methods and Determination of Sample Size

## 8.1 Statistical and Analytical Plans

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.

There are no planned efficacy objectives for this study. The primary safety endpoint is the proportion of subjects who have a sperm concentration $< 15 \times 10^6$/mL by 26 weeks. Approximately 20 subjects (to complete 15 evaluable subjects) with diabetic nephropathy who are taking RAS inhibitors are planned to be enrolled in the study at approximately 20 sites. Subjects will receive 0.75 mg QD of Atrasentan during the 26-week Treatment Period.

In the Treatment Period, semen samples will be collected at Screening (baseline), T5 (Week 13) and T6/EOT (Week 26). Semen samples will be collected at 2 time-points over a 7-day period with each sample being separated by at least 2 days. The average of the 2 samples will be used as the value for that scheduled collection period. Inadequate or missed semen samples can be made up within 14 days of the initial semen sample for that

collection period. In the Observational Period, semen samples will be collected according to the specific windows for semen collection (Section 5.3.2.1), starting at the O1 (Week 13) visit and then every 13 weeks thereafter until the sperm concentration has returned to within 15% of baseline or above, or until the end of the 52-week Observational Period, whichever occurs earlier.

**General Considerations**

Treatment effects will be evaluated based on a 2-sided 80% exact confidence interval.

Unless otherwise specified, for Treatment Period, the baseline observation is defined as the last non-missing measurement collected on or before the date of the first dose of study drug. The final observations 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.

Unless noted otherwise, all analyses will be performed using SAS version 9.2 or higher (SAS Institute Inc., Cary, NC 27513) under the UNIX operating system.

### 8.1.1 Analysis Datasets

**Evaluable Set**

A subject will be considered evaluable if the following is satisfied: (1) the Overall Study Drug compliance status is ≥ 70%; and (2) completes the 26-week treatment period and has all planned sperm samples collected; or has sperm concentration value less than 15 million/mL observed by the end of Treatment Period.

The Safety Analysis Set includes all subjects who receive at least one dose of study drug. Unless otherwise specified, the safety analysis set will serve as the primary population for the safety analysis in this study.

### 8.1.2 Demographic, Other Baseline Characteristics, Subject Disposition, and Concomitant Medication

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.

### 8.1.3 Safety Analyses

**Study Drug Exposure and Compliance**

The duration of study drug exposure and the average daily dose will be summarized for safety analyses set. 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.

#### 8.1.3.1 Primary Safety Analyses

The primary safety endpoint is the proportion of subjects who have a sperm concentration $< 15 \times 10^6$/mL during the 26-week Treatment Period. The simple percentage of subjects and a 2-sided 80% exact confidence interval will be calculated. The primary safety analysis will be conducted on the evaluable set. When 15 evaluable subjects are available, if 4 or more subjects have a sperm concentration $< 15 \times 10^6$/mL, the trial will claim that Atrasentan has a statistically significant effect on the primary endpoint.

### 8.1.3.2 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.

The secondary analysis on 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 will be performed on the evaluable set. The other secondary safety analyses will be conducted on the Safety population. For proportion endpoints, the simple percentage of subjects and a 2-sided exact 80% confidence interval will be calculated.

The continuous variable of the secondary endpoints will be summarized by sample size (N), mean, standard deviation, minimum and maximum.

### 8.1.3.3 Adverse Events (AEs) Analyses

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs (i.e., AEs that begin or worsen in severity after initiation of study drug) throughout the 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. The incidence rates of treatment-emergent AEs will be summarized. Additionally, the treatment-emergent AEs 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 adverse events will be evaluated in a similar manner.

Specifically, adverse events 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.

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.

#### 8.1.3.4 Clinical Laboratory Data

For each laboratory test, the mean change from baseline to the minimum, maximum, and to each 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.

#### 8.1.3.5 Vital Signs Data

The mean change from baseline to each visit in vital signs, including weight, will be summarized.

#### 8.1.3.6 ECG Analyses

The number and percentage of subjects with shifts from baseline in the categories of normal, abnormal as indicated by the study site investigators will be summarized.

### 8.1.4 Interim Analysis

An interim analysis will be performed after all the subjects have completed or prematurely discontinued from the 26-week Treatment Period. The database will be formally locked and versioned. The primary, applicable secondary and other safety analyses will be performed on this version of the clinical database. There is no need to adjust significance level since the primary analysis will be conducted using data from the 26-week Treatment Period.

## 8.2 Determination of Sample Size

The proportion of subjects with sperm concentration < 15 million/mL in an unscreened population of otherwise healthy males is reported to be approximately 10%.[22] With 15 evaluable subjects, this single-arm study will have approximately 80% power to detect a 20% difference between the incidence rate in the Atrasentan group and the null hypothesis of 10% at 2-sided significance level of 0.2.

# 9.0 Ethics

## 9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

## 9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical investigator are specified in Appendix A.

### 9.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related Screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy. Enrollment of subjects who cannot read, sponsor employees, site employees and employee family members are not permissible in this study. In addition, the use of legally authorized representatives is prohibited for this protocol.

Information regarding incentives for the subject and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

In the event a subject withdraws consent to participate from the study, stored samples will continue to be used for research and analysis. In the event a subject would like to withdraw consent for research using these samples, the subject may request their samples be withdrawn. Once AbbVie receives this request, the remaining samples will be destroyed. If the subject changes his consent, and the samples have already been tested, those results will still remain as part of the overall research data.

## 10.0 Source Documents and Case Report Form Completion

### 10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or

evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

The investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

## 10.2 Case Report Forms

Case report forms (CRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic case report forms (eCRFs) will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The Investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

The Investigator or an authorized member of the Investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The

Investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the Investigator at that time as a durable record of the site's eCRF data. It will be possible for the Investigator to make paper printouts from that media.

## 11.0 Data Quality Assurance

Prior to the initiation of the study, the study personnel at each site will be trained on the study procedures by a CRA at a study initiation visit. This training will include a detailed discussion of the protocol, performance of study procedures, CRF completion, and specimen collection methods. In addition, the study personnel at each site will be given an eCRF completion workbook for reference.

The CRAs will monitor each site throughout the study. Source document verification will be performed against entries on the eCRF and a quality assurance check will be performed to ensure that the Investigator is complying with the protocol and regulations. In addition, after eCRFs are retrieved by the CRA, a review of the data will be conducted by a physician and a clinical review team at AbbVie. Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF and documented via addenda or audit trail.

Routine hematology, serum chemistry, urinalysis, and other lab tests will be conducted using a central laboratory. The data from these analyses will be electronically transferred from the central laboratory to the study database. A final review of all laboratory results will be conducted by a physician and clinical review team at AbbVie.

Semen analysis will be conducted at qualified semen analysis laboratories. Data from these analyses will be entered by the site into the eCRF. A final review of all laboratory results will be conducted by a physician and clinical review team at AbbVie.

## 12.0 Use of Information

All information concerning Atrasentan and AbbVie operations, such as AbbVie patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by AbbVie and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by AbbVie in connection with the development of Atrasentan. This information may be disclosed as deemed necessary by AbbVie to other clinical investigators, other pharmaceutical companies, to the US Food and Drug Administration (FDA) and to other governmental agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the Investigator is obligated to provide AbbVie with complete test results and all data developed in this study and to provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review and regulatory inspection.

This confidential information shall remain the sole property of AbbVie, shall not be disclosed to others without the written consent of AbbVie and shall not be used except in the performance of this study.

The Investigator will maintain a confidential subject identification code list of all subjects enrolled in the study (by name and subject number). This list will be maintained at the site and will not be retrieved by AbbVie.

## 13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the time frame specified in the contract between the Investigator and

AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the Investigator and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The Investigator must retain any records related to the study according to local requirements. If the Investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory Investigator from the Investigators who participate in the study. Selection criteria for this Investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory Investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last visit.

## 14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for Atrasentan.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

| | |
|---|---|
| Protocol Title: | A Multicenter, Single-Arm Study of the Effects of Atrasentan on Spermatogenesis and Testicular Function |
| Protocol Date: | 08 April 2016 |

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

## 15.0 Reference List

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## Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.

10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

## Appendix B. List of Protocol Signatories

| Name | Title | Functional Area |
|---|---|---|
| [redacted] | | Clinical |
| | | Clinical |
| | | Clinical |
| | | Pharmacokinetics |
| | | Statistics |

## Appendix C. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

**Specific Protocol Changes:**

**Section 1.0 Title Page**
**Protocol title previously read:**

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

**Has been changed to read:**

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

**Section 1.0 Title Page**
**Add: "EudraCT Number:"**

| | |
|---|---|
| EudraCT Number: | 2016-000722-19 |

**Section 1.0 Title Page**
**"Investigators:," "Sponsor:," and "Sponsor/Emergency Contact:" previously read:**

| | |
|---|---|
| Investigators: | Multicenter (Investigator information on file at AbbVie). |
| Sponsor: | AbbVie Inc. (AbbVie) |
| Sponsor/Emergency Contact: | [redacted] |

**Has been changed to read:**

| | |
|---|---|
| Investigators: | Multicenter (Investigator information is on file at AbbVie). |
| Sponsor: | AbbVie* |
| Sponsor/Emergency Contact: | [redacted] |

**Section 1.0 Title Page**
**Add: new table note "*"**

*The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

## Section 1.2 Synopsis
## Previously read:

| | |
|---|---|
| **AbbVie Inc.** | **Protocol Number:** M12-919 |
| **Name of Study Drug:** Atrasentan | **Phase of Development:** 2 |
| **Name of Active Ingredient:** Atrasentan | **Date of Protocol Synopsis:** 06 May 2015 |
| **Protocol Title:** A Single-Country, Multicenter, Single-Arm Study of the Effects of Atrasentan on Spermatogenesis and Testicular Function | |
| **Objectives:** The study objective is to evaluate the effect of Atrasentan on spermatogenesis and testicular function in men with diabetic nephropathy. | |
| **Investigators:** Multicenter | |
| **Study Sites:** Approximately 10 sites. | |
| **Study Population:** Subjects that have diabetic nephropathy as defined by micro or macro albuminuria. | |
| **Number of Subjects to be Enrolled:** Approximately 20 subjects will be enrolled to complete 15 evaluable subjects. | |
| **Methodology:**<br>This is a prospective, single-country, multicenter, single-arm study. Eligible subjects will be treated with Atrasentan 0.75 mg once daily (QD) for 26 weeks. Semen samples will be collected at Screening (baseline), Week 6, Week 13, and Week 26/End of Treatment (EOT) visit. Duplicate samples will be collected at each time-point over a 7-day period with each sample being separated by at least 2 days. The average of the 2 samples will be used as the value for that time-point. Subjects will be discontinued from study drug and enter into an Observational Period of up to an additional 52 weeks if sperm concentration drops below 15 million/mL at any time during the Treatment Period or at the Week 26/EOT visit. If at the end of the 26-Week Treatment Period, there was a ≥ 50% reduction in sperm concentration from baseline the subject will also enter into the Observational Period. During the Observational Period, semen samples will be collected at Weeks 6 and 13 and then every 13 weeks until sperm concentration returns to baseline (± 15%) or until the end of the Observational Period. | |
| **Diagnosis and Main Criteria for Inclusion/Exclusion:**<br>**Main Inclusion:**<br>1. Male subject 30 to 75 years of age, inclusive at the time of Screening.<br>2. Subject has voluntarily signed and dated an Informed Consent Form, approved by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC), after the nature of the study has been explained and the subject has had the opportunity to ask questions. The informed consent must be signed before any study-specific procedures are performed.<br>3. Subject has type 1or 2 diabetes and has been treated with at least one anti-hyperglycemic medication and ACEi or ARB (RAS inhibitor) for at least 2 months prior to the Screening Period.<br>4. Subject has an eGFR ≥ 50 mL/min with the CKD-EPI formula and UACR ≥ 30 to < 5,000 mg/g creatinine.<br>5. Subject has a serum BNP < 200 ng/L.<br>6. Subject has systolic blood pressure ≥ 110 and ≤ 160 mmHg. | |

**Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):**

**Main Inclusion (Continued):**

7. Subject has a serum potassium ≥ 3.5 and ≤ 5.5 mEq/L.
8. Subject is able to provide a semen specimen at the required intervals.
9. Subject has baseline sperm concentration ≥ 30 million per mL.
10. Subject must be practicing at least two of the following methods of contraception, from initial study drug administration through 90 days after the last dose of study drug unless the subject's partner(s) is post-menopausal or has been surgically sterilized:
    - Partner(s) using an IUD;
    - Partner(s) using hormonal contraceptives (oral, vaginal, parenteral or transdermal);
    - Subject and/or partner(s) using barrier method (condoms, contraceptive sponge, diaphragm, or vaginal ring with spermicidal jellies or creams);
    - Total abstinence from sexual intercourse as the preferred life style of the subject; periodic abstinence is not acceptable.
11. Subject must agree not to donate sperm from initial study drug administration through 90 days after last dose of study drug.
12. $HbA_{1C} \leq 12\%$.
13. Subject has a Follicle Stimulating Hormone (FSH) between 1.30 – 19.30 IU/L.
14. Subject has a Luteinizing Hormone (LH) between 1.2 – 8.6 IU/L.
15. Subject has a total Testosterone between 3.0 – 10.0 ng/mL (300 – 1000 ng/dL) inclusive.
16. Subjects currently using alpha blockers must be on a stable dose for at least 3 months prior to screening and expected to remain on a stable dose during the study.
17. Subject currently using 5 alpha reductase inhibitors must be on a stable dose for at least 6 months prior to screening and expected to remain on a stable dose during the study.

**Main Exclusion:**

1. Prior history of prostate cancer with or without treatment.
2. Untreated retrograde ejaculation or prior prostate surgery. Subjects with treated retrograde ejaculation will be allowed with approval of the Study Designated Physician.
3. Prior history of vasectomy.
4. Prior history of radiation to the testes.
5. Recent history (within 6 months) of STD, UTI, documented prostatitis, orchitis, epididymitis.
6. History of male infertility.
7. Prior history of occupational exposure to environmental toxins within the past 6 months.
8. Drug, alcohol or substance abuse within the last 6 months.
9. Treatment with hormone suppressive agents, including androgens, estrogens, anabolic steroids, glucocorticoids, ketoconazole, cyclosporine, or cancer chemotherapy within the past 6 months or planned during the study.
10. Subject has a body mass index (BMI) > 45.
11. Subject has a history of hormone replacement therapy.
12. Subject has evidence or history of hypogonadism.
13. Current hot tub/Jacuzzi/sauna use or within the previous 12 weeks.

**Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):**

**Main Exclusion (Continued):**

14. Renal transplant.
15. Subject has a history of moderate or severe peripheral edema, pulmonary edema or facial edema unrelated to trauma or a history of myxedema in the prior 6 months to Screening.
16. Subject has a history of pulmonary hypertension requiring either oxygen therapy and/or endothelin receptor antagonist or phosphodiesterase therapy or any lung diseases requiring oxygen therapy (e.g., chronic obstructive pulmonary disease, emphysema, pulmonary fibrosis).
17. Subject has a documented diagnosis of heart failure, previous hospitalization for heart failure or current or constellation of symptoms (dyspnea on exertion, pedal edema, orthopnea, paroxysmal nocturnal dyspnea) felt to be compatible with heart failure, that was not explained by other causes, and for which there was a change in medication or other management directed at heart failure.
18. Subject has elevated liver enzymes (serum alanine aminotransaminase [ALT] and/or serum aspartate aminotransaminase [AST]) > 3 × the upper limit of normal (ULN).
19. Subject has a hemoglobin < 9 g/dL.
20. Subject has a history of an allergic reaction or significant sensitivity to Atrasentan (or its excipients) or similar compounds.
21. Subject has significant comorbidities (e.g., advanced malignancy, advanced liver disease) with a life expectancy of less than 1 year.
22. Subject has clinically significant cerebrovascular disease (CVD) or coronary artery disease (CAD) within 3 months prior to the Screening Period, defined as one of the following:
    a. Hospitalization for MI or unstable angina; or
    b. New onset angina with positive functional study or coronary angiogram revealing stenosis; or
    c. Coronary revascularization procedure; or
    d. Transient ischemic attack (TIA) or stroke.
23. Subject has received any investigational drug within 3 months prior to Screening.
24. Subject is currently receiving rosiglitazone, moxonidine, aldosterone blockers, aliskiren or a combination of ACEi and ARB.
25. Subjects with known allergy to thiazide or loop diuretics.
26. Is considered by the Investigator unsuitable to participate in the trial for any other reason, for instance due to a significant serious underlying condition.

| | |
|---|---|
| **Investigational Product:** | Atrasentan |
| **Dose:** | 0.75 mg QD |
| **Mode of Administration:** | Oral |
| **Reference Therapy:** | Not applicable |
| **Dose:** | Not applicable |
| **Mode of Administration:** | Not applicable |

**Duration of Treatment:** 26 weeks

**Criteria for Evaluation:**

**Primary Safety Endpoint:**

The proportion of subjects who have a sperm concentration < $15 \times 10^6$/mL by 26 weeks.

**Criteria for Evaluation (Continued):**

**Secondary Safety Measures up to the End of Study:**

1. The proportion of subjects who enter the Observation Period and do not return to within 15% of baseline by 52 weeks after treatment discontinuation.
2. Change from baseline to each visit in sperm concentration.
3. Change from baseline to each visit in each of the components of the semen analysis (sperm motility, sperm morphology, sperm concentration, semen volume).
4. Change from baseline to each visit in serum testosterone, estradiol, LH, FSH, and inhibin B.

**Pharmacokinetic:**

Atrasentan apparent oral clearance (CL/F) and volume of distribution (V/F) may be estimated using population pharmacokinetic techniques.

**Statistical Methods:**

**Sample Size Justification:**

The proportion of subjects with sperm concentration < 15 million/mL in an unscreened population of healthy male subjects is reported to be approximately 10% (Cooper et al 2010). With 15 evaluable subjects, this single-arm 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.

**Safety:**

**Primary Safety Endpoint**: The proportion of subjects who have a sperm concentration < 15 million /mL by 26 weeks. The primary safety analysis of primary endpoint will be performed on evaluable subjects. A subject will be considered evaluable for the primary analysis if the following is satisfied: (1) The Overall Study Drug compliance status = YES; and (2) Completes the 26-week TP and has all planned sperm samples collected; or has a sperm concentration value less than 15 million/mL observed prior to the end of treatment period. The simple percentage of subjects and a 2-sided 80% exact confidence interval will be calculated. Thus, when 15 subjects are evaluable, if 4 or more subjects have a sperm concentration < 15 million/mL, the trial will claim that Atrasentan has a statistically significant effect on the primary endpoint.

Adverse events will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects who report treatment-emergent adverse events in treatment period will be tabulated by system organ class (SOC) and preferred term by treatment group. The number and percentage of subjects who report protocol-related adverse events in Observational Period will be also be summarized.

For each laboratory test, the mean change from baseline to the minimum, maximum, and to each visit will be summarized. Additionally for selected laboratory tests of particular 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. The mean change from baseline to each visit in vital signs, including weight, will be summarized.

**Reference:**

1. Cooper TG, Noonan E, von Eckardstein S, et al. World Health Organization reference values for human semen characteristics. Hum Reprod Update. 2010;16(3):231-45.

## Has been changed to read:

| | |
|---|---|
| **AbbVie** | **Protocol Number:** M12-919 |
| **Name of Study Drug:** Atrasentan | **Phase of Development:** 2 |
| **Name of Active Ingredient:** Atrasentan | **Date of Protocol Synopsis:** 08 April 2016 |
| **Protocol Title:** A Multicenter, Single-Arm Study of the Effects of Atrasentan on Spermatogenesis and Testicular Function | |
| **Objectives:** The study objective is to evaluate the effect of Atrasentan on spermatogenesis and testicular function in men with diabetic nephropathy. | |
| **Investigators:** Multicenter | |
| **Study Sites:** Approximately 20 sites. | |
| **Study Population:** Subjects with type 1 or 2 diabetes and nephropathy (e-GFR ≥ 35 ml/min/1.73 $m^2$ and a urinary albumin to creatinine ratio (UACR) ≥ 30 mg/g creatinine and < 5,000 mg/g (≥ 3.4 mg/mmol and < 565 mg/mmol)). | |
| **Number of Subjects to be Enrolled:** Approximately 20 subjects will be enrolled to complete 15 evaluable subjects. | |
| **Methodology:**<br>This is a prospective, open-label, multicenter, single-arm study. Eligible subjects will be treated with Atrasentan 0.75 mg once daily (QD) for 26 weeks while remaining on their RAS inhibitors. Semen samples will be collected at Screening (baseline), Week 13 and Week 26/End of Treatment (EOT) visits. 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) for each scheduled collection period. The average of the 2 semen samples will be used as the value for that collection period. If at any time during the Treatment Period or at the Week 26/EOT visit, the subjects' sperm concentration drops below 15 million/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 baseline, the subject will 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. Subjects who do not meet the criteria to enter the Observational Period will have a follow-up contact from the Investigator (or designee) 30 to 35 days after the last dose of study drug. Subjects, whose sperm concentration returns to within 15% of baseline or above during the Observational Period, will have a follow-up contact from the Investigator (or designee) within 14 days of the collection of the second semen sample. | |
| **Diagnosis and Main Criteria for Inclusion/Exclusion:**<br>**Main Inclusion:**<br>• Male subject 30 to 75 years of age, inclusive at the time of Screening.<br>• Subject has type 1 or 2 diabetes and is receiving treatment with at least one anti-hyperglycemic medication and ACEi or ARB (RAS inhibitor). | |

**Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):**

**Main Inclusion (Continued):**

- Subject has an eGFR ≥ 35 mL/min/1.73 m2 with the CKD-EPI formula and UACR ≥ 30 to < 5,000 mg/g creatinine (≥ 3.4 mg/mmol and < 565 mg/mmol).
- Subject is able to provide a semen specimen at the required intervals.
- Subject has a baseline sperm concentration ≥ 30 million per mL at Screening.

**Main Exclusion:**

- Subject has had treatment with hormone suppressive agents, including androgens, estrogens, anabolic steroids, glucocorticoids, ketoconazole, cyclosporine, or cancer chemotherapy within the 6 months prior to the initial screening visit or planned during the study.
- Subject is currently receiving or has received hormone replacement therapy within the last 6 months prior to the Screening Period.
- Subject has a history of severe peripheral edema or facial edema unrelated to trauma or a history of myxedema in the prior 4 weeks to the initial screening visit.
- Subject has a history of pulmonary hypertension, pulmonary fibrosis or any lung disease requiring either oxygen therapy (e.g., chronic obstructive pulmonary disease, emphysema).
- Subject has a documented diagnosis of heart failure, previous hospitalization for heart failure or current or constellation of symptoms (dyspnea on exertion, pedal edema, orthopnea, paroxysmal nocturnal dyspnea) felt to be compatible with heart failure, that was not explained by other causes, and for which there was a change in medication or other management directed at heart failure.

| | |
|---|---|
| **Investigational Product:** | Atrasentan |
| **Dose:** | 0.75 mg QD |
| **Mode of Administration:** | Oral |
| **Reference Therapy:** | Not applicable |
| **Dose:** | Not applicable |
| **Mode of Administration:** | Not applicable |

**Duration of Treatment:** 26 weeks

**Criteria for Evaluation:**

**Safety:**

**Primary Safety Endpoint:**

The proportion of subjects who have a sperm concentration < $15 \times 10^6$/mL during the 26-week Treatment Period.

**Criteria for Evaluation (Continued):**

**Safety (Continued):**

**Secondary Safety Measures up to the End of Study:**

- 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.

**Pharmacokinetic:**

Atrasentan apparent oral clearance (CL/F) and volume of distribution (V/F) may be estimated using population pharmacokinetic techniques.

**Statistical Methods:**

**Analysis Datasets:**

The following datasets will be used for the analysis of safety endpoints:

- The Evaluable Set will consist of all subjects who achieve the following: 1) ≥ 70% overall study drug compliance; and 2) having completed the 26-week treatment period and having all planned sperm samples collected; or having a sperm concentration value < $15 \times 10^6$/mL observed by the end of the Treatment Period.
- The Safety Analysis Set includes all subjects who receive at least one dose of Atrasentan.

**Sample Size Justification:**

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 open label, single-arm 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.

**Safety:**

**Primary Safety Analysis:**

The primary safety analysis will be conducted on the evaluable set for the primary safety endpoint. The simple percentage of subjects and a 2-sided 80% exact confidence interval will be calculated. When 15 evaluable subjects are available, if 4 or more subjects have a sperm concentration < $15 \times 10^6$/mL, the trial will claim that Atrasentan has a statistically significant effect on the primary endpoint.

**Secondary Safety Analysis:**

The secondary analysis on 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 will be performed on the evaluable set. The other secondary safety analyses will be conducted on the Safety population. For proportion endpoints, the simple percentage of subjects and a 2-sided exact 80% confidence interval will be calculated.

The continuous variable of the secondary endpoints will be summarized by sample size (N), mean, standard deviation, minimum and maximum.

**Statistical Methods (Continued):**

**Adverse Events (AEs) Analysis:**

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs (i.e., AEs that begin or worsen in severity after initiation of study drug) throughout the 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. The incidence rates of treatment-emergent AEs will be summarized. Additionally, the treatment-emergent AEs 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 adverse events will be evaluated in a similar manner.

For the Observational Period, the protocol related AEs will be summarized similarly from 30 days after the last dose of study drug through study completion. The number and percentage of subjects who report protocol-related adverse events in the Observational Period will also be summarized.

**Laboratory Data:**

For each laboratory test, the mean change from baseline to the minimum, maximum, and to each visit will be summarized. Additionally for selected laboratory tests of particular 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. The mean change from baseline to each visit in vital signs, including weight, will be summarized.

**Interim Analysis:**

An interim analysis will be performed after all the subjects have completed or prematurely discontinued from the 26-week Treatment Period. The database will be formally locked and versioned. The primary, applicable secondary and other safety analyses will be performed on this version of the clinical database. There is no need to adjust significance level since the only comparison is in the primary analysis which will be conducted using data from the 26-week Treatment Period.

**Section 1.3 List of Abbreviations and Definition of Terms**
**Subsection Abbreviations**
**Previously read:**

| | |
|---|---|
| ACEi | Angiotensin-converting enzyme |
| AE | Adverse event |
| AKI | Acute kidney injury |
| ALT | Serum alanine aminotransaminase |
| AQOL-4D | Assessment of Quality of Life – 4 Dimensions |
| AST | Serum aspartate aminotransaminase |
| ARB | Angiotensin II receptor blocker |
| BMI | Body mass index |
| BNP | Brain natriuretic peptide |
| BP | Blood pressure |
| BUN | Blood urea nitrogen |
| CAD | Coronary artery disease |
| CCB | Calcium channel blocker |
| CFR | Code of federal regulations |
| CHF | Congestive heart failure |
| CKD | Chronic kidney disease |
| CL/F | Oral clearance |
| Cr | Creatinine |
| CRF | Case report form |
| CV | Cardiovascular |
| CVD | Cerebrovascular disease |
| DBP | Diastolic blood pressure |
| DNA | Deoxyribonucleic acid |
| EAC | Events adjudication committee |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| EDTA | Edetic acid (ethylenediaminetetraacetic acid) |
| eGFR | Estimated glomerular filtration rate |
| EMEA | European agency for the evaluation of medicinal products |
| EPI | Epidemiology collaboration |

| | |
|---|---|
| ESRD | End stage renal disease |
| ET | Endothelins |
| $ET_A$ | Endothelin-A |
| $ET_B$ | Endothelin-B |
| FMV | First morning void |
| FSH | Follicle stimulating hormone |
| GCP | Good Clinical Practice |
| GI | Gastrointestinal |
| $HBA_{1c}$ | Glucosylated hemoglobin $A_{1c}$ |
| HDL | High density lipoprotein |
| HOMA-IR | Homeostatic model assessment |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IEF | Index of Erectile Function |
| IMP | Investigational medicinal product |
| IND | Investigational new drug |
| IRB | Institutional Review Board |
| IUD | Intrauterine device |
| IWRS | Interactive voice response/Interactive Web Response System |
| IVRS | Interactive voice response system |
| LDL | Low density lipoprotein |
| LDH | Lactic dehydrogenase |
| LH | Luteinizing hormone |
| MI | Myocardial infarction |
| MMRM | Mixed model of repeated measures |
| MTLDD | Maximum tolerated labeled daily dose |
| NSAIDS | Non-steroidal anti-inflammatory drugs |
| OLE | Open-label extension |
| PD | Premature discontinuation |
| PG | Pharmacogenetic |
| PI | Principal investigator |
| PK | Pharmacokinetic |
| QD | Once daily |
| MedDRA | Medical dictionary for regulatory activities |

| | |
|---|---|
| RAS | Renin angiotensin system |
| RAAS | Renin-angiotensin-aldosterone system |
| RBC | Red blood cell |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SBP | Systolic blood pressure |
| SGPT | Serum glutamic pyruvic transaminase |
| SGOT | Serum glutamic oxaloacetic transaminase |
| SI | Standard International Units |
| SOP | Standard operating procedure |
| SUSAR | Suspected unexpected serious adverse reactions |
| T | Testosterone |
| TGF-β | Transforming growth factor beta |
| UACR | Urinary albumin to creatinine ratio |
| ULN | Upper limit of normal |
| V/F | Volume of distribution |
| VLDL | Very low density lipoprotein |
| WBC | White blood cell |

**Has been changed to read:**

| | |
|---|---|
| ACEi | Angiotensin-converting enzyme inhibitor |
| AE | Adverse event |
| ALT | Serum alanine aminotransaminase |
| AST | Serum aspartate aminotransaminase |
| ARB | Angiotensin II receptor blocker |
| BNP | Brain natriuretic peptide |
| BP | Blood pressure |
| BUN | Blood urea nitrogen |
| CAD | Coronary artery disease |
| CFR | Code of federal regulations |
| CHF | Congestive heart failure |
| CKD | Chronic kidney disease |
| CL/F | Oral clearance |
| CRA | Clinical Research Associate |
| CRF | Case report form |
| CV | Cardiovascular |
| CVD | Cerebrovascular disease |
| DBP | Diastolic blood pressure |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| EDTA | Edetic acid (ethylenediaminetetraacetic acid) |
| eGFR | Estimated glomerular filtration rate |
| EPI | Epidemiology collaboration |
| EOS | End of Study |
| EOT | End of Treatment |
| ESRD | End stage renal disease |
| ET | Endothelins |
| $ET_A$ | Endothelin-A |
| $ET_B$ | Endothelin-B |
| FMV | First morning void |
| FSH | Follicle stimulating hormone |
| GCP | Good Clinical Practice |

| | |
|---|---|
| GI | Gastrointestinal |
| $HBA_{1c}$ | Glucosylated hemoglobin $A_{1c}$ |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IMP | Investigational medicinal product |
| IND | Investigational new drug |
| IRB | Institutional Review Board |
| IUD | Intrauterine device |
| IWRS | Interactive voice response/Interactive Web Response System |
| IVRS | Interactive voice response system |
| LH | Luteinizing hormone |
| MI | Myocardial infarction |
| MTLDD | Maximum tolerated labeled daily dose |
| OLE | Open-label extension |
| PD | Premature discontinuation |
| PK | Pharmacokinetic |
| QD | Once daily |
| MedDRA | Medical dictionary for regulatory activities |
| RAS | Renin angiotensin system |
| RBC | Red blood cell |
| SAE | Serious adverse event |
| SBP | Systolic blood pressure |
| SGPT | Serum glutamic pyruvic transaminase |
| SGOT | Serum glutamic oxaloacetic transaminase |
| SI | Standard International Units |
| SOP | Standard operating procedure |
| SUSAR | Suspected unexpected serious adverse reactions |
| T | Testosterone |
| TGF-β | Transforming growth factor beta |
| UACR | Urinary albumin to creatinine ratio |
| ULN | Upper limit of normal |
| US | United States |
| V/F | Volume of distribution |
| WBC | White blood cell |

**Section 1.3 List of Abbreviations and Definition of Terms**
**Subsection Definition of Terms**
**"First morning void urine" previously read:**

First morning void urine The first void of the morning collected after 5:00 am.

**Has been changed to read:**

First morning void urine The first void of the morning collected after 5:00 am or upon raising for the day.

**Section 1.3 List of Abbreviations and Definition of Terms**
**Subsection Definition of Terms**
**Delete: "Observation Period criteria"**

Observation Period criteria Subjects whose sperm concentration drops below < 15 million/mL at any time during the Treatment Period. Subjects who experience a ≥ 50% reduction in sperm concentration from baseline at the end of the 26-week Treatment Period will enter the Observational Period.

**Section 1.3 List of Abbreviations and Definition of Terms**
**Subsection Definition of Terms**
**Add: "Duplicate semen samples"**

Duplicate semen samples Set of two semen samples collected over a 7-day period with each sample being separated by at least 2 days (48 hours) for a scheduled collection period. Each collection period lasts up to 14 days and is associated with a specific study visit.

**Section 3.0 Introduction**
**Last paragraph, first sentence previously read:**

The Phase 3 study (Study M11-352) is ongoing to characterize the efficacy and safety of Atrasentan in subjects with type 2 diabetes and nephropathy who have residual albuminuria while receiving MTLDD of RAS inhibitors (Section 4.0), in delaying renal disease progression.

**Has been changed to read:**

The Phase 3 study (Study M11-352) is ongoing to characterize the safety and efficacy of Atrasentan in delaying renal disease progression in subjects with type 2 diabetes and nephropathy who have residual albuminuria while receiving MTLDD of RAS inhibitors.

**Section 3.0 Introduction**
**Subsection Effect of Atrasentan on Testicular Function in Clinical Studies**
**Fifth paragraph, third and fourth sentence previously read:**

These results are noted in the US prescribing information for both bosentan and ambrisentan. In ARIES-E, a clinical study with chronic ambrisentan administration, there was no clear evidence of a detrimental effect on sperm count; however, a decrease in plasma inhibin B and an increase in plasma FSH not associated with a change in testosterone were observed.

**Has been changed to read:**

These results are noted in the US prescribing information for both bosentan and ambrisentan.[19,20] In ARIES-E, a clinical study with chronic ambrisentan administration, there was no clear evidence of a detrimental effect on sperm count; however, a decrease in plasma inhibin B and an increase in plasma FSH not associated with a change in testosterone were observed.[21]

**Section 3.0 Introduction**
**Subsection Effect of Atrasentan on Testicular Function in Clinical Studies**
**Last paragraph previously read:**

The purpose of this study (Study M12-919) is to evaluate the effect of prolonged administration of Atrasentan on spermatogenesis and testicular function.

**Has been changed to read:**

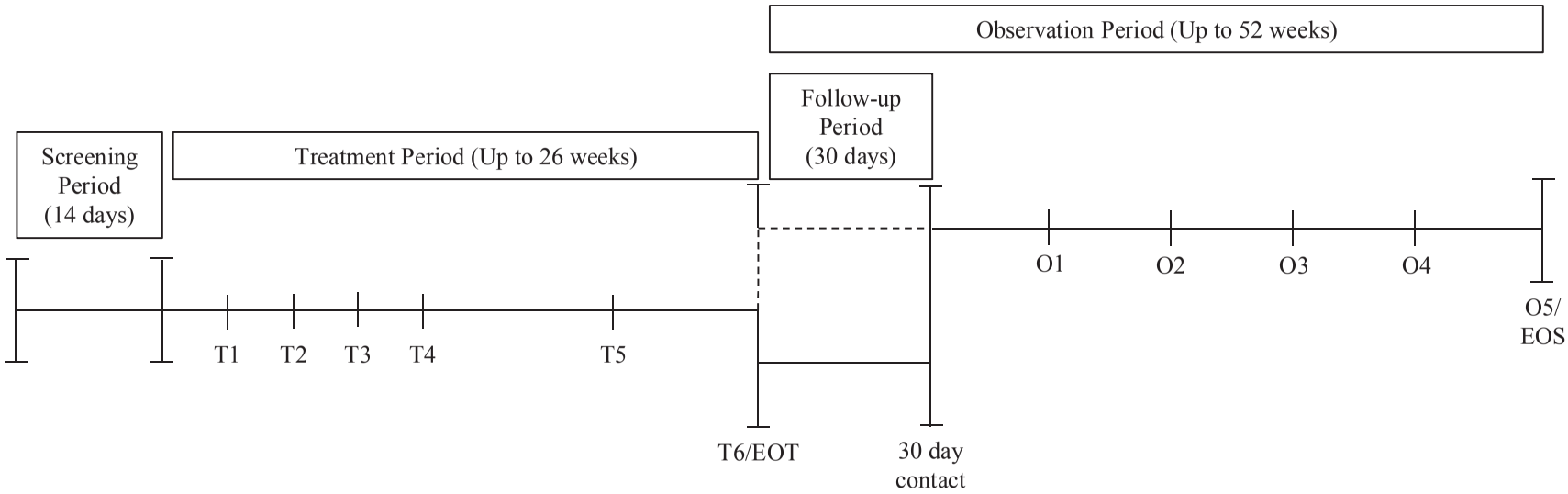
The purpose of this study (Study M12-919) is to evaluate the effect of prolonged administration of Atrasentan on spermatogenesis and testicular function (Section 4.0).

**Section 5.1 Overall Study Design and Plan: Description**
**Previously read:**

This is a Phase 2, open-label, single-country, single-arm study designed to demonstrate the effect of Atrasentan on spermatogenesis and testicular function in men with diabetic nephropathy. Approximately 20 subjects (to complete 15 evaluable subjects) with diabetic nephropathy who are taking RAS inhibitors are planned to be enrolled in the study at approximately 15 sites. Subjects will receive 0.75 mg once daily (QD) of Atrasentan for 26 weeks. The duration of the study will be up to approximately 80 weeks. Semen samples will be collected at Screening (baseline), Week 6, Week 13, and Week 26/End of Treatment (EOT). A duplicate sample will be collected at each time-point over a 7-day period with each sample being separated by at least 2 days. If for any reason one of the two required samples is inadequate or not obtained, then a replacement sample will be collected to ensure that two samples are available for each time-point. All semen samples for a time-point must be collected within a 14-day period. Subject must abstain from ejaculation for at least 2 days but not more than 7 days prior to semen sample collection. The average of the 2 semen samples will be used as the value for that time-point. Subjects will be discontinued from study drug and enter into an Observational Period of up to an additional 52 weeks if sperm concentration drops below 15 million/mL at any time during the Treatment Period or at the Week 26/EOT visit. If at the end of the 26-Week Treatment Period there is a ≥ 50% reduction in sperm concentration from baseline the subject will also enter into the Observational Period. During the Observational Period, semen samples will be collected 6 weeks after the end of treatment visit, Week 13 and then every 13 weeks until all values have returned to the baseline sperm concentration (± 15%) or until the end of the Observational Period.

The study was designed to enroll approximately 20 subjects to obtain 15 evaluable subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled.

**Figure 1. Study Schematic**



**Screening Period**

The Screening Period will last up to 14 days. Procedures to be performed at the Screening visit are noted in Table 1. Subjects will return to the site within the 14-day Screening Period to return the two consecutive first morning void urine samples. In addition, the two semen samples should be scheduled within the 14-day window. See Section 5.3.2.1 for semen collection requirements and time windows. Subjects who fail to meet eligibility criteria will be allowed to re-screen twice.

**Treatment Period**

Subjects should return for the Day 1 visit after all eligibility criteria has been reviewed and the subject is deemed eligible within 14 days from the initial screening laboratory assessments. Subjects who return for the Day 1 visit outside of 14 days from the initial screening laboratory assessments, must repeat Screening laboratory assessments. In addition, if 14 days have passed from the second semen sample, the subjects must repeat the Screening semen assessments.

All subjects will be contacted 30 to 35 days after their last dose of study drug to solicit AEs and SAEs. This follow-up contact will be the final visit for subjects who do not meet the criteria for entering the Observational Period.

**Observational Period**

Subjects meeting the criteria for entering the Observational Period will complete study visits and assessments as noted in Table 1. Subjects who have a sperm concentration returning to baseline (± 15%) will return for their O5/End of Study visit within 14 days. All other subjects will continue study visits until the End of Study visit.

**Has been changed to read:**

This is a Phase 2, prospective, open-label, multicenter, single-arm study designed to evaluate the effect of Atrasentan on spermatogenesis and testicular function in men with diabetic nephropathy. Approximately 20 subjects (to complete 15 evaluable subjects)

with diabetic nephropathy who are taking RAS inhibitors are planned to be enrolled in the study at approximately 20 sites.

Subjects who provide consent, will enter a Screening Period to assess eligibility. Eligible subjects will enter a 26-week Treatment Period, followed by an Observational Period if the subject qualifies. General laboratory tests (including hematology, chemistry and urinalysis) will be collected for safety monitoring and semen samples will be collected throughout the subject's study participation.

If at any time during the Treatment Period or at the T6/End of Treatment (EOT) (Week 26) visit the subject's sperm concentration drops below 15 million/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 baseline the subject will also enter into the Observational Period.

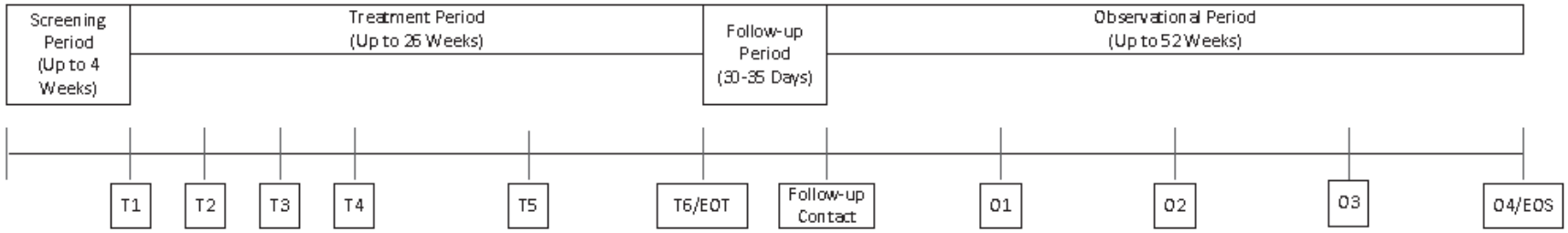
During the Observational Period, laboratory tests and semen samples will be collected.

Subjects who do not meet the criteria for entering the Observational Period will have a contact from the Investigator (or designee) 30 to 35 days after their last dose of study drug.

The study was designed to enroll approximately 20 subjects to obtain 15 evaluable subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled.

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

**Figure 1. Study Schematic**



**Screening Period**

The Screening Period will last up to 4 weeks. Procedures to be performed during the Screening Period are outlined in the Study Activities Table (Table 1). Subjects will be given supplies and instructions for obtaining the first morning void urine sample and scheduled to return to the site within the 4-week Screening Period to return the first morning void urine sample. In addition, the subject will provide the semen samples according to the specific windows for semen collection (Section 5.3.2.1) within the 4-week Screening Period. Tests for eligibility may be repeated within the subject's 4-week Screening Period. Subjects who fail to meet eligibility criteria will be allowed to re-screen at the investigator's discretion.

**Treatment Period**

Eligible subjects will return for the T1 visit (Day 1) no more than 4 weeks from the initial screening visit. The procedures to be performed at the T1 visit are outlined in the Study Activities Table (Table 1), including initial administration of open-label study drug (Atrasentan).

The Treatment Period consists of five additional site visits over a 26 week period.

- The T2 (Week 2) visit will take place 2 weeks (± 7 days) after the T1 visit.
- The T3 (Week 4) visit will take place 2 weeks (± 7 days) after the T2 visit.
- The T4 (Week 6) visit will take place 2 weeks (± 7 days) after the T3 visit.
- The T5 (Week 13) visit will take place 7 weeks (± 7 days) after the T4 visit. At this visit, subjects will be provided with supplies and instructions for the collection of the duplicate semen samples and will be scheduled for the collection of the semen samples according to the specific windows for semen collection (Section 5.3.2.1). Supplies and instructions for obtaining the first morning void urine sample within 1 day of the T6 visit will also be given to the subjects. The site will also call into IVRS/IWRS at this visit and dispense study drug to the subject.

If the average of the two semen samples is < 15 million/mL, the subject will discontinue from study drug and return to the End of Treatment Visit (EOT) 5 days (± 3 days) of the last dose of study drug. For this subject, semen samples will not be collected at the EOT visit.

The T6/EOT (Week 26) visit will take place 13 weeks (± 7 days) after the T5 visit. Subjects will be provided with supplies and instructions for the collection of the duplicate semen samples, and will be scheduled for the collection of the semen samples according to the specific windows for semen collection (Section 5.3.2.1). If the average of the two semen samples is < 15 million/mL or there is a ≥ 50% reduction in sperm concentration from Screening at T6/EOT (Week 26) visit, the subject will enter the Observational Period.

The procedures to be performed at each visit are outlined in the Study Activities Table (Table 1).

**Follow-Up Contact**

Only those subjects who do not meet criteria to enter the Observational Period will be contacted by the Investigator (or designee) approximately 30 to 35 days after their last dose of study drug to solicit changes to concomitant medications and AEs and SAEs. This follow-up contact will be the final contact for these subjects.

**Observational Period**

Only those subjects with a sperm concentration below 15 million/mL at any time during the Treatment Period or with a ≥ 50% reduction from Screening (baseline) at the end of the 26-week Treatment Period will enter the Observational Period.

The Observational Period will consist of up to 4 study visits and last up to 52 weeks.

- The O1 (Week 13) visit will take place 13 weeks (± 7 days) after the subject's EOT visit.

- The O2 (Week 26) visit will take place 13 weeks (± 7 days) after the O1 visit with the remaining visits (O3 [Week 39] and O4 /End of Study [EOS; Week 52]) following every 13 weeks (± 7 days) thereafter.

The procedures to be performed at these visits are outlined in the Study Activities Table (Table 1).

During the Observational Period duplicate semen samples will be collected until the subject's sperm concentration returns to within 15% of baseline or above, or until the end of the Observational Period. At each visit, subjects will be provided with supplies and instructions for the collection of the semen samples, and will be scheduled for the collection of the semen samples according to the specific windows for semen collection (Section 5.3.2.1). If at any time during the Observational Period the sperm concentration returns to within 15% of baseline or above, subjects will have completed their participation in the Observational Period. The visit at which their sperm concentration returned to within 15% of baseline or above will be considered their End of Study visit. These subjects will also be contacted by the Principal Investigator (or designee) within 14 days of the collection of the second semen sample. This contact will be the final contact for these subjects.

All other subjects will continue study visits until the End of Study visit.

**Section 5.2.1 Inclusion Criteria**
**Previously read:**

1. Male subject 30 to 75 years of age, inclusive at the time of Screening.
2. Subject has voluntarily signed and dated an Informed Consent Form, approved by an Institutional Review Board (IRB)/Independent Ethics (IEC), after the nature of the study has been explained and the subject has had the opportunity to ask questions. The informed consent must be signed before any study-specific procedures are performed.

3. Subject has type 1or 2 diabetes and has been treated with at least one anti-hyperglycemic medication and ACEi or ARB (RAS inhibitor) for at least 2 months prior to the Screening Period.
4. Subject has an eGFR ≥ 50 mL/min with the CKD-EPI formula and UACR ≥ 30 to < 5,000 mg/g creatinine.
5. Subject has a serum BNP < 200 ng/L.
6. Subject has systolic blood pressure ≥ 110 and ≤ 160 mmHg.
7. Subject has a serum potassium ≥ 3.5 and ≤ 5.5 mEq/L.
8. Subject is able to provide a semen specimen at the required intervals.
9. Subject has baseline sperm concentration ≥ 30 million per mL.
10. Subject must be practicing at least two of the following methods of contraception, from initial study drug administration through 90 days after last dose of study drug unless subject's partner(s) is post-menopausal or has been surgically sterilized:
    - Partner(s) using an IUD;
    - Partner(s) using hormonal contraceptives (oral, vaginal, parenteral or transdermal);
    - Subject and/or partner(s) using barrier method (condoms, contraceptive sponge, diaphragm, or vaginal ring with spermicidal jellies or creams).
    - Total abstinence from sexual intercourse as the preferred life style of the subject; periodic abstinence is not acceptable.
11. Subject must agree not to donate sperm from initial study drug administration through 90 days after last dose of study drug.
12. $HbA_{1C}$ ≤ 12%.
13. Subject has a Follicle Stimulating Hormone (FSH) between 1.30 – 19.30 IU/L.
14. Subject has a Luteinizing Hormone (LH) between 1.2 – 8.6 IU/L.

15. Subject has a total Testosterone between 3.0 – 10.0 ng/mL (300 – 1000 ng/dL) inclusive.
16. Subjects currently using alpha blockers must be on a stable dose for at least 3 months prior to screening and expected to remain on a stable dose during the study.
17. Subject currently using 5 alpha reductase inhibitors must be on a stable dose for at least 6 months prior to screening and expected to remain on a stable dose during the study.

**Rationale for the Inclusion Criteria**

(1, 3 – 7, 12) To select the appropriate subject population with diabetes-related kidney disease.

(2) In accordance with harmonized GCP.

(8, 9) To select a patient population with an acceptable sperm concentration for the evaluation.

(10, 11, 13 – 15) The impact of Atrasentan on pregnancies is unknown.

**Has been changed to read:**

1. Male subject 30 to 75 years of age, inclusive at the time of Screening.
2. Subject has voluntarily signed and dated an Informed Consent Form, approved by an Institutional Review Board (IRB)/Independent Ethics (IEC), after the nature of the study has been explained and the subject has had the opportunity to ask questions. The informed consent must be signed before any study-specific procedures are performed.
3. Subject has type 1or 2 diabetes and is receiving treatment with at least one anti-hyperglycemic medication and ACEi or ARB (RAS inhibitor).

4. Subject has an eGFR ≥ 35 mL/min/1.73 $m^2$ with the CKD-EPI formula and UACR ≥ 30 to < 5,000 mg/g creatinine (≥ 3.4 mg/mmol and < 565 mg/mmol).
5. Subject has a serum BNP ≤ 200 pg/L (200 ng/mL).
6. Subject has systolic blood pressure ≥ 110 and ≤ 180 mmHg at Screening.
7. Subject has a serum potassium ≥ 3.5 (3.5 mmol/L) and ≤ 6.0 mEq/L (6.0 mmol/L).
8. Subject is able to provide a semen specimen at the required intervals.
9. Subject has a baseline sperm concentration ≥ 30 million per mL at Screening.
10. If the subject is sexually active with female partner(s) of childbearing potential, he must agree, from initial study drug administration through 90 days after the last dose of study, to practice the protocol specified contraception (Section 5.2.4).
11. Subject must agree not to donate sperm from initial study drug administration through 90 days after the last dose of study drug.
12. (intentionally left blank; criterion deleted)
13. (intentionally left blank; criterion deleted)
14. (intentionally left blank; criterion deleted)
15. Subject has a total Testosterone > 150 ng/dL (5.20 nmol/L).
16. Subjects currently using alpha blockers must be on a stable dose for at least 2 weeks prior to the initial screening visit and expected to remain on a stable dose during the study.
17. Subject currently using 5 alpha reductase inhibitors must be on a stable dose for at least 3 months prior to the initial screening visit and expected to remain on a stable dose during the study.

**Rationale for the Inclusion Criteria**

(1, 3 – 7) To select the appropriate subject population with diabetes-related kidney disease.

(2) In accordance with harmonized GCP.

(8, 9, 15 – 17) To select a patient population with an acceptable sperm concentration for the evaluation.

(10, 11) The impact of Atrasentan on pregnancies is unknown.

**Section 5.2.2 Exclusion Criteria**
**Previously read:**

1. Prior history of prostate cancer with or without treatment.
2. Untreated retrograde ejaculation or prior prostate surgery. Subjects with treated retrograde ejaculation will be allowed with approval of the Study Designated Physician.
3. Prior history of vasectomy.
4. Prior history of radiation to the testes.
5. Recent history (within 6 months) of STD, UTI, documented prostatitis, orchitis, epididymitis.
6. History of male infertility.
7. Prior history of occupational exposure to environmental toxins within the past 6 months.
8. Drug, alcohol or substance abuse within the last 6 months.
9. Treatment with hormone suppressive agents, including androgens, estrogens, anabolic steroids, glucocorticoids, ketoconazole, cyclosporine, or cancer chemotherapy within the past 6 months or planned during the study.
10. Subject has a body mass index (BMI) > 45.
11. Subject has a history of hormone replacement therapy.
12. Subject has evidence or history of hypogonadism.

13. Current hot tub/Jacuzzi/sauna use or within the previous 12 weeks.
14. Renal transplant.
15. Subject has a history of moderate or severe peripheral edema, pulmonary edema or facial edema unrelated to trauma or a history of myxedema in the prior 6 months to Screening.
16. Subject has a history of pulmonary hypertension requiring either oxygen therapy, and/or endothelin receptor antagonist or phosphodiesterase therapy or any lung diseases requiring oxygen therapy (e.g., chronic obstructive pulmonary disease, emphysema, pulmonary fibrosis).
17. Subject has a documented diagnosis of heart failure, previous hospitalization for heart failure or current or constellation of symptoms (dyspnea on exertion, pedal edema, orthopnea, paroxysmal nocturnal dyspnea) felt to be compatible with heart failure, that was not explained by other causes, and for which there was a change in medication or other management directed at heart failure.
18. Subject has elevated liver enzymes (serum alanine aminotransaminase [ALT] and/or serum aspartate aminotransaminase [AST]) > 3 × the upper limit of normal (ULN).
19. Subject has a hemoglobin < 9 g/dL.
20. Subject has a history of an allergic reaction or significant sensitivity to Atrasentan (or its excipients) or similar compounds.
21. Subject has significant comorbidities (e.g., advanced malignancy, advanced liver disease) with a life expectancy of less than 1 year.
22. Subject has clinically significant cerebrovascular disease (CVD) or coronary artery disease (CAD) within 3 months prior to the Screening Period, defined as one of the following:
    - Hospitalization for MI or unstable angina; or

- New onset angina with positive functional study or coronary angiogram revealing stenosis; or
- Coronary revascularization procedure; or
- Transient ischemic attack (TIA) or stroke.

23. Subject has received any investigational drug within 3 months prior to Screening.
24. Subject is currently receiving rosiglitazone, moxonidine, aldosterone blockers, aliskiren or a combination of ACEi and ARB.
25. Subjects with known allergy to thiazide or loop diuretics.
26. Is considered by the Investigator unsuitable to participate in the trial for any other reason, for instance due to a significant serious underlying condition.

**Rationale for the Exclusion Criteria**

(10, 13 – 29) To ensure the safety of subjects throughout the study.

(11, 12, 23) To avoid bias for the evaluation of safety by concomitant use of other medications.

(1 – 10) To exclude an inappropriate subject population.

**Has been changed to read:**

1. Prior history of prostate cancer with or without treatment.
2. Untreated retrograde ejaculation or anejaculation; history of prostatectomy with aspermia. Subjects with treated retrograde ejaculation will be allowed with approval of the Study Designated Physician.
3. Prior history of vasectomy unless subject has undergone reversed vasectomy.
4. (intentionally left blank; criterion deleted)
5. Currently symptomatic and receiving treatment for sexually transmitted disease (STD), prostatitis, orchitis or epididymitis.

6. (intentionally left blank; criterion deleted)
7. (intentionally left blank; criterion deleted)
8. Drug, alcohol or substance abuse within the 3 months prior to the initial screening visit.
9. Subject has had treatment with hormone suppressive agents, including androgens, estrogens, anabolic steroids, glucocorticoids, ketoconazole, cyclosporine, or cancer chemotherapy within the 6 months prior to the initial screening visit or planned during the study.
10. (intentionally left blank; criterion deleted)
11. Subject is currently receiving or has received hormone replacement therapy within the 6 months prior to the initial screening visit.
12. (intentionally left blank; criterion deleted)
13. (intentionally left blank; criterion deleted)
14. Renal transplant.
15. Subject has a history of severe peripheral edema or facial edema unrelated to trauma or a history of myxedema in the prior 4 weeks prior to the initial screening visit.
16. Subject has a history of pulmonary hypertension, pulmonary fibrosis or any lung diseases requiring oxygen therapy (e.g., chronic obstructive pulmonary disease, emphysema).
17. Subject has a documented diagnosis of heart failure, previous hospitalization for heart failure or current or constellation of symptoms (dyspnea on exertion, pedal edema, orthopnea, paroxysmal nocturnal dyspnea) felt to be compatible with heart failure, that was not explained by other causes, and for which there was a change in medication or other management directed at heart failure.

18. Subject has elevated liver enzymes (serum alanine aminotransaminase [ALT] and/or serum aspartate aminotransaminase [AST]) > 3 × the upper limit of normal (ULN) during the Screening Period.
19. Subject has a hemoglobin < 9 g/dL during the Screening Period.
20. Subject has a history of an allergic reaction or significant sensitivity to Atrasentan (or its excipients) or similar compounds.
21. Subject has significant comorbidities (e.g., advanced malignancy, advanced liver disease) with a life expectancy of less than 1 year.
22. Subject has clinically significant cerebrovascular disease (CVD) or coronary artery disease (CAD) within 3 months prior to the initial screening visit, defined as one of the following:
    - Hospitalization for Myocardial Infarction or unstable angina; or
    - New onset angina with positive functional study or coronary angiogram revealing stenosis; or
    - Coronary revascularization procedure; or
    - Transient ischemic attack (TIA) or stroke.
23. Subject has received any investigational drug within 3 months prior to the initial screening visit.
24. Subject is currently receiving rosiglitazone, moxonidine, aldosterone blockers, aliskiren or a combination of ACEi and ARB.
25. Subjects with known allergy to both thiazide and loop diuretics.
26. The subject is considered by the Investigator unsuitable to participate in the trial for any other reason, for instance due to a significant serious underlying condition.

**Rationale for the Exclusion Criteria**

(1 – 3, 5, 8, 26) To exclude an inappropriate subject population.

(9, 11) To avoid bias for the evaluation of safety by concomitant use of other medications.

(14 – 25) To ensure the safety of subjects throughout the study.

**Section 5.2.3 Prior and Concomitant Therapy**
**Previously read:**

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of Screening, or receives during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency.

If medically necessary, interruption of ACEi or ARB doses during the Treatment or Observational Periods of the study will be allowed. When returning to RASi therapy, the subject should return to the previous regimen of ACEi or ARB therapy that was prescribed prior to the interruption, although it will not be a requirement. Conversions from one product to another (e.g., ACEi to ARB) must be at equivalent doses. Combinations of ACEi/ARB medications and/or concomitant use of aldosterone blockers or aliskiren are not allowed.

Plasma levels of Atrasentan may be affected by concomitant use of CYP3A or OATP inhibitors (e.g., protease inhibitors, clarithromycin, ketoconazole, gemfibrozil, ciclosporin). Potent P-gp inhibitors may potentially increase the plasma exposure of Atrasentan. In addition, plasma levels of sensitive P-gp substrates (e.g., dabigatran) may be affected by concomitant use of Atrasentan. Caution should be used in patients taking any of these medications during the trial.

The AbbVie study designated physician should be contacted if there are any questions regarding concomitant or prior therapy(ies).

**Has been changed to read:**

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of Screening, or receives during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency.

The AbbVie study designated physician (listed in Section 6.5) should be contacted if there are any questions regarding concomitant or prior therapy(ies).

#### 5.2.3.1 Prior Therapy

Subjects currently using alpha blockers should have been on a stable dose for at least 2 weeks prior to the initial screening visit and must be on a stable dose during the study.

Subjects currently using 5-alpha reductase inhibitors should have been on a stable dose for at least 3 months prior to the initial screening visit and must be on a stable dose during the study.

#### 5.2.3.2 Concomitant Therapy

If medically necessary, changes to or interruption of ACEi or ARB doses during the Treatment or Observational Periods of the study will be allowed. Plasma levels of Atrasentan may be affected by concomitant use of CYP3A or OATP inhibitors (e.g., protease inhibitors, clarithromycin, ketoconazole, gemfibrozil, ciclosporin). Potent P-gp inhibitors may potentially increase the plasma exposure of Atrasentan. In addition, plasma levels of sensitive P-gp substrates (e.g., dabigatran) may be affected by concomitant use of Atrasentan. Caution should be used in patients taking any of these medications during the trial.

**Section 5.2.3.1 Prohibited Therapy**
**First paragraph, first sentence previously read:**

Subjects should not enter into the study if they have a documented history of receiving testosterone or hormone replacement therapy within 6 months of Screening.

**Has been changed to read:**

Subjects should not enter into the study if they are currently receiving or have received testosterone or hormone replacement therapy within 6 months of the initial screening visit.

**Section 5.2.3.1 Prohibited Therapy**
**Add: new third paragraph**

Combinations of ACEi/ARB medications and/or concomitant use of aldosterone blockers or aliskiren are not allowed.

**Section 5.2.3.1 Prohibited Therapy**
**Third paragraph previously read:**

Hot tub/Jacuzzi/sauna use are prohibited 12 weeks prior to Screening and during the study.

**Has been changed to read:**

Use of hot tub/Jacuzzi/sauna are prohibited during the study.

**Section 5.2.3.2 Guidance for Managing Edema or Weight Gain**
**First paragraph, first sentence previously read:**

Weight will be measured at each visit during the study, preferably using the same device and under the same circumstances (i.e., same time of the day, no shoes or coats during measurement).

**Has been changed to read:**

Weight will be measured at each visit during the Treatment Period of the study, preferably using the same device and under the same circumstances (i.e., same time of the day, no shoes or coats during measurement).

**Section 5.2.3.2 Guidance for Managing Edema or Weight Gain**
**Seventh paragraph previously read:**

If weight continues to increase (i.e., > 3 kg in 6 weeks or the previous visit during the Treatment Period), despite the modification in the doses of diuretics, contact the study designated physician for the study.

**Has been changed to read:**

If weight continues to increase (i.e., > 3 kg in 6 weeks or the previous visit during the Treatment Period) despite the modification in the doses of diuretics, contact the study designated physician.

**Section 5.2.4 Contraception Recommendations**
**Add: new section title and text**

### 5.2.4 Contraception Recommendations

If the male subject has a female partner who is postmenopausal or permanently sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy), no contraception is required.

If the subject is sexually active with female partner(s) of childbearing potential, he must agree from initial study drug administration through 90 days after the last dose of study drug to practice contraception with:

- Condom use and female partner(s) using at least one of the following contraceptive measures
  - Intrauterine device (IUD);
  - hormonal contraceptives (oral, vaginal, parenteral or transdermal);

- Barrier method (contraceptive sponge, diaphragm, or vaginal ring with spermicidal jellies or creams).

- True abstinence: refraining from sexual intercourse when this is line with the preferred and usual lifestyle of the subject. (Note: Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

Additionally, subject agrees not to donate sperm from initial study drug administration through 90 days after the last dose of study drug.

**Section 5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart**
**Add: new first paragraph**

Study procedures described in this protocol are summarized in Table 1.

## Table 1. Study Activities
## Previously read:

| Activity | Screening Period (–14 Days)[a] | Treatment Period[b] | | | | | | Observational Period[b] | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Screening | T1[c] (Day 1) | T2 (Week 2) | T3 (Week 4) | T4 (Week 6) | T5 (Week 13) | T6/EOT (Week 26)[m] | O1 (Week 6) | O2, O3, O4 (Weeks 13, 26, 39) | O5/End of Study[n] (Week 52) |
| Informed Consent[d] | X | | | | | | | | | |
| Medical History | X | X | | | | | | | | |
| Concurrent Medications | X | X | X | X | X | X | X | X | X | X |
| Complete Physical Exam | X | | | | | | X | | | |
| Vital Signs[e] | X | X | X | X | X | X | X | X | X | X |
| Semen Samples[f] | X | | | | X | X | X | X | X | X[g] |
| Assess Peripheral Edema | X | X | X | X | X | X | X | X | X | X |
| 12-Lead ECG | | X | | | | | X | | | |
| Hematology | X | X | | X | X | X | X | | X | X |
| Limited Chemistry | | | | X | X | | | | X | |
| Complete Chemistry | X | X | | | | X | X | | | X |
| Lipid Profile (fasting)[h] | | X | | | | X | X | | | |
| BNP | X | | | | X | | X | X | | |
| $HbA_{1c}$ | X | | | | | | X | | | X |
| Urinalysis | X | | | | | | X | | | X |

| Activity | Screening Period (–14 Days)[a] | Treatment Period[b] | | | | | | Observational Period[b] | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Screening | T1[c] (Day 1) | T2 (Week 2) | T3 (Week 4) | T4 (Week 6) | T5 (Week 13) | T6/EOT (Week 26)[m] | O1 (Week 6) | O2, O3, O4 (Weeks 13, 26, 39) | O5/End of Study[n] (Week 52) |
| FMV Urine Collection for UACR[i] | X | | | | | | X | X | | |
| Serum total T, estradiol, LH, FSH, inhibin B[j] | X | | | X | X | X | X | X | X | X |
| IVRS Call | X | X | | | | X | X | | | |
| Monitor AEs and SAEs[k] | X | X | X | X | X | X | X | X | X | X |
| PK Analysis[l] | | | | X | X | X | | | | |
| Drug Accountability/ Compliance Assessment | | | X | X | X | X | X | | | |

a. Screening procedures and laboratory tests may be repeated during the Screening Period, per the Investigator's discretion. Semen samples may be repeated per Section 5.3.2.5.

b. All Treatment and Observation Period visits must be completed be completed with + 5/–0 days of the expected visit date.

c. Day 1 should be completed within 14 days from initial screening assessments or screening laboratory assessments must be repeated.

d. Informed consent can be collected up to 30 days prior to Screening. Informed consent should be obtained prior to performing any study procedures.

e. Vital signs include BP, weight, temperature and pulse rate will be collected at every visit. Height will be collected at initial Screening visit only. Weight gain will be assessed at each visit. Resting BP will be measured two times in the non-dominant arm using the appropriate cuff size at least 2 minutes apart.

f. Two samples should be collected within a 7-day period, with each sample separated by at least 2 days. Subject must abstain from ejaculation 2 days but no more than 7 days prior to collection. For Screening, subjects will be scheduled for the duplicate semen collections to be completed within the 14 day Screening Period and adhering to the specific windows for semen collection noted in Section 5.3.2.1. If Day 1 is not completed within 14 days from the second screening semen sample, the screening semen collections must be repeated.

g. Subjects completing the End of Study visit after returning to sperm concentration baseline (± 15%) during the Observational Period will not provide a semen sample during the EOS visit.

h. Lipid profile tests will be done under fasting conditions.

i. For Screening, subjects will be given supplies and instructions for the two consecutive FMV urine collections, which should be collected and returned to the study site within the 14-day Screening Period. For Treatment and Observation visits, the first morning void (FMV) urine collection will consist of one first morning void sample collected within 1 day of the visit.

j. Total testosterone sample should be collected at approximately the same time of day at each visit.

k. Only serious adverse events (SAEs) will be collected from informed consent until Day 1. All adverse events (serious and nonserious) will be captured beginning the time of informed consent through 30 days after the last dose of study drug. For subjects entering the Observational Period, protocol-related adverse events (serious and nonserious) will be collected beginning 30 days after the last dose of study drug through the End of Study.

l. Blood samples only to be collected for Atrasentan PK analysis and possible metabolites of atrasentan at the following visits: T3 (immediately before dose and 15 minutes, 30 minutes, 1 hour post dose), T4 (immediately before dosing), T5 (immediately before dosing).

m. All subjects should be contacted 30 to 35 days after the last dose of study drug to solicit AEs and SAEs. For subjects not entering the Observational Period, this contact will be the final study contact.

n. During the Observational Period, when subjects return to their baseline sperm concentration value (± 15%), they will return within 14 days for the End of Study visit.

**Has been changed to read:**

| Activity | Screening Period (Up to 4 Weeks)[a] | Treatment Period[b] | | | | | | Observational Period[b,c] | | | FU Contact[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | T1[e] (Day 1) | T2 (Week 2) | T3 (Week 4) | T4 (Week 6) | T5 (Week 13) | T6/EOT (Week 26)[f] | O1 (Week 13) | O2, O3 (Weeks 26, 39) | O4/End of Study (Week 52) | |
| Informed Consent[g] | X | | | | | | | | | | |
| Medical History | X | X[h] | | | | | | | | | |
| Concomitant Medications | X | X | X | X | X | X | X | X | X | X | X |
| Complete Physical Exam | | X | | | | | X | | | | |
| Vital Signs[i] | X | X | X | X | X | X | X | X | X | X | |
| Semen Sample Collection[j] | X | | | | | X | X | X | X | X | |
| Assess Peripheral Edema | X | X | X | X | X | X | X | | | | |
| 12-Lead ECG | | X | | | | | X | | | | |
| Hematology | X | X | | X | X | X | X | X | X | X | |
| Limited Chemistry | | | | X | X | | | | | | |
| Complete Chemistry | X | X | | | | X | X | X | X | X | |
| BNP | X | | | | X | | X | | | | |
| $HbA1_c$ | X | | | | | | X | X | | | |
| Urinalysis | X | | | | | | X | X | | | |
| FMV Urine Collection for UACR[k] | X | | | | | | X | | | | |
| Serum total T, estradiol, LH, FSH, inhibin B[l] | X | X | | X | X | X | X | X | X | X | |
| IVRS Call | X | X | | | | X | X | | | | |

| Activity | Screening Period (Up to 4 Weeks)[a] | Treatment Period[b] | | | | | | Observational Period[b,c] | | | FU Contact[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | T1[e] (Day 1) | T2 (Week 2) | T3 (Week 4) | T4 (Week 6) | T5 (Week 13) | T6/EOT (Week 26)[f] | O1 (Week 13) | O2, O3 (Weeks 26, 39) | O4/End of Study (Week 52) | |
| Monitor AEs and SAEs[m] | X | X | X | X | X | X | X | X | X | X | X |
| PK Analysis[n] | | | | X | X | X | | | | | |
| Dispense Study Drug | | X | | | | X | | | | | |
| Drug Accountability/Compliance Assessment | | | X | X | X | X | X | | | | |

a. Screening procedures and laboratory tests may be repeated during the Screening Period, per the Investigator's discretion. Semen samples may be repeated per Section 5.3.2.5.

b. All Treatment and Observational Period visits must be completed within ± 7 days of the expected visit date.

c. If at any time during the Observational Period, the sperm concentration returns to within 15% of baseline or above, subjects will have completed their participation in the Observational Period. The visit at which their sperm concentration returned to within 15% of baseline or above will be considered their End of Study visit.

d. Subjects not entering the Observational Period should be contacted by the Principal Investigator (or designee) 30 – 35 days after the last dose of study drug. Subjects who have returned to within 15% of their baseline sperm concentration or above during the Observational Period should be contacted by the Principal Investigator (or designee) within 14 days of the collection of the second semen sample.

e. The T1/Day 1 visit should be completed within 4 weeks from the initial screening visit.

f. Subjects completing the End of Treatment Visit because their sperm concentration has dropped below 15 million/mL during the Treatment Period will not provide duplicate semen samples at the T6/EOT visit.

g. Informed consent can be collected up to 30 days prior to conduct of initial study procedures.

h. Updates only.

i. Vital signs include BP, weight, temperature and pulse rate will be collected at every visit. Height will be collected at initial Screening visit only. Weight gain will be assessed at each visit during the Treatment Period.

j. Subjects will be scheduled for the collection of the duplicate semen samples according to the specific windows for semen collection noted in Section 5.3.2.5.

k. For Screening, subjects will be given supplies and instructions for the FMV urine collection, which should be collected and returned to the study site within the 4-week Screening Period. For the T6/EOT visit, the first morning void (FMV) urine collection will be collected within 1 day before the visit.

l. Total testosterone sample should be collected at approximately the same time of day at each visit.

m. Protocol-related non-serious and serious adverse events (SAEs) will be collected from the time the subject signs the study-specific informed consent. All adverse events (serious and nonserious) will be captured from the time of study drug administration through 30 days after the last dose of study drug. For subjects entering the Observational Period, protocol-related non-serious and serious adverse events will be collected beginning 30 days after the last dose of study drug through the post-therapy Observational Period.

n. Blood samples only to be collected for atrasentan PK analysis and possible metabolites of atrasentan at the following visits: T3/Week 4 (immediately before dose and 15 minutes, 30 minutes, 1 hour post dose), T4/Week 6 (immediately before dosing) and T5/Week 13 (immediately before dosing).

**Section 5.3.1.1 Study Procedures**
**Subsection Informed Consent**
**First sentence previously read:**

A signed informed consent will be obtained from the patient before any study procedures are undertaken at the Screening visit.

**Has been changed to read:**

A signed informed consent will be obtained from the patient before any study procedures are undertaken at the initial screening visit.

**Section 5.3.1.1 Study Procedures**
**Subsection Medical History**
**First paragraph, first sentence previously read:**

A complete medical history, including history of tobacco and alcohol use and colonoscopy history, will be obtained from each patient during the initial Screening visit and updated during the Screening Period and Day 1 visit, as necessary.

**Has been changed to read:**

A complete medical history, including history of tobacco and alcohol use and colonoscopy history, will be obtained from each patient during the initial Screening visit and updated during the Screening Period and at the T1/Day 1 visit, as necessary.

**Section 5.3.1.1 Study Procedures**
**Subsection Physical Examination**
**First paragraph, first sentence previously read:**

A complete physical examination will be performed at the Screening visit (baseline) and the T6/EOT visit.

**Has been changed to read:**

A complete physical examination will be performed at the T1/Day 1 visit (baseline) and the T6/EOT visit.

**Section 5.3.1.1 Study Procedures**
**Subsection Vital Signs**
**First, second, and third sentence previously read:**

Vital sign determination of sitting BP, weight, temperature and pulse rate will be obtained at all visits. Vital signs performed at the Day 1 visit will serve as the baseline. Weight gain will be assessed at every visit.

**Has been changed to read:**

Vital sign determination of sitting BP, weight, temperature and pulse rate will be obtained at all on-site visits. Vital signs performed at the T1/Day 1 Visit will serve as the baseline. Weight gain will be assessed at every visit during the Treatment Period.

**Section 5.3.1.1 Study Procedures**
**Subsection Assessment of Edema**
**First paragraph, first sentence previously read:**

Assessment of edema will be performed at every visit.

**Has been changed to read:**

Assessment of edema will be performed at Screening and at every Treatment Visit.

**Section 5.3.1.1 Study Procedures**
**Subsection 12-Lead Electrocardiogram (ECG)**
**Previously read:**

A 12-lead resting ECG will be obtained at the Day 1 visit and the T6/EOT visit. The ECG measurements at the Day 1 visit will serve as the baseline measurements for clinical assessment.

**Has been changed to read:**

A 12-lead resting ECG will be obtained at the T1/Day 1 visit prior to initial dose of study drug and at the T6/EOT visit. The ECG measurements at the T1/Day 1 visit will serve as the baseline measurements for clinical assessment.

**Section 5.3.1.1 Study Procedures**
**Subsection First Morning Void (FMV) Urine Sample Collection**
**First paragraph, first, second, and third sentence previously read:**

Two first morning void urine collections will be obtained during the Screening Period. One first morning void urine sample will be obtained prior to the T6 (EOT) and O1 visits. The first morning void is defined as the subject's first void after 5:00 AM.

**Has been changed to read:**

One first morning void urine collection will be obtained during the Screening Period, and prior to the T6/EOT visit. The first morning void is defined as the subject's first void after 5:00 AM or upon rising for the day.

**Section 5.3.1.1 Study Procedures**
**Subsection Safety Contact**
**Delete: subsection title and text**

**Safety Contact**

All subjects should be contacted 30 – 35 days after the last dose of study drug to solicit adverse events (serious and nonserious).

**Section 5.3.1.1 Study Procedures**
**Subsection Randomization and Assignment of Subject Numbers**
**Delete: subsection title and text**

**Randomization and Assignment of Subject Numbers**

All inclusionary screening laboratory results must be reviewed prior to registering the subject for treatment in IVRS/IWRS. At the Screening visit, each subject will be assigned a unique 4-digit subject number by the IVRS/IWRS. The first 2 digits will be the site number (i.e., 10 to 99), the third and fourth digits will be assigned in ascending numerical order at each site.

**Section 5.3.1.1 Study Procedures**
**Subsection Laboratory Tests**
**Previously read:**

Samples will be obtained for the laboratory tests listed in Table 2 at the visits specified in Table 1. Blood draws should be performed after vital sign determinations have been completed for each visit.

The CKD-EPI formula will be used to calculate eGFR at the Screening visit to determine eligibility for the study.

One hormone measurement will be taken at each visit as noted in Table 1. The testosterone sample should be collected at approximately the same time of the day at each visit.

A central laboratory will be utilized for the clinical laboratory tests. Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory chosen for this study.

The Investigator will review all laboratory test results in a timely manner. All laboratory test results that are considered clinically significant by the Investigator will be followed to a satisfactory resolution.

**Table 2. Clinical Laboratory Tests**

| **Hematology** | **Clinical Chemistry** | **Urinalysis** |
|---|---|---|
| Hematocrit<br>Hemoglobin<br>Red Blood Cells (RBC)<br>White Blood Cells (WBC)<br>Neutrophils<br>Bands<br>Lymphocytes<br>Monocytes<br>Basophils<br>Eosinophils<br>Platelet count (estimate not acceptable) | Albumin<br>Alkaline phosphatase<br>ALT (SGPT)<br>AST (SGOT)<br>Bicarbonate<br>Blood Urea Nitrogen (BUN)<br>Calcium<br>Cystatin C<br>Potassium<br>Chloride<br>Cholesterol*<br>Creatinine<br>Direct Bilirubin<br>Glucose*<br>HDL*<br>Insulin (HOMA-IR)*<br>LDH<br>Lipoprotein A*<br>LDL*<br>Phosphorus<br>Sodium<br>Total bilirubin<br>Total protein<br>Triglycerides*<br>Uric acid<br>VLDL* | Blood<br>Glucose<br>Ketones<br>pH<br>Protein<br>Specific gravity |
| **Limited Chemistry** | | **Urine Tests** |
| Sodium<br>Albumin<br>Potassium<br>Bicarbonate<br>Creatinine<br>Chloride<br>BUN | | First morning void urine:<br>UACR,<br>sodium,<br>potassium,<br>chloride, urea nitrogen |
| | | **Additional Tests** |
| | | BNP<br>Pharmacokinetic measurement<br>$HbA_{1c}$<br>Serum total T<br>Estradiol<br>LH<br>FSH<br>Inhibin B |

* Lipid and metabolic profile tests (obtained under fasting conditions).

**Has been changed to read:**

A central laboratory will be utilized for the clinical laboratory tests. Samples will be obtained for the laboratory tests listed in Table 2 at the visits specified in Table 1. Blood draws should be performed after vital sign determinations have been completed for each visit.

The Investigator will review all laboratory test results in a timely manner. All laboratory test results that are considered clinically significant by the Investigator will be followed to a satisfactory resolution.

Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory chosen for this study.

**Table 2. Clinical Laboratory Tests**

| **Hematology** | **Clinical Chemistry** | **Urinalysis** |
|---|---|---|
| Hematocrit<br>Hemoglobin<br>Red Blood Cells (RBC)<br>White Blood Cells (WBC)<br>Neutrophils<br>Bands<br>Lymphocytes<br>Monocytes<br>Basophils<br>Eosinophils<br>Platelet count (estimate not acceptable) | Albumin<br>Alkaline phosphatase<br>ALT (SGPT)<br>AST (SGOT)<br>Bicarbonate<br>Blood Urea Nitrogen (BUN)<br>Calcium<br>Potassium<br>Chloride<br>Cholesterol<br>Creatinine<br>Direct Bilirubin<br>Glucose<br>LDH<br>Phosphorus<br>Sodium<br>Total bilirubin<br>Total protein<br>Triglycerides<br>Uric acid | Blood<br>Glucose<br>Ketones<br>pH<br>Protein<br>Specific gravity |
| **Limited Chemistry** | | **Urine Tests** |
| Sodium<br>Albumin<br>Potassium<br>Bicarbonate<br>Creatinine<br>Chloride<br>BUN | | First morning void urine:<br>UACR |
| | | **Additional Tests** |
| | | BNP<br>Pharmacokinetic measurement<br>$HbA_{1c}$<br>Serum total T*<br>Estradiol<br>LH<br>FSH<br>Inhibin B |

* The testosterone sample should be collected at approximately the same time of the day at each visit.

The CKD-EPI formula will be used to calculate eGFR at the Screening visit to determine eligibility for the study. The central laboratory will also calculate the eGFR on the laboratory profile report at each visit during the Treatment and Observational Periods.

**Section 5.3.2.1 Blood Samples for Pharmacokinetic Analysis**
**Section title previously read:**

Blood Samples for Pharmacokinetic Analysis

**Has been changed to read:**

Collection of Samples for Pharmacokinetic Analysis

**Section 5.3.2.1 Blood Samples for Pharmacokinetic Analysis**
**First paragraph previously read:**

For all subjects, blood samples for assay of Atrasentan and possible metabolites of Atrasentan will be collected by venipuncture into a 4 mL evacuated K2 EDTA containing collection tube at the T3 (Week 4) visit at immediately prior to dose and 15 minutes, 30 minutes and 1 hour post dose and at the T4 (Week 6) visit and the T5 (Week 13) immediately before dosing.

**Has been changed to read:**

For all subjects, blood samples for assay of Atrasentan and possible metabolites of Atrasentan will be collected by venipuncture into a 4 mL evacuated K2 EDTA containing collection tube at the T3 (Week 4) visit at immediately prior to dose and 15 minutes, 30 minutes and 1 hour post dose and at the T4 (Week 6) visit immediately before dosing and the T5 (Week 13) immediately before dosing.

**Section 5.3.2.1 Blood Samples for Pharmacokinetic Analysis**
**Second paragraph, last sentence previously read:**

The date and time that each blood sample will be noted and the date and time of the two previous doses of study drug will be recorded to the nearest minute on the appropriate eCRF.

**Has been changed to read:**

The date and time of collection of each blood sample will be noted and the date and time of the two previous doses of study drug will be recorded to the nearest minute on the appropriate eCRF.

**Section 5.3.2.5 Collection of Semen Samples for Analysis**
**Previously read:**

Samples will be obtained for the tests listed in Table 3 at the time-points specified in Table 1. Duplicate semen samples should be collected at each time-point over a 7-day period with each sample being separated by at least 2 days. If for any reason one of the duplicate samples is inadequate or not obtained, then a replacement sample will be collected to ensure that two samples are available for each time-point. If clinically relevant confounding symptoms, illness or conditions are suspected, a replacement sample/samples may be obtained at the investigator's discretion. All semen samples for a time-point must be collected within a 14-day period. Subjects must abstain from ejaculation for at least 2 days but not more than 7 days prior to semen sample collection. The average of the 2 semen samples will be used as the value for that time-point. Samples should be collected at the required visits after all study procedures have been completed. Semen sample will be sent for processing as soon as possible after collection. Semen motility analysis should be started with 1 hour of sample collection. The full ejaculate must be captured at each semen collection. Subjects should be evaluated, per the site's standard procedure, for retrograde ejaculation if the full ejaculate is < 1.0 mL. The Study Designated Physician should be consulted if retrograde ejaculation is identified or diagnosed at any time during the study. If the full ejaculate is not captured in the collection container, then a replacement specimen should be collected.

**Has been changed to read:**

Semen samples will be obtained for the tests listed in Table 3 during the scheduled collection period for the visits specified in Table 1. Semen samples should be collected at 2 time-points over a 7-day period with each sample being separated by at least 2 days. If for any reason one of the duplicate samples is inadequate or not obtained, then a replacement sample will be collected to ensure that two samples are available for each scheduled collection period. If clinically relevant confounding symptoms, illness or conditions are suspected, replacement sample/samples may be obtained at the investigator's discretion. All semen samples for a scheduled collection period must be

collected within 14 days of the collection of the first semen sample. Subjects must abstain from ejaculation for at least 2 days but not more than 7 days prior to semen sample collection. The average of the 2 semen samples will be used as the value for that collection period. If the semen sample is collected at the scheduled study visit, the sample should be obtained after all study procedures have been completed.

The semen sample will be sent for processing as soon as possible after collection. Semen motility analysis should be started with 1 hour of sample collection. The full ejaculate must be captured at each semen collection. Subjects should be evaluated, per the site's standard procedure, for retrograde ejaculation if the full ejaculate is < 1.0 mL. The Study Designated Physician should be consulted if retrograde ejaculation is identified or diagnosed at any time during the study. If the full ejaculate is not captured in the collection container, then a replacement specimen should be collected.

**Section 5.3.2.6 Handling/Processing of Samples**
**Previously read:**

Detailed instructions regarding collection and preparation of the semen samples will be provided by the local laboratory processing the semen specimen. The specimen container should be kept at ambient temperature, between 30° and 37°C, to avoid temperature changes that may affect the spermatozoa. It must be labeled, per the instructions provided by the morphology laboratory, with the subject's initials, subject number, study visit, sample identifier, and the date and time of collection.

**Has been changed to read:**

Detailed instructions regarding collection and preparation of the semen samples will be provided by the local laboratory processing the semen specimen. The specimen container should be kept at ambient temperature, between 30° and 37°C, to avoid temperature changes that may affect the spermatozoa.

The local laboratory processing the semen specimens will analyze the samples for volume, concentration and motility following their standard operating procedures, and

will prepare 4 slides for morphology analysis to be conducted by the central morphology laboratory (Tulane Andrology Laboratory). Written instructions on preparation and fixing of sperm morphology slides and shipment to the central morphology laboratory will be provided to the site semen analysis laboratory. Slides must be labeled, per the instructions provided by the morphology laboratory, with the subject's initials, subject number, study visit, sample identifier, and the date and time of collection.

Morphology slides will be sent for morphology analysis to:

Tulane Andrology Laboratory
1430 Tulane Ave., SL-42; [redacted]
New Orleans, LA 70112-2699
United States

**Section 5.3.4.1 Primary Safety Variable**
**Previously read:**

The proportion of subjects who have a sperm concentration $< 15 \times 10^6$/mL by 26 weeks.

**Has been changed to read:**

The primary safety variable is the proportion of subjects who have a sperm concentration $< 15 \times 10^6$/mL during the 26-week Treatment Period.

**Section 5.3.4.2 Secondary Safety Variables**
**First bullet list**
**First bullet previously read:**

The proportion of subjects who enter the Observation Period and do not return to within 15% of baseline by 52 weeks after treatment discontinuation.

**Has been changed to read:**

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.

**Section 5.3.4.2 Secondary Safety Variables**
**First bullet list**
**Third bullet previously read:**

Change from baseline to each visit in each of the components of the semen analysis (sperm motility, sperm morphology, sperm concentration, semen volume).

**Has been changed to read:**

Change from baseline to each visit in each of the components of the semen analysis (sperm motility, sperm morphology, sperm count, semen volume).

**Section 5.3.4.2 Secondary Safety Variables**
**First paragraph, first sentence previously read:**

Safety data will be analyzed for the data collected throughout Treatment Period and up to 30 days post-treatment.

**Has been changed to read:**

Safety data will be analyzed for the data collected throughout Treatment Period and up to 35 days post-treatment.

**Section 5.4.1 Discontinuation of Individual Subjects**
**Previously read:**

Subjects will be discontinued from study drug immediately if any of the following events occur:

- Subject has a weight gain of > 3 kg compared to T1/Day 1 AND a BNP of > 300 ng/L at the T4 (Week 6) visit.
- Subject has an **increase in serum creatinine** > 0.5 mg/dL (> 48 umol/L) **AND > 20% increase** from baseline at the T4 (Week 6) visit.
- Clinically significant deterioration of the subject's medical status that is thought to possibly or probably be related to study drug by the Investigator.
- The subject requests withdrawal from the study.

- Investigator request (for any reason).
- Achievement of the primary study endpoint (sperm concentration sperm concentration < $15 \times 10^6$/mL).
- ESRD as defined by confirmed eGFR < 15 mL/min/1.73 $m^2$.
- Subject is lost to follow-up.

If the subject is permanently discontinued from study drug, the procedures outlined for the T6/End of Treatment visit must be completed within 5 days (±2 days) of the last dose of study drug. Following discontinuation of the study drug, the subject will continue to be monitored until sperm concentration returns to baseline (±15%) or through the O5/EOS visit, whichever occurs first unless the subject withdraws consent.

Subjects who prematurely discontinue from the Treatment Period will not be replaced unless the discontinuation rate exceeds 25% in the Treatment Period. Subjects may be added to ensure that 15 evaluable subjects are assessed.

If the subject is permanently discontinued from the Observation Period, the procedures outlined for the O5/End of Study visit must be completed within 5 days (± 2 days) of the discontinuation. The date and reason for premature discontinuation in either period will be recorded in the subject's source documents and on the appropriate eCRF.

**Has been changed to read:**

Subjects will be discontinued from study drug immediately if any of the following events occur:

- Clinically significant deterioration of the subject's medical status that is thought to possibly or probably be related to study drug by the Investigator.
- The subject requests withdrawal from the study.
- Investigator request (for any reason).
- Achievement of the primary study endpoint (sperm concentration < $15 \times 10^6$/mL).
- Chronic dialysis or renal transplant.

- Subject is lost to follow-up.

If the subject is permanently discontinued from study drug and does not meet the criteria to enter the Observational Period, the procedures outlined for the T6/End of Treatment visit must be completed 5 days (± 3 days) of the last dose of study drug. Additionally, the subject will be contacted by the Investigator (or designee) approximately 30 to 35 days after their last dose of study drug.

If the subject meets the criteria to enter the Observational Period during the Treatment Period, the subject will permanently discontinue from study drug and the procedures outlined for the T6/End of Treatment visit should be completed 5 days (± 3 days) of the last dose of study drug. Following discontinuation of the study drug, the subject will continue to be monitored during the Observational Period until sperm concentration returns to within 15% of baseline or above, or through the O4/EOS visit, whichever occurs first unless the subject withdraws consent.

Subjects who prematurely discontinue from the Treatment Period for other reasons than achievement of the primary study endpoint, will not be replaced unless the discontinuation rate exceeds 25% in the Treatment Period. Subjects may be added to ensure that 15 evaluable subjects are assessed.

If the subject is permanently discontinued from the Observational Period for other reasons than returning to within 15% of their baseline sperm concentration or above, the procedures outlined for the O4/End of Study visit must be completed 5 days (± 3 days) of the discontinuation.

The date and reason for premature discontinuation in either period will be recorded in the subject's source documents and on the appropriate eCRF.

**Section 5.5.1 Treatments Administered**
**Previously read:**

Each subject will receive 0.75 mg Atrasentan once daily for 26 weeks.

**Has been changed to read:**

Each subject will receive 0.75 mg Atrasentan once daily for up to 26 weeks.

**Table 4. Identity of Investigational Products**
**Delete: table note**

Note: All tablets will be identical in appearance.

**Section 5.5.2.2 Storage and Disposition of Study Drugs**
**Previously read:**

The study drug must be stored between (15° to 25°C/59° to 77°F), in the supplied bottle which contains a desiccant. Desiccant canister should be returned to the bottle directly after each tablet removal. The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or returned to AbbVie.

**Has been changed to read:**

The study drug must be stored between (15° to 25°C/59° to 77°F), in the supplied bottle which contains a desiccant. Desiccant canister should be returned to the bottle directly after each tablet removal. Each clinical site should have a temperature recording device in the drug storage area. A temperature log is to be maintained to document proper storage conditions. The temperature must be recorded every business day. If the storage temperature falls outside the allowed range, the excursion must be reported immediately, either by contacting AbbVie directly, or through the ATEMS module of the IVRS/IWRS system. In the event of a temperature excursion, affected study drug should be quarantined and should not be dispensed until notification of the final assessment and disposition is received.

The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label

until dispensed for subject use, destroyed at the site according to local regulations and instructions from AbbVie or returned to AbbVie or a local depot for destruction.

**Section 5.5.3 Method of Assigning Subjects to Treatment Groups**
**Second sentence previously read:**

Subjects meeting entry criteria will be will be centrally registered using an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS).

**Has been changed to read:**

Subjects meeting entry criteria will be centrally registered using an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS).

**Section 5.5.6 Treatment Compliance**
**Delete: third, fourth, and fifth paragraph**

To calculate compliance per bottle at each visit:

[(# of tablets dispensed – # of tablets returned)/# of days from previous visit] * 100% = Compliance

Note: The previous visit should be included in the count when calculating number of days from previous visit. The current visit should not be included in the count when calculating the number of days from previous visit.

**Section 5.6.1 Discussion of Study Design and Choice of Control Groups**
**Add: new paragraph**

This study is designed to assess the effects of Atrasentan on spermatogenesis and testicular function during treatment period and up to 52 weeks follow-up. The open-label design is chosen for this study because no change in spermatogenesis or testicular function is expected without treatment in healthy volunteers.

**Section 5.6.3 Suitability of Subject Population**
**Add: new first and second paragraph**

The purpose of this study is to assess the effects of Atrasentan on spermatogenesis and testicular function by assessing sperm concentration in subjects with Type 1 or 2 diabetes and nephropathy who are also being treated with a RAS inhibitor.

Therefore, subjects who have been treated with a RAS inhibitor (ACEi or ARBs), who have an estimated GFR ≥ 35 mL/min/1.73 $m^2$ with the CKD-EPI formula and UACR ≥ 30 to < 5,000 mg/g creatinine (≥ 3.4 mg/mmol and < 565 mg/mmol) with sperm and testosterone levels within normal ranges have been selected as the target population. Subjects who have underlying diseases/conditions and/or on medications affecting spermatogenesis or testicular function, history of allergic reaction or significant sensitivity to atrasentan or drugs similar to the study drug will be excluded to avoid confounding factors related to the effects being studied.

**Section 5.6.4 Selection of Doses in the Study**
**Add: new first and second paragraph**

The dose of 0.75 mg was selected following analysis of the results of the Phase 2b trials. The rationale for selecting a single dose of Atrasentan is based on the narrow therapeutic index of this drug and the need to balance the efficacy in reducing albuminuria with the safety and blood pressure change parameters. Subjects that enroll in the study will receive 0.75 mg QD of Atrasentan for up to 26 weeks during theTreatment Period.

Dose selection for the Phase 2b studies was based on the exposure-response analyses and clinical results from Study M10-815. Statistically significant exposure-response relationships for both the efficacy (UACR reduction) and the incidence of edema were then quantified from all Phase 2 studies. The simulations showed that a proportion of subjects achieving a 40% reduction in UACR increase with increasing dose from 0.25 mg per day approximately reaching a nadir in the range of 0.75 to 1.25 mg per day dose. The simulations, however, also showed that the probability of edema increases with increasing atrasentan exposure with predicted incidences of 32% and 38% at a dose of 1.25 mg and

1.5 mg per day. Although a slightly higher efficacy is predicted at doses greater than 1.25 mg per day, the predicted rate of edema is higher at these doses.

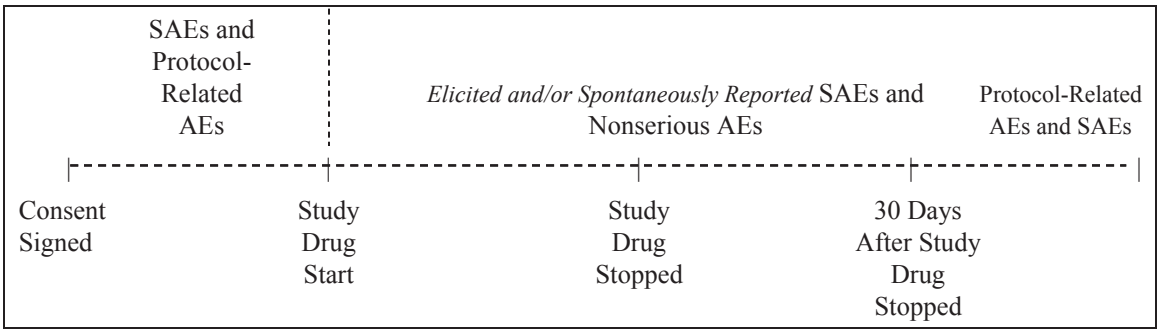
**Section 6.4 Adverse Event Collection Period**
**First paragraph previously read:**

All serious adverse events and protocol-related nonserious adverse events will be collected from the signing of the study specific informed consent until study drug administration. All adverse events (nonserious and serious) reported from the time of study drug administration until 30 days following discontinuation of study drug administration have elapsed will be collected, whether solicited or spontaneously reported by the subject. In addition, protocol-related nonserious and serious adverse events will be collected through the post-therapy Observational Period.

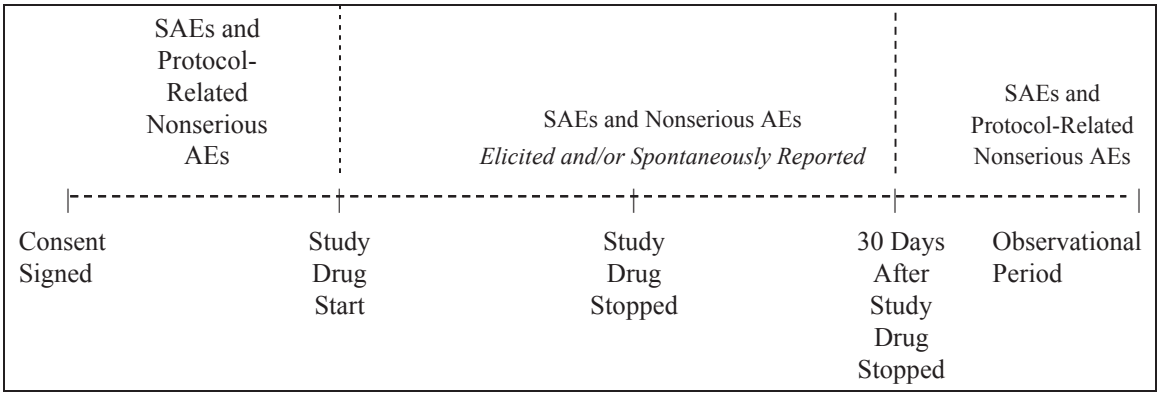
**Has been changed to read:**

All adverse events reported from the time of study drug administration until 30 days following discontinuation of study drug administration have elapsed will be collected, whether solicited or spontaneously reported by the subject. In addition, protocol-related nonserious and serious adverse events will be collected from the time the subject signed the study-specific informed consent through the post-therapy Observational Period.

**Figure 2. Adverse Event Collection**
**Previously read:**



**Has been changed to read:**




**Section 6.5 Adverse Event Reporting**
**First paragraph, last sentence previously read:**

Serious adverse events that occur prior to the site having access to the RAVE® system or if RAVE is not operable should use the SAE Non-CRF paper forms and fax to Clinical Pharmacovigilance within 24 hours of being made aware of the serious adverse event.

**Has been changed to read:**

Serious adverse events that occur prior to the site having access to the RAVE® system or if RAVE is not operable, should be documented on the SAE Non CRF paper forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of being made aware of the serious adverse event.

**Section 6.5 Adverse Event Reporting**
**Contact box previously read:**

| |
|---|
| **FAX to:** [redacted] |
| **Email:** [redacted] |

**Has been changed to read:**

| |
|---|
| **Email:** [redacted] |
| **FAX to:** [redacted] |

**Section 6.5 Adverse Event Reporting**
**"Primary Study Designated Physician:"**
**Title previously read:**

Associate Medical Director

**Has been changed to read:**

Medical Director

**Section 6.5 Adverse Event Reporting**
**Fourth paragraph previously read:**

In case of subject safety concerns or medical emergencies and the Primary Study Designated Physician is unavailable, please call the following central back-up number:

**Has been changed to read:**

In emergency situations involving study subjects when the Study Designated Physician is unavailable, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated back-up AbbVie Renal Medical Director.

**Section 6.6 Pregnancy**
**Second paragraph previously read:**

Information regarding a pregnancy occurrence in a study subject partner and the outcome of the pregnancy will be collected.

**Has been changed to read:**

In the event of pregnancy occurring in the partner of an enrolled subject, written informed consent for release of medical information from the partner must be obtained prior to the collection of any pregnancy-specific information and the pregnancy will be followed to outcome.

**Section 7.0 Protocol Deviations**
**Contact information previously read:**

Primary Contact: Alternate Contact:

**Has been changed to read:**

Primary Contact: Alternate Contact:

**Section 8.1 Statistical and Analytical Plans**
**First paragraph previously read:**

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

**Has been changed to read:**

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.

**Section 8.1 Statistical and Analytical Plans**
**Second paragraph, third sentence previously read:**

Approximately 20 subjects (to complete 15 evaluable subjects) with diabetic nephropathy who are taking RAS inhibitors are planned to be enrolled in the study at approximately 10 sites.

**Has been changed to read:**

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

**Section 8.1 Statistical and Analytical Plans**
**Third paragraph previously read:**

In the Treatment Period, semen samples will be collected at Screening (baseline), T4 (Week 6), T5 (Week 13), and T6/EOT (Week 26). Duplicate samples will be collected at each visit over a 7-day period with each sample being separated by at least 2 days. The average of the 2 samples will be used as the value for that visit. Inadequate or missed semen samples can be made up within 14 days of the initial semen sample from that time-point. In the Observational Period, semen samples will be collected at 6 and

13 weeks after the last dose of study drug then every 13 weeks thereafter until all values have returned to baseline (± 15%) or until the end of the Observational Period, whichever occurs earlier.

**Has been changed to read:**

In the Treatment Period, semen samples will be collected at Screening (baseline), T5 (Week 13) and T6/EOT (Week 26). Semen samples will be collected at 2 time-points over a 7-day period with each sample being separated by at least 2 days. The average of the 2 samples will be used as the value for that scheduled collection period. Inadequate or missed semen samples can be made up within 14 days of the initial semen sample for that collection period. In the Observational Period, semen samples will be collected according to the specific windows for semen collection (Section 5.3.2.1), starting at the O1 (Week 13) visit and then every 13 weeks thereafter until the sperm concentration has returned to within 15% of baseline or above, or until the end of the 52-week Observational Period, whichever occurs earlier.

**Section 8.1 Statistical and Analytical Plans**
**Subsection General Considerations**
**First paragraph previously read:**

Treatment effects will be evaluated based on a 2-sided significance level of 0.200 (when rounded to 3 decimal places).

**Has been changed to read:**

Treatment effects will be evaluated based on a 2-sided 80% exact confidence interval.

**Section 8.1.1 Analysis Datasets**
**Subsection Evaluable Set**
**First paragraph previously read:**

A subject will be considered evaluable if the following is satisfied: (1) the Overall Study Drug compliance status = YES; and (2) completes the 26-week treatment period and has

all planned sperm samples collected; or has sperm concentration value less than 15 million/mL observed prior to the end of Treatment Period.

**Has been changed to read:**

A subject will be considered evaluable if the following is satisfied: (1) the Overall Study Drug compliance status is ≥ 70%; and (2) completes the 26-week treatment period and has all planned sperm samples collected; or has sperm concentration value less than 15 million/mL observed by the end of Treatment Period.

**Section 8.1.3 Safety Analyses**
**Subsection <u>Study Drug Exposure and Compliance</u>**
**First sentence previously read:**

The duration of study drug exposure and average daily dose will be summarized for safety analyses set.

**Has been changed to read:**

The duration of study drug exposure and the average daily dose will be summarized for safety analyses set.

**Section 8.1.3.1 Primary Safety Analyses**
**First sentence previously read:**

The primary safety endpoint is the proportion of subjects who have a sperm concentration $< 15 \times 10^6$/mL by 26 weeks.

**Has been changed to read:**

The primary safety endpoint is the proportion of subjects who have a sperm concentration $< 15 \times 10^6$/mL during the 26-week Treatment Period.

**Section 8.1.3.2 Secondary Safety Endpoints**
**First paragraph, first bullet previously read:**

The proportion of subjects who enter the Observation Period and do not return to within 15% of baseline by 52 weeks after treatment discontinuation.

**Has been changed to read:**

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.

**Section 8.1.3.2 Secondary Safety Endpoints**
**Second paragraph, first sentence previously read:**

The secondary analysis on the proportion of subjects who enter the Observation Period and do not return to within 15% of baseline by 52 weeks after treatment discontinuation will be performed on the evaluable set.

**Has been changed to read:**

The secondary analysis on 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 will be performed on the evaluable set.

**Section 8.1.3.3 Adverse Events (AEs) Analyses**
**Number list previously read:**

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

3. 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.
4. 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.
5. 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.
6. 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.
7. A summary of subject numbers associated with treatment-emergent adverse events by primary MedDRA system organ class and preferred term.

**Has been changed to read:**

- 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.

**Section 8.1.3.3 Adverse Events (AEs) Analyses**
**Fourth paragraph previously read:**

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

**Has been changed to read:**

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.

**Section 8.1.4 Interim Analysis**
**First sentence previously read:**

An interim analysis will be performed after all the subjects have completed or prematurely discontinued from 26-week Treatment Period.

**Has been changed to read:**

An interim analysis will be performed after all the subjects have completed or prematurely discontinued from the 26-week Treatment Period.

**Section 8.1.4 Interim Analysis**
**Last sentence previously read:**

There is no need to adjust significance level since the primary analysis will be conducted using data from 26-week Treatment Period.

**Has been changed to read:**

There is no need to adjust significance level since the primary analysis will be conducted using data from the 26-week Treatment Period.

**Section 8.2 Determination of Sample Size**
**First sentence previously read:**

The proportion of subjects with sperm concentration < 15 million/mL in an unscreened population of otherwise healthy males is reported to be approximately 10% (Cooper et al 2010).

**Has been changed to read:**

The proportion of subjects with sperm concentration < 15 million/mL in an unscreened population of otherwise healthy males is reported to be approximately 10%.[22]

**Section 9.3 Subject Information and Consent**
**Add: new second and third paragraph**

Information regarding incentives for the subject and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

In the event a subject withdraws consent to participate from the study, stored samples will continue to be used for research and analysis. In the event a subject would like to withdraw consent for research using these samples, the subject may request their samples be withdrawn. Once AbbVie receives this request, the remaining samples will be destroyed. If the subject changes his consent, and the samples have already been tested, those results will still remain as part of the overall research data.

**Section 14.0 Investigator's Agreement**
**Item "1." previously read:**

I have received and reviewed the Investigator's Brochure for Atrasentan and the product labeling for marketed drug name.

**Has been changed to read:**

I have received and reviewed the Investigator's Brochure for Atrasentan.

**Section 14.0 Investigator's Agreement**
**"Protocol Title:" previously read:**

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

**Has been changed to read:**

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

**Section 15.0 Reference List**
**Reference 19, 20, 21, 22, and 23 previously read:**

19. Cooper TG, Noonan E, von Eckardstein S, et al. World Health Organization reference values for human semen characteristics. Hum Reprod Update. 2010;16(3):231-45.

20. Anantharanman P, Schmidt RJ. Sexual function in chronic kidney disease. Adv Chronic Kidney Dis. 2007;14(2):119-25.

21. Hellstrom WJ, Overstreet JW, Yu A, et al. Tadalafil has no detrimental effect on human spermatogenesis or reproductive hormones. J Urol. 2003;170(3):887-91.

22. Pierik FH, Vreeburg JT, Stijnen Y, et al. Serum inhibin B as a marker of spermatogenesis. J Clin Endocrinol Metab. 1998;83(9):3110-4.

23. Letairis® [package insert]. Foster City, CA; Gilead Sciences Inc., 2012.

**Has been changed to read:**

19. Tracleer® [package insert]. South San Francisco, CA; Actelion Pharmaceuticals US, Inc., 2011.

20. Letairis® [package insert]. Foster City, CA; Gilead Sciences Inc., 2012.

21. Volibris® [package insert]. Brentford, Middlesex, UK; Glaxo Group Ltd, 2013.

22. Cooper TG, Noonan E, von Eckardstein S, et al. World Health Organization reference values for human semen characteristics. Hum Reprod Update. 2010;16(3):231-45.

## Appendix B. List of Protocol Signatories

**Previously read:**

| Name | Title | Functional Area |
|---|---|---|
| [redacted] | | Clinical |
| | | Clinical |
| | | Clinical |
| | | Pharmacokinetics |
| | | Statistics |

**Has been changed to read:**

| Name | Title | Functional Area |
|---|---|---|
| [redacted] | | Clinical |
| | | Clinical |
| | | Clinical |
| | | Pharmacokinetics |
| | | Statistics |