# A Phase 3b, Multi-center, Open-label Trial to Evaluate the Long Term Safety of Immediate-release Tolvaptan (OPC-41061, 30 mg to 120 mg/day, Split dose) in Subjects with Autosomal Dominant Polycystic Kidney Disease

Published: 06-11-2014
Last updated: 21-04-2024

The primary objective of this trial is to evaluate and describe the long-term safety of tolvaptan.

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Nephropathies |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON41781

**Source**
ToetsingOnline

**Brief title**
Otsuka 156-13-211

### Condition

- Nephropathies

**Synonym**
Autosomal Dominant Polycystic Kidney Disease

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Quintiles
**Source(s) of monetary or material Support:** Farmaceutical Industry

## Intervention

**Keyword:** OPC-41061, Phase 3b, Tolvaptan

## Outcome measures

### Primary outcome

Safety: AEs, vital signs, clinical laboratory assessments, serum transaminase elevations for frequency (2x, 3x, 5x and 10x ULN), time to onset, time to peak levels, time of offset (< 3x, 2x, or 1x ULN), response to de-challenge and re-challenge and frequency of progression to Hy*s laboratory criteria (ALT or AST > 3x ULN and BT > 2x ULN without alkaline phosphatase 2x ULN), Serum sodium excursions above 145, 150, or 155 mmol/L or below 135, 130, or 125 mmol/L.

### Secondary outcome

Exploratory: PKD outcomes survey, Medical resource utilization (office/emergency room, healthcare visits, hospital admissions, procedures and therapies) and productive days lost due to PKD outcomes as part of the ADPKD outcomes surve.

# Study description

### Background summary

Tolvaptan (OPC-41061) is a selective arginine vasopressin (AVP) type 2 (V2) receptor antagonist that is currently approved in the United States (US), Europe, Australia, Canada, China, Hong Kong, Indonesia, Japan, Republic of Korea, and Taiwan for various forms of hyponatremia, and in Japan for volume overload in heart failure or liver cirrhosis.Tolvaptan is also being

investigated for the use in adults to treat autosomal dominant polycystic kidney disease (ADPKD), an inherited condition which leads to progressive destruction of normal kidney structure leading to end-stage renal disease (ESRD). Though ADPKD is a rare genetic disease, it ranks as the 6th leading cause of ESRD in the US (2.3% of the new ESRD cases).

There are currently no therapies which can slow the deterioration of kidney function in ADPKD. Current management focuses on ameliorating symptoms of pain, control of blood pressure, and treatment of infections with antibiotics. None of these treatments target the underlying cause of the disease. Often, the only definitive intervention for renal complications in ADPKD is kidney transplantation, which typically occurs after years of hemodialysis.

In the US, the development program for tolvaptan for ADPKD was granted Fast-track designation on 20 Jan 2006 and orphan drug designation on 06 Apr 2012. Tolvaptan was designated as an orphan drug for prevention of the progression of ADPKD in Japan on 11 Aug 2006. The European Medicines Agency (EMA) granted orphan designation for the use of tolvaptan for the treatment of ADPKD on 5 Aug 2013. If approved, tolvaptan would be the first available therapy to slow kidney disease progression in adults with ADPKD.

Tolvaptan was clinically effective in delaying decline of renal function, as determined by changes in serum creatinine concentrations over 3 years, in an international, multicenter, clinical trial in subjects with chronic kidney disease (CKD) stage 1 to 3 due to ADPKD. This trial also demonstrated an acute and persistent reduction on rate of kidney cystic growth.

**Study objective**

The primary objective of this trial is to evaluate and describe the long-term safety of tolvaptan.

**Study design**

This trial is a phase 3b, multi-center, open-label extension trial. Subjects will be eligible for screening into this trial if they:
1. Participated in the double-blind Trial 156-13-210 (only upon successful completion of their randomized 12-month period including post-treatment follow-up, regardless of whether this was on-treatment or offtreatment), or
2. Participated in the open-label Trial 156-08-271. After consenting and screening, eligible subjects will be assigned a new subject number and administered tolvaptan at asplit-dose of 45/15 mg. Subjects will have the opportunity for either up or down-titration to a maximum split tolvaptan dose of 90/30 mg or a minimum split dose of 15/15 mg at the discretion of the

investigator according to individual tolerability.
Subjects entering the trial from Trial 156-08-271 may receive up to 33 months of open-label tolvaptan therapy, and subjects entering the trial from Trial 156-13-210 may receive up to 15 to 21 months of open-label tolvaptan therapy.

For purposes of ensuring subject safety, all subjects will be monitored for hepatic safety monthly until they have accumulated 18 months of tolvaptan exposure. After that, and following the approval from the medical monitor, hepatic monitoring will be required every 3 months. If subjects approaching the 18-month threshold have had prior transaminase abnormalities (> 2 × upper limit of normal [ULN]), the investigator is responsible for contacting the medical monitor to confirm the change in frequency from monthly to every 3 months. Until their prior treatment assignment is unblinded, all Trial 156-13-210 subjects who are eligible for this trial are scheduled to have trial visits/ hepatic monitoring monthly for the first 18 months of this trial. Once unblinding occurs, it can be determined which subjects received tolvaptan in Trial 156-13-210. These subjects may have their trial visits/hepatic transaminase monitoring change to every 3 months sooner as their previous tolvaptan exposure in Trial 156-13-210 can count towards the 18-month threshold. Enrollment in this trial will be closed when the final eligible subject from Trial 156-13-210 enrolls in this trial.

**Intervention**

The dose regimens to be used in this trial are 15/15 mg, 30/15 mg, 45/15 mg, 60/30 mg, and 90/30 mg. Tolvaptan tablets (15 mg or 30 mg) will be self-administered orally as split-dose regimens, twice daily, once upon awakening and another approximately 8 to 9 hours later. Doses will be recorded as early dose/late dose (eg, 60/30 mg).

**Study burden and risks**

Clinical studies have shown that after the drug breaks down, by-products can build up in the body. While these products do not appear to be active and long-term studies in animals and in humans have been conducted, we do not know whether there are other very long term effects in humans.

Frequent adverse effects (seen in at least 3% of all participants who received tolvaptan regardless of their health before participating) that have been reported during studies of tolvaptan and placebo include increased thirst, increased severity of heart failure in individuals who already have heart failure, dry mouth, nausea, increased urination (frequency and volume at day and night), dizziness, constipation, low blood pressure, high blood pressure, diarrhea, tiredness, trouble sleeping, increases or decreases in the level of potassium in the blood, low blood count, kidney or bladder infection, increased creatinine in the blood (a waste product taken to the kidneys for filtering),

vomiting, cough, decreased appetite, infection in the lung, swelling in the arms or legs, headache, pain in the chest, kidneys, abdomen, back, arms, or legs, fever, increased levels of uric acid in the blood, and shortness of breath.

Less frequent but serious medical problems have been seen in some study participants. These include heart failure, stroke, glaucoma, skin cancers or even death. Because such serious medical problems are infrequent, and given the seriousness of the participant's medical condition before the study it is not known if such problems would have occurred whether the patient had participated in the study or not.

During an investigational clinical study of tolvaptan for the treatment of ADPKD, an increased risk of liver injury was found. Liver test abnormalities and liver injury occurred more frequently in patients taking tolvaptan compared to those taking placebo. These findings indicate that tolvaptan may cause permanent liver injury. No ADPKD patient in a clinical trial has had signs of permanent liver damage but it can occur and may require a liver transplant or cause death. In other clinical trials of tolvaptan, (including the trials in hyponatremia, heart failure, cirrhosis and hepatic edema patients), signs of drug-induced liver damage have not been seen.

## Contacts

**Public**
Quintiles

Siriusdreef 10
Hoofddorp 2132 WT
NL
**Scientific**
Quintiles

Siriusdreef 10
Hoofddorp 2132 WT
NL

## Trial sites

### Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

Male and female subjects aged >18 years with ADPKD who have completed 156-13-210, or who have participated in a previous tolvaptan ADPKD trial and do not qualify for 156-13-210.

## Exclusion criteria

1. Women of child bearing potential who are unwilling to adhere to abstinence or double-barrier contraceptive requirements
2. Women who are breast-feeding and/or who have a positive pregnancy test result prior to receiving IMP.
3. Need for chronic diuretic use
4. Hepatic impairment based on liver function or abnormalities other than that expected for ADPKD with cystic liver disease during screening
5. Subjects with contraindications to required trial assessments (contraindications to optional assessments, eg MRI, are not a limitation)
6. Subjects who, in the opinion of the trial investigator or Medical Monitor, have a medical history or medical findings inconsistent with safety or compliance with trial. This includes prior evidence of significant hepatic injury deemed to be related to tolvaptan use.

# 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): | 09-03-2015 |
| Enrollment: | 69 |
| Type: | Actual |

## Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | Samsca |
| Generic name: | Tolvaptan |

# Ethics review

| | |
|---|---|
| Approved WMO Date: | 06-11-2014 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 09-03-2015 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 28-08-2015 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 16-09-2015 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 12-08-2016 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO | |

| | |
|---|---|
| Date: | 15-08-2016 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 24-08-2016 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 19-06-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 29-06-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 21-12-2017 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 26-04-2018 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 18-05-2018 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 17-10-2018 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 04-12-2018 |
| 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 | EUCTR2014-001516-19-NL |
| ClinicalTrials.gov | NCT02251275 |
| CCMO | NL50567.042.14 |