An exploratory, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety, tolerability and pharmacokinetics of orally administered GLPG2737 for 52 weeks, followed by an open-label extension period of 52 weeks in subjects with autosomal dominant polycystic kidney disease (ADPKD).

Published: 06-11-2019
Last updated: 12-04-2024

Main objective- To characterize the effect of GLPG2737 on growth in total kidneyvolume (TKV) compared to placebo.- To evaluate the safety and tolerability of oral doses of GLPG2737compared to placebo.Secondary objectives: - To characterize the...

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

Summary

ID

NL-OMON55300

Source
ToetsingOnline

Brief title
GLPG2737-CL-203

Condition

- Other condition
- Renal and urinary tract disorders congenital
- Nephropathies

Synonym
kidney disease, Polycystic kidney disease

Health condition

neonetal diseases

Research involving
Human

Sponsors and support

Primary sponsor: Galagapos NV
Source(s) of monetary or material Support: the pharmaceutical industry

Intervention

Keyword: GLPG2737, pharmacokinetics, placebo-controlled, polycystic kidney disease

Outcome measures

Primary outcome

- Mean percent change from baseline of height-adjusted TKV (htTKV).

- Frequency and severity of treatment-emergent adverse events

(TEAEs), treatment-emergent serious AEs (SAEs), and TEAEs leading to

treatment discontinuation.

Secondary outcome

- Mean change from baseline and estimated GFR (eGFR).

- Estimated exposure (area under the curve [AUC], maximum plasma

concentration [Cmax]), based on population PK analyses of GLPG2737

and its major metabolite M4.

Study description

Background summary

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney
disease with an estimated prevalence of 1-5 in 10.000 individuals.
Its course is characterized by the development and inexorable expansion of multiple cysts
scattered throughout the kidney parenchyma. Progressive loss of kidney function takes place over
many decades and frequently leads to end-stage kidney disease during or after the sixth decade of
life.
ADPKD is caused by loss-of-function mutation in the PKD1 or PKD2 genes that encode
polycystin-1 (PC-1) and polycystin-2 (PC-2), respectively. In 75% of cases of ADPKD, the
mutations occur in PKD1, 15% present mutations in PKD2, and the other 10% are undetermined.
PC-1 is an important regulator of several signaling pathways, and PC-2 is a non-selective calcium
channel. Mutations in PC-1 and PC-2 appear to disrupt intracellular calcium regulation, leading
to reduced intracellular Ca2+ levels. It is believed that reduced intracellular Ca2+ levels contribute
to the increased cyclic adenosine monophosphate (cAMP) levels observed in ADPKD human
kidney epithelial cells. Increased levels of cAMP contribute to the progression of
cystogenesis, by stimulating epithelial cell proliferation as well as by stimulating fluid secretion.
cAMP-dependent anion secretion to the cyst lumen has been reported to be mediated by the
luminal cystic fibrosis transmembrane conductance regulator (CFTR).

The mechanism underlying this regulation has not been totally elucidated, although the CFTR
chloride channel has been shown to contribute to disease progression by driving fluid secretion to
the cyst lumen, promoting cyst growth. Cyst and kidney growth is hypothesized to cause loss of
functioning renal mass, and eventually leads to end-stage kidney disease.
GLPG2737 is a CFTR inhibitor. In vitro, CFTR inhibitors have been shown to reduce cyst

growth in mouse and human cells of renal tubular origin. In vivo, CFTR inhibitors have been shown to reduce cyst growth in models of ADPKD, in conditional PKD1 knock-out (KO) mouse. In patients with both ADPKD and cystic fibrosis (CF) with a deletion of phenylalanine in position 508 of the CFTR (F508del-CFTR; lacking functional CFTR), renal function declines at a slower rate than that in family members who have ADPKD alone.

Therefore it is expected that administration of the CFTR inhibitor GLPG2737 to patients with ADPKD will lead to a reduction in cyst growth, slowing down kidney volume growth, and reducing the rate of decline of renal function and delay progression to end-stage kidney disease.

Study objective

Main objective
- To characterize the effect of GLPG2737 on growth in total kidney volume (TKV) compared to placebo.
- To evaluate the safety and tolerability of oral doses of GLPG2737 compared to placebo.

Secondary objectives:
- To characterize the effect of GLPG2737 on renal function (estimated glomerular filtration rate; eGFR) compared to placebo.
- To characterize the pharmacokinetics (PK) of oral doses of GLPG2737 and its major metabolite G1125498 (M4) using population PK analyses.

Study design

An exploratory, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety, tolerability and pharmacokinetics of orally administered GLPG2737 for 52 weeks, followed by an open-label extension period of 52 weeks, in subjects with autosomal dominant polycystic kidney disease

Intervention

Patients should visit the clinics and be willing to receive their study drug comparator an/or placebo according to the dosing scheme. Furthermore their data of Medical history and demographic data will be collected They must undergo physicial and vital signs examinations. ECG and MRI tests will be done. made. Blood and urine will be collected and a patient diary needs to be kept.

Study burden and risks

The study drug may reduce cyst growth, slowing down kidney volume growth, and reducing the rate of decline of renal function, but this is not certain. The disease may return or worsen at any time during this study.
In previous studies, GLPG2737 was well tolerated by healthy adults who took single doses in the range of 25 mg to 600 mg, and daily doses for 14 days in the range of 25 mg to 250 mg. The most common adverse effects in previous studies were:
Dry mouth, throat, or skin
Inflammation of nose/throat
Acne
Sore throat
Tiredness
Headache

Participation in the study also means:
- additional time;
- additional or longer hospital visits;
- additional tests;
- instructions the patient need to follow.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Main inclusion criteria for the double-blind period of the study:
1. Male and female subject aged 18 to 50 years, inclusive.
2. Documented diagnosis of typical ADPKD, using the Ravine criteria.
3. Rapidly progressive disease, defined as presence of all of the following:
-TKV >750 mL, as determined on imaging not older than 5 years before screening. If historical imaging is not available or older than 5 years, imaging can be performed during the screening period according to local clinical practice (i.e. echography, magnetic resonance imaging [MRI]).
-Mayo ADPKD Classification Classes 1C to 1E.
4. eGFR at screening between 30-90 mL/min/1.73 m2 for subjects aged 18 to 40 years (inclusive), and between 30-60 mL/min/1.73 m2 for subjects aged 40 to 50 years.
5. Blood pressure <= 150/90 mmHg. In case the subject is treated for hypertension, he/she should be on a stable treatment regimen of antihypertensive therapy for at least 8 weeks prior to the screening visit, and during the screening period.

Main inclusion criteria for the open-label extension period of the study:
1. Male and female subjects who completed the 52-week double-blind treatment period on IP.
2. Subject, according to the investigator's judgment, may benefit from long-term treatment with GLPG2737.

Exclusion criteria

Main exclusion criteria for the double-blind period of the study:
1. Congenital absence of 1 kidney, or subject had a previous nephrectomy or has a transplanted kidney or a transplantation is planned in the foreseeable future.
2. Administration of polycystic kidney disease-modifying agents (e.g. tolvaptan, somatostatin analogues) or interventions (such as cystaspiration or cyst fenestration) within 12 weeks prior to the screening visit and during the screening period. In case tolvaptan is not being administered, this should be because of e.g. non-availability, intolerance, or physician's clinical judgement.
3. Any condition or circumstances that, in the opinion of the investigator, may make a subject unlikely or unable to complete the study or comply with study

procedures and requirements (e.g. unable to undergo MRI. For example subject's weight exceeds weight capacity of the MRI, ferromagnetic metal prostheses, aneurysm clips, severe claustrophobia, etc.).

Main exclusion criterion for the open-label extension period of the study:
1. Clinically significant abnormalities detected on 12-lead ECG of either rhythm or conduction, QTcF >450 ms, or long QT syndrome.

Study design

Design

Study phase:	2
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):	26-11-2020
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	GLPG2737
Generic name:	GLPG2737

Ethics review

Approved WMO

Date:	06-11-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-03-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-04-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-04-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-08-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-08-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-10-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-11-2021
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	EUCTR2019-003521-21-NL
CCMO	NL71863.056.19