A Phase 3, Multi-center, Double-blind, Placebo-controlled, Parallel-arm Trial to Determine Long-term Safety and Efficacy of Oral Tolvaptan Tablet Regimens in Adult Subjects with Autosomal Dominant Polycystic Kidney Disease

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Primary objective:* Evaluate long-term effect of tolvaptan in ADPKD through rate of renal volume change(%) for tolvaptan-treated compared to placebo-treated subjects.Secondary objectives:* Evaluate long-term efficacy of tolvaptan in ADPKD through a...

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

Summary

ID

NL-OMON30613

Source
ToetsingOnline

Brief title
Fase III trial in adult subjects with ADPKD

Condition

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

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

Research involving
Human

Sponsors and support

Primary sponsor: Otsuka America Pharmaceutical
Source(s) of monetary or material Support: Otsuka Pharmaceutical Development & Commercialization Inc.

Intervention

Keyword: ADPKD, Fase III, Tolvaptan, Vasopressin V2 receptor antagonist

Outcome measures

Primary outcome

Rate of renal volume (total, both kidneys) change (normalized as percentage)

for tolvaptan (combining all doses) relative to placebo

Secondary outcome

Composite endpoint

Time to multiple ADPKD clinical progression events (ie, onset or progression

hypertension, severe renal pain (requiring medical intervention), worsening

albuminuria, worsening renal function for tolvaptan (combining all doses)

relative to placebo while on treatment.

Non-composite endpoints

For tolvaptan compared to placebo:

1. Rate of GFR change from postdose baseline (End of titration) to last on-drug

trial visit (using l/serumcreatinine as primary measure while Cockcroft-Gault

results will be exploratory).

2. For subjects who are non-hypertensive at baseline, change from baseline for

resting mean arterial pressure (MAP) at scheduled clinic visits up to point of exposure to anti-hypertensive therapy for any reason.

3. For subjects who are non-hypertensive at baseline, time to progress to a) high-pre-hypertension (sBP > 129 and/or dBP > 84) or b) hypertension (sBP > 139 and/or dBP > 89 mm Hg) or c) requiring anti-hypertensive therapy

4. For subjects who are taking anti-hypertensive therapy at baseline, percentage with clinically sustained decrease of BP leading to a sustained reduction in anti-hypertensive therapy compared to baseline (while taking investigational product) at visit Months 12, 24 and 36 for hypertensive subjects.

5. Change from baseline in kidney pain as assessed by 1-10 pain scale as average AUC between baseline and last trial visit prior to initiating medical (eg, narcotic or tricyclic) or surgical therapy for pain.

Study description

Background summary

Tolvaptan as a specific AVP V2 receptor antagonist, has shown to produce a dose-related, transient, aquaresis. ADPKD patients have shown a high AVP plasma concentration.
Animal trials show that treatment with vasopressine antagonist inhibits cyst growth and in some cases regresses cyst growth.

Three previous studies have shown that ADPKD patients on tolvaptan responded with potent vasopressine inhibition leading to a delay in the development of kidney cysts.

Preliminary results from an open-label trial with tolvaptan in ADPKD confirm that effectivity improves with each higher dose of tolvaptan but also that higher doses were less tolerated by the patients. As a large degree of variability in subject response was seen, this trial will implement a titration

strategy. Subjects will start at the relatively low daily dose of 45/15 mg mg and will progress in three weeks to the highest tolerated dose of 90/30 mg. Throughout the trial, subjects will have the option to up and down titrate, as circumstances warrant.

Study objective

Primary objective:
* Evaluate long-term effect of tolvaptan in ADPKD through rate of renal volume change(%) for tolvaptan-treated compared to placebo-treated subjects.

Secondary objectives:
* Evaluate long-term efficacy of tolvaptan in ADPKD through a composite of ADPKD progression clinical markers (ie, hypertension, renal pain, albuminuria and renal function)
* Evaluate long-term efficacy of tolvaptan in ADPKD using single clinical markers of ADPKD progression
* Evaluate long-term safety of tolvaptan through standard clinical measures
Evaluate pharmacokinetic (PK), pharmacodynamic (PD) and exploratory parameters for tolvaptan in ADPKD

Study design

This is a multi-centre, double-blind, placebo-controlled, parallel-arm trial in adult subjects with ADPKD
* After determining eligibility, and monitoring of the available data from screening subjects for baseline event rates, tolvaptan or placebo will be titrated from lowest to highest tolerated levels when given in split dose regimens of 45/15, 60/30 or 90/30 mg PO, given BID, on awakening and approximately 9 hours later for up to 36 months.

Intervention

Tolvaptan (using 15 or 30 mg strengths) or matching placebo (randomized in 2:1 ratio) will be self-administered for 36 months, as oral tablets given in split-dose separated by approximately 9 hours, first dose being given on awakening.
Regimens include 45/15, 60/30 and 90/30 mg of the standard tolvaptan formulation and will be titrated to tolerability.
Treatment duration on this trial is 3 years.

Study burden and risks

Possible side effect of tolvaptan, see also page 27-28 of the protocol and page 7-9 of the patient information form version 3.0.
The most commonly reported side effects with tolvaptan were thirst, dry mouth,

frequent urination and non-specific headache.
Some people 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

*GFR estimated at >= 60mL/min
*Expected rapidly progressive kidney growth (total volume >=750cc) by Magnetic Resonance Imaging (MRI) at randomization

Exclusion criteria

* Safety contraindications including: non-compliance with therapies, insufficient or no reproductive precautions, unawareness of thirst, severe allergic reactions to compounds with similar chemical structure
* Contraindications to or interference with MRI assessments
* Concurrent conditions or taking therapies likely to confound endpoint assessments or prevent completion of the trial.

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):	27-08-2007
Enrollment:	70
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:	19-03-2007

Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-06-2007
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-07-2007
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-08-2007
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-03-2008
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-03-2010
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)

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	EUCTR2006-002768-24-NL
ClinicalTrials.gov	NCT00428948
CCMO	NL13875.042.06