A Phase 2a, Single-Center Study Investigating the Short-Term Renal Hemodynamic Effects, Safety and Pharmacokinetics/ Pharmacodynamics of Oral Tolvaptan in Subjects with Autosomal Dominant Polycystic Kidney Disease at Various Stages of Renal Function

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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-OMON34527

Source
ToetsingOnline

Brief title
Phase 2a 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, Autosomal Dominant Polycystic Kidney Disease, Phase 2, Tolvaptan, Vasopressin V2 receptor antagonist

Outcome measures

Primary outcome

Pharmacodynamics:

GFR as determined by iothalamate clearance, ERPF as determined by hippuran

clearance and filtration fraction (GFR/ERPF).

Secondary outcome

- Pharmacodynamics:

Urine concentrations of sodium, potassium, osmoles, creatinine, urea, uric

acid, aldosterone and albumin and urine volume.

The calculated urinary excretion of sodium, potassium, creatinine, urea, uric

acid, albumin and aldosterone.

Serum or plasma concentrations of sodium, potassium, osmoles, creatinine, urea,

uric acid, albumin, cystatin C, active plasma renin, copeptin, and aldosterone.

The calculated clearances of free water, sodium, potassium, osmoles,

creatinine, urea, and uric acid and the fractional clearances of free water,

sodium, potassium, urea and uric acid to creatinine clearance.

The calculated ratio of urine albumin to creatinine.

Mean arterial blood pressure.

Short-term changes in total kidney volume (TKV) as percent change from baseline at the Final Treatment Visit (after approximately 3 weeks of treatment) and at the Post Treatment Visit (after approximately 3 weeks off treatment) measured by MRI.

- Safety:

Adverse events (AEs), vital signs, clinical laboratory tests, physical examinations, and electrocardiograms (ECG).

- Pharmacokinetics:

Peak plasma concentration (Cmax), time to peak plasma concentration (tmax), and area under the concentration-time curve calculated to the time of the last observable concentration (AUCt*) of tolvaptan and its metabolites (DM-4103 and DM-4107) in plasma.

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 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 effective tolvaptan will be in treating ADPKD.

Study objective

The purpose of the trial is to determine the effect of multiple doses of tolvaptan on renal function in patients with autosomal dominant polycystic kidney disease (ADPKD) at various stages of renal function. Additionally, the short-term renal hemodynamic safety of tolvaptan will be assessed.

PRIMARY OBJECTIVE is to determine the effect of maximally tolerated doses of tolvaptan at steady state on the measured glomerular filtration rate (GFR), effective renal plasma flow (ERPF), and filtration fraction in subjects with ADPKD, including those with severely impaired renal function.

SECUNDARY OBJECTIVES are:
- To assess the short-term renal hemodynamic safety of tolvaptan
- To determine the effect of tolvaptan on urine concentrations and excretion of sodium, potassium, osmoles, creatinine, urea, uric acid, aldosterone and albumin and the urine albumin/creatinine concentration ratios, urine volume, plasma or serum concentrations of sodium, potassium, osmoles, creatinine, urea, uric acid, albumin, cystatin C, active plasma renin, copeptin, and aldosterone, the clearances of free water, sodium, potassium, osmoles, creatinine, urea, and uric acid and the fractional clearances of free water, sodium, potassium, urea and uric acid to creatinine clearance
- To determine the effect of tolvaptan on mean arterial blood pressure
- To characterize the plasma concentrations of tolvaptan and its metabolites (DM-4103 and DM-4107)
- To determine short-term effects of tolvaptan on total kidney volume (TKV) as measured by changes from baseline

Study design

This study is a single-center, sequential trial of the effect of multiple doses of tolvaptan on renal function in subjects diagnosed with ADPKD.

This trial will include up to 36 male and female subjects aged 18 to 70 years, inclusive, without previous exposure to tolvaptan.

Inclusion will be stratified for estimated glomerular filtration rate (eGFR) using the 4 variable modification of diet in renal disease (MDRD) equation (Levey AS, Bosch JP, Lewis JB, et al. Ann Intern Med, 1999; 130:461-470), with 3 strata:
1) > 60 mL/min*1.73 m2
2) 30-60 mL/min*1.73 m2
3) < 30 mL/min*1.73 m2.
Each stratum will contain a minimum of 6 subjects and up to 12 subjects.

The study medication is: 15 mg and 30 mg tolvaptan tablets for oral administration.

During the treatment phase of 3 weeks, each subject will Initially receive a daily split dose of 45/15 mg tolvaptan for 1 week, with the larger dose upon awakening each day followed by the smaller dose approximately 8 hours later. If the subject tolerates this dose, the daily split dose will be increased to 60/30 mg for a week, followed by a daily split dose of 90/30 mg the successive week as tolerated.

Study participation for each subject will be up to 12 weeks: a 2- to 42-day screening period, 3 week treatment period, and 3 week post-treatment period. The expected duration of this trial from first subject screened to last subject completed is 12 months.

Intervention

During the 3-week treatment phase, each subject will receive a daily split dose of 45/15 mg tolvaptan for 1 week, with the larger dose upon awakening each day followed by the smaller dose approximately 8 hours later. If the subject tolerates this dose, the daily split dose will be increased to 60/30 mg for a week, followed by a daily split dose of 90/30 mg the successive week as tolerated.

Study burden and risks

For an overview of possible side effects of tolvaptan, see page 20-21 of the protocol and page 7-8 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.

Part of this study is the renal function investigation. This investigation is being done in UMCG routinely to assess the renal function; we have ample experience with these tests. For the renal function investigation the patient will receive an infuse. Via this infuse the patient will be administered a low dose of isotopes (0,4 ml/kg) as 'priming solution'. This solution consists of 0.04 MBq 125I-iothalamate and 0.03 MBq 131I-hippuran with 0.6 MBq 125I-iothalamate dissolved in NaCl 0,9%. Thereafter, a lower dose of isotopes is administered via the infuse (0,015 MBq 125I-iothalamate and 0,02 MBq 131I-hippuran). In total, the patient will be at the infuse for 5,5 hours. A 'steady state' of the concentration of iothalamate en hippuran is reached after 1,5 hours. Thereafter, every hour blood is taken and every two hours urine is captured to measure the amount of radiation. Risks of this investigation are minimal (risk of hematomes at the place of the injection and flebitis). The total dose of isotopes used during this investigation is so low that it amounts to a lower dose of radiation than needed to make a photo of the thorax. Therefore we can state that there is no increased radiation risk for the patient.

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

This study will be started in subjects with eGFR >30 mL/min*1.73m2. Other important inclusion criteria are: confirmed diagnosis of ADPKD, body mass index of <35 kg/m2, in good health determined by: medical history, physical examination, ECG, serum/urine biochemistry, hematology tests. See protocol page 29.
Following determination of the effects in patients with eGFR >30 mL/min*1.73m2, subjects with eGFR <30 mL/min*1.73m2 will be entered as appropriate. If necessary, subjects withdrawn from the trial will be replaced.

Exclusion criteria

- Subjects with previous exposure to tolvaptan
- Subjects with recent (within last 6 months) renal surgery
- Subjects with evidence of renal cystic disease other than ADPKD (e.g. renal cancer)
- Safety contraindications including: reproductive precautions, unawareness of thirst, severe allergic reactions to compounds with similar chemical structure as tolvaptan, significant risk factors for renal impairment other than ADPKD (e.g. advanced diabetes), a history of significant coagulation defects, critical electrolyte inbalances, low blood volume, clinically

significant anemia, history of substance abuse, uncontrolled hypertension.
- Contraindications to or interference with MRI assessments
See protocol page 30 for further details.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-09-2011
Enrollment:	36
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:	26-07-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	31-08-2010

Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-09-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-10-2010
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-05-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-06-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-06-2013
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	EUCTR2010-019025-33-NL
CCMO	NL32771.042.10