

1.0 Title Page

Clinical Study Protocol M11-352

**A Randomized, Multicountry, Multicenter,
Double-Blind, Parallel, Placebo-Controlled Study of
the Effects of Atrasentan on Renal Outcomes in
Subjects with Type 2 Diabetes and Nephropathy
SONAR: Study of Diabetic Nephropathy
with Atrasentan**

**Incorporating Amendments 1 and 2, Administrative
Change 1, Amendment 3, Administrative Change 2,
Amendment 4, Administrative Changes 3 and 4, and
Amendments 5, 6 and 7**

AbbVie Investigational
Product: Atrasentan (ABT-627)
Date: 19 May 2017
Development Phase: 3
Study Design: Phase 3, randomized, double-blind, parallel design,
placebo-controlled, enriched-population, multicenter study.
EudraCT Number: 2012-005848-21
Investigators: Multicenter (Investigator information is on file at AbbVie)
Sponsor: AbbVie Inc.*

Sponsor/Emergency
Contact:



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.

*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.

Confidential Information

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	01 April 2013
Amendment 1	17 July 2013
Amendment 2	13 August 2013
Administrative Change 1	29 August 2013
Amendment 3*	08 October 2014
Administrative Change 2	09 December 2014
Amendment 4	11 February 2015
Administrative Change 3	20 March 2015
Administrative Change 4	13 July 2016
Amendment 5*	17 November 2016
Amendment 6*	10 February 2017

* Amendment was not released to study sites for implementation.

The purpose of this amendment is to:

Substantial Changes (from Amendment 4 through Amendment 7 and includes Administrative Changes 3 and 4)

Statistical Design Parameters

- Update figures throughout protocol:
 - Revise number of subjects to be enrolled from 4,148 to 3,500.
 - Revise responders (UACR reduction $\geq 30\%$ from baseline) figures in the Overall Study Diagram and [Figure 1](#), Study Schematic from 1574 to 1250. Also specify study visits extend past the Follow-Up Visit (F1) visit for subjects that prematurely discontinued study drug administration.
 - Revise number of responders from 3,148 to 2,500.
 - Clarify treatment visits continue past T48.

Rationale: *The reduction in the responder population and total study enrollment is resulted from the change of study duration of Double-Blind Period from 48 months to approximately 6 years.*

- Update Statistical Methods, Sample Size Determination:
 - Revise accrual period from 24 to 42 months.
 - Update duration of the Double-Blind Period from 48 months to approximately 6 years.
 - Add an annualized lost-to-follow-up rate of 2%.
 - Revised the plan for interim analysis of efficacy to be conducted when the number of accrued primary events in the responder population is in the range of 50% to 75% of the targeted 425 events for the study.
 - Specify "approximately" 1,000 non-responders will be randomized into the study to align throughout protocol.

Rationale: *Reflects current enrollment accrual rate and lost-to-follow-up rate. Interim analysis revised to include the assessment of efficacy.*

- Update Statistical Methods, Definition of Baseline
Rationale: *Clarification.*
- Update Statistical Methods, Primary Efficacy Analysis
Rationale: *Clarification.*
- Update Statistical Methods, Derivation of Safety Endpoints
Rationale: *Clarification.*
- Update Statistical Methods, Interim Analysis
Rationale: *Interim analysis revised to include the assessment of efficacy.*
- Update text in Section 8.1, Statistical and Analytical Plans
Rationale: *To align language throughout protocol.*
- Update text in Section 8.1.2, Demographic, Other Baseline Characteristics, Subject Disposition and Concomitant Medication.
Rationale: *Align definition of baseline for consistency throughout protocol.*
- Revise title and text in Section 8.1.3.1, Primary Efficacy Analyses
Rationale: *Clarification.*

- Update text in second paragraph of Section 8.1.3.5, Multiplicity
Rationale: To align with protocol text.
- Update text in Section 8.1.4, Safety Analyses
Rationale: Clarification.
- Revise text in Section 8.1.4.1, Adverse Events (AEs) Analyses
Rationale: Clarification.
- Add sentence to Section 8.1.4.4, ECG Analyses
Rationale: To more accurately describe planned analysis of ECG data.
- Revise text in Section 8.1.5, Interim Analysis
Rationale: Interim analysis revised to include the assessment of efficacy.
- Modify text in Section 8.1.6, Independent Data Monitoring Committee (IDMC) and Independent External Statistician.
Rationale: Change incorporated to specify which events trigger the IDMC meetings and clarify committee recommendations are provided to the sponsor.
- Update text in Section 8.2, Determination of Sample Size
Rationale: Align text throughout protocol.
- Update bullet point three in Section 8.3, Randomization Methods
Rationale: Clarification.

Increase in Study Duration

- Update duration of the Double-Blind Period from 48 months to approximately 6 years.
Rationale: Sentence clarifies approximate duration of the double-blind treatment period.
- Revise Section 1.2, Synopsis, Duration of Treatment
Rationale: Clarification

Study Procedures

- Define visit completion sequence at study completion and align open-label extension study text.

Rationale: Clarification.

- Add text to Inclusion Criterion 5, bullet point one, to highlight eGFR range of 25 to 75 mL/min/1.73 m² is valid until the eGFR cap is met.

Rationale: Clarification.

- Add End Stage Renal Disease text.

Rationale: Clarify laboratory sample collection is not required at the discretion of the Investigator after the Premature Discontinuation visit for subjects that receive chronic dialysis or renal transplantation.

- Revise study assessment text.

Rationale: Clarify on-site visits are preferred and telephone assessments should only be utilized when necessary to complete study assessments.

- Add Home Visits text.

Rationale: Presents optional visit plan to reduce number of discontinued subjects.

- Add lead in sentence before Inclusion Criterion 8 to specify male subjects must meet both Inclusion Criterion 8 and 9 from initial study drug administration through 90 days after last dose of study drug.

Rationale: Clarification.

- Modify lead in sentence before Exclusion Criterion 1 to specify subjects will not be eligible for entry into the Run-In Period of the study if any exclusion criteria are met.

Rationale: Clarification.

- Modify Exclusion Criterion 19 to re-define premenopausal women are not eligible for study participation.

Rationale: Clarification.

- Update [Table 1](#), Study Activities footnotes
 - Delete footnote "j." for Complete Chemistry
 - Revise footnote "d." to extend yearly visits past T48
 - Specify footnote "i." procedures to be conducted during Medical History.
 - Clarify footnote "k." sentence.

- Revise footnote "w." description of IVRS/IWRS transaction at Final Treatment/PD visit.

Rationale: *Administrative error and clarification.*

- Update [Table 2](#), Reminder Phone Calls
 - Extend Yearly Visits past T48
 - Administrative Change 3 update of naming convention of Final Treatment/Premature Discontinuation Visit to align with terminology used in rest of protocol.
 - Delete reference to 24-hour urine collection at Final Treatment/Premature Discontinuation Visit as sample is not collected at either visit.
 - Add statement to F1 visit for subjects that consented to initiate their 24-hour urine collection.

Rationale: *Clarification.*

- Added Clinical Laboratory Tests text

Rationale: *Provides option to utilize local laboratory test results.*

- Update Section [5.3.1.1.1](#), 24-Hour Urine Collection Sub-Study (Additional Consent Needed)
 - Reference [Table 4](#), Study Activities for Optional 24-hour Urine Sub-Study, schedule for urine sample collection frequency.
 - Administrative Change 3 raised the number of subjects participating in the sub-study to 800 to increase the sample size and mitigate potential response variation.
 - Define yearly visits in [Table 4](#), Study Activities for Optional 24-hour Urine Sub-Study.

Rationale: *Clarification.*

- Delete number of planned PK samples in Section [5.3.2.1](#), Collection of Samples for Pharmacokinetic Analysis

Rationale: *Clarification.*

- Update Section [5.3.3.3](#), Additional Endpoints

Rationale: *Clarification.*

- Update text in Section [5.4.2](#), Discontinuation of Entire Study

Rationale: Clarification.

- Update text in Section 5.4.3, Study Completion

Rationale: Clarification.

- Revise Figure 2, Adverse Event Collection table to clarify collection period for Potential Endpoints and SAEs.

Rationale: Clarification.

- Update Section 6.5.1, Potential Endpoint Reporting title and text to specify events to be reported for subjects in the Enrichment Period.

Rationale: Clarification.

- Modify urine collection time points in Section 8.1.3.4, Efficacy Analyses for the 24-Hour Urine Sub-Study.

Rationale: Clarification.

Administrative Changes

- Administrative Change 4 update Sponsor/Emergency contact

Rationale: Clarification.

- Revise Sponsor/Emergency contact

Rationale: Clarification.

- Delete reference in Section 1.2, Synopsis

Rationale: Clarification.

- Added Kaplan-Meier and Hazard ratio abbreviations to List of Abbreviations and Definition of Terms

Rationale: Clarification.

- Administrative Change 3 inclusion of visit window for Run-In Treatment Period.

Rationale: Clarification.

- Administrative Change 4 deletion of international system of units in Section 5.1, Overall Study Design and Plan: Description.

Rationale: Application of inclusion criteria consistently across all geographic regions.

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- Administrative Change 3 removal of the specific ratio for the chronologic distribution of non-responders to responders randomized.
Rationale: Allows for flexibility to alter the ratio if necessary to ensure proportional distribution of the two populations.
 - Update Section 5.1, Overall Study Design and Plan: Description, Randomization Visit.
Rationale: Clarification.
 - Administrative Change 3 inclusion of visit windows during the Double-Blind Treatment Period.
Rationale: Clarification.
 - Modify End Stage Renal Disease text.
Rationale: Clarify acceptance of confirmatory values within intended visit window, and correct typographical error.
 - Add Subject Withdrawal header and revise text.
Rationale: Clarification.
 - Modify Open-Label Extension Study text
Rationale: To clarify participation will be based on subject eligibility and site agreement to participate in the open-label study.
 - Administrative Change 4 delete international system of units for Inclusion Criterion 7, bullet point four.
Rationale: Application of inclusion criteria consistently across all geographic regions.
 - Delete extra word in Exclusion Criterion 3
Rationale: Typographical error.
 - Add country code to Sample Receiving contact numbers
Rationale: Clarification.
 - Administrative Change 3 update PK samples preparation instructions to remove the requirements for an ice bath.
Rationale: Clarification.
 - Revise title and add parenthesis brackets in Section 5.3.3.1, Primary Variables
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Rationale: Clarification.

- Reference [Table 1](#), Study Activities, in Section [5.3.5](#), Pharmacokinetic Variables for PK collection time points.

Rationale: Clarification.

- Revise text in Section [5.5.5](#), Blinding

Rationale: Clarification.

- Revise text in Section [5.5.5.1](#), Blinding of Data for Independent Data Monitoring Committee (IDMC)

Rationale: Clarification.

- Revise Renal Safety Management Team contact information in Section [6.5](#), Adverse Event Reporting.

Rationale: Clarification.

- Administrative Change 4 update primary study designated physician in Section [6.5](#), Adverse Event Reporting.

Rationale: Clarification.

- Update Section [7.0](#), Protocol Deviations.
 - Administrative Change 3 update of primary contact.
 - Administrative Change 4 update of alternate contact.

Rationale: Clarification.

- Update country code for primary contact office number in Section [7.0](#), Protocol Deviations

Rationale: Clarification.

- Administrative Change 4 addition of missing parentheses bracket in Section [8.1.3.5](#), Multiplicity.

Rationale: Clarification.

- Administrative Change 3 removed the specific ratio for the chronologic distribution of non-responders to responders randomized, to allow for flexibility to alter the ratio if necessary to ensure proportional distribution of the two populations.

Rationale: Clarification.

- Update [Appendix B](#), List of Protocol Signatories

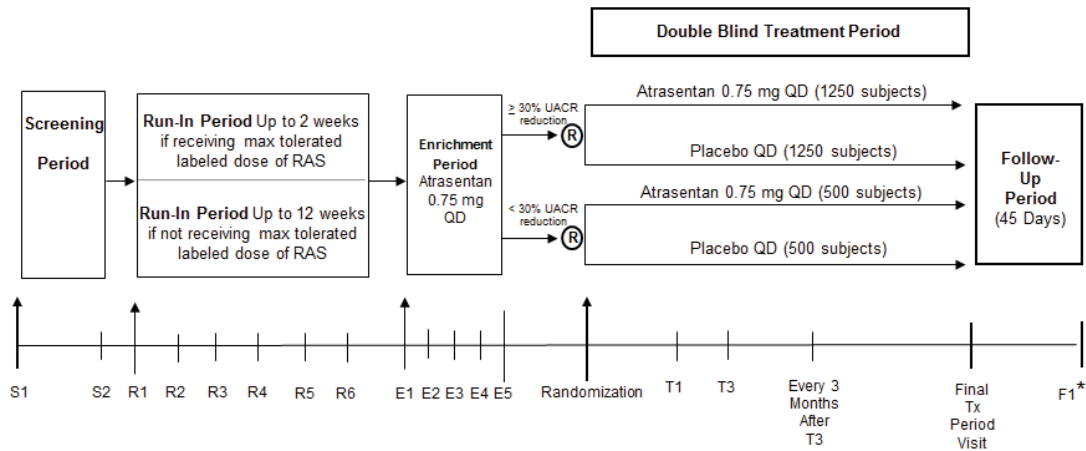
***Rationale:** Clarification.*

An itemized list of all changes made to the protocol under this amendment can be found in [Appendix C](#).

1.2 Synopsis

AbbVie Inc.	Protocol Number: M11-352
Name of Study Drug: Atrasentan (ABT-627)	Phase of Development: 3
Name of Active Ingredient: (2R,3R,4S)-4-(1,3-benzodioxol-5-yl)-1-[2-(dibutylamino)-2-oxoethyl]-2-(4-methoxyphenyl) pyrrolidine-3-carboxylic acid, monohydrochloride	Date of Protocol Synopsis: 19 May 2017
Protocol Title: A Randomized, Multicountry, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Atrasentan on Renal Outcomes in Subjects with Type 2 Diabetes and Nephropathy - SONAR: Study of Diabetic Nephropathy with Atrasentan	
Objectives: The study objective is to evaluate the effect of Atrasentan compared with placebo on time to doubling of serum creatinine or the onset of end stage renal disease (ESRD) in subjects with type 2 diabetes and nephropathy who are treated with the maximum tolerated labeled daily dose (MTLDD) of a Renin-Angiotensin System (RAS) inhibitor. In addition, the study will assess the effects of Atrasentan compared with placebo on cardiovascular morbidity and mortality, urine albumin excretion, changes in estimated glomerular filtration rate (eGFR), as well as on the impact on quality of life in subjects with type 2 diabetes and nephropathy.	
Investigators: Multicenter study	
Study Sites: 800 – 900 sites globally.	
Study Population: Subjects that have type 2 diabetes with nephropathy (eGFR of 25 – 75 ml/min/1.73 m ² and a urinary albumin to creatinine ratio (UACR) ≥ 300 mg/g creatinine and < 5,000 mg/g).	
Number of Subjects to be Enrolled: Approximately 3,500 subjects will be randomized to the Double-Blind Treatment Period.	

Overall Study Design:



* Subjects permanently discontinued from study drug during the Double-Blind Treatment Period should complete the Final Treatment/Premature Discontinuation visit and Follow-Up visit and then continue with all scheduled study visits as referenced in Section 5.3.1.1, Post-Discontinuation Visits/Phone Calls.

Methodology:

This is a prospective, randomized, double-blind, enriched-population, placebo-controlled, multicenter study. Eligible subjects will proceed to a run-in period to optimize RAS inhibitor and diuretic doses. Following the Run-in period, eligible subjects will enter the Enrichment Period in which all will receive Atrasentan 0.75 mg once daily (QD) to determine their UACR response and to assess tolerability of Atrasentan. Approximately 2,500 responders (UACR reduction $\geq 30\%$ from baseline) and approximately 1,000 non-responders (UACR reduction $< 30\%$ from baseline) will then be randomized 1:1 into the double-blind treatment period.

Methodology (Continued):

The duration of the Double-Blind Period is estimated to be approximately 6 years. Subjects' doses of RAS inhibitors and diuretic should be stable during the treatment period and remain unchanged through the end of the study. If at any time during the study there is an interruption or decrease of RAS inhibitor dose, resumption of the previous dose should be attempted within 1 month, according to the Investigator's medical judgment. If there is significant worsening of peripheral edema or other symptoms of fluid overload, such as dyspnea with walking or lying down, during any of the treatment visits, the Investigator may adjust the diuretic dose as needed. The study will continue until 425 distinct primary renal composite events (doubling of serum creatinine or the onset of ESRD) occurring in the responder population have been adjudicated by an independent Events Adjudication Committee (EAC). Subjects who reach the endpoint of doubling of serum creatinine or eGFR < 15 ml/min/1.73 m² will remain on study drug until they reach chronic dialysis, renal transplantation or renal death or the completion of the trial. If a subject stops taking study drug, every attempt will be made to keep him/her in the study by continuing scheduled study visits and restarting study drug if medically appropriate at the discretion of the Investigator. After 425 events have occurred in the responder population, all subjects who have not permanently discontinued study drug will return for a Final Treatment visit and 45-day follow-up visit. Subjects who were permanently discontinued from study drug will complete the next scheduled visit. Upon study completion, eligible subjects will be invited to participate in an open-label study if their site is participating in the extension study to determine the long-term safety of Atrasentan.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

To be eligible for initial entry into the study, subjects must meet all of the following criteria:

- Subject is 18 – 85 years of age at the initial Screening visit (S1).
- Subject, or legal representative, 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.
- Subject has type 2 diabetes (including patients with latent autoimmune diabetes or insulin-treated patients without a history of diabetic ketoacidosis who also have a negative anti-glutamic acid decarboxylase test AND an elevated post-prandial serum C-peptide level) and has been treated with at least one anti-hyperglycemic medication and ACEi/or ARB (RAS inhibitor) for at least 4 weeks prior to the Screening S2 visit.

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

Main Inclusion (Continued):

For entry into the Run-In Period, the subject must satisfy the following criteria:

- Screening laboratory values:
 - Estimated GFR 25 to 75 ml/min/1.73 m² [until the eGFR cap on subjects (approximately 300) with a baseline of > 60 mL/min/1.73 m² is reached] and a UACR ≥ 300 and < 5,000 mg/g (≥ 34 mg/mmol and < 565 mg/mmol);
 - Serum albumin ≥ 2.5 g/dL (25 g/L);
 - BNP ≤ 200 pg/mL (200 ng/L);
 - Serum Potassium ≥ 3.5 mEq/L (3.5 mmol/L) ≤ 6.0 mEq/L (6.0 mmol/L); and
 - SBP ≥ 110 and ≤ 180 mmHg at any time during the Screening Period.
- Subjects on a MTLDD of a RAS inhibitor for ≥ 4 weeks and on a diuretic at the time of screening, and who satisfy the above criteria may proceed directly to the last visit in the Run-In Period (R6 visit).
- Subjects on a MTLDD RAS inhibitor for ≥ 4 weeks and not on a diuretic (unless medically contra-indicated) at the time of Screening will start with a diuretic and participate in Run-In for at least 2 weeks.

Main Exclusion:

Subjects meeting any of the following criteria will be excluded from the study:

- Subject has a history of severe peripheral edema or facial edema requiring diuretics unrelated to trauma or a history of myxedema in the prior 4 weeks to the initial Screening S1 visit.
- Subject has a history of pulmonary hypertension, pulmonary fibrosis or any lung disease requiring 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.
- Subject has known non-diabetic kidney disease (other than kidney stones).
- Subject has elevated liver enzymes (serum alanine aminotransaminase [ALT] and/or serum aspartate aminotransaminase [AST]) > 3 × the upper limit of normal (ULN).
- Subject is currently receiving rosiglitazone, moxonidine, aldosterone blockers, aliskiren, or a combination of ACEi and ARB.

Investigational Product:	Atrasentan
Dose:	0.75 mg once daily (QD)
Mode of Administration:	Oral
Reference Therapy:	Placebo
Dose:	Not Applicable
Mode of Administration:	Oral

Duration of Treatment: Subjects will continue on randomized study treatment until discontinued from study drug.

Criteria for Evaluation:

Efficacy:

Primary Efficacy Endpoint:

Time to the first occurrence of a component of the composite renal endpoint: doubling of serum creatinine (confirmed by a 30-day serum creatinine) or the onset of ESRD (eGFR < 15 ml/min/1.73 m² confirmed by a 90-day eGFR, receiving chronic dialysis, renal transplantation or renal death).

Secondary Efficacy Endpoints:

- Time to a 50% eGFR reduction.
- Time to cardio-renal composite endpoint: confirmed doubling of serum creatinine, ESRD, CV death, nonfatal myocardial infarction, nonfatal stroke.
- Time to first occurrence of a component of composite renal end-point: confirmed doubling of serum creatinine, or the onset of ESRD for all randomized subjects (pooled).
- Time to the CV composite endpoint: CV death, nonfatal myocardial infarction and nonfatal stroke.

Pharmacokinetic:

Atrasentan clearance (CL/F) and volume of distribution (V_{ss}/f) will be determined using population pharmacokinetic techniques.

Pharmacodynamic:

The relationship between Atrasentan exposure and clinical efficacy and/or safety response(s) may be explored.

Statistical Methods:

Analysis Datasets:

The following datasets will be used for the analysis of all efficacy and other non-safety endpoints. For these analyses, subjects will be analyzed in the treatment group to which they were randomized.

- The **Intention-to-treat (ITT) Responder Set** will serve as the primary dataset for the analysis of efficacy in this study. It will consist of all randomized subjects who achieve at least 30% reduction in UACR in the Enrichment Period (responders).
- The **ITT Non-responder Set** will consist of all randomized subjects who achieve less than 30% reduction in UACR in the Enrichment Period (non-responders).
- The **ITT Pooled Set** will consist of all randomized subjects (both responders and non-responders) and will be used for a pooled analysis of efficacy.

The following datasets will be used for the analysis of safety endpoints. For these analyses, subjects will be analyzed according to the treatment they actually receive during the double-blind phase.

- The **All Treated Responder Set** includes all randomized subjects who achieve at least 30% reduction in UACR in the Enrichment Period and receive at least one dose of study drug during double-blind phase.
- The **All Treated Non-responder Set** includes all randomized subjects who achieve less than 30% reduction in UACR in the Enrichment Period and receive at least one dose of study drug during double-blind phase.

Statistical Methods (Continued):

Analysis Datasets (Continued):

- The **All Treated Set** includes all randomized subjects who receive at least one dose of study drug during double-blind phase.

Additionally, an **All Atrasentan Set** comprising all subjects who receive at least one dose of Atrasentan, including both Enrichment and Double-Blind Treatment Periods, is defined for the purposes of data analysis.

Sample Size Determination:

The sample size for the Double-Blind Treatment Period is based on the primary efficacy endpoint of time to the renal composite event comparing Atrasentan to placebo. A total of 425 events in the ITT set is required to detect a 27% hazard reduction (HR of 0.73) with approximately 90% power using a log-rank test at a two sided significance level of 0.05. Based on the annual event rate in RENAAL study (~13%) and ALTITUDE (~3%), the estimate of the annual placebo event rate in the SONAR study is 6%. With the assumption of annual event rate of 6% in placebo group, 42-month accrual period, approximate 6 year duration of the Double-Blind Period and an annualized lost to follow-up rate of 2%, a total of about approximately 2,500 subjects who achieve at least 30% UACR reduction (responders) in the Enrichment Period (1,250 subjects per group) would be needed to be randomized.

In addition, approximately 1,000 subjects who achieve less than 30% UACR reduction in the Enrichment Period will also be randomized in a 1:1 ratio to Atrasentan or placebo.

Definition of Baseline:

For treatment comparisons and summaries based on the Double-Blind Treatment Period, baseline values refer to the last non-missing value observed prior to or at the time of randomization. This includes treatment comparisons performed for the ITT analysis sets (ITT responder set, ITT non-responder set and the ITT pooled set).

For purposes of summarizing safety and efficacy for the Enrichment Period and the entire study treatment period (Enrichment and Double-Blind Treatment Period combined), baseline values refer to the last non-missing value observed prior to or pre-dose on the first day of Atrasentan therapy (Treatment Day 1) at the beginning of the Enrichment Period.

For specific purposes, e.g., determination of doubling of serum creatinine, baseline values refer to the last non-missing value observed prior to or pre-dose on the first day of Atrasentan therapy at the beginning of the Enrichment Period.

Primary Efficacy Analysis:

A Cox proportional-hazard regression model will be performed on the ITT responder set to estimate the hazard ratio of Atrasentan to placebo and its 95% confidence interval. The primary efficacy analysis for treatment comparison will also be conducted using a stratified log-rank test, adjusting for the following stratification factors:

- UACR level at the beginning of the Enrichment Period ($\leq 1,000$ mg/g [113 mg/mmol] or $> 1,000$ mg/g [113 mg/mmol]), and
- UACR reduction during Enrichment Period (30% – $< 45\%$, 45% – $< 60\%$, and $\geq 60\%$).

Kaplan-Meier (KM) estimates for cumulative event rates will be plotted.

Statistical Methods (Continued):

Primary Efficacy Analysis (Continued):

In addition, the individual components of the primary efficacy endpoint, i.e., the time to the first occurrence of doubling of serum creatinine (confirmed by a 30-day serum creatinine) and the time to the first occurrence of the onset of ESRD will be analyzed separately using the same methods as specified above. In analyzing the individual components, first occurrence of only that specific endpoint will be considered as events.

Subgroup analyses for subgroups based on age, gender, race, geographical region and important baseline characteristics will also be performed.

Secondary Efficacy Analysis:

These pre-specified secondary efficacy endpoints are listed according to their clinical importance and will be analyzed in a hierarchical (step-down) fashion. The analyses of these time-to-event endpoints of a 50% eGFR reduction (ITT responder set), a cardio-renal composite endpoint (ITT responder set), the composite renal endpoint (ITT pooled set), and the CV composite endpoint (ITT responder set), will follow the same methods as specified for the primary efficacy analysis.

Pharmacokinetics:

Population modeling techniques will be used to estimate population central values for Atrasentan clearance (CL/F) and volume of distribution (V_{ss}/f), and post hoc values of these parameters for the individual subjects will also be estimated. Additional parameters may be estimated if useful in the interpretation of the data.

Safety:

All safety analyses will be conducted on the all treated analysis sets (i.e., all treated responder set, all treated non-responder set and all treated set, respectively) and the all Atrasentan analysis set (where indicated). No formal statistical tests of treatment difference are planned.

Derivation of Safety Endpoints:

Safety data collected from the first dose up to 45-days post last dose in the double blind period will be included in the relevant analyses for the all treated analysis sets, unless otherwise specified in the Statistical Analysis Plan (SAP) document. Safety data collected during the Enrichment Period will be summarized for exploratory purposes for the all Atrasentan analysis set.

Study Drug Exposure and Compliance:

The number of days on study drug will be summarized by treatment group and overall. The number and percentage of subjects with at least 70% compliance with study drug at each visit will be summarized by treatment group and overall.

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 follow-up period of the study will be summarized by the treatment group in descending order of overall frequency by MedDRA preferred term, as well as by system organ class (SOC) and MedDRA preferred term. The incidence rates of treatment-emergent AEs for each treatment group will be summarized. Additionally, the treatment-emergent AEs and serious adverse events (SAEs) will also be summarized by the relationship to study drug and their maximum severity.

Statistical Methods (Continued):

Laboratory Data:

For each laboratory test, the mean change from baseline to the minimum, maximum, and to each visit will be summarized by treatment groups. 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 by treatment group.

Interim Analysis:

An interim analysis of efficacy will be performed when the number of accrued primary events in the responder population is in the range of 50% to 75% of the targeted 425 events for the study. An alpha-spending function approach will be used to ensure that the overall one-sided type I error rate will be controlled at 0.025 or less. In addition, an interim analysis of efficacy data for futility only may be performed at an earlier time point. No adjustment to the type I error rate will be made for the futility assessment.

To preserve the integrity and the validity of trial data, an external Statistical Analysis Center will perform the requisite interim analyses and present the results to IDMC. Further details of the interim analysis plan will be provided in the Statistical Analysis Plan (SAP) and IDMC Charter. In making any decision to recommend discontinuation of the study, either for superior efficacy of Atrasentan or for futility, the IDMC shall be guided by a formal stopping rule described in the SAP.

Independent Data Monitoring Committee:

This study will have an IDMC composed of at least two external clinicians and one external statistician to review and make recommendations based on the results of the unblinded interim analysis and periodic reviews of the safety of Atrasentan.

Adjudication of Potential Outcome Events:

An independent events adjudication committee (EAC), blinded to study treatment assignment, will adjudicate all events that have the potential to be considered endpoints that will be specified in the EAC charter.

Steering Committee:

A steering committee will be involved in the design and implementation of the study. Its membership will be representative of the global nature of the study sites and regular meetings will be conducted to evaluate the conduct of the trial, including evaluations from the IDMC and EAC.

References:

Westfall PH, Krishen A. Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. *J Stat Plan Inference*. 2001;99:25-40.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

ABP	Ambulatory blood pressure
ACE _i	Angiotensin-converting enzyme
AE	Adverse event
AKI	Acute kidney injury
ALT	Serum alanine aminotransaminase
ANOVA	Analysis of variance
AQOL-4D	Assessment of Quality of Life – 4 Dimensions
ARB	Angiotensin II receptor blocker
AST	Serum aspartate aminotransaminase
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
CYP3A	Cytochrome P450, family 3, subfamily A
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
EMA	European agency for the evaluation of medicinal products
EPI	Epidemiology collaboration
EQ-5D	EuroQol 5 Dimensions
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
HR	Hazard ratio
Hb	Hemoglobin
HBA _{1c}	Glucosylated hemoglobin A _{1c}
HDL	High density lipoprotein
HOMA-IR	Homeostatic model assessment
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IND	Investigational new drug
IRB	Institutional Review Board
ITT	Intention to treat
IUD	Intrauterine device
IVR	Interactive voice response
IVRS	Interactive voice response system
IWRS	Interactive Web response system
K	Potassium
KDQOL	Kidney disease quality of life
KM	Kaplan-Meier
LDL	Low density lipoprotein
LDH	Lactic dehydrogenase
MI	Myocardial infarction

MMRM	Mixed model of repeated measures
MTLDD	Maximum tolerated labeled daily dose
Na	Sodium
NSAIDS	Non-steroidal anti-inflammatory drugs
PD	Premature discontinuation
PG	Pharmacogenetic
P-gp	P-glycoprotein
PI	Principal Investigator
PK	Pharmacokinetic
POC	Point of care
QD	Once daily
QOL	Quality of life
QT	QT interval
QTc	QT interval corrected for heart rate
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
SDT	Study drug termination
SGPT	Serum glutamic pyruvic transaminase
SGOT	Serum glutamic oxaloacetic transaminase
SI	Standard International Units
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reactions
TGF- β	Transforming growth factor beta
TIA	Transient Ischemic Attack
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

WHO World Health Organization

Definition of Terms

First morning void urine	The first void of the morning collected after 5:00 a.m. or upon rising for the day.
CKD-EPI (epidemiology collaboration) calculation for SCr based eGFR	$GFR = 141 \times \min(SCr/\kappa, 1)^\alpha \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age}$ $\times 1.018$ [if female] $\times 1.159$ [if black] Where SCr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of SCr/ κ or 1, and max indicates the maximum of SCr/ κ or 1.
HOMA-IR calculation for Insulin resistance	Homeostatic model assessment: (fasting plasma insulin [FPI] \times fasting plasma glucose [FPG])/22.5.
Stable Dose	Same type and regimen of medication.
Maximum Tolerated Labeled Daily Dose (MTLDD)	The subject's daily dose of ACEi or ARB, at or below the maximum dose on the label, that does not exhibit any intolerable adverse effects (i.e., hypotension or hyperkalemia), based on the Investigator's assessment.
Baseline UACR	Baseline UACR will be the average of the UACR values collected at the last week of Run-In (Visit R6) and the first day of Enrichment (Visit E1).
Responders	Subjects who achieve at least a $\geq 30\%$ UACR reduction at the end of the Enrichment Period compared to baseline.
Non-Responders	Subjects who achieve $< 30\%$ UACR reduction at the end of the Enrichment Period compared to baseline.
End-Stage Renal Disease (ESRD)	eGFR < 15 ml/min/1.73 m ² (confirmed by a 90-day eGFR), receiving chronic dialysis, renal transplant, or renal death.
Study Completion	Study Completion is defined as the occurrence of 425 distinct primary renal events in the responder population.

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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} ET_A 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 cells¹¹ 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 hypertension¹² and they correlate with long-term control of the disease in type I 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,3R,4S)-4-(1,3-benzodioxol-5-yl)-1-[2-(dibutylamino)-2-oxoethyl]-2-(4-methoxyphenyl) pyrrolidine-3-carboxylic acid, monohydrochloride 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 TGFβ).^{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, [REDACTED] 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. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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, one-sided $P = 0.023$) and 1.75 mg per day (35% reduction, one-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 the M12-812 study 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 the M12-830 study 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).

A detailed discussion of the preclinical toxicology, metabolism, clinical safety and pharmacology can be found in the Investigator's Brochure.¹⁹

The purpose of this Phase 3 study is 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. The primary endpoint will be the time to doubling of serum creatinine or end stage renal disease (ESRD).

3.1 Differences Statement

This is the first Phase 3 study in subjects with type 2 diabetes and nephropathy to utilize the Atrasentan tablet formulation. This study differs from the previous Phase 2 studies in that it is an event driven trial, with time to doubling of serum creatinine or ESRD as the primary composite endpoint, and including cardiovascular events as secondary endpoints.

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.

Atrasentan has been evaluated in 5 studies in subjects with diabetic nephropathy: one Phase 2a study in subjects with type 1 diabetic nephropathy who were not receiving renin-angiotensin-aldosterone system (RAS) inhibitors [REDACTED] 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 subjects 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. This study will provide definitive long-term efficacy and safety information of Atrasentan for slowing the progression of chronic kidney disease (CKD). There is a potential for fluid retention as CKD progresses over time.

The hypothesis of this Phase 3 study is that Atrasentan 0.75 mg QD is superior to placebo in delaying renal disease progression in subjects with type 2 diabetes and nephropathy.

4.0 Study Objectives

The study objective is to evaluate the effect of Atrasentan compared with placebo on time to doubling of serum creatinine or the onset of end stage renal disease (ESRD) in subjects with type 2 diabetes and nephropathy who are treated with the maximum tolerated labeled

daily dose (MTLDD) of a renin-angiotensin system (RAS) inhibitor. In addition, the study will assess the effects of Atrasentan compared with placebo on cardiovascular morbidity and mortality, urine albumin excretion, changes in estimated glomerular filtration rate (eGFR), as well as on the impact on quality of life in subjects with type 2 diabetes and nephropathy.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a prospective, randomized, double-blind, enriched-population, placebo-controlled, multicenter study.

The study was designed to randomize approximately 3,500 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 randomized, there is a possibility that additional subjects in screening will not be enrolled.

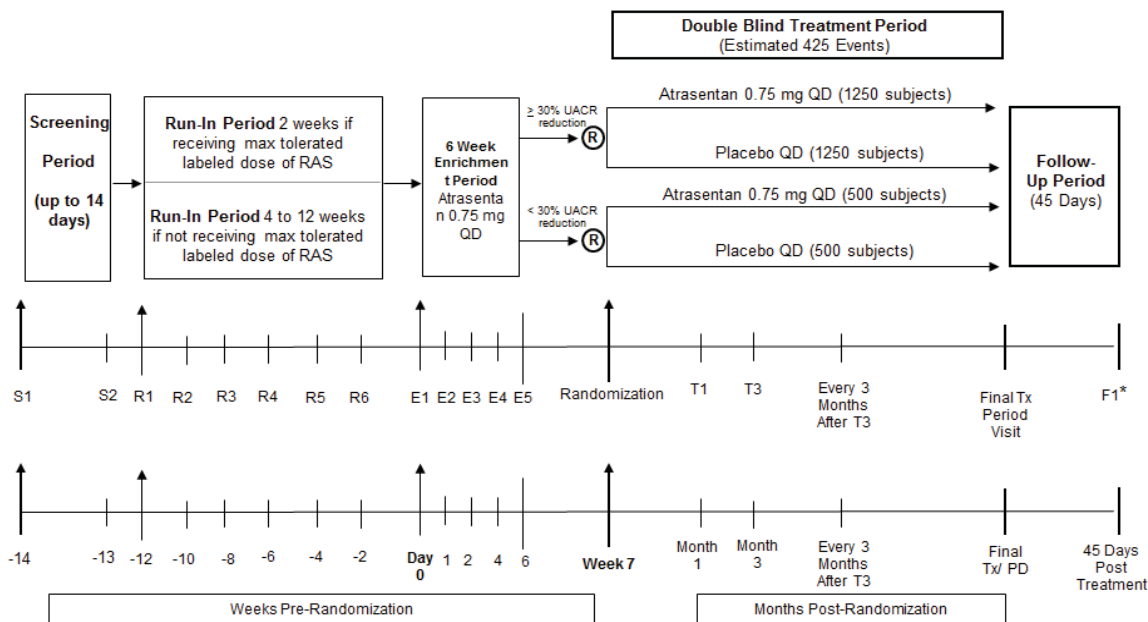
Subjects who meet the inclusion for initial study entry and none of the exclusion criteria will be eligible to proceed to the Run-In Period to optimize RAS inhibitor prior to receiving study drug (Atrasentan) in an Enrichment Period.

The study will be performed in five to six periods in the following sequence:

- Pre-Screening Period (optional)
- Screening Period
- Run-In Period
- Enrichment Period
- Double-Blind Treatment Period
- Follow-Up Period

A schematic of the study design is shown below in [Figure 1](#).

Figure 1. Study Schematic



* Subjects permanently discontinued from study drug during the Double-Blind Treatment Period should complete the Final Treatment/Premature Discontinuation visit and Follow-Up visit and then continue with all scheduled study visits as referenced in Section 5.3.1.1, Post-Discontinuation Visits/Phone Calls.

A description of the study periods is noted below. Study procedures for each visit are outlined in [Table 1](#).

Pre-Screening Period (Optional)

The Pre-Screening Period is for subjects who do not have recent documented eGFR and/or UACR values. Subjects will sign a pre-screening informed consent and will need to complete the Pre-Screening Visit activities. The activities include collection of a blood and urine sample to measure eGFR and UACR with the point of care (POC) devices.

Data collected during the pre-screening will not be recorded on an electronic case report form (eCRF) and included in the study database.

Screening Period (Visits S1 and S2)

The Screening Period will consist of 2 visits. The procedures to be performed at the initial Screening visit (S1) are outlined in the Study Activities Table (Table 1). The site will also call into the Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) to register the subject and obtain the subject number. All subjects will be given supplies and instructions for obtaining 2 consecutive first morning void (FMV) urine collections that need to be collected within 2 days of the second visit in the Screening Period.

The second Screening visit (S2) will be scheduled within 2 weeks after the initial Screening visit. The procedures to be performed at the second Screening visit (S2) are outlined in Table 1. At this visit, the subject will bring in their 2 consecutive FMV urine collections that will be used to determine the UACR for assessing the subject's eligibility.

While subject is in screening, tests for eligibility may be repeated within the screening window. Subjects who screen fail will be allowed to rescreen per investigator's judgment.

During Screening, the Investigator should document in the source if the subject is or is not on a MTLDD of a RAS inhibitor and which Run-In visit the subject should proceed to (as described below in the Run-In Period). If the subject is currently on the MTLDD of a RAS inhibitor and a diuretic, he/she will be given supplies and instructions for obtaining 3 consecutive FMV urine collections that need to be collected within the 3 days of his/her next visit (Run-In R6 visit).

Run-In Period (Up to 12 Weeks) (Visits R1 – R6)

If the subject meets inclusion criteria for run-in, the subject will be allowed to proceed to the Run-In Period within 1 – 2 weeks of confirmed eligibility. IVRS/IWRS will be called to confirm eGFR cap has not been met in order for the subject to continue. The Run-In Period will consist of up to 6 visits.

The purpose of the Run-In Period is to optimize RAS inhibitor doses to a MTLDD for optimal blood pressure (BP) control according to local guidelines and to add a diuretic (if possible) for blood pressure control as well as to enhance RAS inhibitor effects on UACR reduction.²³ The procedures to be performed at each Run-In visit are outlined in [Table 1](#). Subjects will be given supplies and instructions for collecting 3 consecutive FMV urine samples that need to be collected within the 3 days of the last visit in the Run-In Period (R6).

The subject will enter into the Run-In Period as follows:

- If the subject is already receiving a MTLDD of a RAS inhibitor, such as angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB), and a diuretic at Screening, he/she may proceed to the last visit in the Run-In Period (R6) and then proceed to the Enrichment Period approximately 2 weeks later.
- If the subject is already receiving a MTLDD of a RAS inhibitor but not on a diuretic (unless medically contraindicated), he/she will proceed to the first visit of the Run-In Period (R1) to be placed on a diuretic for a minimum of 2 weeks, then proceed to the R6 visit.
- If the subject is currently not receiving a MTLDD of a RAS inhibitor, the dose will be titrated up to the MTLDD over the course of up to 12 weeks.
- If subject is currently receiving a RAS inhibitor and has hyperkalemia the dose of RAS inhibitor may be down titrated according to the Investigator's judgment. The new lower dose would be the MTLDD and the subject would proceed to Run-In (R1) for 4 weeks of stable MTLDD of RAS inhibitor, then proceed to the R6 visit.

During the Run-In Period, BP control and tolerance to the new therapeutic doses will be assessed approximately every other week (\pm 2 days). The RAS inhibitor dose should remain stable during the 4 weeks immediately prior to the Enrichment Period; however, dose adjustments of non-RASi may be necessary based on the clinical discretion of the Investigator for BP control and worsening or new onset of edema. Diuretic discontinuation or decrease in dose will be allowed for clinical signs and symptoms of

volume depletion (e.g., orthostatic hypotension, unexplained dizziness). If a subject is on the MTLDD of a RAS inhibitor and a diuretic and experiences symptomatic hypotension, dose reductions of non-RAS antihypertensive medications should be performed first. If the subject continues to have hypotension after an additional week, the diuretic dose should be reduced or withdrawn at the discretion of the Investigator. If the subject continues to have symptomatic hypotension after an additional week, the subject should be discontinued from the RAS inhibitor and discontinued from the study as a screen failed subject.

Non-RAS blood pressure medications (calcium channel blockers, beta blockers, central acting agents) may be adjusted during the Run-In Period, if needed, to achieve optimal blood pressure control according to local guidelines. Refer to Section 5.2.3 guidance for managing concomitant medications.

Subjects who fail to meet eligibility criteria for the Enrichment Period may be re-screened. If at Run-In R5 visit, the dose of the RAS inhibitor is not tolerated in the opinion of the Investigator, the Run-In R5 visit can be repeated 2 weeks (± 10 days) after the RAS inhibitor adjustments.

If at the Run-In R6 visit, the dose of the RAS inhibitor is not tolerated in the opinion of the Investigator, the Run-In R6 visit can be repeated 4 weeks (± 10 days) after the RAS inhibitor adjustments. The Run-In R6 visit may not be repeated if the Run-In R5 visit was repeated.

If the subject meets the inclusion criteria for the Enrichment Period at the last Run-In visit (R6), the subject will be allowed to proceed to the Enrichment Period 2 weeks (± 10 days) after his/her last Run-In visit. Subjects will be given supplies and instructions for collection of 3 consecutive FMV urine samples within 3 days of the first visit of the Enrichment Period (E1).

Enrichment Period (6 Weeks) (Visits E1 – E5)

The Enrichment Day 1 (E1) visit will occur 2 weeks (± 10 days) after the Run-In R6 visit. The procedures to be performed at the first Enrichment Period E1 visit are outlined in [Table 1](#), including administration of open-label study drug (Atrasentan). At this visit, the subject will bring in his/her 3 consecutive FMV urine collections. The site will call into the IVRS/IWRS and dispense open-label study drug (Atrasentan) to the subject. Subjects will remain on open-label Atrasentan until Randomization into the Double-Blind Treatment Period.

All Enrichment visits should take place the same day of the week, if possible (i.e., if Enrichment visit E1 occurred on a Wednesday then Enrichment visit E2 should take place the following Wednesday). Subject compliance to study drug administration will be assessed by the Investigator or designee at each visit during the Enrichment Period (Section 5.5.6).

The Enrichment E2 visit will take place 1 week (± 2 days) after the E1 visit. The Enrichment E3 visit will take place 1 week (± 2 days) after the E2 visit. The procedures to be performed at Enrichment E2 and E3 visits are outlined in [Table 1](#). At the Enrichment E3 visit, subjects will be given supplies and instructions for collection of 3 consecutive FMV urine samples that need to be collected within 3 days of the Enrichment E4 visit.

The Enrichment E4 visit will take place 2 weeks (± 2 days) after the E3 visit. The procedures to be performed at the Enrichment E4 visit are outlined in [Table 1](#). Supplies and instructions for collection of 3 consecutive FMV urine samples that need to be collected within the 3 days prior to the last visit (E5) in the Enrichment Period will be given to the subject. The site will also call into the IVRS/IWRS at this visit and provide the subject with study drug (Atrasentan).

The Enrichment E5 visit will take place 2 weeks (± 2 days) after the E4 visit. The procedures to be performed at the E5 visit are listed in [Table 1](#).

The geometric mean of the FMV urine samples collected at Enrichment E4 and E5 visits will be used to determine the response group for each subject as compared to the baseline UACR. Initial UACR for the Enrichment Period is defined as the geometric mean of the 3 UACR values at the last Run-In visit (R6) and the 3 UACR values at the first Enrichment visit (E1). Every subject should have 6 FMV samples analyzed from R6 and E1 visits to calculate the initial UACR; however, the subject will be allowed to enter the Enrichment period if a minimum of three FMVs have been collected between the two visits. In addition, every subject should have 6 FMV samples analyzed (from E4 and E5 visits); however, the subject may be allowed to enter the Double-Blind Treatment period if a minimum of three FMVs have been collected between the two visits.

If the subject meets the inclusion criteria for randomization at the last Enrichment Period visit, the subject will be allowed to proceed to the Double-Blind Treatment Period; however, if the subject meets one of the primary or secondary endpoints, as defined for the Double-Blind Treatment Period (refer to Section 6.5.1), during Enrichment or if the subject has a significant increase in serum creatinine (defined below), he/she will be discontinued from the study and will not be allowed to proceed to the Double-Blind Treatment Period.

Serum Creatinine Elevation During Enrichment

Subjects must not have an increase in serum creatinine > 0.5 mg/dL AND $> 20\%$ from E1 to the E5 visit. Subjects that experience an increase in serum creatinine > 0.5 mg/dL and 20% from baseline (E1) should be permanently discontinued from study drug, return for the Premature Discontinuation visit within 9 days, and be followed weekly, up to 4 weeks, to test for serum creatinine until serum creatinine returns to baseline $\pm 10\%$. In addition, the 45-day Follow-Up (F1) visit should be completed.

The number of subjects with eGFR $60 - 75$ ml/min/1.73 m² at the E1 visit who are randomized in the responder population will be capped at approximately 300 subjects. After the cap has been reached, subjects with an eGFR of > 60 ml/min/1.73 m² at

Screening (S1) will not be allowed to enter into the study. Such subjects will be considered screen failures. Even after the cap has been reached, subjects who have entered the Run-In Period or are already receiving Atrasentan in the Enrichment Period who have an eGFR 60 – 75 ml/min/1.73 m² at the E1 visit will be allowed to move into the Double-Blind Treatment Period.

A responder/non-responder ratio design was set up to ensure proportional distribution to the expected enrollment. The implementation of this ratio will be through the IRT system. The ability to randomize non-responders will "turn on and off" based on the responder/non-responder ratio of randomization. The non-responder arm will re-open to enrollment at any given time without notice, as the randomization scheme is applied, until enrollment of approximately 1,000 subjects in the non-responder arm of the protocol is complete.

Subjects discontinued in the Enrichment Period may be re-screened and re-enrolled at the S1 visit after 3 months have passed from last dose of study drug at the discretion of the Investigator.

Randomization Visit

The Randomization visit will occur 1 – 2 weeks after the subject's last Enrichment Period visit. The site will call into the IVRS/IWRS to obtain the blinded treatment. If the non-responder cap is met and a subject has achieved < 30% UACR reduction at the end of the Enrichment Period compared to baseline, the IVRS/IWRS will inform the site that the subject cannot continue into the Double-Blind Treatment Period. Procedures to be performed at this visit are outlined in [Table 1](#). Subjects that have consented to the separate pharmacogenetic (PG) analysis will have a sample collected at this visit. Subjects who have met the entry criteria will be randomized in a 1:1 ratio to receive Atrasentan or placebo; the subject will receive a drug supply adequate until the first Treatment Period visit (T1). Subjects should be administered the first dose of study drug at the Randomization visit. Subjects will be given supplies and instructions for the collection of 1 FMV urine sample that needs to be collected within 1 day of the T1 visit.

Subjects will be randomized in the Treatment Period if the subject did not experience a serious adverse event(s) or reaction(s) possibly related to the study drug during the Enrichment Period. Randomization will be based on UACR response to Atrasentan from the Enrichment Period (Please refer to Section 8.3 for details of the stratification factors).

Approximately 1,000 subjects in the non-responder population will be randomized. For subjects who present for the Randomization visit that are determined to be ineligible for the Double-Blind Treatment Period or if the non-responder cap has been reached, a Premature Discontinuation visit can be conducted instead. Collection of the FMV urine sample for the Premature Discontinuation visit will not be required for these subjects.

Double-Blind Treatment Period (Randomization – Final Treatment Visit)

Subjects will be contacted by telephone at 1 and 2 weeks after the subject's Randomization visit to inquire about symptoms of hypotension (dizziness, dizziness with standing, falling, excess thirst). If necessary, unscheduled visits should be made during this time for a limited physical exam and to measure blood pressure. Dosages of diuretics or other blood pressure medications may be adjusted during these unscheduled visits.

The first Treatment Period visit (T1) will occur 1 month (± 7 days) after the Randomization visit. Procedures to be performed at the Treatment T1 visit are outlined in Table 1. The subject will bring in his/her 1 FMV urine sample that was collected within 1 day of the T1 visit. The site will call into the IVRS/IWRS at this visit and provide the subject with study drug and perform drug accountability (Section 5.5.6).

T3 will occur 3 months (± 2 weeks) after randomization (2 months after T1).

The procedures conducted at the 3-month visits during the Treatment Period are listed in Table 1. The visit window for all Treatment Visits after T1 is ± 2 weeks. The site will call into the IVRS/IWRS at each of these visits, collect unused study drug dispensed at the previous visit, perform drug accountability (Section 5.5.6), and provide the subject with adequate supply of study drug. Subjects will also be given supplies and instructions when

required for the collection of 1 FMV urine sample that needs to be collected within 1 day of the yearly treatment visit (T12, T36, T48, etc).

For the T24 visit, 3 FMV urine samples are needed. At the T21 visit, subjects will be given supplies and instructions for the collection of 3 FMV urine samples that need to be collected within the 3 days of the T24 visit.

At the Final Treatment/PD visit, IVRS/IWRS will be called. Subjects will return study drug and site staff will perform and document drug accountability.

Subjects' doses of RAS inhibitor and diuretic should remain stable during the Double-Blind Treatment Period and remain unchanged through the end of the study, unless there is a medical need to alter the doses. Subjects will be provided diaries to collect information regarding weight between visits, with instructions on actions to be taken if significant weight gain occurs.

If at any time during the study there is an interruption or decrease of the RAS inhibitor dose, the subject should be returned to the previous dose within 1 month, if possible, according to the Investigator's medical judgment. If there is significant worsening of peripheral edema during any of the treatment visits, the Investigator may increase the diuretic dose as needed.

If at any time during the study there is an interruption of the study drug administration, the reason for interruption should be captured on the eCRF and the subject should be re-started as soon as possible according to the Investigator's judgment. The study drug should only be restarted if it is medically appropriate. There is no time limit for a subject to be off the study drug that would prevent re-starting it. The subject would not be considered a premature discontinuation unless the subject permanently discontinues study drug administration.

Primary Efficacy Endpoints

Doubling of Serum Creatinine

Once a doubling of serum creatinine has been recorded, the Investigator will be informed by the central laboratory; subsequently, the site personnel will contact the subject to schedule a return visit sometime between 30 and 40 days from the last visit to have blood sampling for serum creatinine to confirm doubling of serum creatinine. If the subject misses the return visit during the 30 – 40 day window, the subject will continue to be followed until a return visit can be conducted. The Investigator will make all reasonable attempts to exclude reversible causes of elevation of serum creatinine such as volume depletion or nephrotoxic medication. Once doubling of serum creatinine is confirmed, the site will report the event in eClinical[®], as described in Section 6.5.1, to begin the process of collecting the information required to have the event properly adjudicated by the independent Event Adjudication Committee (EAC). Subjects who reach the endpoint of doubling of serum creatinine will remain on study drug until they receive chronic dialysis or experience renal transplantation or the occurrence of renal death or until completion of the trial.

End Stage Renal Disease

ESRD will be defined as eGFR < 15 ml/min/1.73 m² receiving chronic dialysis, renal transplantation or the occurrence of renal death. Once an eGFR < 15 ml/min/1.73 m² is reported the Investigator will be informed by the central laboratory. The lab should be confirmed at the next 3 month scheduled visit or at an unscheduled visit at approximately 90 days (confirmatory values within the intended study visit window will be acceptable). If the subject misses the return visit, the visit should be rescheduled as soon as possible. The Investigator will make all reasonable attempts to exclude reversible causes of elevation of serum creatinine such as volume depletion or nephrotoxic medication. Once an eGFR < 15 ml/min/1.73m² is confirmed, the site will report the event in eClinical[®], as described in Section 6.5.1, to begin the process of collecting the information required to have the event properly adjudicated by the independent EAC. Subjects who reach the endpoint of an eGFR < 15 ml/min/1.73 m² will remain on study drug until they receive

chronic dialysis or experience renal transplantation or the occurrence of renal death or until completion of the trial.

Renal death as an event is defined as death that occurs when: 1) the patient refuses renal replacement therapy (RRT) because they believe their current quality of life, with their expected lifespan, outweighs the quality and quantity of life following RRT, or 2) when both the clinician and the subject consider RRT futile and believe that the patient's current quality of life, with their expected lifespan, outweighs the quality and quantity of life following RRT. Such events will be classified as renal death when the subject dies following refusal of dialysis AND no other cause of death is adjudicated. The diagnosis of renal death is not intended for subjects in whom dialysis is not offered or withdrawn because of advanced cancer, severe sepsis, advanced heart failure, or terminal organ failure. In such instances, the primary diagnosis that led to withholding RRT will be designated the cause of death. Renal death is intended for those events in which dialysis is deliberately withheld due to advanced age of the subject, lack of availability of dialysis, or the wishes of the subject not to be dialyzed. When a more specific cause of death is adjudicated, such as sepsis, pneumonia, or trauma, such more specific causes will be designated as the primary cause of death.

Subjects who reach the endpoint of confirmed doubling of serum creatinine or confirmed $eGFR < 15$ ml/min will remain on study drug until they experience chronic dialysis, or renal transplantation. If the subject receives chronic dialysis or renal transplantation, he/she will permanently discontinue study drug administration and complete the Premature Discontinuation visit procedures and Follow-Up (F1) visit. For subjects receiving chronic dialysis or renal transplantation, laboratory samples will be collected at the Follow-Up (F1) visit or any remaining study visits at the discretion of the Investigator. In addition, they will be encouraged to continue the study visit assessments or be followed by quarterly phone calls or allow medical record review until the completion of the trial (refer to Premature Discontinuation and Retention section below).

Premature Discontinuation and Retention

Subjects who have received at least one dose of study drug (i.e., enrolled in the Enrichment Period) will be considered a Premature Discontinuation if he/she has permanently discontinued study drug administration before study completion. Subjects permanently discontinued during the Enrichment Period should have a Final Treatment/Premature Discontinuation visit within 9 days and a Follow-Up (F1) visit 45 days (± 14 days) of the last dose of study drug. These subjects should not continue further in the study. Subjects permanently discontinued during the Double-Blind Treatment Period should have a Final Treatment/Premature Discontinuation visit within 9 days and a Follow-Up (F1) visit 45 days (± 14 days) of the last dose of study drug. These subjects should continue with all scheduled study visits if possible as specified in Section 5.3.1.1.

It is recommended that subjects not be permanently discontinued from the study drug administration or from the study until the Investigator discusses the reason for permanent discontinuation with the Sponsor. The Investigator may have a subject pause study drug at any time for any reason.

As noted above, if a subject permanently discontinues study drug, the Final Treatment/Premature Discontinuation visit should occur within 9 days of the last dose of study drug. Procedures to be performed at the Final Treatment/Premature Discontinuation visit are outlined in Table 1. The reason for discontinuation will be documented in the subject's source documents at the site and the electronic case report forms (eCRF).

If the study drug administration is temporarily stopped for an individual subject, the Investigator should make every attempt to re-start study drug, if medically appropriate, regardless of the time passed from discontinuation. A premature discontinuation visit and F1 visit will not be performed on the subjects that temporarily stop study drug administration. Whenever possible, Investigators should encourage subjects to continue with on-site study assessments even after they discontinue taking study drug during the Double-Blind Treatment Period. Study assessments and visits would occur following the

schedule of activities (Table 1). IVRS/IWRS, dispense study drug, drug accountability, and PK sampling would not occur at these visits unless study drug administration has resumed. If the subject is unable or unwilling to undergo on-site assessments for an upcoming quarterly visit, study staff should make telephone contact and encourage subjects to allow further assessments. Telephone assessments should only be utilized when necessary. As part of the telephone assessment, the site will elicit or collect information regarding, but not limited to, concurrent medications, occurrence of renal and cardiovascular events including chronic dialysis, and local laboratory reports (if available). If the subject is unwilling to receive phone calls, he/she should be encouraged to allow collection of data about renal and cardiovascular events and recent laboratory values from medical records or through contacts with the treating physician. An authorization to release information from the subject should be obtained.

Home Visits

In exceptional cases, visiting nurse services may be available for use, as needed. Sponsor approval will be required prior to implementation of the nursing service. Study activities such as local or central laboratory sample collection and processing may be conducted in the home or non-hospital/clinic environment by qualified individuals.

Subject Withdrawal

Withdrawal refers to the complete withdrawal from the study for any reason before the end of the study, including death. A subject who withdraws consent will discontinue taking study drug and will be encouraged to return for the Final Treatment/Premature Discontinuation visit within 9 days and the Follow-Up F1 visit 45 days (± 14 days) of the last dose of study drug. Withdrawal of consent for follow-up should be accompanied by documentation of the reason for withdrawal. Withdrawal of consent for study drug should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-subject contact follow-up (e.g., medical records checks). Subjects requesting withdrawal should be informed that withdrawal of consent for follow-up will jeopardize the public health value of the study. Subjects who withdraw should be

explicitly asked about the contribution of possible adverse events to their decision to withdraw consent and any adverse event information elicited should be documented. Subjects who withdraw should do so in writing and failure to do that should be documented by the site and include the reason for the subject's failure to provide written withdrawal of consent. It is expected that subjects who permanently discontinue study drug will agree to remain for follow-up status evaluations. For subjects who are lost to follow-up without withdrawing consent, attempts will be made by the Investigator (or designee) to obtain further information.

Follow-Up Period (45 Days) (Visit F1)

Upon permanent discontinuation of study drug administration or study completion (425 distinct primary renal events have occurred in the responder population), all subjects will have one scheduled Follow-Up (F1) visit occurring 45 days (± 14 days) after the last dose of study drug. Procedures to be performed at the F1 visit are outlined in [Table 1](#). If the subject indicates that he/she will not be able to return for the F1 visit, a telephone contact should be made to assess for the occurrence of adverse events (AEs), serious adverse events (SAEs), and potential endpoints.

Unscheduled Visits

Unscheduled visits may occur for various reasons, including the following: management of an AE or SAE, performing additional investigation(s) for clinically abnormal laboratory test values (e.g., confirming an elevated transaminase value) or other signs and symptoms, any time the investigator feels that it is appropriate for subject safety, dispensing of study drug, etc. If a scheduled visit was missed, all procedures and tests for the missed visit should be performed at an unscheduled visit.

Open-Label Extension Study

Upon study completion, eligible subjects will be invited to participate in an open-label study if their site is participating in the extension study to determine the long-term safety of Atrasentan.

5.2 Selection of Study Population

5.2.1 Inclusion Criteria

A subject will be eligible for initial entry into the study if he/she meets any of the following criteria:

1. Subject is 18 – 85 years of age at the initial Screening S1 visit.
2. Subject, or legal representative, 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.
3. Subject has type 2 diabetes (including patients with latent autoimmune diabetes or insulin-treated patients without a history of diabetic ketoacidosis who also have a negative anti-glutamic acid decarboxylase test AND an elevated post-prandial serum C-peptide level) and has been treated with at least one anti-hyperglycemic medication and ACEi/or ARB (RAS inhibitor) for at least 4 weeks prior to the Screening S2 visit.
4. (intentionally left blank; criterion deleted)

For entry into the **Run-In Period**, the subject must satisfy the following criteria:

5. Screening laboratory values:
 - Estimated GFR 25 to 75 mL/min/1.73 m² [until the eGFR cap on subjects (approximately 300) with a baseline of > 60 mL/min/1.73 m² is reached] and a UACR ≥ 300 and < 5,000 mg/g (≥ 34 mg/mmol and < 565 mg/mmol);
 - Serum albumin ≥ 2.5 g/dL (25 g/L);
 - BNP ≤ 200 pg/mL (200 ng/L);
 - Serum Potassium ≥ 3.5 mEq/L (3.5 mmol/L) ≤ 6.0 mEq/L (6.0 mmol/L); and
 - SBP ≥ 110 and ≤ 180 mmHg at any time during the Screening Period.

Subjects on a MTLDD of a RAS inhibitor for ≥ 4 weeks and on a diuretic at the time of screening, and who satisfy the above criteria may proceed directly to the last visit in the Run-In Period (R6 visit).

Subjects on a MTLDD RAS inhibitor for ≥ 4 weeks and not on a diuretic (unless medically contra-indicated) at the time of Screening will start with a diuretic and participate in Run-In for at least 2 weeks.

For entry into the **Enrichment Period**, the subject must satisfy the following criteria:

6. Based on the last visit of the Run-In Period:
 - Subject received a RAS inhibitor at the MTLDD for the previous 4 weeks with no adjustments of the dose;
 - Subject was on a MTLDD RAS inhibitor and not on a diuretic (unless medically contra-indicated) at the time of Screening and has been in Run-In for at least 2 weeks.

For entry into the **Double-Blind Treatment Period**, the subject must satisfy the following criteria:

7. Based on his/her last visit of the Enrichment Period:
 - Subject has taken a RAS inhibitor at the MTLDD for the previous 6 weeks during the Enrichment Period with no adjustments of the dose;
 - Subject has taken a diuretic at any dose unless medically contraindicated or clinically intolerable in the investigator's judgment (i.e., hypotension or hypokalemia);
 - Subject must not have a **weight change** ≥ 3 kg from the beginning of Enrichment (E1) to the end of the Enrichment Period **AND absolute serum BNP** ≥ 300 pg/mL (300 ng/L) at the last Enrichment visit;
 - Subject must not have an **increase in serum creatinine** > 0.5 mg/dL **AND** **> 20% increase** from the beginning of Enrichment (E1) to the end of the Enrichment Period.

Male subjects must satisfy the following criteria from initial study drug administration through 90 days after last dose of study drug:

8. If male, subject must be surgically sterile or 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.
9. If male, subject must agree not to donate sperm from initial study drug administration through 90 days after the last dose of study drug.

Rationale for the Inclusion Criteria:

- (1) For the safety of the study subjects.
- (2) In accordance with harmonized GCP.
- (3 – 7) To select the adequate subject population with appropriate disease severity for the evaluation.
- (8 – 9) The impact of Atrasentan on pregnancies is unknown.

5.2.2 Exclusion Criteria

A subject will not be eligible for entry into the Run-in Period if he/she meets any of the following criteria:

1. Subject has a history of severe peripheral edema or facial edema requiring diuretics unrelated to trauma or a history of myxedema in the prior 4 weeks to the initial Screening S1 visit.
2. Subject has a history of pulmonary hypertension, pulmonary fibrosis or any lung diseases requiring oxygen therapy (e.g., chronic obstructive pulmonary disease, emphysema).
3. Subject has a documented diagnosis of heart failure, previous hospitalization for heart failure or current 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.
4. Subject has known non-diabetic kidney disease (other than kidney stones).
5. (intentionally left blank; criterion deleted)
6. (intentionally left blank; criterion deleted)
7. Subject has elevated liver enzymes (serum alanine aminotransaminase [ALT] and/or serum aspartate aminotransaminase [AST]) $> 3 \times$ the upper limit of normal (ULN).
8. Subject has a hemoglobin < 9 g/dL (90 g/L).
9. Subject has a sensitivity to loop diuretics.
10. Subject has a history of an allergic reaction or significant sensitivity to Atrasentan (or its excipients) or similar compounds.
11. Subject has a history of chronic gastrointestinal disease, which, in the Investigator's opinion, may cause significant GI malabsorption.
12. Subject has a history of secondary hypertension (i.e., hemodynamically significant renal artery stenosis, primary aldosteronism or pheochromocytoma).
13. Subject has significant comorbidities (e.g., advanced malignancy, advanced liver disease) with a life expectancy of less than 1 year.

14. Subject has clinically significant cerebrovascular disease (CVD) or coronary artery disease (CAD) within 3 months prior to the Screening S1 visit, 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 or Stroke.
15. Subject has received any investigational drug including Atrasentan within 3 months prior to Screening S1 visit.
16. Subject receives dialysis treatments or is expected to receive dialysis or renal transplant within 6 months of screening.
17. Subject is currently receiving rosiglitazone, moxonidine, aldosterone blockers, aliskiren or a combination of ACEi and ARB.
18. (intentionally left blank; criterion deleted)
19. Subject is a premenopausal woman defined as (for study purposes) any female subject with a menses in the past 2 years. For women who are < 50 years old, serum FSH must be greater than 35 IU/L. Women who are surgically sterile or have a history of hysterectomy may not necessarily be postmenopausal, and must also have an FSH > 35 IU/L.
20. Subject is at high risk for QT/QTc prolongation such as a family history of Long QT Syndrome, defined as QTc prolongation exceeding 450 ms in men, or 460 ms in women.
21. Subject has type 1 diabetes.
22. Subject is considered to be clinically unstable regarding general, metabolic or cardiovascular health as determined by the Investigator.

The Rationale for the Exclusion Criteria

(1 – 22) The rationale for the exclusion criteria is 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 the initial Screening S1 visit and 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 Double-Blind Treatment or Follow-Up Periods of the study will be allowed. When returning to treatment, 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). 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 subjects taking any of these medications during the study.

The AbbVie Study Designated Physician (listed in Section 6.5) should be contacted if there are any questions.

5.2.3.1 Guidance for Blood Pressure Management

Recommendations for treatment of hypertension throughout the study will be based on accepted published guidelines for diabetic patients with CKD (e.g., KDIGO, JNC 8) that

utilize various combinations of anti-hypertensive medications which are applied in a step-wise manner to achieve the blood pressure target as recommended by clinical guidelines (standard of care). Diuretics and MTLDDs of RAS inhibitors are essential treatments for blood pressure management in patients with type 2 diabetes and nephropathy.²⁰

Step-wise addition of maximum tolerated labeled doses of anti-hypertensive drugs, such as CCBs (e.g., amlodipine, verapamil or diltiazem) or beta 1-selective agents (e.g., atenolol, metoprolol) have shown benefit in diabetic patients. Alpha-1 blockers (e.g., doxazosin), central alpha-2 agonists or other centrally acting drugs (e.g., clonidine, methyldopa, reserpine) and direct vasodilators (e.g., hydralazine, minoxidil) should only be considered for the most resistant forms of hypertension, recognizing that orthostatic hypotension and edema are commonly observed side-effects.

In cases of orthostatic hypotension, CCBs or beta blocker agents should be first modified or withdrawn at the discretion of the Investigator. The Investigator may be contacted by the Sponsor regarding decreases in blood pressure.

5.2.3.2 Guidance for Using RASi and Other Blood Pressure Lowering Drugs During the Study

- Investigators should attempt to maintain the blood pressure within the range recommended by local guidelines (e.g., KDIGO).
- Per protocol, the MTLDD is defined as the subject's dose of ACEi or ARB, at or below the labeled dose, that does not exhibit any intolerable adverse effects (e.g., hypotension, hyperkalemia), based on the Investigator's assessment.
- If the subject is currently receiving one drug (ACEi or ARB) below the maximum labeled dose, the drug should be titrated to the MTLDD during the Run-In period. Subject's dose of ACEi or ARB will be titrated based on the assessment of tolerability by the Investigator and according to local practice guidelines.
- Subjects should be encouraged to limit their dietary salt intake (< 5 grams per day of sodium chloride) as recommended by the WHO.

- The ACEi or ARB must be stable the 4 weeks before Enrichment. The diuretic should be administered at stable doses during 2 weeks before Enrichment.
- Diuretics may be titrated to help maintain BP target levels.
- If a subject is on the maximum tolerated labeled dose of RAS inhibitor and a diuretic at the lowest possible dose and experiences an adverse medical condition, such as hypotension:
 - The non-RASi blood pressure medications should be down titrated (calcium channel blockers, beta blockers, etc.) before altering the diuretic dose.
 - Subjects under these circumstances are eligible to proceed to the Enrichment period.
- Any changes in RAS inhibitor use or diuretic therapy should be preceded by consideration of any relevant contraindications as per the local product information.

5.2.3.3 Guidance for Managing Elevated Serum Creatinine During Enrichment Period

Reductions in blood pressure may be associated with elevated serum creatinine in patients with CKD. In addition, medications which improve renovascular resistance and glomerular filtration fraction (e.g., RAS inhibitors and ETA receptor blockers like Atrasentan) may cause temporary increases in serum creatinine independent of any blood pressure lowering effect. Subjects who receive Atrasentan during the Enrichment Period may experience elevations of serum creatinine that reflect its effect on renal hemodynamics. For those subjects that demonstrate elevated serum creatinine during enrichment, it is recommended to implement the following activities and re-measure blood for serum creatinine as needed:

1. If the decrease in SBP is > 20 mm Hg from the E1 visit or the absolute value is < 110 mmHg and weight gain from E1 visit is:
 - a. < 2 kg: stop or reduce the dose of diuretic before reducing the dose of non-RAS blood pressure lowering drugs

- b. ≥ 2 kg: reduce the dose of non-RAS blood pressure lowering drugs
- 2. If the decrease in systolic BP is < 20 mm Hg from E1 and the absolute value is > 110 mmHg evaluate for other causes of elevated serum creatinine:
 - a. Use of nonsteroidal anti-inflammatory drugs (NSAIDs)
 - b. Use of cimetidine
 - c. Volume depletion assessed by presence of orthostatic hypotension
 - d. Urinary tract obstruction

5.2.3.4 Guidance for Hyperkalemia Management (Serum Potassium > 5.5 mmol/L)

When serum potassium is > 5.5 mmol/L at any period of the study (including run-in, enrichment and double-blind treatment period), it is recommended to implement the following activities:

1. If serum potassium is ≥ 6.5 mmol/L, emergency management is recommended.
2. If serum potassium is > 5.5 and < 6.5 mmol/L, rule out measurement errors or obvious reasons for the increase (i.e., hemolysis of the sample, subject stopped taking diuretics/lack of compliance, diet transgression, e.g., salt substitutes, bananas, dried fruits, potatoes).
3. If all obvious reasons are ruled out and the subject is receiving a diuretic, increase the dose of the diuretic by 50%. Reassess the subject's tolerability within 1 week as well as their blood pressure, eGFR, Na and K.
4. If all obvious reasons are ruled out and the subject is not receiving a diuretic, it is recommended to start a diuretic. The choice of a thiazide or loop diuretic is at the discretion of the Investigator. Reassess the subject's tolerability within 1 week as well as their blood pressure, eGFR, Na and K.
5. In both of the above noted scenarios (numbers 3 and 4), adjust the dose of diuretic accordingly after 1 week. If the subject's serum potassium is still > 5.5 mmol/L,

reinforce diet counseling/restrictions and consider increasing the dose of the diuretic. If, after another additional week the serum potassium is still > 5.5 mmol/L, reduce the dose of RAS inhibitors by 50%. If hyperkalemia persists or recurs, the RAS inhibitor may be discontinued and the subject may continue in the trial if they are in the Double-Blind Treatment Period.

6. Chronic hyperkalemia should be managed according to the standard of care.
7. Kayexalate treatment may be used for chronic hyperkalemia at the discretion of the Investigator. Because kayexalate can result in sodium loading, susceptible subjects may be at increased risk for fluid retention.

5.2.3.5 Guidance for Stopping RAS Inhibitors During the Double-Blind Treatment Period

1. Hyperkalemia (serum potassium > 5.5 mmol/L) not responding to other interventions (such as diet and diuretics or down-titration of RAS inhibitor).
2. Hypotension where RASi is the only anti-hypertensive medication.
3. Discontinuing RASi is discouraged as a method to delay ESRD.

5.2.3.6 Guidance for Managing Edema or Weight Gain

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). Results will be compared with the previous visit and the site may be contacted by the Sponsor. If there is an increase of ≥ 2 kg during the Enrichment Period or in the Double-Blind Treatment Period, it is recommended to implement the following activities:

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

2. Evaluate for the presence of edema. This may be indicative of fluid retention as the cause for weight gain.
3. Ascertain whether the subject has exceeded the recommended daily dietary salt intake (≤ 5 grams of sodium chloride).
4. 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.
5. If the asymptomatic 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 20 – 40 mg per day of furosemide or equivalent OR Chlorthalidone 25 mg per day or equivalent	Loop diuretic 20 mg per day of furosemide or equivalent OR Chlorthalidone 12.5 – 25 mg per day or equivalent	Chlorthalidone 12.5 mg per day or equivalent
Re-check for BP, weight, edema, eGFR and Hb	1 week SBP target 110 – 140		

6. 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.
7. If weight continues to increase (i.e., > 3 kg in 6 weeks or the previous visit during the Double-Blind Treatment Period), despite the modification in the doses of diuretics, contact the Study Designated Physician for the study.
8. Discontinuation of a diuretic may be allowed under the following conditions:

- 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.
9. An unscheduled visit may be utilized at any time to assess and/or intervene per the Investigator's clinical judgment.
 10. The AbbVie Study Designated Physician should be contacted if there are any questions.

5.2.3.7 Guidance for Glucose Control

1. Adjust anti-diabetic medications to A1C target levels that are recommended by local guidelines.
2. Rosiglitazone should not be used throughout the study.
3. Any changes in anti-diabetic therapy should be preceded by consideration of any relevant contraindications as per the local product information.

5.2.3.8 Guidance for the Diagnosis of Acute Kidney Injury (AKI)

1. It is suggested that the KDOQI Commentary of the 2012 KDIGO Clinical Practice Guideline for Acute Kidney Injury be used for the assessment and treatment of AKI (Am J Kidney Dis 2013).²⁰
2. The cause of AKI should be determined whenever possible.
3. Evaluate subject with AKI promptly to determine the cause, with special attention to reversible causes, such as use of NSAIDs, hypotension, volume depletion or urinary tract obstruction.
4. Diuretics should not be used to prevent or treat AKI except in the management of volume overload.

In the presence of AKI, study drug can be stopped or discontinued temporarily based on the Investigator judgment.

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

Visit Duration in Weeks until Randomization	Screening (2 Weeks)		Run-In Period ^a (1 to 12 Weeks)		Enrichment Period						Double-Blind Treatment Period						F/U Period		
	Wk -14	Wk -13	Wk -12	Week -10, -8, -6, -4	Wk -2	Day 1	Wk 1	Wk 2	Wk 4	Wk 6	Wk 7	Wk 1 Call	Wk 2 Call	T1	Every 3 Mths*	Yearly ^d		Final Treatment/ PD ^e	F1 ^f
Activities	S1	S2	R1	R2, R3, R4, R5	R6	E1	E2	E3	E4	E5 ^b	Randomization ^c	Wk 1 Call	Wk 2 Call	T1	Every 3 Mths*	Yearly ^d	Final Treatment/ PD ^e	F1 ^f	
Informed Consent ^g	X																		
Medical History	X	X ⁱ	X ⁱ	X ⁱ	X ⁱ	X ⁱ													
Concurrent Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Exam ^t						X											X		
Vital Signs ^h	X	X	X	X	X	X	X	X	X	X	X				X	X	X	X	X
Assess Peripheral Edema	X	X	X	X	X	X	X	X	X	X	X				X	X	X	X	X
12-Lead ECG						X										X	X		
Hematology	X				X	X	X	X	X	X	X				X	X	X	X	X
Limited Chemistry	X		X	X	X				X	X					X				
Complete Chemistry						X	X	X			X					X	X	X	X
Liver Function	X					X					X				X	X	X	X	X
Lipid Profile (fasting) ^j						X								X		X			X

Table 1. Study Activities (Continued)

Visit Duration in Weeks until Randomization	Screening (2 Weeks)		Run-In Period ^a (1 to 12 Weeks)		Enrichment Period					Double-Blind Treatment Period					F/U Period		
	Wk -14	Wk -13	Wk -12	Week -10, -8, -6, -4	Wk R6	Day 1	Wk 1	Wk 2	Wk 4	Wk 6	Wk 7	Wk 1 Call	Wk 2 Call	T1		Every 3 Mths* Yearly ^d	Final Treatment/PD ^e
Activities	S1	S2	R1	R2, R3, R4, R5	R6	E1	E2	E3	E4	E5 ^b	Randomization ^c						
BNP	X					X				X				X			X
HbA _{1c}	X										X						X
Urinalysis	X										X						X
FMV Urine Collection for UACR ^k		X			X	X			X	X				X			X
RAS Dose Adjustment	X ^l	X ^l	X ^l														
Call into IVRS ^w	X		X			X			X		X			X			X
Dispense Study Drug ^m						X			X		X			X			
Monitor AEs and SAEs ⁿ	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient (QOL) Questionnaires ^o					X						X				T3, T6 and T9 only		X
Serum and Urine Biomarkers						X				X					T3 only		X

Table 1. Study Activities (Continued)

Visit Duration in Weeks until Randomization	Screening (2 Weeks)		Run-In Period ^a (1 to 12 Weeks)		Enrichment Period					Double-Blind Treatment Period				F/U Period							
	Wk -14	Wk -13	Wk -12	Week -10, -8, -6, -4	Wk R1	Wk R2, R3, R4, R5	Wk R6	Day 1	Wk 1	Wk 2	Wk 4	Wk 6	Wk 7		Wk 1 Call	Wk 2 Call	T1	Every 3 Mths*	Yearly ^d	Final Treatment/PD ^e	F1 ^f
PG Sample																					
PK Analysis ^{g,y}											X	X	X	X ^v			X ^y	X ^y	X ^y	X	
Drug Accountability/Compliance Assessment ^p									X	X	X	X	X				X	X	X	X	
Serum FSH ^f	X																				
Review Subject Diary ^s																	X	X	X	X	
Telephone Contact ^u															X	X					

* From the randomization visit.

- If the subject is already receiving a maximum tolerated labeled daily dose of RAS inhibitor and a diuretic then they will proceed to the Run-In Period R6 visit. The first Run-In visit may start immediately after the subject has met all of the inclusion and none of the exclusion criteria. If the subject is currently not receiving a maximum tolerated labeled daily dose of RAS inhibitor, then the subject will be in the Run-In Period for a minimum of 4 weeks and a maximum of 12 weeks.
- If the subject has a change in serum creatinine > 0.5 mg/dL and > 20% from the beginning of Enrichment to the last visit of the Enrichment Period, a PD visit should be completed within 9 days, and be followed weekly until serum creatinine returns to baseline ± 10%, up to 4 weeks. Subject should also have an F1 visit.
- The number of subjects with eGFR 60 – 75 ml/min/1.73 m² at the Enrichment Period E1 visit who are randomized in the responder population will be capped at approximately 300 subjects.

Table 1. Study Activities (Continued)

- d. T12, T24, T36, T48, etc.
- e. Premature Discontinuation visit should be performed within 9 days after the last dose of study drug for subjects that permanently discontinue study drug prior to study completion.
- f. Upon permanent discontinuation of study drug administration or study completion (425 distinct primary renal events have occurred in the responder population), all subjects will have one scheduled Follow-Up (F1) visit occurring 45 days (\pm 14 days) after the last dose of study drug.
- g. Informed consent can be collected up to 30 days prior to the initial Screening (S1) visit. Informed consent should be obtained prior to the performance of any study procedures.
- h. Vital signs including BP, weight and pulse rate will be collected at every visit. Height will be collected at initial Screening visit only. Temperature will be collected at Randomization visit only. Weight gain will be assessed at each visit. Subject will be queried on an intervening occurrence of laser photocoagulation for diabetic retinopathy.
- i. Complete medical history, including history of tobacco and alcohol use and colonoscopy history, will be obtained during initial Screening visit and updated through the Enrichment Period E1.
- j. Lipid profile tests should be done under fasting conditions.
- k. For Screening, the first morning void (FMV) urine collection will consist of two consecutive FMV samples collected within 2 days of the second Screening visit. For Run-In and Enrichment, the FMV urine collection will consist of three consecutive FMV samples collected within 3 days of the Run-In R6 Visit, E1 visit, E4 visit and the E5 visit. For Treatment and the F1 visit, the FMV urine collection will consist of one FMV sample collected within 1 day of the required Treatment Period Visit (with the exception of 3 FMVs to be collected at the T24 visit). FMV is not required for subjects who present for the Randomization visit and are not randomized and a Final Treatment visit is conducted instead of a Randomization visit.
- l. Only adjust the RAS dose in the Screening or Run-In Period if required to reach the MTLDD.
- m. Doses of the study drug for scheduled visit days should be administered to the subject by site personnel at the clinical site.
- n. Serious adverse events will be recorded after informed consent. Adverse events (serious and non-serious) will be captured beginning at the E1 visit through 45 days after last dose of study drug. Serious adverse event monitoring will continue to be captured 45 days after last dose of study drug and through study completion.
- o. The KDQoL-SFT™ Version 1.3, AQOL-4D (for Australia only) and EQ-5D-5L questionnaires should be administered and completed prior to any study procedures being performed.
- p. Calculation instructions are provided in Section 5.5.6.
- q. Blood samples only to be collected for Atrasentan PK analysis and possible metabolites of Atrasentan.
- r. For women under 50 years of age.

Table 1. Study Activities (Continued)

- s. Subjects will be provided a diary at the Randomization visit and will be instructed to record their weekly weights on the diary under the same circumstances (i.e., same time of day, no shoes or coat during measurement) using the same scale.
- t. Symptom directed physical exam should be performed at all other subsequent visits.
- u. The Investigator or designee will contact each subject 1 and 2 weeks post-randomization to assess for signs and symptoms of hypotension.
- v. For subjects who provide consent and are moving forward into the Double-Blind Treatment Period, if the PG sample is not collected at this visit, it may be collected at any subsequent visit.
- w. IVRS/IWRS will be called at the S1 visit to obtain the subject's screening number and at the first Run-In visit for that subject to confirm the eGFR cap has not been met in order for the subject to continue. The IVRS/IWRS call at the Final Treatment/PD visit is only for the discontinuation of study drug. An IVRS/IWRS call will not be completed at visits for subjects who will not be dispensed study drug.
- y. Samples to be collected at T3, T6, T9, T12 and every 6 months thereafter.

5.3.1.1 Study Procedures

The study procedures outlined in [Table 1](#) are discussed in detail in this section with the exception of the collection of adverse event information (discussed in [Section 6.0](#)) and Pre-screening activities (discussed in [Section 5.1](#)). All study data will be recorded on the appropriate eCRF.

Informed Consent

A signed informed consent will be obtained from the subject before any study procedures are undertaken. Informed consent can be collected up to 30 days prior to the initial Screening (S1) visit. 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 subject during the initial Screening visit and updated through the Enrichment Period E1 visit. 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
	Drinker: consumes at least 3 drinks per year
	Light: less than 2 drinks per day
	Moderate: 2 to 4 drinks per day
	Heavy: more than 4 drinks per day

Physical Examination

A complete physical examination will be performed at the Enrichment E1 visit (baseline physical), and the Final Treatment/Premature Discontinuation visit.

Symptom directed physical exam should be performed at all other visits.

Any clinically significant changes occurring after the baseline physical will be documented as adverse events.

Vital Signs

Vital sign determination of sitting BP, weight and pulse rate will be obtained at all visits. Vital signs performed at the Randomization visit will serve as the baseline. Weight gain will be assessed at every visit. Careful consideration should be used to ensure that the appropriate cuff size is used for all sitting BP determinations. BP will be measured twice according to local standards. One such method includes obtaining BP (using the appropriate cuff size) in the non-dominant arm two times at 2-minute intervals after 5 minutes of rest in the seated position. All BP readings should be collected by experienced site personnel using appropriate technique and equipment. BP should be measured consistently by the same method for all visits. Temperature will be obtained at the Randomization visit only. Height will be collected at the initial Screening visit only. Subjects will be queried for an intervening occurrence of laser photocoagulation for diabetic retinopathy at each visit.

12-Lead Electrocardiogram (ECG)

A 12-lead resting ECG will be obtained at the E1 visit, the yearly Double-Blind Treatment Period visits, and Final Treatment/PD visit. The ECG measurements at the E1 visit will serve as the baseline measurements for clinical assessment.

Patient Reported Quality of Life (QOL) Questionnaires: EQ-5D-5L, AQOL-4D (Australia only) and Kidney Disease Quality of Life (KDQOL-SF™ v1.3)

Subjects will be asked to complete standard quality of life (QOL) questionnaires, EQ-5D-5L, AQOL-4D (for Australia only) and Kidney Disease Quality of Life (KDQOL-SF™ v1.3) as noted in [Table 1](#). The questionnaires should be administered and completed prior to any other study procedures being performed at these visits. Questionnaires will be completed by subjects directly onto paper case report forms (CRF).

When possible, subjects should complete the questionnaires on their own. Subjects with applicable limitations may have the questionnaires completed for them based on their verbal responses by study personnel and/or a legally authorized representative, following questionnaire administration instructions. The site will document in the source Document whether the QOL questionnaires were completed by subject on their own or if their verbal responses were captured by study personnel and/or a legally authorized representative.

Subject questionnaires such as health related QOL or functional status will be captured via subject self-administration to assess treatment efficacy, as outlined elsewhere in the protocol. The subject questionnaires included in this trial are measures of treatment efficacy, data collected in this manner will not be analyzed in any way that would impact the blinded nature of the study, and therefore will only be analyzed at pre-specified time periods where other measures of efficacy are assessed. As part of their guidance on subject reported outcomes, the FDA recommends that adverse effects of treatment be captured separately from measures of treatment effectiveness (i.e., collected within separate instruments). Therefore, given the focus of subject questionnaire data on measuring treatment efficacy, and the fact that these data are not analyzed until database lock (and therefore will not be available to assess safety during the study), these data would not be expected to be reconciled with the safety database nor would they be reported to the Independent Data Monitoring Committee.

Assessment of Edema

Assessment of edema will be performed at every visit. The assessment of edema should be performed by qualified 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.

Subject Diaries

Subjects will be given a diary at the Randomization visit to record their weight on a weekly basis during the double-blind treatment period. Subjects will bring their diary to each visit and site personnel will review the weight changes recorded.

Subjects will be instructed to record their weight every week under the same circumstances (i.e., same time of day, no shoes or coats during measurement) using the same scale. Subjects will be instructed to notify the Investigator if they notice a weight change greater than 2 kilograms over a 2 week period.

Post-Discontinuation Visits/Phone Calls

Subjects who have permanently discontinued study drug administration during the Double-Blind Treatment Period will continue with study assessments and visits following the schedule of activities ([Table 1](#)). IVRS/IWRS, dispense study drug, drug accountability, and PK sampling would not occur at these visits.

If the subject is unable or unwilling to undergo on-site planned assessments, study staff should make telephone contact and encourage subjects to allow further assessments. Telephone assessments should only be utilized when necessary. The telephone assessments will consist of a phone call to the subject every 3 months until the study end. Procedures to be performed during the telephone contact include, but not limited to, eliciting and collecting information regarding concurrent medications, occurrence of renal

and cardiovascular events, SAEs, local laboratory reports (if available), and inquire as to whether the subject has started receiving chronic dialysis. If the subject is unwilling to receive phone calls, he/she should be encouraged to allow collection of data about renal and cardiovascular events and recent laboratory values from medical records or through contacts with the treating physician. An authorization to release information from the subject should be obtained.

Reminder Phone Calls

Subjects will be required to perform several study procedures at home. Therefore, it is recommended that reminder phone calls be performed by Study Site Personnel at specified intervals. [Table 2](#) is an outline for the description and timing of the reminder calls.

Contact

One and two weeks after Randomization, the Investigator or designee will contact the subject to query about occurrence of signs and symptoms of hypotension.

Table 2. Reminder Phone Calls

Study Period	Study Day	Call Description
Screening Period	Approximately 3 days prior to the S2 visit.	Call the subject to remind them to initiate their two consecutive first morning void urine sample collections the 2 days prior to the S2 visit.
Run-In Period	Approximately 4 days prior to the R6 visit.	Call the subject to remind them to initiate their three consecutive first morning void urine samples the 3 days prior to their R6 visit.
Run-In Period	Approximately 4 days prior to the E1 visit (for those subjects that have passed the Run-In Period).	Call the subject to remind them to initiate their three consecutive first morning void urine samples the 3 days prior to their E1 visit and that they must fast for 8 hours prior to the visit and hold their morning dose of antihyperglycemic agents prior to the E1 visit. Also remind them to initiate their 24-hour urine collection (if the subject consented) immediately after their third first morning void urine has been collected.
Enrichment Period	Approximately 4 days prior to the E4 visit (for those subjects that have entered the Enrichment Period).	Call the subject to remind them to initiate their three consecutive first morning void urine samples the 3 days prior to their E4 visit.
Enrichment Period	Approximately 4 days prior to the E5 visit (for those subjects that have entered the Enrichment Period).	Call the subject to remind them to initiate their three consecutive first morning void urine samples the 3 days prior to their E5 visit. Also remind them to initiate their 24-hour urine collection (if the subject consented) immediately after their third first morning void urine has been collected.
Randomization	Approximately 1 day prior to the visit.	Call the subject to remind them of their Randomization visit.

Table 2. Reminder Phone Calls (Continued)

Study Period	Study Day	Call Description
Treatment T1 Visit	Approximately 2 days prior to the visit.	Call the subject to remind them to initiate their first morning void urine sample the day prior to their T1 visit. At this time, also remind the subject that they must fast for 8 hours prior to the visit and hold their morning dose of antihyperglycemic agents prior to their T1 visit. Subjects should be reminded to bring their diary to the visit.
Treatment Visits Every 3 Months	Approximately 2 days prior to the visit.	Call to remind the subject to bring their diary to the visit.
Yearly Visits (i.e., T12, T36, T48, etc).	Approximately 2 – 3 days prior to the visit.	Call the subject to remind them to initiate their first morning void urine sample the day prior to their yearly Treatment visit. Also remind them to initiate their 24-hour urine collection (if the subject consented) immediately after the first morning void urine has been collected. At this time, also remind the subject that they must fast for 8 hours prior to the visit and hold their morning dose of antihyperglycemic agents prior to their yearly Treatment visit. Remind the subject to bring their diary to the visit.
Yearly Visit T24	Approximately 4 days prior to the visit.	Call the subject to remind them to initiate their three consecutive first morning void urine samples the 3 days prior to their yearly Treatment visit. Also remind them to initiate their 24-hour urine collection (if the subject consented) immediately after their third first morning void urine has been collected. At this time, also remind the subject that they must fast for 8 hours prior to the visit and hold their morning dose of antihyperglycemic agents prior to their yearly Treatment visit. Remind the subject to bring their diary to the visit.

Table 2. Reminder Phone Calls (Continued)

Study Period	Study Day	Call Description
Final Treatment/ Premature Discontinuation Visit	Approximately 2-3 days prior to the Final Treatment/ Premature Discontinuation visit.	Call the subject to remind them to initiate their first morning void urine sample the day prior to their Final Treatment/Premature Discontinuation visit. Remind the subject to bring their diary to the visit.
F1 Visit	Approximately 2 days prior to the F1 visit.	Call the subject to remind them to initiate their first morning void urine sample the 2 days prior to their F1 visit. Also remind them to initiate their 24-hour urine collection (if the subject consented) immediately after the first morning void urine has been collected. At this time, also remind the subject that they must fast for 8 hours prior to the visit and hold their morning dose of antihyperglycemic agents prior to their F1 visit.

Clinical Laboratory Tests

Blood draws should be performed before the dose of study drug and after vital sign determinations have been completed at each visit.

A certified central laboratory will be utilized to process and provide results for all clinical laboratory tests throughout the study. In exceptional cases, test results from a local laboratory may be acceptable. Samples will be obtained for the laboratory tests listed in [Table 3](#) according to the schedule of activities in [Table 1](#). The subject should fast (nothing by mouth except water) for 8 hours prior to lipid profile assessments collected at the study visits identified in [Table 1](#). If a subject is not able to fast due to unforeseen circumstances, the non-fasting status will be recorded in the study source documentation. The central laboratory will provide instructions regarding the collection, processing and shipping of these samples.

The Investigator will review all laboratory test results. All laboratory test results that are considered clinically significant by the Investigator will be followed to satisfactory resolution. Laboratory abnormalities 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 an adverse event. The Investigator and AbbVie will be blinded to the UACR laboratory results during the Double-Blind Treatment Period.

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

Covance CLS
8211 SciCor Drive
Indianapolis, IN 46214-2985 USA
Tel: (+1) 317-271-1200
Fax: (+1) 317-273-4030

Laboratory samples will be sent to the following Covance CLS locations depending on the geographic location of the site:

- Indianapolis, IN, USA
- Geneva, Switzerland
- Singapore
- Shanghai, China
- Saitama, Japan

Table 3. Clinical Laboratory Tests

Hematology	Complete Chemistry	Urinalysis	
Hematocrit Hemoglobin Red Blood Cells (RBC) White Blood Cells (WBC) Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable)	Albumin Alkaline phosphatase* ALT (SGPT)* AST (SGOT)* Bicarbonate Blood Urea Nitrogen (BUN) Calcium Cystatin C Potassium Chloride Cholesterol** Creatinine Direct Bilirubin* Glucose** HDL** Insulin (HOMA-IR)** LDH Lipoprotein A** LDL** Phosphorus Sodium	Blood Glucose Ketones pH Protein Specific gravity	
		Urine Tests	
		First morning void urine: UACR 24-hour urine: Albumin Creatinine Sodium Potassium Chloride	
		Additional Tests	
		BNP Pharmacokinetic measurement HbA _{1c} Serum and Urine samples for biological markers Serum FSH	
		Limited Chemistry	Total bilirubin* Total protein Triglycerides** Uric acid VLDL**
		Sodium Albumin Potassium Bicarbonate Creatinine Chloride BUN	

* Liver enzymes.

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

Estimated Glomerular Filtration Rate (eGFR)

The CKD-EPI formula will be used to calculate eGFR at the Screening S1 visit to determine eligibility for the Run-In Period. The central laboratory will also calculate the GFR on the laboratory profile report at each visit during the treatment period.

First Morning Void (FMV) Urine Sample Collections

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.

Three first morning void urine sample collections will be obtained prior to the Run-In R6 visit, Enrichment E1 visit, Enrichment E4 visit, Enrichment E5 visit, and the Treatment T24 visit. One first morning void sample collection will be obtained prior to the Treatment visit T1, the yearly visits (T12, T36, T48, etc.), the Final Treatment/Premature Discontinuation visit, and the Follow-Up Visit F1.

Two first morning void urine sample collections will be obtained prior to the second screening visit.

If a subject did not collect the required samples at any of these visits, re-dispense supplies and instructions for collection of the FMV samples. Once the FMV samples are collected by the subject, he/she will return the samples to the site.

If the FMV sample collection needs to be recollected for a Treatment Period visit, the site should make every effort to maintain the original visit schedule for that subject.

During the Screening and Run-In Periods, the UACR values will be reported to the Investigator by the central laboratory on the laboratory reports.

Subjects who are in the Enrichment Period and present for the randomization visit and who are determined to be ineligible for participation in the Double-Blind Treatment Period or if the non-responder cap has been reached, a premature discontinuation visit can be conducted instead. An FMV for the premature discontinuation visit will not be required for these subjects.

5.3.1.1.1 24-Hour Urine Collection Sub-Study (Additional Consent Needed)

The 24-hour urine collection will be collected as outlined in [Table 4](#) during the study for each subject that consents to participate in this optional sub-study up to a limit of 800 subjects. The subject will be provided with urine collection containers prior to each visit where 24-hour urine is required as outlined in [Table 4](#). The central laboratory will provide specific instructions for collection and storage of the specimens. Subjects will initiate the 24-hour collection within 1 day prior to the respective visit (where 24-hour urine collections are required) and after the third FMV is collected during Enrichment and after the one FMV is collected during Treatment. The 24-hour urine collection will end on the morning of the subject's scheduled study visit. The specimen will be brought to the study visit. All 24-hour urine collections should be initiated on an empty bladder. Each 24-hour urine sample will be analyzed at the central laboratory for the following: albumin, chloride, creatinine, potassium and sodium.

For the Enrichment E1 visit, Enrichment E5 visit and the F1 visit, where subjects must collect their FMVs and a 24-hour urine collection, the procedure is as follows:

- The FMV urine samples will be collected the 3 days prior to (for Enrichment) and the 1 day prior to (for Treatment) the scheduled study visit in the morning. The third (for Enrichment and the T24 visit) or only (for Treatment, with the exception of the T24 visit) FMV is collected the day prior to the scheduled study visit. Immediately after the final FMV is collected (the day before the subject's visit), the subject will then start collecting their 24-hour urine collection. The subject will complete the 24-hour urine collection on the morning of their scheduled study visit.

If a subject did not complete the 24-hour urine collection at the E1 (baseline) visit, the subject should not continue in the 24-hour sub-study. If a subject did not complete the 24-hour urine collection at a subsequent visit, re-dispense supplies and repeat the instructions for the 24-hour urine collection.

If the 24-hour urine collection needs to be recollected for a Treatment Period visit and the subject has consented, the site should make every effort to maintain the original visit schedule.

Table 4 is an outline of the schedule for the 24-hour urine collection sub-study.

Table 4. Study Activities for Optional 24-hour Urine Sub-Study

Activities	Screening		Run-In Period		Enrichment Period					Double-Blind Treatment Period			F/U Period	
	S1	S2	R1	R2, R3, R4, R5	E1	E2	E3	E4	E5	Randomization	T1	Yearly*		Final Treatment/ PD
24-hour urine collection					X					X		X		F1
														X

* T12, T24, T36, T48, etc.

Serum and Urine Samples for Biological Markers

Additional samples of serum and urine will be collected according to the schedule outlined in [Table 1](#). These samples will be sent to the central laboratory (stored at -70°C at the central laboratory) for exploratory analyses of additional biomarkers. The results of serum and urine biomarkers may not be reported in the study summary.

Randomization and Assignment of Subject Numbers

A unique 6-digit Subject Number will be assigned by the IVR to all subjects that complete their first Screening visit. This number will be used to identify the subject throughout the study.

All Screening and Run-In R6 laboratory results must be reviewed by the Investigator prior to the Enrichment Period. Subjects who meet the eligibility criteria will proceed to the Enrichment Period for treatment with Atrasentan 0.75 mg QD. All E5 visit laboratory results must be reviewed by the Investigator and subject eligibility assessed prior to the subject proceeding to randomization.

Eligible subjects will be randomized to receive either placebo or Atrasentan 0.75 mg once daily at the Randomization visit. Unique 8-digit randomization numbers will be assigned as subjects are enrolled in the study and will be captured in the eCRF.

5.3.1.2 Blood Samples for Pharmacogenetic Analysis

One 4 mL whole blood sample for DNA isolation will be collected from each subject who enters the Double-Blind Treatment Period and consents to provide samples for pharmacogenetic analysis. If the sample is not collected at the required visit, it may be collected at any subsequent visit. The procedure for obtaining and documenting informed consent is discussed in [Section 9.3](#).

Whole blood will be collected by standard phlebotomy techniques as described below:

- Collect approximately 4 mL of blood into an appropriately labeled EDTA tube.
- Immediately invert the collection tube 8 to 10 times to reduce the likelihood of clot formation.
- Store samples at -20°C or colder within 30 minutes of the blood draw until shipped/transported to the central laboratory on dry ice sufficient to last during shipment/transport.

Samples will be shipped frozen to AbbVie for DNA extraction and long-term storage. Samples should not be allowed to thaw prior to arrival at AbbVie. Arrangements will be made with the central laboratory for the shipment of samples to AbbVie:

AbbVie Sample Receiving



For China, arrangements will be made with the central laboratory for shipment of samples to the reference laboratories following separately provided instructions.

The sample collection tubes will minimally be labeled with "Pharmacogenetic Sample," the drug number, protocol number, subject number and the study day. AbbVie will store the DNA samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on Atrasentan (or drugs of this class) continues but no longer than 20 years from the end of the study.

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 timepoints outlined in [Table 1](#). 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.

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.

Arrangements will be made with the central laboratory for shipment of samples to the reference laboratories following separately provided instructions.

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 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.

5.3.3 Efficacy Variables

5.3.3.1 Primary Endpoint (Adjudicated)

Time to the first occurrence of a component of the composite renal endpoint: doubling of serum creatinine (confirmed by a 30-day serum creatinine) or the onset of ESRD (eGFR < 15 ml/min/1.73m² (confirmed by a 90-day eGFR), receiving chronic dialysis, renal transplantation or renal death).

5.3.3.2 Secondary Efficacy Endpoints

- Time to a 50% eGFR reduction.
- Time to cardio-renal composite endpoint: confirmed doubling of serum creatinine, ESRD, CV death, nonfatal myocardial infarction, nonfatal stroke.
- Time to first occurrence of a component of composite renal endpoint: confirmed doubling of serum creatinine or the onset of ESRD for all randomized subjects (pooled).
- Time to the CV composite endpoint: CV death, nonfatal myocardial infarction and nonfatal stroke.

5.3.3.3 Additional Endpoints

- Time to 40% reduction in eGFR.
- Change in eGFR slope.
- Change in eGFR after 3 months post randomization treatment.
- Change in eGFR to 45 days after end of treatment (or final observation on treatment).

- Change from baseline to Month 24 post-randomization visit on UACR.
- Time to major vascular event: CV death, nonfatal myocardial infarction, nonfatal stroke, hospitalized unstable angina.
- Time to any vascular event: CV death, nonfatal myocardial infarction, nonfatal stroke, hospitalized unstable angina, or arterial revascularization (coronary, carotid or peripheral).
- Time to congestive heart failure (hospitalized and non-hospitalized).
- Time to major coronary disease events: fatal coronary event, non-fatal myocardial infarction, hospitalized unstable angina.
- Time to Total Stroke: fatal and non-fatal stroke.
- Number of new onset atrial fibrillation/flutter events.
- Cumulative number of acute kidney injury (AKI) events after randomization that are associated with temporary dialysis (< 30 days duration of dialysis).
- Change from baseline to each post-baseline assessment in EQ-5D-5L Index Score and AQOL-4D (Australia only) and KDQOL SF™ version 1.3 parameters.
- Time to all-cause mortality.
- Time to first laser photocoagulation for diabetic retinopathy.
- Cumulative number of laser photocoagulations for diabetic retinopathy (where a laser treatment is considered new if it occurs more than 10 weeks after the last treatment).

5.3.4 Safety Variables

Safety data will be analyzed for the data collected throughout Treatment Period and up to 45 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 treatment visits outlined in [Table 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 parameters may be calculated if useful in the interpretation of the data. Relationship between Atrasentan exposure and clinical efficacy response will be explored using population modeling techniques.

5.3.6 Pharmacogenetic Variables

DNA samples may be analyzed for genetic factors contributing to the subject's response to Atrasentan, or other study treatment, in terms of pharmacokinetics, efficacy, tolerability and safety. Such genetic factors may include genes for drug metabolizing enzymes, drug transport proteins, genes within the target pathway, or other genes believed to be related to drug response. Some genes currently insufficiently characterized or unknown may be understood to be important at the time of analysis. The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to Atrasentan or drugs of this class. The samples may also be used for the development of diagnostic tests related to Atrasentan (or drugs of this class). The results of pharmacogenetic analyses may not be reported with the study summary.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

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

- Chronic dialysis, or renal transplant.
- The subject or subject's legally authorized representative requests withdrawal from the study.
- Investigator request (for any reason).

Subjects who have had study drug discontinuation for any reason other than the above should be encouraged to restart study drug as soon as practically and medically appropriate at the discretion of the Investigator.

If the subject permanently discontinues from study drug administration, after discussion with the Sponsor, the procedures outlined for the Premature Discontinuation/Final Treatment visit must be completed within 9 days of the last dose of study drug. In addition, the procedures outlined for the F1 visit must be completed 45 days (± 14 days) of the last dose of study drug. Following discontinuation of the study drug during the Double-Blind Treatment Period, the subject will continue to be monitored for potential primary and cardiovascular outcome events, including CV death and all SAEs. Events requiring adjudication will continue to be adjudicated using the eClinical[®] system (Section 6.5.1). Subjects who prematurely discontinue from the study will not be replaced. The date and reason for premature discontinuation will be recorded in the subject's source documents and on the appropriate eCRF.

A subject may withdraw at any time without prejudice. If the Investigator, for any reason, decides it is in the best interest of the subject to permanently discontinue study drug, treatment should be stopped but the subject should be encouraged to continue in the study so that important and complete safety information can be obtained. If a subject withdraws or is lost to follow-up, such should be noted, along with the reason for withdrawal on the eCRF. Safety-related reasons for withdrawal are reported to AbbVie as adverse events.

Every effort will be made to retain all randomized subjects in the study. All subjects that are unreachable after at least three documented attempts every 3 months for 9 months, including attempts to contact the subject via phone, email, certified letter, and/or to attempt to reach the subject's secondary contact that was provided on the informed consent, will be considered lost to follow-up.

For subjects who are lost to follow-up during the study, the Sponsor will take reasonable actions to ascertain vital status at the end of the study. The Sponsor will make every effort to encourage investigational sites to match subjects lost to follow-up against the

National Death Registries, and against national/regional cancer registries and vital registries.

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 (e.g., early study termination after interim futility or efficacy analyses) provided that written notice is submitted to the site(s) 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 or designee will immediately notify the Investigator by telephone and subsequently provide written instructions for study termination.

Following study termination for any reason, all subjects must be contacted. At this time, subjects who have not permanently discontinued study drug will be scheduled for the Final Treatment visit and Follow-Up Visit (F1). In subjects who were permanently discontinued from study drug, the next scheduled on-site visit (preferred) or phone call (only if the subject is unable or unwilling to undergo on-site assessments) should be completed to solicit and collect information about any potential endpoint events, SAEs, and local laboratory reports for values such as serum creatinine and eGFR since the previous visit or phone call.

5.4.3 Study Completion

Study Completion is defined as the occurrence of 425 distinct primary renal events in the responder population. Upon reaching Study Completion, the Sponsor (or designee) will contact the Investigators to inform them of Study Completion and request all subjects be contacted. Subjects who have not permanently discontinued from study drug will be scheduled for the Final Treatment Visit and Follow Up visit (F1). Subjects who were permanently discontinued from study drug should complete the next scheduled visit or phone call to solicit information about any potential endpoint events, SAEs, and

laboratory values such as serum creatinine and eGFR since the previous visit or phone call (refer to Premature Discontinuation and Retention section).

The Sponsor will track the number of positively adjudicated primary renal events and the events undergoing adjudication. Because all potential events occurring on or before each subject's last contact will be adjudicated and due to the time it will take to have every subject complete a follow-up visit, there is a possibility the EAC will positively adjudicate more than 425 primary efficacy events.

5.5 Treatments

5.5.1 Treatments Administered

Before randomization, each subject will receive 0.75 mg of Atrasentan once daily during an Enrichment Period. The subjects will continue to take study drug until the Randomization visit and be stratified according to geographic region, baseline albuminuria, and percentage of UACR reduction. Within each stratum, subjects will be randomly assigned in a 1:1 ratio to one of the following blinded treatments:

- Placebo once daily
- Atrasentan 0.75 mg once daily

5.5.2 Identity of Investigational Products

The individual study drug information is presented in [Table 5](#).

Table 5. Identity of Investigational Products

Study Drug	Dosage Strength	Formulation	Manufacturer
Atrasentan	0.75 mg	Film-coated tablet	AbbVie
Placebo for Atrasentan	N/A	Film-coated tablet	AbbVie

Note: All tablets will be identical in appearance.

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.

In the Enrichment Period, subjects will receive open-label Atrasentan 0.75 mg. Subjects will be instructed to take 1 tablet daily.

In the Double-Blind Treatment Period, subjects will receive bottles containing either Atrasentan 0.75 mg or matching Placebo. Subjects will be instructed to take 1 tablet daily. To provide blinded subject doses of Placebo or Atrasentan 0.75 mg once daily, tablets will be manufactured such that they are identical in appearance, and will be packaged and labeled in an identical fashion.

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), protected from moisture, 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. The Investigator will keep a current and accurate inventory of clinical supplies provided by AbbVie. All original study medication containers supplied by AbbVie, whether empty or containing unused medications, will be kept until instructions are provided from the Clinical Monitor, in conjunction with AbbVie.

5.5.3 Method of Assigning Subjects to Treatment Groups

The randomization schedules will be computer generated by the Clinical Statistics Department at AbbVie, North Chicago, IL prior to the start of the study. The original randomization schedules will be securely stored at AbbVie, and a hard copy and electronic file of the randomization schedules will be supplied to Perceptive Informatics in accordance with AbbVie's standard operating procedures (SOP).

At the Screening visit, each subject will be assigned a unique 6-digit subject number by the IVRS/IWRS. [REDACTED]

Subjects meeting entry criteria into the Double-Blind Treatment Period will be randomized via IVRS/IWRS supplied by Perceptive Informatics. The kit bottle number will be 7 digits.

A stratified randomization scheme will be used to ensure desired subject allocation ratio among treatment groups within geographic region (North America, Latin America, Europe, Asia Pacific and Japan), baseline UACR level \leq or $>$ 1000 mg/g, and UACR reduction achieved during the Enrichment Period ($<$ 0%, 0% – $<$ 15%, 15% – $<$ 30%, 30%

– < 45%, 45% – < 60% and \geq 60%). The randomization methods are described in Section 8.3.

Through the IVRS/IWRS, subjects will be assigned in a 1:1 ratio to one of the two treatment groups: placebo once daily or Atrasentan 0.75 mg once daily. All clinical drug supplies (Atrasentan and matching placebo) will be supplied by AbbVie.

5.5.4 Selection and Timing of Dose for Each Subject

Before randomization, each subject will receive Atrasentan 0.75 mg once daily during an Enrichment Period. The subjects will continue to take study drug until the Randomization visit and be randomized to one of the two treatment groups described in Section 5.5.1. Subjects should be administered the first dose of blinded study drug during the Randomization visit. Subjects will be instructed to take study drug once daily at approximately the same time each day (preferably in the morning).

5.5.5 Blinding

Both the Investigator and the subject will remain blinded to the subject's treatment group during the double-blind period of the study. The IVRS/IWRS will be programmed with blind-breaker instructions. The study blind may be broken if, in the opinion of the Investigator, it is in the subject's best interest to know the study drug assignment. The Sponsor (AbbVie) MUST be notified before breaking the blind unless identification of the study drug is required for emergency therapeutic measures. If an emergency therapeutic measure is necessary which warrants breaking of the blind, the Sponsor must be notified within 24 hours of the blind being broken. The date and reason for blind breakage must be recorded in source documentation and on the appropriate eCRF.

5.5.5.1 Blinding of Data for Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) comprised of external physicians and an external statistician will review unblinded safety data periodically throughout the study. The objective of the IDMC is to review key safety information in Study M11-352

and make recommendations to the Sponsor and the Steering Committee (described in Section 5.5.5.3) regarding continuation, modification, or termination of the study without compromising study blind from the perspective of the Sponsor or any other party involved in conduct of the study. The IDMC membership and responsibilities are defined in the IDMC Charter. In addition, the IDMC will review the pre-planned interim analyses and make recommendations guided by the formal stopping rules described in the statistical analysis results plan (SAP).

5.5.5.2 Blinding of Data for Events Adjudication Committee (EAC)

An independent EAC, blinded to study treatment assignment, will adjudicate all events that have the potential to be considered as doubling of serum creatinine, ESRD, cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, heart failure (hospitalized and non-hospitalized), and possibly other endpoints of interest. The EAC Charter describes the roles and responsibilities of the EAC and defines the events to be adjudicated and the manner in which they will be adjudicated. The EAC will judge whether an event meets the predetermined definitions. The Investigator will notify George Clinical of a potential endpoint through a Web portal as outlined in Section 6.5.1. George Clinical will give the Investigator instructions for collecting documentation for the EAC review.

5.5.5.3 Steering Committee

A steering committee will be involved in the design and implementation of the study. Its membership will be representative of the global nature of the study sites and regular meetings will be conducted to evaluate the conduct of the trial, including evaluations from the IDMC and EAC. A separate Steering Committee charter describes the roles and responsibilities of the Steering Committee.

5.5.6 Treatment Compliance

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 visit. The study site

personnel will document compliance during the Enrichment Period by recording the total number of doses returned (brought back) per bottle during each visit in the source document and on the appropriate eCRF page.

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.

To calculate compliance at each visit:

$$\frac{[(\# \text{ of tablets dispensed} - \# \text{ of tablets returned}) / \# \text{ of days from previous visit}] * 100\%}{100\%} = \% \text{ compliance}$$

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.

Subjects will be encouraged to take study drug as prescribed. At each visit, compliance will be assessed and the subject will be counseled if there is evidence of non-compliance. The Investigator or designee will investigate and document the reason for non-compliance.

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 by the site in the 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 or destroyed per instructions from AbbVie and according to local regulations.

The Investigator and/or designated and qualified representatives 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

The design of this study provides a placebo control to assess the efficacy and safety of Atrasentan. Double-blind, parallel group designs are generally acknowledged as standard for unbiased estimates of treatment group differences.

5.6.1.1 Use of an Independent Data Monitoring Committee (IDMC)

Use of an IDMC, comprised of independent experts, to perform the unbiased and consistent evaluation of safety is a well-established component of ethical, well-run clinical studies.

5.6.2 Appropriateness of Measurements

All efficacy measurements in this study are standard. 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 efficacy and safety of Atrasentan on slowing the progression of chronic kidney disease (CKD) as adjudicated by assessing time to doubling of serum creatinine or time to ERSD (composite primary endpoint) in subjects with type 2 diabetes and nephropathy that are currently being treated with the MTLDD of a RAS inhibitor.

Therefore, subjects who have been treated with a stable dose of ACEi or ARBs, who have an estimated GFR ≥ 25 and ≤ 75 mL/min/1.73 m² by epidemiology collaboration (EPI)

formula, who have a UACR ≥ 300 and ≤ 5000 mg/g, and who are ≥ 18 years of age have been selected as the target population for this study. Subjects who have a history of an allergic reaction or significant sensitivity to Atrasentan or to drugs similar to the study drug will be excluded to avoid confounding factors related to the active disease process.

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 ABT-627 for up to 7 weeks during the Enrichment Period. After enrichment, subjects may be randomized to receive a maximum of 0.75 mg QD of ABT-627 for up to approximately 6 years.

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. [REDACTED]

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 (non-serious and serious) reported from the time of study drug administration until 45 days following discontinuation of study drug administration have elapsed will be collected, whether solicited or spontaneously reported by the subject. In addition, serious adverse events will be collected from the time the subject signed the study-specific informed consent.

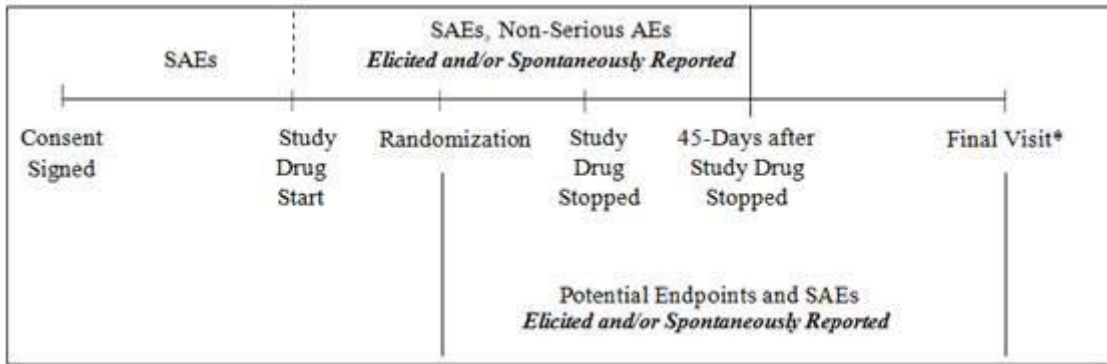
In the event that study drug is interrupted, adverse events and serious adverse events will be collected throughout the interruption. If treatment with study drug is discontinued for any reason the reason will be recorded and the subject should be encouraged to remain in the study so important safety information can be obtained. All adverse events and serious adverse events leading to discontinuation of study drug or discontinuation of study will be collected. Once a subject withdraws consent to participate in the study, no further information can be collected from the subject.

For subjects who permanently discontinue study drug and continue in the study, beginning after the 45-day post study drug discontinuation period, the Investigator will

monitor each subject for potential endpoints and SAEs for the duration of the study (refer to Section 5.1 and Section 6.5.1).

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

Figure 2. Adverse Event Collection



* Final visit refers to final subject contact as referenced in Section 5.4.2 and Section 5.4.3.


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 use the SAE non-CRF paper forms and be faxed to the Clinical Pharmacovigilance within 24 hours of site being made aware of the serious adverse event:

FAX to: [REDACTED]
Email: [REDACTED]

For safety concerns, contact the Renal Safety Management Team at:

Renal Safety Management


AbbVie Inc.
1 North Waukegan Road
North Chicago, IL 60064

Office: 

Email: 

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

Primary Study Designated Physician:



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:

Phone: 

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.

In Japan, the Investigator will provide documentation of all protocol-related serious adverse events to the Director of the investigative site and the Sponsor.

6.5.1 Potential Endpoint Reporting for Adjudication

The Investigator or designee will report potential endpoints through a Web Portal (eClinical[®]) within 5 days of being aware of potential event. The vendor (George Clinical) will work with the site to obtain pertinent information to complete a case packet. Once the packet is confirmed complete by George Clinical, they will assign to the EAC committee for review and adjudication. Details of the endpoint reporting process are listed in the Endpoint Reporting site manual.

The following events will be reported by the site in eClinical[®] for subjects in the Enrichment Period:

- Death
- Nonfatal Stroke
- Nonfatal MI
- Heart Failure (hospitalized and non-hospitalized)

The following events will be reported by the site in eClinical[®] for subjects in the Double-Blind Treatment Period including subjects who continue follow-up after premature discontinuation of study drug during the Double-Blind Treatment Period:

- Doubling of Serum Creatinine
- ESRD
- Death
- Nonfatal Stroke
- Nonfatal MI
- Heart Failure (hospitalized and non-hospitalized)

The Sponsor may request reporting of additional safety-related events into eClinical[®].

6.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued immediately (Section 5.4.1).

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

Pregnancy in a study subject 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. 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.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol. The 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 Investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and their assigned CRO Clinical Monitor or AbbVie:

Primary Contact:

Alternate Contact:



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.

In Japan, the Investigator will record all protocol deviations in the appropriate medical records at site.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

All statistical analyses with between treatment comparisons are conducted for the Double-Blind Period. Testing of treatment group differences for efficacy endpoints between the Atrasentan arm and placebo arm will be conducted at a two-sided significance level of 0.05 (suitably adjusted for group-sequential testing and multiplicity for the primary and secondary endpoints). Safety data involving the Enrichment Period will be presented for exploratory purposes and no statistical comparisons will be made.

The primary efficacy endpoint of the study is the time to first occurrence of an adjudicated renal composite event defined as either doubling of serum creatinine (confirmed by a 30-day serum creatinine) or the onset of ESRD in subjects who achieve at least 30% reduction in UACR in the Enrichment Period (responders). Approximately 3,500 subjects (2,500 subjects who achieve at least 30% reduction in UACR in the Enrichment Period and approximately 1,000 subjects who achieve less than 30% reduction in UACR in the

Enrichment Period) will be randomized in a 1:1 ratio to 2 treatment groups: placebo or Atrasentan 0.75 mg/day.

For summarizing continuous variables (e.g., weight) the mean, standard deviation, median, minimum and maximum values will be provided. For selected variables, appropriate percentiles may also be provided. For categorical variables (e.g., gender), frequencies and percentages will be provided.

Unless noted otherwise, all analyses will be performed using SAS version 9.3 (SAS Institute Inc., Cary, NC 27513) under the UNIX operating system.

8.1.1 Analysis Datasets

The following datasets will be used for the analysis of all efficacy and other non-safety endpoints. For these analyses, subjects will be classified according to the treatment group to which they were randomized.

- The **Intention-to-treat (ITT) Responder Set** will serve as the primary dataset for the analysis of efficacy in this study. It will consist of all randomized subjects who achieve at least 30% reduction in UACR in the Enrichment Period (responders).
- The **ITT Non-responder Set** will consist of all randomized subjects who achieve less than 30% reduction in UACR in the Enrichment Period (non-responders).
- The **ITT Pooled Set** will consist of all randomized subjects (both responders and non-responders) and will be used for a pooled analysis of efficacy.

The following datasets will be used for the analysis of safety endpoints. For these analyses, subjects will be analyzed according to the treatment they actually receive during the double-blind phase.

- The **All Treated Responder Set** includes all randomized subjects who achieve at least 30% reduction in UACR in the Enrichment Period and receive at least one dose of study drug during double-blind phase.

- The **All Treated Non-responder Set** includes all randomized subjects who achieve less than 30% reduction in UACR in the Enrichment Period and receive at least one dose of study drug during double-blind phase.
- The **All Treated Set** includes all randomized subjects who receive at least one dose of study drug during double-blind phase.

Additionally, an **All Atrasentan Set** comprising all subjects who receive at least one dose of Atrasentan, including both Enrichment and Double-Blind Treatment Periods, is defined for the purposes of data analysis.

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

Definition of Baseline

For treatment comparisons and summaries based on the Double-Blind Period, baseline values refer to the last non-missing value observed prior to or at the time of randomization. This includes treatment comparisons performed for the ITT responder set, ITT non-responder set and the ITT pooled set (Section 8.1.1).

For determination of doubling of serum creatinine, baseline values refer to the last non-missing value observed prior to or pre-dose on the first day of Atrasentan therapy at the beginning of the Enrichment Period.

For purposes of summarizing safety and efficacy for the Enrichment Period and the entire study treatment period (Enrichment and Double-Blind Treatment Periods combined), baseline values refer to the last non-missing value observed prior to or pre-dose on the first day of Atrasentan therapy (Treatment Day 1) at the beginning of the Enrichment Period. For the Enrichment Period, initial UACR is computed as the geometric mean of UACR collected at Visits R6 and E1, and final UACR is computed as the geometric mean of the UACR values collected at Visits E4 and E5, provided at least three UACR values are available in each case. UACR will be considered to be missing otherwise.

Analysis

All demographic and baseline characteristics such as gender, race, age, weight, etc., will be summarized by treatment group to assess comparability of treatment groups for the ITT analysis sets.

Subject disposition, completion of study, or discontinuation from the study (along with the primary reason for discontinuation), will be summarized by treatment group for the ITT analysis sets. The primary reasons for discontinuation of study drug during the Double-Blind Treatment Period will be summarized by treatment group. A summary of subject disposition and discontinuation during the Enrichment Period will be provided using the all Atrasentan set.

Concomitant medications will be reported by generic name assigned by the World Health Organization (WHO) dictionary and their usage will be summarized by treatment group for the ITT analysis sets.

In addition, the concomitant use of RAS inhibitors will be summarized for the ITT analysis sets as follows:

- For each medication in the RAS inhibitor class, the average daily dose will be calculated across the Double-Blind Treatment Period and summary statistics of the average daily dose will be provided by treatment group.
- The number and percentage of subjects who change their dosage or initiate prescriptions of another RAS inhibitor during the Double-Blind Treatment Period of the study will be tabulated by treatment group.

The concomitant use of diuretics will be summarized for the ITT analysis sets as follows:

- For each medication in the diuretics class, the average daily dose will be calculated across the days that diuretics are taken during the Double-Blind Treatment Period and summary statistics for the average daily dose will be provided by treatment group.

- The number of days that a subject is on any diuretics during the Double-Blind Treatment Period and the percentage of such days over the subject's total duration of the Double-Blind Treatment Period will be computed. Summary statistics will be provided for the percentage of days on any diuretics by treatment group.
- The number and percentage of subjects who take diuretics, change their dosage, or initiate prescriptions of another diuretic medication during the Double-Blind Treatment Period will be tabulated by treatment group.

8.1.3 Efficacy Analyses

Efficacy analyses for treatment comparisons will be performed on the ITT responder population, ITT analysis sets as follows.

For UACR value for the screening visit, the geometric mean of UACR values from two consecutive FMV urine samples collected prior to that visit will be used. For scheduled visits during the Run-In and Enrichment Period, the geometric mean of values from all FMV urine samples available for that visit will be used. The initial UACR value (at the beginning of enrichment) is defined as the average (geometric mean) of the UACR values collected at the last week of Run-In (Visit R6) and the first day of Enrichment (Visit E1) (a minimum of three UACR values are required). The final UACR in the Enrichment period is defined as the average (geometric mean) of the UACR values collected from the Enrichment Week 4 (Visit E4) to Enrichment Week 6 (Visit E5) (a minimum of three UACR values are required). The initial (or final) average UACR value will be considered to be missing if less than three values are available for its calculation. The percent change in UACR that is used to define responders and non-responders at the end of the Enrichment Period is calculated with the initial UACR as the reference value. For on-treatment visits and the 45-day follow-up, the FMV urine samples will consist of a single collection within 1 day of the yearly Treatment visits (with the exception of 3 FMVs to be collected just prior to the T24 visit).

8.1.3.1 Primary Efficacy Analyses (Responders)

The primary efficacy endpoint is the time to the first occurrence of a component of the composite renal endpoint: doubling of serum creatinine (confirmed by a 30-day serum creatinine) or the onset of ESRD. Only events adjudicated by the Events Adjudication Committee (EAC) will be considered in defining this endpoint. The time of randomized treatment assignment will be considered "time zero" (time origin) for the derivation of the primary endpoint. In defining the composite endpoint, reaching any component of the composite will be considered as attaining the endpoint. For subjects for whom an event is not recorded, the time-to-event will be right-censored at the date of the last visit/assessment at which there is complete information for all components of the composite.

A Cox proportional-hazard regression model will be performed on the ITT responder set to estimate the hazard ratio of Atrasentan to placebo and its 95% confidence interval. The primary efficacy analysis for treatment comparison will be conducted using a stratified log-rank test, adjusting for the following stratification factors.

- UACR level at the beginning of the Enrichment Period ($\leq 1,000$ mg/g [113 mg/mmol] or $> 1,000$ mg/g [113 mg/mmol]) and
- UACR reduction during Enrichment Period (30% – $< 45\%$, 45% – $< 60\%$, and $\geq 60\%$).

Kaplan-Meier estimates for cumulative event rates will be plotted. A Cox proportional-hazards regression model with treatment group and the relevant factors (defined in the Statistical Analysis Plan) as explanatory variables will be performed to estimate the hazard ratio of events comparing placebo to Atrasentan and its 95% confidence interval.

In addition, the individual components of the primary efficacy endpoint, i.e., the time to the first occurrence of doubling of serum creatinine (confirmed by a 30-day serum creatinine) or eGFR < 15 ml/min (confirmed by a 90 day eGFR) and the time to the

first occurrence of the onset of dialysis, renal transplant or renal death will be analyzed separately using the same methods as specified above. In analyzing the individual components, first occurrence of only that specific endpoint will be considered as events.

Subgroup analyses for subgroups based on age, gender, race, geographical regions and important baseline characteristics will also be performed.

8.1.3.2 Secondary Efficacy Analysis

These pre-specified secondary efficacy endpoints are listed according to their clinical importance (Section 5.3.3.2) and will be analyzed in a hierarchical (step-down) fashion as described in Section 8.1.3.5.

The analyses of these time-to-event endpoints will follow the same methods as specified for the primary efficacy analysis.

8.1.3.3 Additional Efficacy Analysis

The additional time-to-event endpoints will be analyzed for all ITT analysis sets using the same methodology as specified for the primary efficacy endpoint.

The additional endpoints of change from baseline in eGFR to 45 days after end of treatment, change from baseline to Month 24 post-randomization visit on UACR, change from baseline to each post-baseline assessment in EQ-5D-5L Index Score and AQOL-4D (Australia only) and KDQOL SF™ version 1.3 parameters will be analyzed using a mixed model of repeated measures (MMRM). In this model, the response vector consists of the change from baseline values at each post-randomization assessment. The model will include the fixed effects of treatment, time (treated as a categorical variable), treatment-by-time interaction, baseline value and baseline-by-visit interaction. An unstructured covariance matrix will be used to model the correlation among longitudinal measurements, and Satterthwaites's approximation will be used to estimate the denominator degrees of freedom. The treatment difference between placebo and Atrasentan 0.75 mg QD at Month 24 will be estimated from the model using a

CONTRAST statement. *P* value and associated 95% confidence interval will be provided. The treatment effect at each post-baseline visit will be estimated from the model using a CONTRAST statement. The endpoints of change in eGFR after 3 months post-randomization treatment and change in eGFR slope from baseline to 45 days after end of treatment will be analyzed using a linear regression model.

The additional efficacy endpoints of number of new onset atrial fibrillation/flutter events, cumulative number of AKI events after randomization that are associated with temporary dialysis, and cumulative number of laser photocoagulations for diabetic retinopathy (where a laser treatment is considered new if it occurs more than 10 weeks after the last treatment), will be analyzed using chi-square tests.

Estimates of treatment effects and associated 95% confidence intervals will be provided.

8.1.3.4 Efficacy Analyses for the 24-Hour Urine Sub-Study

Twenty-four-hour urine will be collected prior to dosing in the Enrichment Period (Visit E1), and during enrichment at Visit E5, 12 months after randomization (Visit T12), yearly thereafter and at the follow-up visit (Visit F1) for each subject that consents to participate in this optional sub-study up to a limit of 800 subjects.

Longitudinal analyses of change from baseline in mean 24-hour urine indices (albumin, creatinine, sodium, potassium and chloride) will be performed using an MMRM. The model will include the fixed categorical effects of treatment, country, visit, and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline measurements and baseline-by-visit interaction. Within group LS mean change from baseline to each post-baseline visit as estimated from the MMRM will be presented graphically.

The mean of each 24-hour urine component for each subject is calculated as the average of all the valid measurements taken in that 24-hour period.

8.1.3.5 Multiplicity

There is a single primary efficacy endpoint (time to the first occurrence of a component of the composite renal endpoint: doubling of serum creatinine, eGFR < 15 ml/min or the onset of chronic dialysis, renal transplant or renal death), and one primary comparison between placebo and Atrasentan 0.75 mg QD for the ITT responder set. Other than a group-sequential adjustment for the interim analysis (Section 8.1.5), no additional adjustment for multiplicity is needed for the primary efficacy analysis.

To control the family-wise type I error rate at 0.05, each secondary endpoint will be tested at the interim or final analysis only when the primary endpoint is statistically significant at the corresponding analysis using the same alpha level as the alpha spent for the primary endpoint at the interim or final analysis, respectively, following a hierarchical (step-down) multiple testing procedure. The primary efficacy comparison of the study will serve as the gatekeeper for the test of the secondary endpoints.

8.1.4 Safety Analyses

All safety analyses will be conducted on the all treated analysis sets (i.e., all-treat responder set, all-treated non-responder set, and all treated set, respectively) and the all Atrasentan analysis set (where indicated). No formal statistical testing of treatment difference is planned.

Derivation of Safety Endpoints

Safety data collected from the first dose up to 45 days post last dose in the Double-Blind Period will be included in the relevant analyses for the all treated analysis sets, unless otherwise specified in the Statistical Analysis Plan (SAP) document. Safety data collected during the Enrichment Period will be summarized for exploratory purposes for the all Atrasentan analysis set.

Study Drug Exposure and Compliance

The number of days on study drug will be summarized by treatment group and overall. The number and percentage of subjects with at least 70% compliance with study drug at each visit will be summarized by treatment group and overall.

8.1.4.1 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 follow-up period of the study will be summarized by the treatment group in descending order of overall frequency by MedDRA preferred term, as well as by system organ class (SOC) and MedDRA preferred term. The incidence rates of treatment-emergent AEs for each treatment group 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 by treatment group. Serious adverse events will be evaluated in a similar manner.

Specifically, adverse events will be summarized by treatment group as described below:

1. An overview of the number and percentage of subjects with treatment-emergent adverse events.
2. A summary of the number and percentage of subjects with treatment-emergent adverse events by primary MedDRA system organ class and preferred term.
3. A summary of the number and percentage of subjects with treatment-emergent serious adverse events by primary MedDRA system organ class and preferred term.
4. 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.

5. A summary of the number and percentage of subjects with drug-related treatment-emergent adverse events by primary MedDRA system organ class and preferred term.
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.

8.1.4.2 Clinical Laboratory Data

For each laboratory test, the mean change from baseline to the minimum, maximum, and to each visit will be summarized by treatment groups. 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 by treatment group.

8.1.4.3 Vital Signs Data

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

8.1.4.4 ECG Analyses

The number and percentage of subjects with shifts from baseline to the final in the categories of normal, abnormal as indicated by the study site investigators will be summarized. Shifts from baseline at each visit where ECG data is collected will be summarized similarly.

8.1.4.5 Safety Data in the Enrichment Period

Safety data in Enrichment Period and will be summarized. Descriptive statistics, including the number of observations (N), mean, and standard deviation (SD) for continuous variables and counts and percentages for discrete variables, will be provided

for AE, serious AE, laboratory, vital sign and ECG parameters, for the Enrichment Period. In addition, the cumulative incidence of AE and serious AE adjusting for the duration of exposure on Atrasentan during the Enrichment Period and the Double-Blind Treatment Period will be summarized. For subjects who discontinue prior to randomization or who are randomized to placebo, this duration of exposure on Atrasentan will be their duration of exposure in the Enrichment Period.

8.1.5 Interim Analysis

An interim analysis of efficacy will be performed when the number of accrued primary events in the responder population is in the range of 50% to 75% of the targeted 425 events for the study. An alpha-spending function approach will be used to ensure that the overall one-sided type I error rate will be controlled at 0.025 or less. In addition, an interim analysis of efficacy data for futility only may be performed at an earlier time point. No adjustment to the type I error rate will be made for the futility assessment.

To preserve the integrity and the validity of trial data, an external Statistical Analysis Center will perform the requisite interim analyses and present the results to IDMC. Further details of the interim analysis plan will be provided in the Statistical Analysis Plan (SAP) and IDMC Charter. In making any decision to recommend discontinuation of the study, either for superior efficacy of Atrasentan or for futility, the IDMC shall be guided by a formal stopping rule described in the SAP.

8.1.6 Independent Data Monitoring Committee (IDMC) and Independent External Statistician

This study will have an IDMC composed of at least two external clinicians and one external statistician to review and make recommendations based on the results of the unblinded interim analysis and periodic reviews of the safety of Atrasentan. The IDMC membership and responsibilities, and details of the interim analyses and safety reviews, will be documented in a charter that will be prepared prior to the first IDMC review meeting.

The AbbVie project statistician will serve as an intermediary between the external Statistical Analysis Center and the Sponsor if the IDMC has questions or requests for additional data.

Communications from the IDMC to the Sponsor will not contain information that can potentially unblind the representatives of the Sponsor directly responsible for the study.

The first IDMC meeting will occur after the first 30 subjects with a UACR < 0% (non-responders) are randomized and have completed the T1 visit or after the first 100 subjects have completed the enrichment period, whichever occurs first. The second IDMC meeting will occur after the first 100 subjects are randomized. Subsequently IDMC meetings will occur after 25%, 50%, and 75% of the primary endpoints have occurred. In addition, the IDMC will meet at least every 6 months and, if necessary, at times other than those scheduled if either the Sponsor or the IDMC determines that an unplanned meeting is warranted based on safety concerns.

The IDMC will make recommendation(s) to AbbVie (Sponsor representative) based on their review. The Sponsor representative will accept or reject the IDMC's recommendation.

The IDMC will review unblinded efficacy data as specified in Section 8.1.5.

8.2 Determination of Sample Size

The sample size for the Double-Blind Treatment Period is calculated based on the primary efficacy endpoint of time to the first occurrence of a renal composite event comparing Atrasentan treatment with placebo in the responder population. A total of 425 events in the ITT set are needed to detect a 27% hazard reduction (HR of 0.73) with approximately 90% power at two-sided alpha level of 0.05. Based on the annual event rate in RENAAL study (~13%) and ALTITUDE (~3%), our estimate of the annual placebo event rate in our study is 6%.^{21,22} With the assumption of annual event rate of 6% in placebo group, 42-month accrual period, approximate 6 year duration of the Double-Blind Period, and an annualized lost to follow-up rate of 2%, a total of approximately 2,500 subjects who

achieve at least 30% reduction in UACR (responders) during the Enrichment Period (1,250 subjects per group) are needed for randomization.

In addition, approximately 1,000 subjects who achieve less than 30% reduction in UACR (non-responders) in Enrichment period will also be randomized in a 1:1 ratio to Atrasentan treatment or placebo since it has not been determined whether Atrasentan can reduce long-term CKD progression in this population.

8.3 Randomization Methods

Subjects will be randomized to Placebo QD (plus stable dose of RAS inhibitor) or Atrasentan 0.75 mg QD (plus stable dose of RAS inhibitor) in a 1:1 ratio at the beginning of the Double-Blind Treatment Period. The Randomization will be stratified by the following factors:

- Geographic region (North America, Latin America, Europe, Asia Pacific, and Japan),
- UACR level at the beginning of the Enrichment Period \leq or $>$ 1000 mg/g, and
- UACR reduction during the Enrichment Period: $<$ 0% (approximately at 250); 0% to $<$ 15% and 15% to $<$ 30% (approximately at 750); 30% to $<$ 45%, 45% to $<$ 60% and \geq 60%.

A strategy will be utilized to provide gating of subjects into the responder and non-responder groups in order to allow for temporal similarity in accrual of subjects and relatively similar exposure times on study drug. The implementation of the responder/non-responder ratio will be through the IRT system.

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.

Pre-screening will only be performed if the subject has voluntarily signed and dated a pre-screening informed consent, approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. The pre-screening informed consent must be signed before the pre-screening testing is performed. If the subject does not consent to the pre-screening testing, it will not impact the subject's participation in the study.

Pharmacogenetic sample collection and analysis will only be performed if the subject has voluntarily signed and dated a pharmacogenetic informed consent, approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. The pharmacogenetic informed consent must be signed before the pharmacogenetic testing is performed. If the subject does not consent to the pharmacogenetic testing, it will not impact the subject's participation in the study.

Twenty four-hour urine sub-study testing will only be performed if the subject has voluntarily signed and dated a 24-hour urine informed consent, approved by an IRB/IEC, after the nature of the sub-study testing has been explained and the subject has had an opportunity to ask questions. The 24-hour urine sub-study informed consent must be signed before the 24-hour urine collections are taken. If the subject does not consent to the 24-hour urine sub-study testing, it will not impact the subject's participation in the study.

If the subject has provided consent, the subject's primary physician will be notified about the subject's involvement in the study once the subject has entered the Run-In Period. This is not applicable if the Investigator is the subject's primary physician or if the subject does not have a primary physician.

If the subject is willing, he/she will be asked to provide a name and phone number for a secondary contact in the event that the Investigator is unable to reach the subject for follow-up.

9.3.1 Informed Consent Form and Explanatory Material

In Japan, the Investigator will prepare the consent form and explanatory material required to obtain subject's consent to participate in the study with the cooperation of the sponsor and will revise these documents as required. The prepared or revised consent forms and explanatory material will be submitted to the sponsor. Approval of the IRB will be obtained prior to use in the study.

9.3.2 Revision of the Consent Form and Explanatory Material

In Japan, when important new information related to the subject's consent becomes available, the Investigator will revise the consent form and explanatory material based on the information without delay and will obtain the approval of the IRB prior to use in the study. The Investigator will provide the information, without delay, to each subject already participating in the study, and will confirm the intention of each subject to continue the study or not. The Investigator shall also provide a further explanation using the revised form and explanatory material and shall obtain written consent from each subject of their own free will to continue participating in the study.

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 including adjudicated primary and secondary endpoints.

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 Principal 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.

Subject completed Quality of Life surveys will be recorded directly on the paper questionnaire and the site staff will enter data directly into the eCRF.

11.0 Data Quality Assurance

Prior to the initiation of the study, an Investigator's meeting will be held with AbbVie personnel, the Investigators and appropriate site personnel, and the clinical research associates (CRA) for the study. This meeting will include a detailed discussion of the protocol, performance of study procedures, CRF completion, and specimen collection methods. In addition to the Investigator's meeting, the study personnel at each site will be trained on the study procedures by a CRA at a study initiation visit and 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, and urinalysis 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.

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.

Any pharmacogenetic research that may be done using DNA samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management. Hence, neither the Investigator, the subject, nor the subject's physician (if different from the Investigator) will be informed of individual subject pharmacogenetic results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, genetic researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved

in this research other than for regulatory purposes. Aggregate pharmacogenetic information from this study may be used in scientific publications or presented at medical conventions. Pharmacogenetic information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

The Investigator will conduct the study in compliance with the protocol and complete the study within the timeframe 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 (EMA) Guidance on Investigator's Signature for Study Reports.

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

The Last Subject Last Visit date is defined as the last date of an observation or contact with a subject.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for Atrasentan and the product labeling 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 Randomized, Multicountry, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Atrasentan on Renal Outcomes in Subjects with Type 2 Diabetes and Nephropathy
SONAR: Study of Diabetic Nephropathy with Atrasentan

Protocol Date: 19 May 2017

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
		General Medicine Therapeutic Area
		General Medicine Therapeutic Area
		Clinical
		Data and Statistical Sciences, Statistics
		Bioanalysis
		Pharmacokinetics and Pharmacodynamics
		Clinical Drug Supply Management

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

"Sponsor/Emergency Contact:" previously read:

Sponsor/Emergency
Contact:

Has been changed to read

Sponsor/Emergency
Contact:



Section 1.2 Synopsis

Previously read:

AbbVie Inc.	Protocol Number: M11-352
Name of Study Drug: Atrasentan (ABT-627)	Phase of Development: 3
Name of Active Ingredient: (2R,3R,4S)-4-(1,3-benzodioxol-5-yl)-1-[2-(dibutylamino)-2-oxoethyl]-2-(4-methoxyphenyl) pyrrolidine-3-carboxylic acid, monohydrochloride	Date of Protocol Synopsis: 11 February 2015
Protocol Title: A Randomized, Multicountry, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Atrasentan on Renal Outcomes in Subjects with Type 2 Diabetes and Nephropathy - SONAR: Study of Diabetic Nephropathy with Atrasentan	
Objectives: The study objective is to evaluate the effect of Atrasentan compared with placebo on time to doubling of serum creatinine or the onset of end stage renal disease (ESRD) in subjects with type 2 diabetes and nephropathy who are treated with the maximum tolerated labeled daily dose (MTLDD) of a Renin-Angiotensin System (RAS) inhibitor. In addition, the study will assess the effects of Atrasentan compared with placebo on cardiovascular morbidity and mortality, urine albumin excretion, changes in estimated glomerular filtration rate (eGFR), as well as on the impact on quality of life in subjects with type 2 diabetes and nephropathy.	
Investigators: Multicenter study	
Study Sites: 800 – 900 sites globally.	
Study Population: Subjects that have type 2 diabetes with nephropathy (eGFR of 25 – 75 ml/min/1.73 m ² and a urinary albumin to creatinine ratio (UACR) ≥ 300 mg/g creatinine and < 5,000 mg/g).	
Number of Subjects to be Enrolled: Approximately 4,148 subjects will be randomized to the Double-Blind Treatment Period.	
Overall Study Design:	
<p>The diagram illustrates the study design timeline. It begins with a Screening Period (S1 to S2). This is followed by a Run-In Period (R1 to R6) where subjects receive the maximum tolerated labeled dose of RAS. The Run-In Period is split into two paths: one for subjects receiving the dose for up to 2 weeks and another for up to 12 weeks. Following the Run-In Period is an Enrichment Period (E1 to E5) where subjects receive Atrasentan 0.75 mg QD. Subjects are then randomized based on UACR reduction: those with ≥ 30% reduction are randomized to either Atrasentan 0.75 mg QD (1574 subjects) or Placebo QD (1574 subjects); those with < 30% reduction are randomized to either Atrasentan 0.75 mg QD (500 subjects) or Placebo QD (500 subjects). The Double-Blind Treatment Period follows randomization, leading to a Follow-Up Period (45 Days) ending at F1. Key visits include S1, S2, R1-R6, E1-E5, Randomization, T1, T3, and the Final Tx Period Visit. Visits occur every 3 months after T3.</p>	

Methodology:

This is a prospective, randomized, double-blind, enriched-population, placebo-controlled, multicenter study. Eligible subjects will proceed to a run-in period to optimize RAS inhibitor and diuretic doses. Following the Run-in period, eligible subjects will enter the Enrichment Period in which all will receive Atrasentan 0.75 mg once daily (QD) to determine their UACR response and to assess tolerability of Atrasentan. Approximately 3,148 responders (UACR reduction \geq 30% from baseline) and approximately 1,000 non-responders (UACR reduction $<$ 30% from baseline) will then be randomized 1:1 into the double-blind treatment period.

The double-blind treatment period is estimated to continue for approximately 48 months. Subjects' doses of RAS inhibitors and diuretic should be stable during the treatment period and remain unchanged through the end of the study. If at any time during the study there is an interruption or decrease of RAS inhibitor dose, resumption of the previous dose should be attempted within 1 month, according to the Investigator's medical judgment. If there is significant worsening of peripheral edema or other symptoms of fluid overload, such as dyspnea with walking or lying down, during any of the treatment visits, the Investigator may adjust the diuretic dose as needed. The study will continue until 425 distinct primary renal composite events (doubling of serum creatinine or the onset of ESRD) occurring in the responder population have been adjudicated by an independent Events Adjudication Committee (EAC). Subjects who reach the endpoint of doubling of serum creatinine or eGFR $<$ 15 ml/min/1.73 m² will remain on study drug until they reach chronic dialysis, renal transplantation or renal death or the completion of the trial. If a subject stops taking study drug, every attempt will be made to keep him/her in the study by continuing scheduled study visits and restarting study drug if medically appropriate at the discretion of the Investigator. After 425 events have occurred in the responder population, all subjects will discontinue study drug and return for a Final Treatment visit and 45-day follow-up visit. After the follow-up visit, all subjects who have not reached the endpoints of dialysis, renal transplantation or renal death will be eligible to enroll in a separate open-label extension study where each subject receives Atrasentan.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

To be eligible for initial entry into the study, subjects must meet all of the following criteria:

- Subject is 18 – 85 years of age at the initial Screening visit (S1).
- Subject, or legal representative, 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.
- Subject has type 2 diabetes (including patients with latent autoimmune diabetes or insulin-treated patients without a history of diabetic ketoacidosis who also have a negative anti-glutamic acid decarboxylase test AND an elevated post-prandial serum C-peptide level) and has been treated with at least one anti-hyperglycemic medication and ACEi/or ARB (RAS inhibitor) for at least 4 weeks prior to the Screening S2 visit.

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

Main Inclusion (Continued):

For entry into the Run-In Period, the subject must satisfy the following criteria:

- Screening laboratory values:
 - Estimated GFR 25 to 75 ml/min/1.73 m² and a UACR ≥ 300 and < 5,000 mg/g (≥ 34 mg/mmol and < 565 mg/mmol);
 - Serum albumin ≥ 2.5 g/dL (25 g/L);
 - BNP ≤ 200 pg/mL (200 ng/L);
 - Serum Potassium ≥ 3.5 mEq/L (3.5 mmol/L) ≤ 6.0 mEq/L (6.0 mmol/L); and
 - SBP ≥ 110 and ≤ 180 mmHg at any time during the Screening Period.
- Subjects on a MTLDD of a RAS inhibitor for ≥ 4 weeks and on a diuretic at the time of screening, and who satisfy the above criteria may proceed directly to the last visit in the Run-In Period (R6 visit).
- Subjects on a MTLDD RAS inhibitor for ≥ 4 weeks and not on a diuretic (unless medically contra-indicated) at the time of Screening will start with a diuretic and participate in Run-In for at least 2 weeks.

Main Exclusion:

Subjects meeting any of the following criteria will be excluded from the study:

- Subject has a history of severe peripheral edema or facial edema requiring diuretics unrelated to trauma or a history of myxedema in the prior 4 weeks to the initial Screening S1 visit.
- Subject has a history of pulmonary hypertension, pulmonary fibrosis or any lung disease requiring 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.
- Subject has known non-diabetic kidney disease (other than kidney stones).
- Subject has elevated liver enzymes (serum alanine aminotransaminase [ALT] and/or serum aspartate aminotransaminase [AST]) > 3 × the upper limit of normal (ULN).
- Subject is currently receiving rosiglitazone, moxonidine, aldosterone blockers, aliskiren, or a combination of ACEi and ARB.

Investigational Product: Atrasentan

Dose: 0.75 mg once daily (QD)

Mode of Administration: Oral

Reference Therapy: Placebo

Dose: Not Applicable

Mode of Administration: Oral

Duration of Treatment: Estimated 48-month Double-Blind Treatment Period.

Criteria for Evaluation:

Efficacy:

Primary Efficacy Endpoint:

Time to the first occurrence of a component of the composite renal endpoint: doubling of serum creatinine (confirmed by a 30-day serum creatinine) or the onset of ESRD (eGFR < 15 ml/min/1.73 m² confirmed by a 90-day eGFR, receiving chronic dialysis, renal transplantation or renal death).

Secondary Efficacy Endpoints:

- Time to a 50% eGFR reduction.
- Time to cardio-renal composite endpoint: confirmed doubling of serum creatinine, ESRD, CV death, nonfatal myocardial infarction, nonfatal stroke.
- Time to first occurrence of a component of composite renal end-point: confirmed doubling of serum creatinine, or the onset of ESRD for all randomized subjects (pooled).
- Time to the CV composite endpoint: CV death, nonfatal myocardial infarction and nonfatal stroke.

Pharmacokinetic:

Atrasentan clearance (CL/F) and volume of distribution (V_{ss}/f) will be determined using population pharmacokinetic techniques.

Pharmacodynamic:

The relationship between Atrasentan exposure and clinical efficacy and/or safety response(s) may be explored.

Statistical Methods:

Analysis Datasets:

The following datasets will be used for the analysis of all efficacy and other non-safety endpoints. For these analyses, subjects will be analyzed in the treatment group to which they were randomized.

- The **Intention-to-treat (ITT) Responder Set** will serve as the primary dataset for the analysis of efficacy in this study. It will consist of all randomized subjects who achieve at least 30% reduction in UACR in the Enrichment Period (responders).
- The **ITT Non-responder Set** will consist of all randomized subjects who achieve less than 30% reduction in UACR in the Enrichment Period (non-responders).
- The **ITT Pooled Set** will consist of all randomized subjects (both responders and non-responders) and will be used for a pooled analysis of efficacy.

The following datasets will be used for the analysis of safety endpoints. For these analyses, subjects will be analyzed according to the treatment they actually receive during the double-blind phase.

- The **All Treated Responder Set** includes all randomized subjects who achieve at least 30% reduction in UACR in the Enrichment Period and receive at least one dose of study drug during double-blind phase.
- The **All Treated Non-responder Set** includes all randomized subjects who achieve less than 30% reduction in UACR in the Enrichment Period and receive at least one dose of study drug during double-blind phase.
- The **All Treated Set** includes all randomized subjects who receive at least one dose of study drug during double-blind phase.

Statistical Methods (Continued):

Analysis Datasets (Continued):

Additionally, an **All Atrasentan Set** comprising all subjects who receive at least one dose of Atrasentan, including both Enrichment and Double-Blind Treatment Periods, is defined for the purposes of data analysis.

Sample Size Determination:

The sample size for the Double-Blind Treatment Period is based on the primary efficacy endpoint of time to the renal composite event comparing Atrasentan to placebo. A total of 425 events in the ITT set is required to detect a 27% hazard reduction (HR of 0.73) with 90% power using a log-rank test at a two-sided significance level of 0.05. Based on the annual event rate in RENAAL study (~13%) and ALTITUDE (~3%), the estimate of the annual placebo event rate in the SONAR study is 6%. With the assumption of annual event rate of 6% in placebo group, 24-month accrual period, approximate 48-month double-blind treatment duration and the discontinuation rate of 15%, 3,148 subjects who achieve at least 30% UACR reduction (responders) in the Enrichment Period (1,574 subjects per group) would be needed to be randomized.

In addition, 1,000 subjects who achieve less than 30% UACR reduction in the Enrichment Period will also be randomized in a 1:1 ratio to Atrasentan or placebo.

Definition of Baseline:

For treatment comparisons and summaries based on the Double-Blind Treatment Period, baseline values refer to the last non-missing value observed prior to or at the time of randomization. This includes treatment comparisons performed for the ITT analysis sets (ITT responder set, ITT non-responder set and the ITT pooled set).

For purposes of summarizing safety and efficacy for the Enrichment Period and the entire study treatment period (Enrichment and Double-Blind Treatment Period combined), baseline values refer to the last non-missing value observed prior to or pre-dose on the first day of Atrasentan therapy (Treatment Day 1) at the beginning of the Enrichment Period.

For specific purposes, e.g., determination of doubling of serum creatinine, the values prior to Enrichment may be used as reference values.

Primary Efficacy Analysis:

The primary efficacy analysis for treatment comparison will be conducted on the ITT responder set for the primary efficacy endpoint using a stratified log-rank test, adjusting for the following stratification factors:

- Geographical region (North America, Latin America, Europe, Asia Pacific, and Japan),
- UACR level at the beginning of the Enrichment Period ($\leq 1,000$ mg/g [113 mg/mmol] or $> 1,000$ mg/g [113 mg/mmol]), and
- UACR reduction during Enrichment Period (30% – $< 45\%$, 45% – $< 60\%$, and $\geq 60\%$).

Kaplan-Meier estimates for cumulative event rates will be plotted. A Cox proportional-hazards regression model with treatment group and the above stratification factors as explanatory variables will be performed to estimate the hazard ratio of events comparing placebo to Atrasentan, and its 95% confidence interval.

Statistical Methods (Continued):

Primary Efficacy Analysis (Continued):

In addition, the individual components of the primary efficacy endpoint, i.e., the time to the first occurrence of doubling of serum creatinine (confirmed by a 30-day serum creatinine) and the time to the first occurrence of the onset will be analyzed separately using the same methods as specified above. In analyzing the individual components, first occurrence of only that specific endpoint will be considered as events.

Subgroup analyses for subgroups based on age, gender, race and important baseline characteristics will also be performed.

Secondary Efficacy Analysis:

These pre-specified secondary efficacy endpoints are listed according to their clinical importance and will be analyzed in a hierarchical (step-down) fashion. The analyses of these time-to-event endpoints of a 50% eGFR reduction (ITT responder set), a cardio-renal composite endpoint (ITT responder set), the composite renal endpoint (ITT pooled set), and the CV composite endpoint (ITT responder set), will follow the same methods as specified for the primary efficacy analysis.

Pharmacokinetics:

Population modeling techniques will be used to estimate population central values for Atrasentan clearance (CL/F) and volume of distribution (V_{ss}/f), and post hoc values of these parameters for the individual subjects will also be estimated. Additional parameters may be estimated if useful in the interpretation of the data.

Safety:

All safety analyses will be conducted on the all treated analysis sets (i.e., all treated responder set, all treated non-responder set and all treated set, respectively) and the all Atrasentan analysis set (where indicated). No formal statistical tests of treatment difference are planned.

Derivation of Safety Endpoints:

Safety data collected from randomization up to the 45-day Follow-up visit will be included in the relevant analyses for the all treated analysis sets, unless otherwise specified in the Statistical Analysis Plan (SAP) document. Safety data collected during the Enrichment Period will be summarized for exploratory purposes for the all Atrasentan analysis set.

Study Drug Exposure and Compliance:

The number of days on study drug will be summarized by treatment group and overall. The number and percentage of subjects with at least 70% compliance with study drug at each visit will be summarized by treatment group and overall.

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 follow-up period of the study will be summarized by the treatment group in descending order of overall frequency by MedDRA preferred term, as well as by system organ class (SOC) and MedDRA preferred term. The incidence rates of treatment-emergent AEs for each treatment group will be summarized. Additionally, the treatment-emergent AEs and serious adverse events (SAEs) will also be summarized by the relationship to study drug and their maximum severity.

Statistical Methods (Continued):

Laboratory Data:

For each laboratory test, the mean change from baseline to the minimum, maximum, and to each visit will be summarized by treatment groups. 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 by treatment group.

Interim Analysis:

One interim analysis of the primary efficacy endpoint will be performed when approximately 50% of the events (total of adjudicated and unadjudicated) required for completion of the trial are available. The primary analysis will be based on the EAC-adjudicated events. Supportive analyses will also be based upon both the total of adjudicated and unadjudicated events. A futility stopping boundary is specified using Gamma (-6) as the beta-spending function (Hwang et al).

An alpha spending of 0.0009 using a Gamma (-8) function will also be applied to the interim analysis. Hence for the final analyses, the primary efficacy endpoint will be tested at an expected nominal alpha level of 0.0498. The final adjustment will be based on the exact number of EAC-adjudicated events observed for the interim analysis.

To preserve the integrity and the validity of trial data, an external Statistical Analysis Center will perform the interim analysis.

Independent Data Monitoring Committee:

This study will have an IDMC composed of at least two external clinicians and one external statistician to review and make recommendations based on the results of the unblinded interim analysis and periodic reviews of the safety of Atrasentan.

Adjudication of Potential Outcome Events:

An independent events adjudication committee (EAC), blinded to study treatment assignment, will adjudicate all events that have the potential to be considered endpoints that will be specified in the EAC charter.

Steering Committee:

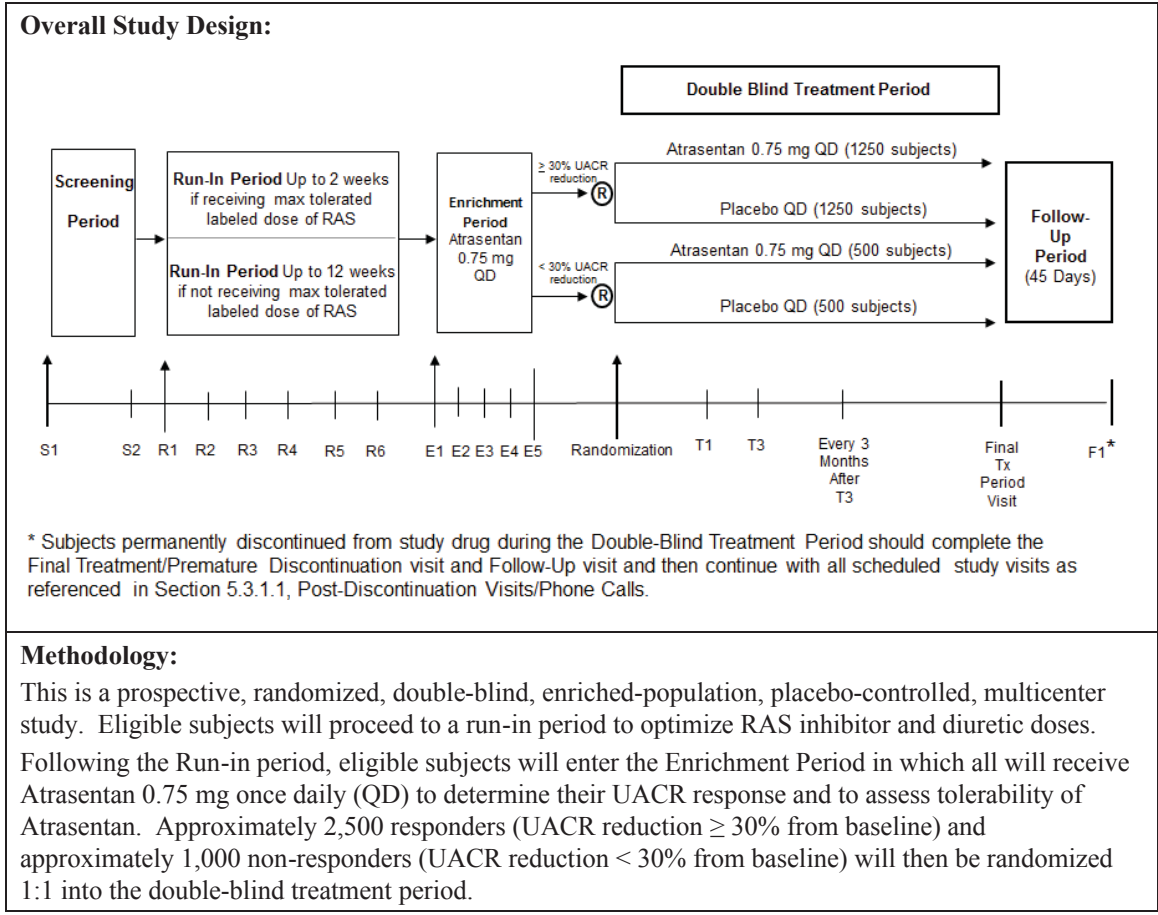
A steering committee will be involved in the design and implementation of the study. Its membership will be representative of the global nature of the study sites and regular meetings will be conducted to evaluate the conduct of the trial, including evaluations from the IDMC and EAC.

References:

Hwang IK, Shih WJ, De Cani JS. Group sequential designs using a family of type I error probability spending functions. *Stat Med.* 1990;9(12):1439-45.
Westfall PH, Krishen A. Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. *J Stat Plan Inference.* 2001;99:25-40.

Has been changed to read:

AbbVie Inc.	Protocol Number: M11-352
Name of Study Drug: Atrasentan (ABT-627)	Phase of Development: 3
Name of Active Ingredient: (2R,3R,4S)-4-(1,3-benzodioxol-5-yl)-1-[2-(dibutylamino)-2-oxoethyl]-2-(4-methoxyphenyl) pyrrolidine-3-carboxylic acid, monohydrochloride	Date of Protocol Synopsis: 19 May 2017
Protocol Title: A Randomized, Multicountry, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Atrasentan on Renal Outcomes in Subjects with Type 2 Diabetes and Nephropathy - SONAR: Study of Diabetic Nephropathy with Atrasentan	
Objectives: The study objective is to evaluate the effect of Atrasentan compared with placebo on time to doubling of serum creatinine or the onset of end stage renal disease (ESRD) in subjects with type 2 diabetes and nephropathy who are treated with the maximum tolerated labeled daily dose (MTLDD) of a Renin-Angiotensin System (RAS) inhibitor. In addition, the study will assess the effects of Atrasentan compared with placebo on cardiovascular morbidity and mortality, urine albumin excretion, changes in estimated glomerular filtration rate (eGFR), as well as on the impact on quality of life in subjects with type 2 diabetes and nephropathy.	
Investigators: Multicenter study	
Study Sites: 800 – 900 sites globally.	
Study Population: Subjects that have type 2 diabetes with nephropathy (eGFR of 25 – 75 ml/min/1.73 m ² and a urinary albumin to creatinine ratio (UACR) ≥ 300 mg/g creatinine and < 5,000 mg/g).	
Number of Subjects to be Enrolled: Approximately 3,500 subjects will be randomized to the Double-Blind Treatment Period.	



Methodology (Continued):

The duration of the Double-Blind Period is estimated to be approximately 6 years. Subjects' doses of RAS inhibitors and diuretic should be stable during the treatment period and remain unchanged through the end of the study. If at any time during the study there is an interruption or decrease of RAS inhibitor dose, resumption of the previous dose should be attempted within 1 month, according to the Investigator's medical judgment. If there is significant worsening of peripheral edema or other symptoms of fluid overload, such as dyspnea with walking or lying down, during any of the treatment visits, the Investigator may adjust the diuretic dose as needed. The study will continue until 425 distinct primary renal composite events (doubling of serum creatinine or the onset of ESRD) occurring in the responder population have been adjudicated by an independent Events Adjudication Committee (EAC). Subjects who reach the endpoint of doubling of serum creatinine or eGFR < 15 ml/min/1.73 m² will remain on study drug until they reach chronic dialysis, renal transplantation or renal death or the completion of the trial. If a subject stops taking study drug, every attempt will be made to keep him/her in the study by continuing scheduled study visits and restarting study drug if medically appropriate at the discretion of the Investigator. After 425 events have occurred in the responder population, all subjects who have not permanently discontinued study drug will return for a Final Treatment visit and 45-day follow-up visit. Subjects who were permanently discontinued from study drug will complete the next scheduled visit. Upon study completion, eligible subjects will be invited to participate in an open-label study if their site is participating in the extension study to determine the long-term safety of Atrasentan.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

To be eligible for initial entry into the study, subjects must meet all of the following criteria:

- Subject is 18 – 85 years of age at the initial Screening visit (S1).
- Subject, or legal representative, 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.
- Subject has type 2 diabetes (including patients with latent autoimmune diabetes or insulin-treated patients without a history of diabetic ketoacidosis who also have a negative anti-glutamic acid decarboxylase test AND an elevated post-prandial serum C-peptide level) and has been treated with at least one anti-hyperglycemic medication and ACEi/or ARB (RAS inhibitor) for at least 4 weeks prior to the Screening S2 visit.

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

Main Inclusion (Continued):

For entry into the Run-In Period, the subject must satisfy the following criteria:

- Screening laboratory values:
 - Estimated GFR 25 to 75 ml/min/1.73 m² [until the eGFR cap on subjects (approximately 300) with a baseline of > 60 mL/min/1.73 m² is reached] and a UACR ≥ 300 and < 5,000 mg/g (≥ 34 mg/mmol and < 565 mg/mmol);
 - Serum albumin ≥ 2.5 g/dL (25 g/L);
 - BNP ≤ 200 pg/mL (200 ng/L);
 - Serum Potassium ≥ 3.5 mEq/L (3.5 mmol/L) ≤ 6.0 mEq/L (6.0 mmol/L); and
 - SBP ≥ 110 and ≤ 180 mmHg at any time during the Screening Period.
- Subjects on a MTLDD of a RAS inhibitor for ≥ 4 weeks and on a diuretic at the time of screening, and who satisfy the above criteria may proceed directly to the last visit in the Run-In Period (R6 visit).
- Subjects on a MTLDD RAS inhibitor for ≥ 4 weeks and not on a diuretic (unless medically contra-indicated) at the time of Screening will start with a diuretic and participate in Run-In for at least 2 weeks.

Main Exclusion:

Subjects meeting any of the following criteria will be excluded from the study:

- Subject has a history of severe peripheral edema or facial edema requiring diuretics unrelated to trauma or a history of myxedema in the prior 4 weeks to the initial Screening S1 visit.
- Subject has a history of pulmonary hypertension, pulmonary fibrosis or any lung disease requiring 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.
- Subject has known non-diabetic kidney disease (other than kidney stones).
- Subject has elevated liver enzymes (serum alanine aminotransaminase [ALT] and/or serum aspartate aminotransaminase [AST]) > 3 × the upper limit of normal (ULN).
- Subject is currently receiving rosiglitazone, moxonidine, aldosterone blockers, aliskiren, or a combination of ACEi and ARB.

Investigational Product:	Atrasentan
Dose:	0.75 mg once daily (QD)
Mode of Administration:	Oral
Reference Therapy:	Placebo
Dose:	Not Applicable
Mode of Administration:	Oral

Duration of Treatment: Subjects will continue on randomized study treatment until discontinued from study drug.

Criteria for Evaluation:

Efficacy:

Primary Efficacy Endpoint:

Time to the first occurrence of a component of the composite renal endpoint: doubling of serum creatinine (confirmed by a 30-day serum creatinine) or the onset of ESRD (eGFR < 15 ml/min/1.73 m² confirmed by a 90-day eGFR, receiving chronic dialysis, renal transplantation or renal death).

Secondary Efficacy Endpoints:

- Time to a 50% eGFR reduction.
- Time to cardio-renal composite endpoint: confirmed doubling of serum creatinine, ESRD, CV death, nonfatal myocardial infarction, nonfatal stroke.
- Time to first occurrence of a component of composite renal end-point: confirmed doubling of serum creatinine, or the onset of ESRD for all randomized subjects (pooled).
- Time to the CV composite endpoint: CV death, nonfatal myocardial infarction and nonfatal stroke.

Pharmacokinetic:

Atrasentan clearance (CL/F) and volume of distribution (V_{ss}/f) will be determined using population pharmacokinetic techniques.

Pharmacodynamic:

The relationship between Atrasentan exposure and clinical efficacy and/or safety response(s) may be explored.

Statistical Methods:

Analysis Datasets:

The following datasets will be used for the analysis of all efficacy and other non-safety endpoints. For these analyses, subjects will be analyzed in the treatment group to which they were randomized.

- The **Intention-to-treat (ITT) Responder Set** will serve as the primary dataset for the analysis of efficacy in this study. It will consist of all randomized subjects who achieve at least 30% reduction in UACR in the Enrichment Period (responders).
- The **ITT Non-responder Set** will consist of all randomized subjects who achieve less than 30% reduction in UACR in the Enrichment Period (non-responders).
- The **ITT Pooled Set** will consist of all randomized subjects (both responders and non-responders) and will be used for a pooled analysis of efficacy.

The following datasets will be used for the analysis of safety endpoints. For these analyses, subjects will be analyzed according to the treatment they actually receive during the double-blind phase.

- The **All Treated Responder Set** includes all randomized subjects who achieve at least 30% reduction in UACR in the Enrichment Period and receive at least one dose of study drug during double-blind phase.
- The **All Treated Non-responder Set** includes all randomized subjects who achieve less than 30% reduction in UACR in the Enrichment Period and receive at least one dose of study drug during double-blind phase.

Statistical Methods (Continued):

Analysis Datasets (Continued):

- The **All Treated Set** includes all randomized subjects who receive at least one dose of study drug during double-blind phase.

Additionally, an **All Atrasentan Set** comprising all subjects who receive at least one dose of Atrasentan, including both Enrichment and Double-Blind Treatment Periods, is defined for the purposes of data analysis.

Sample Size Determination:

The sample size for the Double-Blind Treatment Period is based on the primary efficacy endpoint of time to the renal composite event comparing Atrasentan to placebo. A total of 425 events in the ITT set is required to detect a 27% hazard reduction (HR of 0.73) with approximately 90% power using a log-rank test at a two sided significance level of 0.05. Based on the annual event rate in RENAAL study (~13%) and ALTITUDE (~3%), the estimate of the annual placebo event rate in the SONAR study is 6%. With the assumption of annual event rate of 6% in placebo group, 42-month accrual period, approximate 6 year duration of the Double-Blind Period and an annualized lost to follow-up rate of 2%, a total of about approximately 2,500 subjects who achieve at least 30% UACR reduction (responders) in the Enrichment Period (1,250 subjects per group) would be needed to be randomized.

In addition, approximately 1,000 subjects who achieve less than 30% UACR reduction in the Enrichment Period will also be randomized in a 1:1 ratio to Atrasentan or placebo.

Definition of Baseline:

For treatment comparisons and summaries based on the Double-Blind Treatment Period, baseline values refer to the last non-missing value observed prior to or at the time of randomization. This includes treatment comparisons performed for the ITT analysis sets (ITT responder set, ITT non-responder set and the ITT pooled set).

For purposes of summarizing safety and efficacy for the Enrichment Period and the entire study treatment period (Enrichment and Double-Blind Treatment Period combined), baseline values refer to the last non-missing value observed prior to or pre-dose on the first day of Atrasentan therapy (Treatment Day 1) at the beginning of the Enrichment Period.

For specific purposes, e.g., determination of doubling of serum creatinine, baseline values refer to the last non-missing value observed prior to or pre-dose on the first day of Atrasentan therapy at the beginning of the Enrichment Period.

Primary Efficacy Analysis:

A Cox proportional-hazard regression model will be performed on the ITT responder set to estimate the hazard ratio of Atrasentan to placebo and its 95% confidence interval. The primary efficacy analysis for treatment comparison will also be conducted using a stratified log-rank test, adjusting for the following stratification factors:

- UACR level at the beginning of the Enrichment Period ($\leq 1,000$ mg/g [113 mg/mmol] or $> 1,000$ mg/g [113 mg/mmol]), and
- UACR reduction during Enrichment Period (30% – $< 45\%$, 45% – $< 60\%$, and $\geq 60\%$).

Kaplan-Meier (KM) estimates for cumulative event rates will be plotted.

Statistical Methods (Continued):

Primary Efficacy Analysis (Continued):

In addition, the individual components of the primary efficacy endpoint, i.e., the time to the first occurrence of doubling of serum creatinine (confirmed by a 30-day serum creatinine) and the time to the first occurrence of the onset of ESRD will be analyzed separately using the same methods as specified above. In analyzing the individual components, first occurrence of only that specific endpoint will be considered as events.

Subgroup analyses for subgroups based on age, gender, race, geographical region and important baseline characteristics will also be performed.

Secondary Efficacy Analysis:

These pre-specified secondary efficacy endpoints are listed according to their clinical importance and will be analyzed in a hierarchical (step-down) fashion. The analyses of these time-to-event endpoints of a 50% eGFR reduction (ITT responder set), a cardio-renal composite endpoint (ITT responder set), the composite renal endpoint (ITT pooled set), and the CV composite endpoint (ITT responder set), will follow the same methods as specified for the primary efficacy analysis.

Pharmacokinetics:

Population modeling techniques will be used to estimate population central values for Atrasentan clearance (CL/F) and volume of distribution (V_{ss}/f), and post hoc values of these parameters for the individual subjects will also be estimated. Additional parameters may be estimated if useful in the interpretation of the data.

Safety:

All safety analyses will be conducted on the all treated analysis sets (i.e., all treated responder set, all treated non-responder set and all treated set, respectively) and the all Atrasentan analysis set (where indicated). No formal statistical tests of treatment difference are planned.

Derivation of Safety Endpoints:

Safety data collected from the first dose up to 45-days post last dose in the double blind period will be included in the relevant analyses for the all treated analysis sets, unless otherwise specified in the Statistical Analysis Plan (SAP) document. Safety data collected during the Enrichment Period will be summarized for exploratory purposes for the all Atrasentan analysis set.

Study Drug Exposure and Compliance:

The number of days on study drug will be summarized by treatment group and overall. The number and percentage of subjects with at least 70% compliance with study drug at each visit will be summarized by treatment group and overall.

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 follow-up period of the study will be summarized by the treatment group in descending order of overall frequency by MedDRA preferred term, as well as by system organ class (SOC) and MedDRA preferred term. The incidence rates of treatment-emergent AEs for each treatment group will be summarized. Additionally, the treatment-emergent AEs and serious adverse events (SAEs) will also be summarized by the relationship to study drug and their maximum severity.

Statistical Methods (Continued):

Laboratory Data:

For each laboratory test, the mean change from baseline to the minimum, maximum, and to each visit will be summarized by treatment groups. 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 by treatment group.

Interim Analysis:

An interim analysis of efficacy will be performed when the number of accrued primary events in the responder population is in the range of 50% to 75% of the targeted 425 events for the study. An alpha-spending function approach will be used to ensure that the overall one-sided type I error rate will be controlled at 0.025 or less. In addition, an interim analysis of efficacy data for futility only may be performed at an earlier time point. No adjustment to the type I error rate will be made for the futility assessment.

To preserve the integrity and the validity of trial data, an external Statistical Analysis Center will perform the requisite interim analyses and present the results to IDMC. Further details of the interim analysis plan will be provided in the Statistical Analysis Plan (SAP) and IDMC Charter. In making any decision to recommend discontinuation of the study, either for superior efficacy of Atrasentan or for futility, the IDMC shall be guided by a formal stopping rule described in the SAP.

Independent Data Monitoring Committee:

This study will have an IDMC composed of at least two external clinicians and one external statistician to review and make recommendations based on the results of the unblinded interim analysis and periodic reviews of the safety of Atrasentan.

Adjudication of Potential Outcome Events:

An independent events adjudication committee (EAC), blinded to study treatment assignment, will adjudicate all events that have the potential to be considered endpoints that will be specified in the EAC charter.

Steering Committee:

A steering committee will be involved in the design and implementation of the study. Its membership will be representative of the global nature of the study sites and regular meetings will be conducted to evaluate the conduct of the trial, including evaluations from the IDMC and EAC.

References:

Westfall PH, Krishen A. Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. J Stat Plan Inference. 2001;99:25-40.

Section 1.3 List of Abbreviations and Definition of Terms

Subsection Abbreviations

Add: "HR" and "KM"

HR	Hazard ratio
KM	Kaplan-Meier

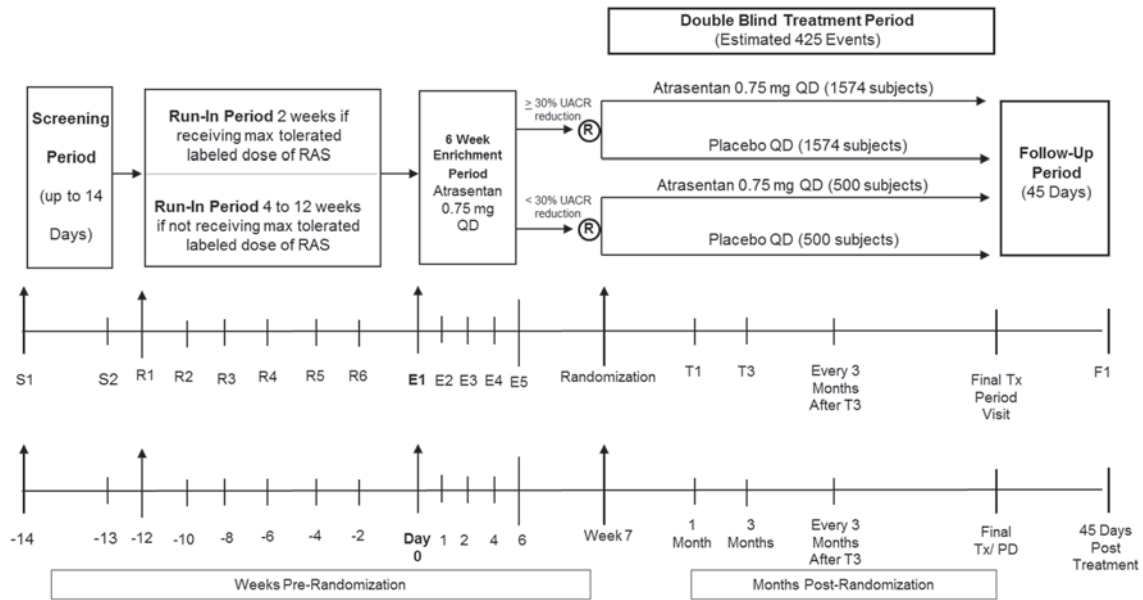
Section 5.1 Overall Study Design and Plan: Description
Second paragraph, first sentence previously read:

The study was designed to randomize approximately 4,148 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.

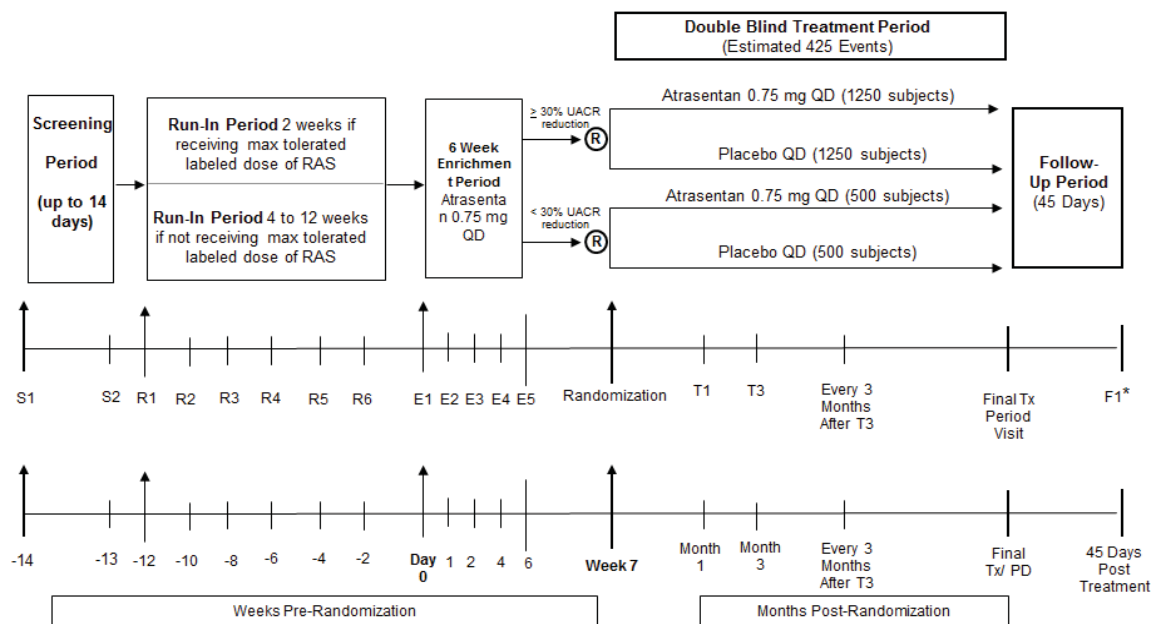
Has been changed to read:

The study was designed to randomize approximately 3,500 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.

Figure 1. Study Schematic
Previously read:



Has been changed to read:



* Subjects permanently discontinued from study drug during the Double-Blind Treatment Period should complete the Final Treatment/Premature Discontinuation visit and Follow-Up visit and then continue with all scheduled study visits as referenced in Section 5.3.1.1, Post-Discontinuation Visits/Phone Calls.

Section 5.1 Overall Study Design and Plan: Description
Subsection Run-In Period (Up to 12 Weeks) (Visits R1 – R6)
Fourth paragraph, first sentence previously read:

During the Run-In Period, BP control and tolerance to the new therapeutic doses will be assessed approximately every other week.

Has been changed to read:

During the Run-In Period, BP control and tolerance to the new therapeutic doses will be assessed approximately every other week (± 2 days).

Section 5.1 Overall Study Design and Plan: Description
Subsection Enrichment Period (6 Weeks) (Visits E1 – E5)
Heading "Serum Creatinine Elevation During Enrichment"
First paragraph, first sentence previously read:

Subjects must not have an increase in serum creatinine > 0.5 mg/dL (> 48 umol/L) AND > 20% from E1 to the E5 visit.

Has been changed to read:

Subjects must not have an increase in serum creatinine > 0.5 mg/dL AND > 20% from E1 to the E5 visit.

Section 5.1 Overall Study Design and Plan: Description
Subsection Enrichment Period (6 Weeks) (Visits E1 – E5)
Heading "Serum Creatinine Elevation During Enrichment"
Third paragraph previously read:

A responder/non-responder ratio design was set up to ensure proportional distribution to the expected enrollment. The implementation of this ratio will be through the IRT system and will allow the randomization of 50 non-responders for every 150 responders that are randomized (1:3 proportion). The ability to randomize non-responders will "turn on and off" based on the responder/non-responder ratio of randomization. The non-responder arm will re-open to enrollment at any given time without notice, as the randomization scheme is applied, until enrollment of the 1000 subject non-responder arm of the protocol is complete.

Has been changed to read:

A responder/non-responder ratio design was set up to ensure proportional distribution to the expected enrollment. The implementation of this ratio will be through the IRT system. The ability to randomize non-responders will "turn on and off" based on the responder/non-responder ratio of randomization. The non-responder arm will re-open to enrollment at any given time without notice, as the randomization scheme is applied, until

enrollment of approximately 1,000 subjects in the non-responder arm of the protocol is complete.

Section 5.1 Overall Study Design and Plan: Description

Subsection Randomization Visit

First paragraph, third sentence previously read:

If the non-responder cap is met, the IVRS/IWRS will inform the site that the subject cannot continue into the Double-Blind Treatment Period.

Has been changed to read:

If the non-responder cap is met and a subject has achieved < 30% UACR reduction at the end of the Enrichment Period compared to baseline, the IVRS/IWRS will inform the site that the subject cannot continue into the Double-Blind Treatment Period.

Section 5.1 Overall Study Design and Plan: Description

Subsection Randomization Visit

Last paragraph, first sentence previously read:

Only 1,000 subjects in the non-responder population will be randomized.

Has been changed to read:

Approximately 1,000 subjects in the non-responder population will be randomized.

Section 5.1 Overall Study Design and Plan: Description

Subsection Double-Blind Treatment Period (Randomization – Final Treatment Visit)

Third paragraph previously read:

T3 will occur 3 months after randomization (2 months after T1).

Has been changed to read:

T3 will occur 3 months (\pm 2 weeks) after randomization (2 months after T1).

Section 5.1 Overall Study Design and Plan: Description
Subsection Double-Blind Treatment Period (Randomization – Final Treatment Visit)

Fourth paragraph

Add: new second sentence

The visit window for all Treatment Visits after T1 is ± 2 weeks.

Section 5.1 Overall Study Design and Plan: Description
Subsection Double-Blind Treatment Period (Randomization – Final Treatment Visit)

Fourth paragraph, last sentence previously read:

Subjects will also be given supplies and instructions when required for the collection of 1 FMV urine sample that needs to be collected within 1 day of the yearly treatment visit (T12, T36, T48).

Has been changed to read:

Subjects will also be given supplies and instructions when required for the collection of 1 FMV urine sample that needs to be collected within 1 day of the yearly treatment visit (T12, T36, T48, etc).

Section 5.1 Overall Study Design and Plan: Description
Subsection End Stage Renal Disease

First paragraph previously read:

ESRD will be defined as $eGFR < 15 \text{ ml/min/1.73 m}^2$ (confirmed by a 90-day $eGFR$), receiving chronic dialysis, renal transplantation or the occurrence of renal death. Once an $eGFR < 15 \text{ ml/min/1.73 m}^2$ is reported the Investigator will be informed by the central laboratory. The lab should be confirmed at the next 3 month scheduled visit or at an unscheduled visit at approximately 90 days. If the subject misses the return visit, the visit should be rescheduled as soon as possible. The Investigator will make all reasonable attempts to exclude reversible causes of elevation of serum creatinine such as volume depletion or nephrotoxic medication. Once an $eGFR < 15 \text{ ml/min/1.73m}^2$ is confirmed at , the site will report the event in eClinical[®], as described in Section 6.5.1, to begin the process of collecting the information required to have the event properly adjudicated by

the independent EAC. Subjects who reach the endpoint of an eGFR < 15 ml/min/1.73 m² will remain on study drug until they receive chronic dialysis or experience renal transplantation or the occurrence of renal death or until completion of the trial.

Has been changed to read:

ESRD will be defined as eGFR < 15 ml/min/1.73 m² receiving chronic dialysis, renal transplantation or the occurrence of renal death. Once an eGFR < 15 ml/min/1.73 m² is reported the Investigator will be informed by the central laboratory. The lab should be confirmed at the next 3 month scheduled visit or at an unscheduled visit at approximately 90 days (confirmatory values within the intended study visit window will be acceptable). If the subject misses the return visit, the visit should be rescheduled as soon as possible. The Investigator will make all reasonable attempts to exclude reversible causes of elevation of serum creatinine such as volume depletion or nephrotoxic medication. Once an eGFR < 15 ml/min/1.73m² is confirmed, the site will report the event in eClinical[®], as described in Section 6.5.1, to begin the process of collecting the information required to have the event properly adjudicated by the independent EAC. Subjects who reach the endpoint of an eGFR < 15 ml/min/1.73 m² will remain on study drug until they receive chronic dialysis or experience renal transplantation or the occurrence of renal death or until completion of the trial.

Section 5.1 Overall Study Design and Plan: Description

Subsection End Stage Renal Disease

Last paragraph

Add: new third sentence

For subjects receiving chronic dialysis or renal transplantation, laboratory samples will be collected at the Follow-Up (F1) visit or any remaining study visits at the discretion of the Investigator.

Section 5.1 Overall Study Design and Plan: Description

Subsection Premature Discontinuation and Retention

Last paragraph, third sentence previously read:

Whenever possible, Investigators should encourage subjects to continue with study assessments even after they discontinue taking study drug during the Double-Blind Treatment Period.

Has been changed to read:

Whenever possible, Investigators should encourage subjects to continue with on-site study assessments even after they discontinue taking study drug during the Double-Blind Treatment Period.

Section 5.1 Overall Study Design and Plan: Description

Subsection Premature Discontinuation and Retention

Last paragraph, sixth, seventh, and eighth sentence previously read:

If the subject is unable or unwilling to undergo planned assessments, study staff should make telephone contact and encourage subjects to allow further assessments. The telephone assessments will consist of a phone call to the subject every 3 months until the study end. Procedures to be performed during the telephone contact include, but not limited to, eliciting information regarding concurrent medications, occurrence of renal and cardiovascular events, ask about recent laboratory values, and inquire as to whether the subject has started receiving chronic dialysis.

Has been changed to read:

If the subject is unable or unwilling to undergo on-site assessments for an upcoming quarterly visit, study staff should make telephone contact and encourage subjects to allow further assessments. Telephone assessments should only be utilized when necessary. As part of the telephone assessment, the site will elicit or collect information regarding, but not limited to, concurrent medications, occurrence of renal and cardiovascular events including chronic dialysis, and local laboratory reports (if available).

Section 5.1 Overall Study Design and Plan: Description

Subsection Premature Discontinuation and Retention

Heading "Home Visits"

Add: new heading title and text

Home Visits

In exceptional cases, visiting nurse services may be available for use, as needed. Sponsor approval will be required prior to implementation of the nursing service. Study activities such as local or central laboratory sample collection and processing may be conducted in the home or non-hospital/clinic environment by qualified individuals.

Subject Withdrawal

Section 5.1 Overall Study Design and Plan: Description

Subsection Premature Discontinuation and Retention

Last paragraph, eighth sentence previously read:

It is expected that subjects who leave the study and stop taking study drug will agree to remain for follow-up status evaluations.

Has been changed to read:

It is expected that subjects who permanently discontinue study drug will agree to remain for follow-up status evaluations.

Section 5.1 Overall Study Design and Plan: Description

Subsection Open-Label Extension Study

Previously read:

Upon study completion, those subjects who have completed the Final Treatment visit and the Follow-Up (F1) visit will be invited to participate in an open-label study to determine the long-term safety and efficacy of Atrasentan 0.75 mg QD.

Has been changed to read:

Upon study completion, eligible subjects will be invited to participate in an open-label study if their site is participating in the extension study to determine the long-term safety of Atrasentan.

Section 5.2.1 Inclusion Criteria

Criterion 5, first bullet previously read:

Estimated GFR 25 to 75 mL/min/1.73 m² and a UACR \geq 300 and < 5,000 mg/g (\geq 34 mg/mmol and < 565 mg/mmol);

Has been changed to read:

Estimated GFR 25 to 75 mL/min/1.73 m² [until the eGFR cap on subjects (approximately 300) with a baseline of > 60 mL/min/1.73 m² is reached] and a UACR \geq 300 and < 5,000 mg/g (\geq 34 mg/mmol and < 565 mg/mmol);

Section 5.2.1 Inclusion Criteria

Criterion 7, last bullet previously read:

- Subject must not have an **increase in serum creatinine** > 0.5 mg/dL (> 48 μ mol/L) **AND** > **20% increase** from the beginning of Enrichment (E1) to the end of the Enrichment Period.

Has been changed to read:

- Subject must not have an **increase in serum creatinine** > 0.5 mg/dL **AND** > **20% increase** from the beginning of Enrichment (E1) to the end of the Enrichment Period.

Male subjects must satisfy the following criteria from initial study drug administration through 90 days after last dose of study drug:

Section 5.2.2 Exclusion Criteria

First paragraph previously read:

A subject will not be eligible for study participation if he/she meets any of the following criteria:

Has been changed to read:

A subject will not be eligible for entry into the Run-in Period if he/she meets any of the following criteria:

Section 5.2.2 Exclusion Criteria

Criterion 3 previously read:

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.

Has been changed to read:

Subject has a documented diagnosis of heart failure, previous hospitalization for heart failure or current 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.

Section 5.2.2 Exclusion Criteria

Criterion 19, last sentence previously read:

Women who are surgically sterile or have a history of hysterectomy may not be premenopausal.

Has been changed to read:

Women who are surgically sterile or have a history of hysterectomy may not necessarily be postmenopausal, and must also have an FSH > 35 IU/L.

Table 1. Study Activities

Activity "Complete Chemistry"^j previously read:

Complete Chemistry^j

Has been changed to read:

Complete Chemistry

Table 1. Study Activities

Table note "d." previously read:

T12, T24, T36, and T48.

Has been changed to read:

T12, T24, T36, T48, etc.

Table 1. Study Activities

Table note "i." previously read:

Updates.

Has been changed to read:

Complete medical history, including history of tobacco and alcohol use and colonoscopy history, will be obtained during initial Screening visit and updated through the Enrichment Period E1.

Table 1. Study Activities

Table note "k.," last sentence previously read:

FMV is not required for subjects who present for the Randomization visit and are not randomized and a Final Treatment visit is conducted instead of a randomization.

Has been changed to read:

FMV is not required for subjects who present for the Randomization visit and are not randomized and a Final Treatment visit is conducted instead of a Randomization visit.

Table 1. Study Activities

Table note "w.," second sentence previously read:

The IVRS/IWRS call at the Final Treatment/PD visit is only for study completion/premature discontinuation.

Has been changed to read:

The IVRS/IWRS call at the Final Treatment/PD visit is only for the discontinuation of study drug.

Section 5.3.1.1 Study Procedures

Subsection Post-Discontinuation Visits/Phone Calls

Last paragraph, first sentence previously read:

If the subject is unable or unwilling to undergo planned assessments, study staff should make telephone contact and encourage subjects to allow further assessments.

Has been changed to read:

If the subject is unable or unwilling to undergo on-site planned assessments, study staff should make telephone contact and encourage subjects to allow further assessments. Telephone assessments should only be utilized when necessary.

Section 5.3.1.1 Study Procedures

Subsection Post-Discontinuation Visits/Phone Calls

Last paragraph, third sentence previously read:

Procedures to be performed during the telephone contact include, but not limited to, eliciting information regarding concurrent medications, occurrence of renal and cardiovascular events, and SAEs, and ask about recent laboratory values, and inquire as to whether the subject has started receiving chronic dialysis.

Has been changed to read:

Procedures to be performed during the telephone contact include, but not limited to, eliciting and collecting information regarding concurrent medications, occurrence of renal and cardiovascular events, SAEs, local laboratory reports (if available), and inquire as to whether the subject has started receiving chronic dialysis.

Table 2. Reminder Phone Calls

Study Period "Yearly Visits (i.e., T12, T36, T48)" previously read:

Yearly Visits (i.e., T12, T36, T48)

Has been changed to read:

Yearly Visits (i.e., T12, T36, T48, etc).

**Table 2. Reminder Phone Calls
Study Period "Final Treatment/Premature Discontinuation Visit" and "F1 Visit"
previously read:**

Study Period	Study Day	Call Description
Final Treatment/ Premature Discontinuation Visit	Approximately 2-3 days prior to the Final Treatment/ Premature Discontinuation visit.	Call the subject to remind them to initiate their first morning void urine sample the day prior to their T48/Premature Discontinuation visit. Also remind them to initiate their 24-hour urine collection (if the subject consented) immediately after their third first morning void urine has been collected. Remind the subject to bring their diary to the visit.
F1 Visit	Approximately 2 days prior to the F1 visit.	Call the subject to remind them to initiate their first morning void urine sample the 2 days prior to their F1 visit. Also remind the subject that they must fast for 8 hours prior to the visit and hold their morning dose of antihyperglycemic agents prior to their F1 visit.

Has been changed to read:

Study Period	Study Day	Call Description
Final Treatment/ Premature Discontinuation Visit	Approximately 2-3 days prior to the Final Treatment/ Premature Discontinuation visit.	Call the subject to remind them to initiate their first morning void urine sample the day prior to their Final Treatment/Premature Discontinuation visit. Remind the subject to bring their diary to the visit.
F1 Visit	Approximately 2 days prior to the F1 visit.	Call the subject to remind them to initiate their first morning void urine sample the 2 days prior to their F1 visit. Also remind them to initiate their 24-hour urine collection (if the subject consented) immediately after the first morning void urine has been collected. At this time, also remind the subject that they must fast for 8 hours prior to the visit and hold their morning dose of antihyperglycemic agents prior to their F1 visit.

**Section 5.3.1.1 Study Procedures
Subsection Clinical Laboratory Tests**

Second paragraph

Add: new second sentence

In exceptional cases, test results from a local laboratory may be acceptable.

Section 5.3.1.1 Study Procedures

Subsection First Morning Void (FMV) Urine Sample Collections

Second paragraph, second sentence previously read:

One first morning void sample collection will be obtained prior to the Treatment visit T1, the yearly visits (T12, T36, and T48), the Final Treatment/Premature Discontinuation visit, and the Follow-Up Visit F1.

Has been changed to read:

One first morning void sample collection will be obtained prior to the Treatment visit T1, the yearly visits (T12, T36, T48, etc.), the Final Treatment/Premature Discontinuation visit, and the Follow-Up Visit F1.

Section 5.3.1.1.1 24-Hour Urine Collection Sub-Study (Additional Consent Needed)

First paragraph, first sentence previously read:

The 24-hour urine collection will be collected six times during the study for each subject that consents to participate in this optional sub-study up to a limit of 400 subjects.

Has been changed to read:

The 24-hour urine collection will be collected as outlined in [Table 4](#) during the study for each subject that consents to participate in this optional sub-study up to a limit of 800 subjects.

Table 4. Study Activities for Optional 24-hour Urine Sub-Study

Header row, column "Yearly" previously read:

Yearly

Has been changed to read:

Yearly*

Table 4. Study Activities for Optional 24-hour Urine Sub-Study

Add: new table note "*"

T12, T24, T36, T48, etc.

Section 5.3.1.2 Blood Samples for Pharmacogenetic Analysis

"AbbVie Sample Receiving," "Phone:" and "Fax:" previously read:

Phone:

Fax:

Has been changed to read:

Phone:

Fax:

Section 5.3.2.1 Collection of Samples for Pharmacokinetic Analysis

First paragraph

Delete: second sentence

A total of 14 blood samples per subject are planned to be collected for pharmacokinetic (PK) analysis.

Section 5.3.2.1 Collection of Samples for Pharmacokinetic Analysis

First paragraph, last sentence previously read:

Immediately after collection, the blood samples will be inverted several times to ensure good mixing of the blood and anticoagulant, and be placed in an ice bath.

Has been changed to read:

Immediately after collection, the blood samples will be inverted several times to ensure good mixing of the blood and anticoagulant.

Section 5.3.3.1 Primary Variables

Section title previously read:

Primary Variables

Has been changed to read:

Primary Endpoint (Adjudicated)

Section 5.3.3.1 Primary Variables

Previously read:

Time to the first occurrence of a component of the composite renal endpoint: doubling of serum creatinine (confirmed by a 30-day serum creatinine) or the onset of ESRD (eGFR < 15 ml/min/1.73m² confirmed by a 90-day eGFR, receiving chronic dialysis, renal transplantation or renal death).

Has been changed to read:

Time to the first occurrence of a component of the composite renal endpoint: doubling of serum creatinine (confirmed by a 30-day serum creatinine) or the onset of ESRD (eGFR < 15 ml/min/1.73m² (confirmed by a 90-day eGFR), receiving chronic dialysis, renal transplantation or renal death).

Section 5.3.3.3 Additional Endpoints

Third bullet previously read:

- Change in eGFR to 45 days after end of treatment.

Has been changed to read:

- Change in eGFR after 3 months post randomization treatment.
- Change in eGFR to 45 days after end of treatment (or final observation on treatment).

Section 5.3.5 Pharmacokinetic Variables

First sentence previously read:

Plasma concentrations of Atrasentan and its possible metabolites will be obtained at all treatment visits.

Has been changed to read:

Plasma concentrations of Atrasentan and its possible metabolites will be obtained at the treatment visits outlined in [Table 1](#).

Section 5.4.2 Discontinuation of Entire Study

First paragraph, first sentence previously read:

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.

Has been changed to read:

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause (e.g., early study termination after interim futility or efficacy analyses) provided that written notice is submitted to the site(s) in advance of the intended termination.

Section 5.4.2 Discontinuation of Entire Study

Last paragraph previously read:

Following study termination for any reason, all subjects who have not withdrawn or died must be contacted. At this time, subjects who have not permanently discontinued study drug will be scheduled for the Final Treatment visit and will be scheduled for the Follow-Up Visit (F1). In subjects who were permanently discontinued from study drug, a phone call can be completed to solicit information about any potential endpoint events and SAEs since the previous visit.

Has been changed to read:

Following study termination for any reason, all subjects must be contacted. At this time, subjects who have not permanently discontinued study drug will be scheduled for the Final Treatment visit and Follow-Up Visit (F1). In subjects who were permanently discontinued from study drug, the next scheduled on-site visit (preferred) or phone call

(only if the subject is unable or unwilling to undergo on-site assessments) should be completed to solicit and collect information about any potential endpoint events, SAEs, and local laboratory reports for values such as serum creatinine and eGFR since the previous visit or phone call.

Section 5.4.3 Study Completion

First paragraph, last sentence previously read:

Upon reaching Study Completion, the sponsor (or designee) will contact the Investigators to inform them of Study Completion and request all subjects who have not withdrawn or died be contacted and scheduled for the Final Treatment Visit and Follow Up visit (F1).

Has been changed to read:

Upon reaching Study Completion, the Sponsor (or designee) will contact the Investigators to inform them of Study Completion and request all subjects be contacted. Subjects who have not permanently discontinued from study drug will be scheduled for the Final Treatment Visit and Follow Up visit (F1). Subjects who were permanently discontinued from study drug should complete the next scheduled visit or phone call to solicit information about any potential endpoint events, SAEs, and laboratory values such as serum creatinine and eGFR since the previous visit or phone call (refer to Premature Discontinuation and Retention section).

Section 5.4.3 Study Completion

Last paragraph, first sentence previously read:

The EAC will track the number of positively adjudicated primary renal events and the events undergoing adjudication.

Has been changed to read:

The Sponsor will track the number of positively adjudicated primary renal events and the events undergoing adjudication.

Section 5.5.5 Blinding

First sentence previously read:

Both the Investigator and the subject will remain blinded to the subject's treatment group during the double-blind treatment period of the study.

Has been changed to read:

Both the Investigator and the subject will remain blinded to the subject's treatment group during the double-blind period of the study.

Section 5.5.5.1 Blinding of Data for Independent Data Monitoring Committee (IDMC)

Fourth and fifth sentence previously read:

In addition, the IDMC will review the pre-planned interim futility analysis results. The study can be stopped for futility if the criteria defined in Section 8.1.5 are met.

Has been changed to read:

In addition, the IDMC will review the pre-planned interim analyses and make recommendations guided by the formal stopping rules described in the statistical analysis results plan (SAP).

Section 5.6.4 Selection of Doses in the Study

First paragraph, last sentence previously read:

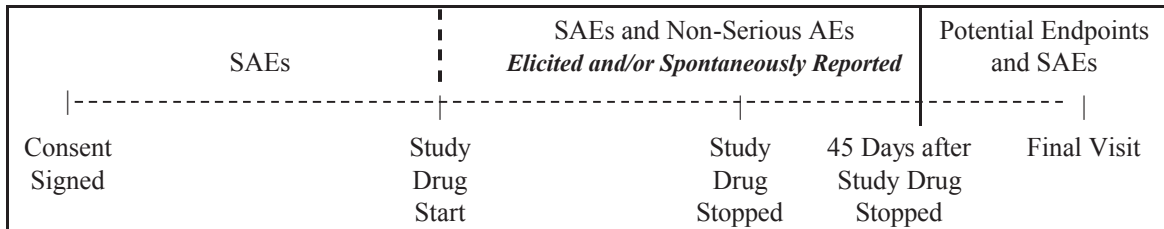
After enrichment, subjects may be randomized to receive a maximum of 0.75 mg QD of ABT-627 for up to 48 months.

Has been changed to read:

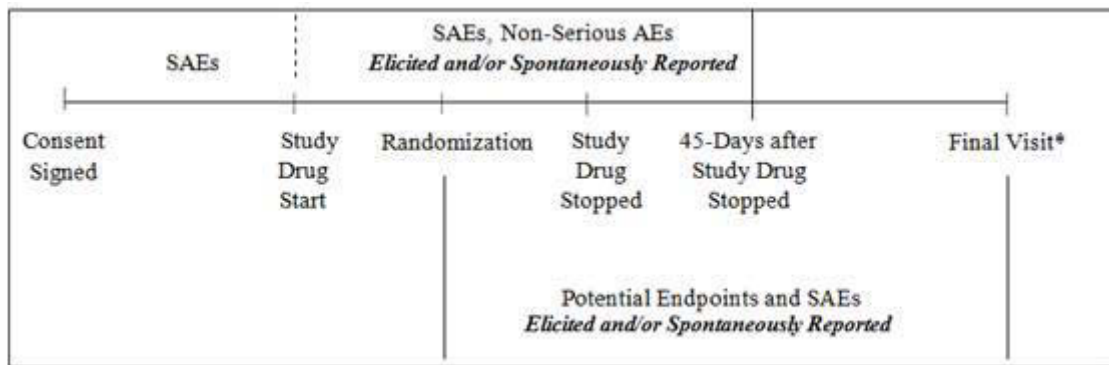
After enrichment, subjects may be randomized to receive a maximum of 0.75 mg QD of ABT-627 for up to approximately 6 years.

Figure 2. Adverse Event Collection

Previously read:



Has been changed to read:



* Final visit refers to final subject contact as referenced in Section 5.4.2 and Section 5.4.3.

Section 6.5 Adverse Event Reporting

"Renal Safety Management:"

Delete: building number



Section 6.5 Adverse Event Reporting

"Primary Study Designated Physician:" previously read:



Has been changed to read:



Section 6.5.1 Potential Endpoint Reporting

Section title and text previously read:

6.5.1 Potential Endpoint Reporting

The Investigator or designee will report potential endpoints through a Web Portal (eClinical[®]) within 5 days of being aware of potential event. The vendor (George Clinical) will work with the site to obtain pertinent information to complete a case packet.

Once the packet is confirmed complete by George Clinical, they will assign to the EAC committee for review and adjudication. The Investigator will be notified on the outcome of the review. Details of the process are listed in the site manual. The following events will be reported by the site in eClinical[®] for subjects in the Double-Blind Treatment Period:

- Doubling of Serum Creatinine
- ESRD
- Death
- Nonfatal Stroke
- Nonfatal MI
- Heart Failure (hospitalized and non-hospitalized; including those events occurring during the Enrichment Period)

Has been changed to read:

6.5.1 Potential Endpoint Reporting for Adjudication

The Investigator or designee will report potential endpoints through a Web Portal (eClinical[®]) within 5 days of being aware of potential event. The vendor (George Clinical) will work with the site to obtain pertinent information to complete a case packet. Once the packet is confirmed complete by George Clinical, they will assign to the EAC committee for review and adjudication. Details of the endpoint reporting process are listed in the Endpoint Reporting site manual.

The following events will be reported by the site in eClinical[®] for subjects in the Enrichment Period:

- Death
- Nonfatal Stroke
- Nonfatal MI
- Heart Failure (hospitalized and non-hospitalized)

The following events will be reported by the site in eClinical[®] for subjects in the Double-Blind Treatment Period including subjects who continue follow-up after premature discontinuation of study drug during the Double-Blind Treatment Period:

- Doubling of Serum Creatinine
- ESRD
- Death
- Nonfatal Stroke
- Nonfatal MI
- Heart Failure (hospitalized and non-hospitalized)

The Sponsor may request reporting of additional safety-related events into eClinical[®].

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, first and second sentence previously read:

All statistical analyses with between treatment comparisons are conducted for the Double-Blind Treatment Period. Testing of treatment group differences between the Atrasentan arm and placebo arm will be conducted at a two-sided significance level of 0.05 (suitably adjusted for group-sequential testing and multiplicity for the primary and secondary endpoints).

Has been changed to read:

All statistical analyses with between treatment comparisons are conducted for the Double-Blind Period. Testing of treatment group differences for efficacy endpoints between the Atrasentan arm and placebo arm will be conducted at a two-sided significance level of 0.05 (suitably adjusted for group-sequential testing and multiplicity for the primary and secondary endpoints).

Section 8.1 Statistical and Analytical Plans

Second paragraph previously read:

The primary efficacy endpoint of the study is the time to first occurrence of a renal composite event defined as either doubling of serum creatinine (confirmed by a 30-day serum creatinine) or the onset of ESRD. Approximately 4,148 subjects (3,148 subjects

who achieve at least 30% reduction in UACR in the Enrichment Period and 1,000 subjects who achieve less than 30% reduction in UACR in the Enrichment Period) will be randomized in a 1:1 ratio to 2 treatment groups: placebo or Atrasentan 0.75 mg/day.

Has been changed to read:

The primary efficacy endpoint of the study is the time to first occurrence of an adjudicated renal composite event defined as either doubling of serum creatinine (confirmed by a 30-day serum creatinine) or the onset of ESRD in subjects who achieve at least 30% reduction in UACR in the Enrichment Period (responders). Approximately 3,500 subjects (2,500 subjects who achieve at least 30% reduction in UACR in the Enrichment Period and approximately 1,000 subjects who achieve less than 30% reduction in UACR in the Enrichment Period) will be randomized in a 1:1 ratio to 2 treatment groups: placebo or Atrasentan 0.75 mg/day.

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

Subsection Definition of Baseline

First paragraph, first sentence previously read:

For treatment comparisons and summaries based on the Double-Blind Treatment Period, baseline values refer to the last non-missing value observed prior to or at the time of randomization.

Has been changed to read:

For treatment comparisons and summaries based on the Double-Blind Period, baseline values refer to the last non-missing value observed prior to or at the time of randomization.

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

Subsection Definition of Baseline

Second paragraph previously read:

For determination of doubling of serum creatinine, values obtained prior to Enrichment will be used as reference values.

Has been changed to read:

For determination of doubling of serum creatinine, baseline values refer to the last non-missing value observed prior to or pre-dose on the first day of Atrasentan therapy at the beginning of the Enrichment Period.

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

Subsection Definition of Baseline

Last paragraph

Add: new second and third sentence

For the Enrichment Period, initial UACR is computed as the geometric mean of UACR collected at Visits R6 and E1, and final UACR is computed as the geometric mean of the UACR values collected at Visits E4 and E5, provided at least three UACR values are available in each case. UACR will be considered to be missing otherwise.

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

Subsection Analysis

Second paragraph

Delete: third sentence

P values for the treatment difference in the discontinuation rate and that for each primary reason will be provided using Fisher's exact test at the significance level of 0.05.

Section 8.1.3.1 Primary Efficacy Analyses

Section title previously read:

Primary Efficacy Analyses

Has been changed to read:

Primary Efficacy Analyses (Responders)

Section 8.1.3.1 Primary Efficacy Analyses

First paragraph

Delete: second sentence

For determination of doubling of serum creatinine, values obtained prior to Enrichment will be used as reference values.

Section 8.1.3.1 Primary Efficacy Analyses

Second paragraph previously read:

The primary efficacy analysis for treatment comparison will be conducted on the ITT responder set for the primary efficacy endpoint using a stratified log-rank test, adjusting for the following stratification factors.

Has been changed to read:

A Cox proportional-hazard regression model will be performed on the ITT responder set to estimate the hazard ratio of Atrasentan to placebo and its 95% confidence interval. The primary efficacy analysis for treatment comparison will be conducted using a stratified log-rank test, adjusting for the following stratification factors.

Section 8.1.3.1 Primary Efficacy Analyses

Delete: first bullet

Geographical region (North America, Latin America, Europe, Asia Pacific, and Japan),

Section 8.1.3.1 Primary Efficacy Analyses

Third paragraph, last sentence previously read:

A Cox proportional-hazards regression model with treatment group and the above stratification factors as explanatory variables will be performed to estimate the hazard ratio of events comparing placebo to Atrasentan and its 95% confidence interval.

Has been changed to read:

A Cox proportional-hazards regression model with treatment group and the relevant factors (defined in the Statistical Analysis Plan) as explanatory variables will be performed to estimate the hazard ratio of events comparing placebo to Atrasentan and its 95% confidence interval.

Section 8.1.3.1 Primary Efficacy Analyses

Last paragraph previously read:

Subgroup analyses for subgroups based on age, gender, race and important baseline characteristics will also be performed.

Has been changed to read:

Subgroup analyses for subgroups based on age, gender, race, geographical regions and important baseline characteristics will also be performed.

Section 8.1.3.4 Efficacy Analyses for the 24-Hour Urine Sub-Study

First paragraph previously read:

Twenty-four-hour urine will be collected at baseline (prior to the Enrichment Period), and subsequently at the E5, T12, visits yearly and F1 visit thereafter in a subset of subjects.

Has been changed to read:

Twenty-four-hour urine will be collected prior to dosing in the Enrichment Period (Visit E1), and during enrichment at Visit E5, 12 months after randomization (Visit T12), yearly thereafter and at the follow-up visit (Visit F1) for each subject that consents to participate in this optional sub-study up to a limit of 800 subjects.

Section 8.1.3.5 Multiplicity

Last paragraph, first sentence previously read:

To control the family-wise type I error rate at 0.05, each secondary endpoint will be tested at a 0.05 level (two-sided) following a hierarchical (step-down) multiple testing procedure.

Has been changed to read:

To control the family-wise type I error rate at 0.05, each secondary endpoint will be tested at the interim or final analysis only when the primary endpoint is statistically significant at the corresponding analysis using the same alpha level as the alpha spent for the primary endpoint at the interim or final analysis, respectively, following a hierarchical (step-down) multiple testing procedure.

Section 8.1.4 Safety Analyses

Subsection Derivation of Safety Endpoints

First sentence previously read:

Safety data collected from randomization up to the 45-day Follow-Up Visit will be included in the relevant analyses for the all treated analysis sets, unless otherwise specified in the Statistical Analysis Plan (SAP) document.

Has been changed to read:

Safety data collected from the first dose up to 45 days post last dose in the Double-Blind Period will be included in the relevant analyses for the all treated analysis sets, unless otherwise specified in the Statistical Analysis Plan (SAP) document.

Section 8.1.4.1 Adverse Events (AEs) Analyses

Item 5 and 6 previously read:

5. 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.

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 relationship to study drug.

Has been changed to read:

5. A summary of the number and percentage of subjects with drug-related treatment-emergent adverse events by primary MedDRA system organ class and preferred term.

Section 8.1.4.4 ECG Analyses

Add: new last sentence

Shifts from baseline at each visit where ECG data is collected will be summarized similarly.

Section 8.1.5 Interim Analysis

Previously read:

One futility analysis of the primary efficacy endpoint will be performed when approximately 50% of the events (total of adjudicated and unadjudicated) required for completion of the trial are available. The primary analysis will be based on the EAC-adjudicated events. Supportive analyses will also be based upon both the total of adjudicated and unadjudicated events. A futility stopping boundary is specified using Gamma (-6) as the beta-spending function (Hwang et al). An alpha spending of 0.0009 using a Gamma (-8) function will also be applied to the interim analysis. Hence for the final analyses, the primary efficacy endpoint will be tested at an expected nominal alpha level of 0.0498. The final adjustment will be based on the exact number of EAC-adjudicated events observed for the interim analysis.

To preserve the integrity and the validity of trial data, an external Statistical Analysis Center will perform the interim analysis.

Has been changed to read:

An interim analysis of efficacy will be performed when the number of accrued primary events in the responder population is in the range of 50% to 75% of the targeted 425 events for the study. An alpha-spending function approach will be used to ensure that the overall one-sided type I error rate will be controlled at 0.025 or less. In addition, an interim analysis of efficacy data for futility only may be performed at an earlier time point. No adjustment to the type I error rate will be made for the futility assessment.

To preserve the integrity and the validity of trial data, an external Statistical Analysis Center will perform the requisite interim analyses and present the results to IDMC. Further details of the interim analysis plan will be provided in the Statistical Analysis Plan (SAP) and IDMC Charter. In making any decision to recommend discontinuation of the study, either for superior efficacy of Atrasentan or for futility, the IDMC shall be guided by a formal stopping rule described in the SAP.

Section 8.1.6 Independent Data Monitoring Committee (IDMC) and Independent External Statistician

First paragraph, second sentence previously read:

The IDMC membership and responsibilities, and details of the interim analysis and safety reviews, will be documented in a charter that will be prepared prior to the first IDMC review meeting.

Has been changed to read:

The IDMC membership and responsibilities, and details of the interim analyses and safety reviews, will be documented in a charter that will be prepared prior to the first IDMC review meeting.

Section 8.1.6 Independent Data Monitoring Committee (IDMC) and Independent External Statistician

Fourth and fifth paragraph previously read:

The first IDMC meeting will occur after the first 30 subjects with a UACR < 30% (non-responders) are randomized and have completed the T1 visit or after the first 100 subjects have completed the enrichment period, whichever occurs first. The second IDMC meeting will occur after the first 100 subjects are randomized. Subsequently IDMC meetings will occur approximately every 6 months and, if necessary, at times other than those scheduled if either the Sponsor or the IDMC determines that an unplanned meeting is warranted based on safety concerns.

The IDMC will review unblinded efficacy data at the single interim futility analysis as specified in Section 8.1.5.

Has been changed to read:

The first IDMC meeting will occur after the first 30 subjects with a UACR < 0% (non-responders) are randomized and have completed the T1 visit or after the first 100 subjects have completed the enrichment period, whichever occurs first. The second IDMC meeting will occur after the first 100 subjects are randomized. Subsequently IDMC meetings will occur after 25%, 50%, and 75% of the primary end-points have occurred. In addition, the IDMC will meet at least every 6 months and, if necessary, at times other than those scheduled if either the Sponsor or the IDMC determines that an unplanned meeting is warranted based on safety concerns.

The IDMC will make recommendation(s) to AbbVie (Sponsor representative) based on their review. The Sponsor representative will accept or reject the IDMC's recommendation.

The IDMC will review unblinded efficacy data as specified in Section [8.1.5](#).

Section 8.2 Determination of Sample Size

First paragraph, second previously read:

A total of 425 events in the ITT set are needed to detect a 27% hazard reduction (HR of 0.73) with 90% power at two-sided alpha level of 0.05.

Has been changed to read:

A total of 425 events in the ITT set are needed to detect a 27% hazard reduction (HR of 0.73) with approximately 90% power at two-sided alpha level of 0.05.

Section 8.2 Determination of Sample Size

First paragraph, last sentence previously read:

With the assumption of annual event rate of 6% in placebo group, 24-month accrual period, approximate 48-month double-blind treatment duration, and the discontinuation rate is 15%, a total of 3,148 subjects who achieve at least 30% reduction in UACR (responders) during the Enrichment Period (1,574 subject per group) are needed for randomization.

Has been changed to read:

With the assumption of annual event rate of 6% in placebo group, 42-month accrual period, approximate 6 year duration of the Double-Blind Period, and an annualized lost to follow-up rate of 2%, a total of approximately 2,500 subjects who achieve at least 30% reduction in UACR (responders) during the Enrichment Period (1,250 subjects per group) are needed for randomization.

Section 8.2 Determination of Sample Size

Second and third paragraph previously read:

In addition, a maximum of 1,000 subjects who achieve less than 30% reduction in UACR (non-responders) in Enrichment period will also be randomized in a 1:1 ratio to Atrasentan treatment or placebo since it has not been determined whether Atrasentan can reduce long-term CKD progression in this population.

A blinded event rate calculation is planned before the enrollment is completed to confirm or potentially revise the event rate assumption and sample size for the study.

Has been changed to read:

In addition, approximately 1,000 subjects who achieve less than 30% reduction in UACR (non-responders) in Enrichment period will also be randomized in a 1:1 ratio to Atrasentan treatment or placebo since it has not been determined whether Atrasentan can reduce long-term CKD progression in this population.

Section 8.3 Randomization Methods

Last bullet previously read:

UACR reduction during the Enrichment Period: < 0% (capped at 250); 0% to < 15% and 15% to < 30% (capped at 750); 30% to < 45%, 45% to < 60% and \geq 60%.

Has been changed to read:

UACR reduction during the Enrichment Period: < 0% (approximately at 250); 0% to < 15% and 15% to < 30% (approximately at 750); 30% to < 45%, 45% to < 60% and \geq 60%.

Section 8.3 Randomization Methods

Last paragraph previously read:

Randomization of non-responders will be distributed chronologically throughout the study in a 1:3 proportion to the number of responders randomized in an attempt to maintain proportionate balance between the two populations (e.g., in terms of rate of primary events and representation of global regions). The implementation of the responder/non-responder ratio will be through the IRT system and will allow the randomization of 50 non-responders for every 150 responders that are randomized.

Has been changed to read:

A strategy will be utilized to provide gating of subjects into the responder and non-responder groups in order to allow for temporal similarity in accrual of subjects and

relatively similar exposure times on study drug. The implementation of the responder/non-responder ratio will be through the IRT system.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[Redacted]		Clinical
		Clinical
		Clinical
		Clinical
		Statistics
		Clinical
		Pharmacokinetics
		Global Drug Supply Management

Has been changed to read:

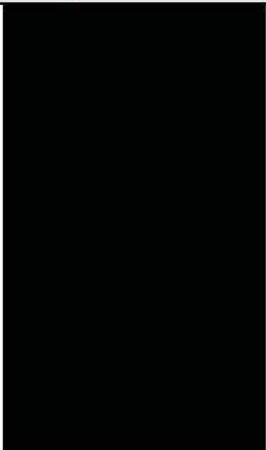
Name	Title	Functional Area
[Redacted]		General Medicine Therapeutic Area
		General Medicine Therapeutic Area
		Clinical
		Data and Statistical Sciences, Statistics
		Bioanalysis
		Pharmacokinetics and Pharmacodynamics
		Clinical Drug Supply Management

Document Approval

Study M11352 - A Randomized, Multicountry, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Atrasentan on Renal Outcomes in Subjects with Type 2 Diabetes and Nephropathy SONAR: Study of Diabetic Nephropathy with Atrasentan - Amendment 7 - EudraCT 2012-005848-21 - 19May2017

Version: 2.0

Date: 22-May-2017 04:57:44 PM Company ID: 05222017-00F9F681534C49-00002-en

Signed by:	Date:	Meaning Of Signature:
	19-May-2017 08:33:51 PM	Approver
	19-May-2017 08:46:45 PM	Approver
	19-May-2017 09:12:43 PM	Approver
	22-May-2017 01:33:37 A	Approver
	22-May-2017 02:04:19 AM	Approver
	22-May-2017 04:44:54 PM	Approver
	22-May-2017 04:57:43 P	Author