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

Published: 25-09-2013
Last updated: 22-04-2024

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...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Diabetic complications
Study type	Interventional

Summary

ID

NL-OMON44825

Source
ToetsingOnline

Brief title
SONAR: Study Of Diabetic Nephropathy with Atrasentan

Condition

- Diabetic complications
- Nephropathies

Synonym
diabetic and neuropathy

Research involving
Human

Sponsors and support

Primary sponsor: Abbvie Deutschland GmbH & Co. KG
Source(s) of monetary or material Support: AbbVie

Intervention

Keyword: atrasentan, diabetic Nephropathy, Phase III

Outcome measures

Primary outcome

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 outcome

Secondairy 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 (Vss/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.

Study description

Background summary

The role of ETa and Etb receptor subtypes in renal and cardiovascular (CV) disease are under investigation.

Study objective

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.

Study design

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 per day for 6 weeks to determine their UACR response and to assess tolerability of atrasentan. Approximately 2,500 Responders (UACR reduction * 30% from baseline) and approximately 1,000 non-responders (UACR < 30% reduction from baseline) will then be randomized 1:1 into the double-blind treatment period.

The duration ofthe 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 at the discretion of the PI. 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 PI's medical judgment. If there is significant worsening of peripheral edema or other symptoms of fluid overload, such as dyspnea with walking or laying down, during any of the treatment visits, the PI may increase 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 subject stops taking drug, every attempt will be made to keep him/her in the study by continuing scheduled 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 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.

Intervention

After screening, this study has three periods: a run-in period where the subject will take their regular medications, an enrichment period where he/she will take 0.75 mg once per day of atrasentan, and a dosing period where he/she will be randomly assigned to receive 0.75 mg per day of atrasentan or placebo (dummy medication) once per day.

There is a 50% chance of receiving atrasentan and a 50% chance of receiving placebo.

Study burden and risks

The participation in this study will last up to 6 years and may include up to 40 study visits to the research center.

During these visits there will be 2x a physical examination, the vital signs will be meassured, the weight will be meassured, blood and morning urine will be collected, 5x an ECG will be taken, and 8x a Quality of Life questoinnaire

is completed.

Reported Side Effects from Clinical Studies with Atrasentan Have Been:
dizziness, decreases in blood presssure, runny/stuffy nose/sinus congestion ,
headache, Diarrhea, Constipation, Fatigue, Fluid retention, Heart Failure,
Decrease Red Blood cell count, Blood Creatinine Increased.

Contacts

Public
Abbvie Deutschland GmbH & Co. KG

Knolltrasse
Ludwigshafen 67061
DE
Scientific
Abbvie Deutschland GmbH & Co. KG

Knolltrasse
Ludwigshafen 67061
DE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

To be eligible for initial entry into the study, subjects must meet 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-glumatic 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 mm Hg 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 Run-In Period (R6);
Subjects already on a MTLDD of a RAS inhibitor for * 4 weeks and not on a diuretic (unless medically contraindicated) 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 based on the last visit of the Run-In Period:;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 contraindicated) 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 judgement (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* 300pg/mL (300ng/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.
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.

Exclusion criteria

Subjects meeting the following criteria will be excluded from the study:
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 × 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 (TIA) 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 two 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 I diabetes.
22. Subject is considered to be clinically unstable regarding general, metabolic or cardiovascular health as determined by the investigator.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-04-2014
Enrollment:	70
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Altrasentan

Ethics review

Approved WMO Date:	25-09-2013
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-01-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-06-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-07-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-10-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-11-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-05-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	19-07-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-08-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-09-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-07-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-10-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-10-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-005848-21-NL
ClinicalTrials.gov	NCT01858532
CCMO	NL45007.056.13