Multi-center, Open-label, Extension Study to Evaluate the Long-term Efficacy and Safety of Oral Tolvaptan Tablet Regimens in Subjects with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Published: 21-06-2010
Last updated: 01-05-2024

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal and urinary tract disorders congenital
Study type	Interventional

Summary

ID

NL-OMON39149

Source
ToetsingOnline

Brief title
Open-label extension study in adult subjects with ADPKD

Condition

- Renal and urinary tract disorders congenital
- Renal disorders (excl nephropathies)

Synonym
Genetic disease whereby the kidneys contain multiple cysts filled with fluid

Research involving
Human

Sponsors and support

Primary sponsor: Covance
Source(s) of monetary or material Support: De Sponsor;Otsuka Pharmaceutical Development & Commercialization;Inc.

Intervention

Keyword: ADPKD, Phase 3b, Tolvaptan, Vasopressin V2 receptor antagonist

Outcome measures

Primary outcome

For subjects continuing from protocol 156-04-251 comparing those previously

treated with tolvaptan (combining all doses) to those subjects previously

treated with placebo, disease modification as measured by:

- Percent change from 156-04-251 baseline in total kidney volume (TKV) at month

24 in trial 156-08-271 as compared to the percent change in TKV at 156-04-251

Month 36 measured by magnetic resonance imaging (MRI)

then,

- Change in renal function (100x1/Serum Creatinine mg/dL) at Month 24 in trial

156-08-271 as compared to change from end of titration in renal function at

Month 36 in protocol 156-04-251.

Secondary outcome

In prior placebo subjects enrolling from protocol 156-04-251:

- Change in annual TKV slope when crossing over to tolvaptan treatment

- Change in annual slope for renal function (100x1/Serum Creatinine mg/dL) when crossing over to tolvaptan treatment

For all subjects enrolled in this trial:

- Change from baseline in TKV by exposure group

- Change from end of titration in renal function (100x1/Serum Creatinine mg/dL) by exposure group

- For subjects who are taking anti-hypertensive therapy at Baseline in this trial, percentage with clinically sustained decreases of blood pressure (BP) leading to a sustained reduction in anti-hypertensive therapy compared to Baseline (while taking investigational product) at visit Months 12 and 24 for hypertensive subjects.

Study description

Background summary

Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC) is studying an investigational drug called tolvaptan (the *Study Drug*). An investigational drug is a drug that is being studied for approval by the United States Food and Drug Administration (FDA) and EMA (European Medicines Agency). Tolvaptan (Samsca®) is a drug approved for use in the United States (2009) in patients with certain types of hyponatremia (hypervolemic and euvolemic hyponatremia). Hyponatremia is low amount of sodium or salt in the blood. Tolvaptan (Samsca®) is approved in the European Union (2009) for treatment for a different type of hyponatremia (hyponatremia secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH)).
The Study Drug has not been approved for use in the United States or in any other country to treat Autosomal Dominant Polycystic Kidney Disease (ADPKD).

ADPKD is a disease that causes kidney cysts (like fluid-filled balloons), worsening kidney function, and blood in the urine, kidney pain, high blood pressure, kidney stones, kidney infections, and cysts in the brain or other parts of the body. Tolvaptan is being studied as a possible treatment for ADPKD. For those people with ADPKD, the kidneys respond abnormally to the hormone vasopressin that may be involved in cyst development or growth in humans. Tolvaptan interferes with vasopressin*s effects on the kidney, and when taken chronically, appears to block cyst growth in animal models of ADPKD. It is hoped that similar effects will be seen in humans. Tests will tell how useful tolvaptan will be in treating ADPKD.

Study objective

The objective of this extension study is to find out the potential long-term benefits and safety of tolvaptan. During this study all participants will receive tolvaptan.

PRIMARY OBJECTIVE is to demonstrate whether tolvaptan modifies ADPKD progression as measured by changes from baseline (from trial 156-04-251) in total kidney volume (TKV) and renal function.
Disease modification is evidenced by the maintenance of treatment group differences (tolvaptan- versus placebo-treated subjects) observed at the end of trial 156-04-251, as compared to the end of trial 156-08-271.

SECUNDARY OBJECTIVES are:
- To determine whether, for placebo-treated subjects from trial 156-04-251, the annual rate of change (slope) in TKV and renal function changes during the crossover from placebo to tolvaptan treatment.
- To explore exposure response relationship among all subjects enrolled in this trial for changes in TKV, renal function and hypertension.

Study design

This is an international, multi-center, open-label, extension trial in adult subjects with ADPKD treated with tolvaptan split-dose regimens for a minimum of 24 months.

During this study all participants will receive tolvaptan.

Tolvaptan (15 or 30 mg oral tablets) will be self-administered given in split-doses separated by approximately 9 hours, first dose being given on awaking, for a minimum of 24 months and up to 60 months. Regimens include 45/15, 60/30 and 90/30 mg of tolvaptan.
All subjects will be titrated to the last assigned dose group from their prior trial.
Subjects will be able to increase, hold or step down in dose level during the

trial.

Intervention

Tolvaptan (15 or 30 mg oral tablets) will be self-administered given in split-doses separated by approximately 9 hours, first dose being given on awaking, for a minimum of 24 months and up to 60 months.
Regimens include 45/15, 60/30 and 90/30 mg of tolvaptan.

All subjects will be titrated to the last assigned dose group from their prior trial with the exception of subjects enrolling from protocol 156-04-250 where titrations requirements may be waived.

Subjects will be able to increase, hold or step down in dose level during the trial.

The subject receives a minimum of 24 months treatment + 7 day follow-up.

Subjects will be allowed to continue in the trial until the last subject completes their Month 24 visit, up to 60 months.

Study burden and risks

For an overview of possible side effects of tolvaptan, see page 23-25 of the protocol and page 8-10 of the patient information letter.
The most frequent side effects of tolvaptan are increased thirst, dry mouth and headache.

Frequent complaints (seen in at least 3% of all participants) that have been reported during studies of tolvaptan include increased thirst, increased heart failure in individuals who already have heart failure, dry mouth, nausea, increased urination (frequency and volume),dizziness, headache, constipation, low blood pressure, soft stool, tiredness, trouble sleeping, chest pain, increased level of potassium in the blood, decreased level of potassium in the blood, low blood count, kidney or bladder infection, irregular heart beat (atrial fibrillation), increased creatinine in the blood (a waste product taken to the kidneys for filtering), vomiting, cough, rapid heart rate, worsening of kidney function, infection in the lung, swelling in the arms or legs, pain in the abdomen, back, arms, or legs, increased levels of uric acid in the blood, and shortness of breath. These side effects may or may not be caused by tolvaptan.

At the area where the blood is taken, there may be mild pain, bruising and swelling. More rarely, the patient may faint and the area may become infected.

Can occur during the MRI scan in rare cases: local infection, irritation,

allergic reaction (at the area of the injection of the contrast fluid). Some patients can feel uncomfortable in the MRI machine.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Successful completion of a previous phase 1, 2, or 3 tolvaptan ADPKD or renal impairment trial, with a confirmed diagnosis of ADPKD.
- Estimated GFR greater than or equal to 30 mL/min/1.73 m2 within 30 days prior to enrollment, or with documented medical monitor approval prior to enrollment.

Exclusion criteria

- Safety contraindications including: non-compliance with therapies, reproductive precautions, unawareness of thirst, severe allergic reactions to compounds with similar chemical structure as tolvaptan
- Contraindications to or interference with MRI assessments
- Concurrent conditions or taking therapies likely to confound endpoint assessments or prevent completion of the trial (Efficacy Analysis Exclusion Only)

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-02-2011
Enrollment:	96
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	nog niet geregistreerd voor deze indicatie
Generic name:	tolvaptan

Ethics review

Approved WMO

Date:	21-06-2010

Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-10-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-01-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-09-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-11-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-12-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-04-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-05-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-11-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-02-2013

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-06-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-07-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-09-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-02-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-06-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-09-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-11-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-02-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-06-2015

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	31-08-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2010-018401-10-NL
CCMO	NL32308.042.10