CLINICAL STUDY PROTOCOL

Project Number:	GLPG2737	Protocol Version:	6.00
Study Number:	GLPG2737-CL-203	Amendment:	5
		Date:	20-Dec-2021

Study Title:	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
Short Title:	A study to evaluate the effects of GLPG2737 in subjects with autosomal dominant polycystic kidney disease

Status	Final	Development Phase:	2a
EudraCT No:	2019-003521-21	CT.gov No:	NCT04578548

IND No:	not applicable
Sponsor:	Galapagos NV, Generaal De Wittelaan L11 A3, 2800 Mechelen, Belgium
Study Physician:	[redacted]
General Protocol / Applicable Country(ies):	General protocol

Confidentiality Statement

EMERGENCY CONTACT INFORMATION

In case of a **serious adverse event (SAE)**, a special situation (see Section 8.1.6) or in case of **pregnancy** during the clinical study the investigator must report this immediately, and under no circumstances later than 24 hours following the knowledge of the SAE or pregnancy, as follows:

SGS Medical Affairs SAE Fax #: [redacted]

or

E-mail: [redacted]

In case of medical **questions** during the course of the study, the investigator must contact the contract research organization (CRO) medical monitor or, if unavailable, his/her back-up. Please refer to the study contact list in the investigator site file for the CRO medical contact details.

Sponsor contact number:

[redacted]

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CLINICAL STUDY PROTOCOL HISTORY

Clinical Study Protocol (CSP) / Amendment #	**Date**	**Main Rationale** **General / Country-Specific**
CSP Version 1.00	16-Sep-2019	Initial Protocol Version General
Amendment 1, CSP Version 2.00	18-Dec-2019	Clarification of prohibited medication was added. General
Amendment 2, CSP Version 3.00	11-Feb-2020	Update of CSP in order to extend treatment period from 24 weeks to 52 weeks. General
Amendment 3, CSP Version 4.00	25-June-2020	Update of CSP: change in contraceptive language, mitigation on the SARS-CoV-2 pandemic, updated wording related to IDMC, collection and storage of biological samples. General
Amendment 4, CSP Version 5.00	13-Aug-2021	Update of CSP: incorporation of an open-label extension period, removal of the interim analysis in combination with a change in the composition from iDMC to DMC, clarification on vaccinations including covid vaccination, and operational changes (including update of timing of MRI assessments). General
Amendment 5, CSP Version 6.00	20-Dec-2021	Update of CSP to change DMC to Independent DMC General

SUMMARY OF CHANGES

Amendment 5 (20-Dec-2021)
The overall reason for this amendment: The protocol was updated to change the composition of the data monitoring committee (DMC) to a fully independent DMC.
The change made to the CSP GLPG2737-CL-203 (Version 5.00, 13-Aug-2021) is listed below, reflecting a brief rationale of each change and the applicable section.
Rationale: The CSP was updated to change the composition of the DMC by removing the sponsor's representative to create a fully independent DMC. **Applicable Section**: 7.1 (Independent Data Monitoring Committee)

Amendment 4 (13-Aug-2021)
The overall reason for this amendment: The protocol was updated to incorporate an open-label extension period after the completion of the double-blind period of the study, removal of the interim analysis in combination with a change in the composition from iDMC to DMC due to the inclusion of a representative from the sponsor, clarification on vaccinations including covid vaccination, as well as operational changes (including update of timing of MRI assessments and timing/collection of assessments).
The changes made to the CSP GLPG2737-CL-203, Version 4.00, 25-Jun-2020, are listed below, reflecting a brief rationale of each change and the applicable sections.
Rationale: The protocol was updated to include the possibility to roll-over to an open-label extension (OLE) period, after the completion of the double-blind period of the study. Due to the chronic, progressive nature of the disease, subjects would be expected to receive long-term treatment. To acquire additional data on long-term safety, tolerability, and efficacy and [redacted] of GLPG2737 in ADPKD, an OLE period is now foreseen. The primary endpoint analysis will be performed at the end of the double-blind period. **Applicable Sections:** List of Abbreviations, Protocol Synopsis, 3.1 (Clinical Study Design), 3.2 (End of Study Definition), 3.4.3 (Other Endpoints), 3.6.1 (Inclusion Criteria), 3.6.2 (Exclusion Criteria), 3.7.2 (Blinding and Unblinding), 4.5.1 (Subject Diary), 5.1 (Timing of Assessments), 5.5.5 (12-lead Electrocardiogram), 5.6 (Pharmacokinetic Assessments), 5.7 (Pharmacodynamic Assessments), 5.8.2 (Future Scientific Research), 5.11.1 (Double-blind Treatment Period), 5.11.2 (Open-label Treatment Period), 6.2 (Population for Analyses), 6.3.1 (General Statistical Considerations), 6.3.4 (Analyses of

Primary Efficacy Parameters), 6.3.5 (Analyses of Primary Safety Data), 6.3.7 (Pharmacodynamic Analyses)
Rationale: The protocol was updated to delete the planned interim analysis in combination with a change in the composition from independent Data Monitoring Committee (IDMC) to DMC due to the inclusion of a sponsor's representative. This change was made as the sponsor will appoint to the DMC a senior medical expert in the field of clinical development who will not be involved in management of the study. By the change in DMC composition, with regular review of unblinded safety and efficacy data, a separate interim analysis is not needed anymore. **Applicable Sections:** List of Abbreviations, Protocol Synopsis, 3.1 (Clinical Study Design), 6.3.2 (Interim Analysis), 7.1 (Independent Data Monitoring Committee)
Rationale: The protocol was updated to add clarification on vaccinations including COVID-19 vaccination prior / during the study and to explain in more detail replacement of a visit by a phone call or a televisit in case travel restrictions apply. **Applicable Sections:** Appendix 4 Mitigation Plan as a Consequence of SARS-CoV-2 Pandemic**)**
Operational changes – **Rationale:** In case MRI at screening is performed according to study specifications and centrally read, this MRI can be used for screening and baseline. In this case, there is no need to repeat MRI at Visit 2 (Day 1). **Applicable Sections: 5.1 (**Timing of Assessments**), 5.4.1 (**htTKV and [redacted] by MRI**), 5.11.1 (**Double-blind Treatment Period**)** – **Rationale:** At the screening visit a random urine sample can be collected instead of first morning urine. **Applicable Section: 5.1 (**Timing of Assessments**), 5.11.1 (**Double-blind Treatment Period**)** – **Rationale:** As an OLE period is now included in the study, a longer time window at Week 56 is foreseen (from +/- 4 days to +/- 10 days), to have some more flexibility to roll-over to the OLE period. **Applicable Section: 5.11.1 (**Double-blind Treatment Period**)** – **Rationale:** As an OLE period is now included in the study, the [redacted] at Week 52 plus 5/6 days is now removed. More data on [redacted] will be collected during the OLE period.

Applicable Sections: 3.1 (Clinical Study Design), 5.1 (Timing of Assessments), 5.6 (Pharmacokinetic Assessments), 5.11.1 (Double-blind Treatment Period)
Administrative changes – **Rationale:** Removal of eGFR as a separate assessment from the section describing the individual study visits, as this is derived from safety laboratory evaluations and not a separate assessment. **Applicable Sections: 5.1** (Timing of Assessments) – **Rationale:** Calcium measurement was clarified in more detail, to explain that it also includes ionized calcium. **Applicable Sections: 5.5.2** (Clinical Laboratory Evaluations) – **Rationale:** Alignment between sections that blood and urine samples can be kept up to 30 years for optional future research. **Applicable Sections:** 5.9 (Sample Management), 5.10 (Long Term Storage of Samples and Associated Data for Future Scientific and Genetic Research).

Amendment 3 (25-June-2020)
The overall reason for this amendment: The protocol was updated to incorporate updates regarding contraceptive language for male subjects participating in the study, to mitigate the impact of the current SARS-CoV-2 pandemic, description of an Independent Data Monitoring Committee, addition of safety parameters, and addition of wording on collection and longterm storage of biological samples.
The changes made to the CSP GLPG2737-CL-203, Version 3.00, 11-Feb-2020, are listed below, reflecting a brief rationale of each change and the applicable sections.
Rationale: The protocol was updated regarding contraceptive language. From existing data it is clear that there is no risk for genotoxicity, teratogenicity/fetotoxicity or gonadal abnormalities. Therefore, no contraceptive measures are required for male subjects participating in the study and no data needs to be collected for female partners of male subjects. **Applicable Section: 1.1** (Background - Nonclinical Studies), **3.6.1** (Inclusion Criteria) **3.6.4.1** (Precautions for Sexual Intercourse), **8.3.3** (Pregnancy), **9.4.2** (Informed Consent)

Rationale: The protocol was updated to mitigate the impact of the current SARS-CoV-2 pandemic for subjects participating in the study. **Applicable Sections: 3.5** (Potential Risks and Benefits)**, 6.1** (Determination of Sample Size)**, Appendix 4** Mitigation Plan as a Consequence of SARS-CoV-2 Pandemic)
Rationale: The protocol was updated to collect optional samples for future scientific and genetic research, and specify long term storage of biological samples. **Applicable Sections: 5.1** (Timing of Assessments), **5.8.2** (Future Scientific Research), **5.10** (Long Term Storage of Samples and Associated Data for Future Scientific and Genetic Research)**, 5.11** (Schedule of Activities)**, 9.4.2** (Informed Consent)
Rationale: The protocol was updated regarding addition of safety parameters, requested by the independent safety reviewer. During compilation of the independent safety review charter it became clear that collection of data regarding pancreas and albumin, creatinine would be of added value to review the safety data during the study. **Applicable Sections: 5.5.2** (Clinical Laboratory Evaluations)
Rationale: The protocol was updated regarding definition of a committee performing the safety review. As a consequence of change of management approach within Galapagos, an Independent Data Monitoring Committee will be implemented. Applicable Section: **7.1** (Independent Data Monitoring Committee)
Rationale: The protocol was updated to include that certain liver enzyme elevations should be reported as an SAE. This definition is included to allow for uniform safety reporting across studies within Galapagos. **Applicable Section: 8.1.5** (Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events)
Rationale: Some minor textual changes have been implemented to improve readability of the protocol. **Applicable Sections:** – Synopsis: addition of the word “baseline” in other endpoint. – 1 (Introduction): deletion of reference occurring twice. – 3.6.5 (Treatment Discontinuation (Temporarily and Permanently), Subject Withdrawal, and Study Termination): Addition of subtitle. – 5.4.1 (htTKV and [redacted] by MRI): addition of “TKV” before MRI. – 5.7 (Pharmacodynamic Assessments): Addition of “blood samples analysis including but not limited to”

– Signature Page: Addition of the word “exploratory” to the title.

Amendment 2 (11-Feb-2020)
The overall reason for this amendment: The protocol was updated in order to incorporate changes regarding treatment duration, definition of primary and secondary outcome, deletion of mGFR as secondary outcome, addition of height-adjusted liver volume as other outcome, update on wording of sample size calculation, description of collection of physical examinations, update on wording of safety review committee, and more detailed information on the dosing rationale.
The changes made to the CSP GLPG2737-CL-203 (Version 2.00, 18-Dec-2019) are listed below, reflecting a brief rationale of each change and the applicable sections.
Rationale: The treatment period has been extended from 24 weeks to 52 weeks. The probability of detecting an effect is higher by increasing the duration of exposure to 52 weeks, as shown in other studies with other compounds in the same indication. **Applicable Sections**: **2** (Clinical Study Objectives), **3.1** (Clinical Study Design), **3.3.2** (Clinical Study Design Rationale), **3.4** (Endpoints), **5.1** (Timing of Assessments), 5.6 (Pharmacokinetic Assessments), **5.11** (Schedule of Activities), **6.1** (Determination of Sample Size)
Rationale: The protocol was updated to clarify the wording of the primary outcome. The wording now clarifies that mean percent change and not absolute change of total kidney volume (TKV) will be determined. **Applicable Sections: 3.4.1** (Primary Endpoint), **6.1** (Determination of Sample Size), **6.3.4.1** (Analysis for Primary Efficacy Endpoint)
Rationale: The protocol was updated to remove measured GFR as secondary objective, due to complexity and burden of the measurement at this stage of product development. **Applicable Sections: 2.2** (Secondary Objectives), **3.4.2** (Secondary Endpoints), **5.1** (Timing of Assessments), Previous Section **5.4.3**, **5.11** (Schedule of Activities)
Rationale: [redacted] **Applicable Sections:** [redacted]

Rationale: Exclusion criterion 3 was updated to clarify that in case tolvaptan is not being administered, this should be because of e.g. non-availability, intolerance, or physician's clinical judgment. **Applicable Sections:** Protocol synopsis, 3.6.2 (Exclusion Criteria)
Rationale: The protocol was adapted to update the wording regarding sample size calculation**.** The description of the sample size calculation changed (power to detect a significant difference increased) as a consequence of the extended treatment period (from 24 weeks to 52 weeks) and the change of the primary outcome (from absolute change to % change). **Applicable Section: 6.1** (Determination of Sample Size)
Rationale: The protocol was updated to change of timing of interim analysis from 4 weeks to 26 weeks, as a consequence of the longer treatment duration. **Applicable Sections: 3.1 (**Clinical Study Design**), 6.3.2 (**Interim Analysis**)**
Rationale: As both safety and efficacy related assessments (i.e. MRI) can be repeated during unscheduled visits, to word safety has been removed. **Applicable Section: 5.2** (Unscheduled Visits)
Rationale: The protocol was updated regarding the description of collection of physical examinations. Physical examination should be reported by the investigator as AE when clinical significant. Therefore, they are already part of the AE listing. **Applicable Section:** Previous Section **6.3.5.4**
Rationale: Analysis for other efficacy endpoints has been added, as this section was missing. **Applicable Section: 6.3.4.2** (Analysis for Other Efficacy Endpoints)
Rationale: The protocol was updated regarding the wording of independent safety review. As the independent safety review will only include safety data and not efficacy data, the name was changed to independent safety review. **Applicable Section: 7.1 (**Independent Data Monitoring Committee**)**
Rationale: The protocol was updated to provide more information regarding expected pharmacological activity at a dose regimen of 150 mg q.d., based on the available clinical data, in vitro pharmacology data, and observed GLPG2737 and M4 plasma concentrations in humans.

Applicable Section: 3.3.1 (Dose Rationale)

Amendment 1 (18-Dec-2019)
The overall reason for this amendment: The protocol was updated in order to clarify prohibited medication.
The changes made to the CSP GLPG2737-CL-203, Version 1.00, 16-sep-2019, are listed below, reflecting a brief rationale of each change and the applicable sections.
Rationale: The protocol was updated to prohibit the use of tolvaptan during the study. If during the course of the study the investigator decides to initiate tolvaptan based on benefit-risk evaluation, then investigational product (IP) needs to be discontinued for the remainder of the study. The patient will continue to be followed up as per protocol. **Applicable Sections:** 3.6.4.2 (Prior and concomitant medications)
Rationale: The protocol was updated to add "Initiation of tolvaptan treatment" as reason for permanent discontinuation of treatment. **Applicable Sections:** 3.6.5 (Permanent discontinuation of treatment)

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

ADL	activities of daily living
ADPKD	autosomal dominant polycystic kidney disease
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
Bpm	beats per minute
[redacted]	[redacted]
cAMP	cyclic adenosine monophosphate
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum plasma concentration
CRF	case report form
CRO	contract research organization
CSP	clinical study protocol
CTCAE	common terminology criteria for adverse events
C_{trough}	trough concentration
DB	double-blind
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
DTP	direct to patient
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ETD	early treatment discontinuation
EoS	end of the study
EoSA	end of study assessments - visit at the end of the foreseen treatment period but when the subject has discontinued IP before the visit

EoST	end of study treatment - visit at the end of the treatment period when the subject has continued taking IP till this visit
ETD	early treatment discontinuation
EU	European Union
FDA	Food and Drug Administration
FIH	first in human
FSH	follicle stimulating hormone
GCP	good clinical practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
HBs Ag	hepatitis B surface antigen
HBs	hepatitis B surface
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HMA	Heads of Medicines Agency
HR	heart rate
htTKV	height-adjusted total kidney volume
[redacted]	[redacted]
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IWRS	interactive web response system
KDOQI	Kidney Disease Outcomes Quality Initiative
KO	knock-out
LFT	liver function test

MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCS	microscopy culture and sensitivity
MCV	mean corpuscular volume
MRI	magnetic resonance imaging
NASH	nonalcoholic steatohepatitis
NOAEL	no observed adverse effect level
OLE	open-label extension
PD	pharmacodynamics
[redacted]	[redacted]
PK	pharmacokinetics
PC	polycystin
q.d.	quaque die, once daily
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
TKV	total kidney volume
[redacted]	[redacted]
t_{max}	time to reach maximum plasma concentration
[redacted]	[redacted]
ULN	upper limit of normal
WOCBP	women of childbearing potential

Definition of Terms

BMI	body mass index: Weight (kg) / (height [m])^2
QTcF	QT interval corrected for heart rate using Fridericia's formula:

$$QTcF = QT/RR^{1/3}$$

PROTOCOL SYNOPSIS

Title of Study

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)

Phase of Development: Phase 2a

Planned Number of Subjects

A total of 60 adult ADPKD subjects (n=40 for GLPG2737 and n=20 for placebo) will be enrolled in this study.

Study Duration

Each subject will be in the study for up to 60 weeks for the double-blind period (up to 4 weeks of screening, double-blind treatment period of 52 weeks, and 4 weeks of follow-up). For subjects who are eligible and consent to roll-over to the open-label extension (OLE) period, another 52 weeks of treatment and 4 weeks follow-up will be added.

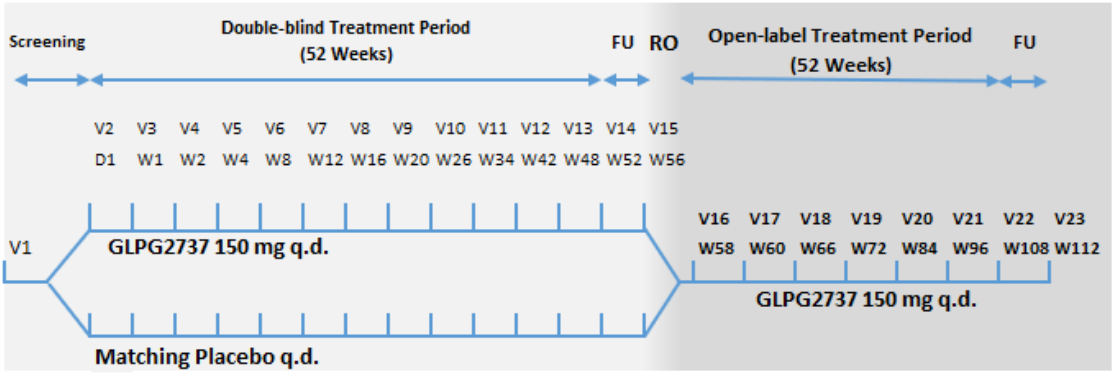
Study Design

This is an exploratory, randomized, double-blind, placebo-controlled, parallel group, multicenter, proof of concept study (Phase 2a), evaluating orally administered GLPG2737 (150 mg q.d.) for a double-blind treatment period of 52 weeks and 4 weeks of follow up as well as an OLE treatment period of 52 weeks and 4 weeks of follow up, in approximately 60 subjects with rapidly progressing ADPKD.

The primary analysis will be performed when all subjects have reached the end of the double-blind period, or discontinued earlier.

A follow-up visit should occur 4 weeks after the 52-weeks double-blind treatment period (Week 56). Subjects will be offered OLE treatment for a period of 52 weeks. The follow-up visit will be used to roll-over to the OLE period.

Refer to the study scheme below for further details.



D: Day; FU: Follow-up period; RO: Roll-over visit; V: Visit; W: Week

Objectives and Endpoints

Objectives	Endpoints
The following objectives will be determined in adult subjects with ADPKD until the end of the double-blind period:	*The following endpoints will be measured from baseline until the end of the double-blind period:*
Primary	*Primary*
– To characterize the effect of GLPG2737 on growth in total kidney volume (TKV) compared to placebo.	– Mean percent change from baseline of height-adjusted TKV (htTKV).
– To evaluate the safety and tolerability of oral doses of GLPG2737 compared to placebo.	– Frequency and severity of treatment-emergent adverse events (TEAEs), treatment-emergent serious AEs (SAEs), and TEAEs leading to treatment discontinuation.
Secondary	*Secondary*
– To characterize the effect of GLPG2737 on renal function (estimated glomerular filtration rate; eGFR) compared to placebo.	– Mean change from baseline of estimated GFR (eGFR).
– To characterize the pharmacokinetics (PK) of oral doses of GLPG2737 and its major metabolite G1125498 (M4) using population PK analyses.	– Estimated exposure (area under the curve [AUC], maximum plasma concentration [C_{max}]), based on population PK analyses for GLPG2737 and its major metabolite M4.
[redacted]	

Main Criteria for Inclusion and Exclusion

Main inclusion criteria for the double-blind period of the study, clinically most relevant for the investigator:

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:
   a. 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]).
   b. Mayo ADPKD Classification Classes 1C to 1E.
4. eGFR at screening between 30-90 mL/min/1.73 m^2 for subjects aged 18 to 40 years[1] (inclusive), and between 30-60 mL/min/1.73 m^2 for subjects aged 40 to 50 years.
5. Blood pressure ≤ 150/90 mmHg. In case the subject is treated for hypertension, it 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 exclusion criteria for the double-blind period of the study, clinically most relevant for the investigator:

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 cyst aspiration 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 judgment.
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 inclusion criteria for the OLE period of the study, clinically most relevant for the investigator:

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.

Main exclusion criterion for the OLE period of the study, clinically most relevant for the investigator:

1. Clinically significant abnormalities detected on 12-lead ECG of either rhythm or conduction, QTcF >450 ms, or long QT syndrome.

Treatment and Treatment Schedule

Subjects will be randomized in a 2:1 ratio to GLPG2737 150 mg q.d., or matching placebo q.d., administered for 52 weeks.

During the OLE period, each subject will receive 150 mg GLPG2737 q.d. for 52 weeks.

Investigational Product, Dosage, and Mode of Administration

GLPG2737 will be provided as 2 capsules for oral use, containing 75 mg [redacted] each [redacted] is the compound code for GLPG2737).

The matching placebo will be provided as 2 capsules for oral use.

Statistical Analysis

Strict statistical criteria were not used to determine the sample size for this study. The number of subjects (n=60) should give reasonable precision around the estimates of the endpoints for design of future studies.

For the primary analysis a longitudinal analysis of the htTKV percent change from baseline until the end of the double-blind period will be performed and appropriate inferential measures on the treatment difference will be obtained.

Safety analysis during the double-blind period will be descriptive and should be focused on changes from baseline and treatment-emergent findings with GLPG2737 treatment as compared to placebo.

Observed GLPG2737 and M4 plasma concentrations will be analyzed using a population PK analysis. PK parameters, estimated based on the population PK model will be reported.

[redacted]

[redacted]

1. INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease with an estimated prevalence of 1-5 in 10.000 individuals (Orphanet, 2019; Willey, et al., 2017). 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. As ADPKD is a multisystem disorder, other organs can also be affected. Hepatic cysts are the most common extra-renal manifestations; occurring in up to 83% of cases (Bae, et al., 2006), with enlarged total liver volume in up to nearly 60 % of cases (van Aerts, et al., 2019).

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 Ca^{2+} levels. It is believed that reduced intracellular Ca^{2+} levels contribute to the increased cyclic adenosine monophosphate (cAMP) levels observed in ADPKD human kidney epithelial cells (Wallace, 2011). 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 (Yang, Sonawane, Zhao, Somlo, & Verkman, 2008). 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 (Xu, et al., 2006). CFTR is present in the apical membrane of the cholangiocytes (Fiorotto & Strazzabosco, 2019).

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.

For more details refer to the investigator's brochure (IB) (GLPG2737-ADPKD, Version 2.0, 20-Nov-2020) and relevant updates/addenda.

This clinical study will be conducted in accordance with the current International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice (ICH-GCP) Guideline E6 (see also Section 9).

1.1. Background - Nonclinical Studies

[redacted]

1.2. Background - Clinical Studies

[redacted]

Clinical Pharmacokinetics

[redacted]

Clinical Safety

[redacted]

[redacted]

2. CLINICAL STUDY OBJECTIVES

The following objectives will be determined in adult subjects with rapidly progressing ADPKD until the end of the double-blind period:

2.1. Primary Objectives

- 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.

2.2. 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.

2.3. Other Objectives

3. INVESTIGATIONAL PLAN

3.1. Clinical Study Design

This is an exploratory, randomized, double-blind, placebo-controlled, parallel group, multicenter, proof of concept study (Phase 2a), evaluating orally administered GLPG2737 (150 mg q.d.) for a treatment period of 52 weeks and 4 weeks follow-up, followed by an open-label extension (OLE) period of 52 weeks and 4 weeks follow-up in approximately 60 subjects with rapidly progressing ADPKD.

The eligibility screening period of maximally 28 days will consist of the assessments as presented in the Schedule of Activities (see Section 5.11). For the in- and exclusion criteria please refer to 3.6.1 and 3.6.2.

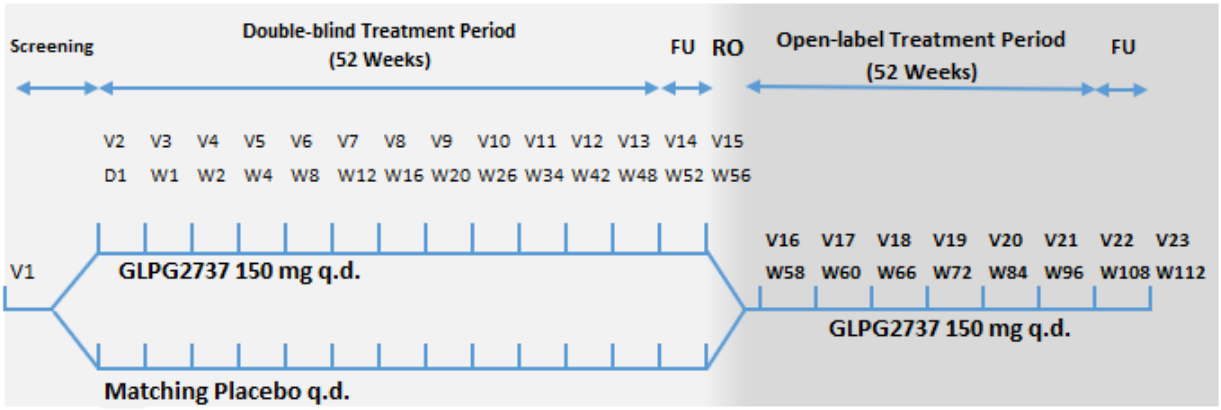
At Day 1 (baseline), subjects will be randomized in a 2:1 ratio to GLPG2737 150 mg q.d. taken as 2 capsules of 75 mg each, or matching placebo q.d. administered for 52 weeks.

An unblinded primary endpoint analysis will be performed when all subjects have reached the end of the double-blind period, or discontinued earlier.

A follow-up visit should occur 4 weeks after the 52-weeks double-blind treatment period (Week 56). Subjects will be offered OLE treatment for a period of 52 weeks. The follow-up visit of the double-blind period will be used to roll-over to the OLE period.

A schematic diagram of clinical study design, procedures and stages is provided in

Figure 1.



D: Day; FU: Follow-up period; RO: Roll-over visit; V: Visit; W: Week

Figure 1 Schematic Diagram

For detailed information regarding dosage form, packaging and labeling of the investigational product (IP) please refer to Section 4.2, "Dosage and Administration" and Section 4.3, "Packaging, Labeling and Distribution".

3.2. End of Study Definition

The end of the study (EoS) is reached when the last follow-up visit (i.e. Week 112 of the OLE period), as planned according to the Schedule of Activities (Section 5.11), of the last subject is performed.

3.3. Clinical Study Rationale

ADPKD is a chronic and progressive disease for which there exists only 1 approved drug at the moment (i.e. the vasopressin receptor antagonist tolvaptan), indicating a high unmet medical need for the development of novel therapies.

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 KO-mouse (Yang, Sonawane, Zhao, Somlo, & Verkman, 2008). In patients with both ADPKD and 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, reducing the rate of decline of renal function, and delay progression to end-stage kidney disease.

3.3.1. Dose Rationale

A dose of GLPG2737 150 mg q.d. for oral administration has been selected for use in this Phase 2a study. This dose is considered safe and well tolerated based on the results of the multiple ascending dose study in healthy subjects (evaluated for 2 weeks up to 250 mg q.d.) and a study in subjects with CF, treated for up to 4 weeks with 150 mg q.d.. GLPG2737 exposure is not expected to be higher in subjects with ADPKD as compared to healthy subjects, as the kidney plays a minor role in the elimination of GLPG2737 and its major active metabolite M4. After repeated once daily dosing of GLPG2737 at 250 mg q.d., less than 1% of the dose was excreted in urine as unchanged GLPG2737, and around 3% of the dose was excreted as M4.

GLPG2737 has been shown to have a clinical effect at 150 mg q.d., by reducing the open probability of rescued CFTR channels in the development of a combination therapy in CF. In addition, modest increases in sweat chloride (a marker of CFTR activity) were observed in healthy subjects, providing indirect proof of ion transport channels being affected (see Section 5.1.5 of the IB).

Furthermore, in an in vitro cyst swelling assay using patient-derived cyst cells, GLPG2737 and M4 showed a decrease in the number of cysts in a concentration-dependent manner, both compounds showing an activity ($p<0.05$) at concentrations starting at 100 nM. In addition to the cyst number quantification, the cyst size was quantified. At 10 µM, GLPG2737 and at 1 µM its metabolite M4 showed a decrease ($p<0.05$) in the area of cysts formed by ADPKD patient-derived cells (see IB addendum). The observed steady-state mean trough and maximum levels at the intended dose level of 150 mg q.d. are respectively 448 ng/mL (730 nM) and 1300 ng/mL (2118 nM) for GLPG2737, and 648 ng/mL (1080 nM) and 921 ng/mL (1536 nM) for M4 (see Section 5.1.1.2 of the IB).

Finally, 2 in vitro target engagement assays involving human CFTR, measuring inhibition of CFTR mediated transport by GLPG2737 and M4, have been performed (YFP halide assay and

TECC assay, see Section 4.1.1.1.1 and 4.1.1.1.3 of the IB). Of these assays the latter is considered to be most physiologically relevant as there was no overexpression of CFTR. The IC_{50} values from this assay were 108 nM for GLPG2737 and 32 nM for M4. Based on this data the combined unbound plasma concentrations for GLPG2737 and M4 (free fraction 0.0205 for GLPG2737 and 0.0240 for M4, see Section 4.2.2.1 of the IB) that are maintained during the dosing interval at the 150 mg q.d. dosing regimen are situated within the pharmacodynamic range observed in the TECC assay.

Taken together, pharmacological activity can be expected at a dose regimen of 150 mg q.d. based on the available clinical data, in vitro pharmacology data and observed GLPG2737 and M4 plasma concentrations in humans.

3.3.2. Clinical Study Design Rationale

Rationale for study design: the placebo-controlled, randomized, parallel group design is a standard design for an exploratory study in patients.

Rationale for selection of progressive ADPKD subjects: to be able to detect a signal, defined as a change in kidney volume, subjects with progressive disease will be selected, as those outcome parameters may change within the timeframe of the study in this study population compared to less severe subjects.

Rationale for 52 weeks treatment: the acute effects on TKV as seen in tolvaptan treated patients are a result of hemodynamic effects and the profound aquaresis. These acute effects have not been seen with GLPG2737 treatment, and are therefore not expected at short study duration. Structural chronic changes are expected at a longer study duration of 52 weeks (Torres, et al., 2012) (Torres, et al., 2017) (Caroli, et al., 2013).

A substantial treatment effect has been defined by the cardio-renal division of the Food and Drug Administration (FDA) as halting the increase in TKV (Smith, et al., 2018). Preventing the growth of the ADPKD kidneys would provide compelling evidence of efficacy and could provide a basis for approval of drugs to treat ADPKD. The average increase in TKV in patients with progressive ADPKD is approximately 6% per year.

Rationale for OLE: due to the chronic, progressive nature of the disease, subjects would be expected to receive long-term treatment. To acquire additional data on long-term safety, tolerability, efficacy and [redacted] of GLPG2737 in ADPKD, an OLE period up to 52 weeks of treatment will be foreseen. In addition, this will enable the subjects assigned to placebo to receive active treatment during the OLE.

3.4. Endpoints

The following endpoints will be measured from baseline until end of the double-blind period:

3.4.1. Primary Endpoint

- 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.

3.4.2. Secondary Endpoints

– Mean change from baseline of estimated GFR (eGFR).
– Estimated exposure (area under the curve [AUC], maximum plasma concentration [C_{max}]), based on population PK analyses for GLPG2737 and its major metabolite M4.

3.4.3. Other Endpoints

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3.5. Potential Risks and Benefits

GLPG2737 has been well tolerated to date in healthy subjects in single and repeated doses up to 150 mg for 14 days. It has been administered to subjects with CF in combination with a CFTR potentiator and a CFTR corrector molecule for up to 28 days at a dose of 150 mg daily. GLPG2737 was well tolerated in this population. To date, no GLPG2737 related SAEs have been reported.

There is a potential risk with drugs that are inhibitors or inducers of CYP3A4. Only the drugs inhibiting CYP3A4, potentially leading to an increase in exposure of GLPG2737, will be prohibited during the study. Refer to Section 3.6.4.2 for prohibited medication.

Based upon its mechanism of action and its potential to decrease the rate of decline of renal function in patients with ADPKD, together with its safety profile and clinical risk mitigation built into the study design it is believed that the GLPG2737 benefit-risk profile is positive.

Given this study may be performed during a SARS-CoV-2 pandemic, appropriate measures should be taken to minimize the risk of SARS-CoV-2 infection for subjects participating in the study as well as study site personnel. Local guidelines to prevent SARS-CoV-2 infection should

be adhered to. Protocol specific instructions in case of travel restrictions due to a pandemic or infection with SARS-CoV-2 are described in Appendix 4.

Subjects presenting with signs and symptoms of infection, including SARS-CoV-2 infection should immediately contact the site investigator, who should inform the sponsor's medical responsible as soon as possible.

3.6. Clinical Study Population

3.6.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in the double-blind period of the study:

1. Able and willing to comply with the protocol requirements and to sign the informed consent form (ICF) as approved by the Independent Ethics Committee (IEC) / Institutional Review Board (IRB), prior to any screening evaluations.
2. Male and female subject aged 18 to 50 years, inclusive.
3. Documented diagnosis of typical ADPKD, using the Ravine criteria (Ravine, et al., 1994).
4. 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.
5. eGFR at screening between 30-90 mL/min/1.73 m^2 for subjects aged 18 to 40 years[1] (inclusive), and between 30-60 mL/min/1.73 m^2 for subjects aged 40 to 50 years.
6. 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.
7. Subject must be able and willing to comply with restrictions on prior and concomitant medication as described in Section 3.6.4.2.
8. Female subjects of childbearing potential must have a negative blood pregnancy test at screening and a negative urinary human chorionic gonadotropin (HCG) test at randomization.
9. Female subjects of childbearing potential are willing to comply with the contraceptive methods described in Section 3.6.4.1 from signing of the ICF, during the clinical study, and for at least 7 days after the last dose of the IP.
10. A body mass index (BMI) between 18–35 kg/m^2, inclusive.
11. Apart from ADPKD, judged to be in good health by the investigator, based upon the results of a medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG), and clinical laboratory safety tests.

[1] Until and including day of 40th birthday

Subjects must meet all of the following inclusion criteria to be eligible for participation in the OLE period of the study:

12. Able and willing to comply with the protocol requirements of the OLE period and to sign the ICF for the OLE period as approved by the Independent Ethics Committee (IEC) / Institutional Review Board (IRB).

13. Male and female subjects who completed the 52-week double-blind treatment period on IP.

14. Subject, according to the investigator's judgment, may benefit from long-term treatment with GLPG2737.

3.6.2. Exclusion Criteria

Subjects meeting 1 or more of the following criteria cannot be enrolled in this clinical study:

1. Known hypersensitivity to IP ingredients or history of a significant allergic reaction to IP ingredients as determined by the investigator, such as anaphylaxis requiring hospitalization.
2. 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.
3. *Original criterion (CSP Version 4.0, dated 25-Jun-2020):*
   Administration of polycystic kidney disease-modifying agents (e.g. tolvaptan) or interventions (such as cyst aspiration 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 judgment.
   3.1 Criterion modified as per Amendment 4, Version 5.0, dated 13-Aug-2021):
   Administration of polycystic kidney disease-modifying agents (e.g. tolvaptan, somatostatin analogues) or interventions (such as cyst aspiration 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.
4. 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.).
5. Subjects with clinically significant incontinence, overactive bladder, or urinary retention (e.g. benign prostatic hyperplasia).
6. Current immunosuppressive condition (e.g. human immunodeficiency virus [HIV] infection).
7. Having any illness, judged by the investigator as clinically significant, in the 12 weeks prior to the screening visit and during the screening period.
8. Presence or sequelae of gastrointestinal, liver, or other conditions known to interfere with the absorption, distribution, metabolism, or excretion of drugs.
9. History of malignancy within the past 5 years (except for carcinoma in situ of the uterine cervix, basal cell carcinoma of the skin that has been treated with no evidence of recurrence, prostate cancer that has been medically managed through active surveillance or watchful waiting, squamous cell carcinoma of the skin if fully resected, and Ductal Carcinoma In Situ).

10. Concurrent participation or participation in a drug, drug/device or biologic investigational research study within 12 weeks or 5 half-lives of the IP, whichever is longer, prior to the screening visit and during the screening period.
11. Positive blood test for hepatitis B surface antigen (HB_S Ag) or hepatitis C virus (antibody, confirmed by hepatitis C virus (HCV) RNA positivity).
    Note: Subjects with a resolved hepatitis A at least 3 months prior to screening can be screened.
12. Clinically significant abnormalities detected on 12-lead ECG of either rhythm or conduction, QTcF >450 ms, or long QT syndrome.
13. Pregnant or breast feeding female or subject intending to become pregnant or breastfeed.
14. Systemic administration of any moderate and strong inhibitor(s) or inducer(s) of CYP3A4 currently taking or going to take 4 weeks prior to screening and during the screening period (see Appendix 2 and Appendix 3 for a list with examples).
15. Moderate to severe hepatic impairment (Child-Pugh B or C) and/or abnormal liver function test (LFT) at screening, defined as AST, and/or ALT ≥2x upper limit of normal (ULN), and/or total bilirubin ≥1.5x ULN. Retesting is allowed once for abnormal LFT.
16. Investigator or other study staff or relative thereof who is directly involved in the conduct of the study.

    Subjects meeting the following criterion cannot be enrolled in the OLE period of the study:

17. Clinically significant abnormalities detected on 12-lead ECG of either rhythm or conduction, QTcF >450 ms, or long QT syndrome.

3.6.3. Rescreening and Retesting

Screen failures will be defined as subjects not complying with 1 or more in-/exclusion criteria. Subjects may only be rescreened with the approval of the sponsor's study physician.

- If a subject is rescreened, all screening assessments will be repeated, apart from historical TKV imaging that was used for screening purposes only (i.e. not centrally read).
- If rescreened, the subject must be reconsented. The subject will be assigned a new subject number which will be linked to the first screening number.

Retesting of individual screening assessment(s) that did not meet eligibility criteria is not permitted, with the following exceptions AND only in case it is still possible to randomize the subject within the per protocol defined screening period of 28 days:

- Laboratory values for LFTs and eGFR can be retested once.
- Assessment of blood pressure.
- Lost or invalid blood or urine samples.

3.6.4. Prohibition and Restrictions

3.6.4.1. Precautions for Sexual Intercourse

Highly effective contraceptive measures for females of childbearing potential must be documented in the source documents.

3.6.4.1.1. Female subjects

In line with the Heads of Medicines Agencies (HMA)'s Clinical Trial Facilitation Group recommendation, female subjects are considered of non-childbearing potential if they meet one of the following criteria:

- No menses for 12 or more months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Permanently surgically sterile (bilateral oophorectomy, surgical removal of ovaries, bilateral salpingectomy or hysterectomy, surgical removal of uterus).

All other female subjects are considered to be of childbearing potential (WOCBP) and must use one of the following highly effective methods of birth control from signing of the ICF, during the clinical study and for at least 7 days after the last dose of IP:

- Combined (estrogen and progesterone containing) (oral, intravaginal, transdermal) hormonal contraception associated with inhibition of ovulation.
- Progesterone-only hormonal (oral, injectable, implantable) contraception associated with inhibition of ovulation.
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject.
  Periodic abstinence (e.g. calendar, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a clinical study, withdrawal, spermicides only, and lactational amenorrhea method are not acceptable as methods of contraception.

In case a WOCBP has a vasectomized partner, provided that partner is the sole sexual partner of the WOCBP clinical study participant and that the vasectomized partner has received medical assessment of the surgical success, then she is not required to use an additional form of contraception.

Within these limits, the specific forms of contraception employed are left to the discretion of the subject, the investigator, and/or the subject's physician.

The safety of GLPG2737 during breastfeeding is unknown. Nursing women are not allowed to take part in this clinical study.

3.6.4.1.2. Male subjects

As there is no risk for genotoxicity, teratogenicity/fetotoxicity, or gonadal abnormalities (see Section 1.1), no contraceptive measures are required for men with WOCBP partners and no restrictions are required for sperm donation.

3.6.4.2. Prior and Concomitant Medications

Should any treatment other than the IP be used during the course of the study, the name of the medication, the dosage, the route, the reason for medication, and the start and stop dates of administration must be recorded in the case report form (CRF).

Concomitant medications taken for the long-term treatment of pre-existing conditions can continue during the study, provided they are in accordance with the in- and exclusion criteria (see Sections 3.6.1 and 3.6.2), as well as the restrictions indicated below. It is required that these medications are stabilized prior to study entry and preferably continue without variation of dose or regimen during the study.

Tolvaptan is prohibited during the study. If during the course of the study the investigator decides to initiate tolvaptan based on benefit-risk evaluation, then the IP needs to be discontinued for the remainder of the study. The patient will continue to be followed up as per protocol.

In case additional concomitant medication needs to be administered or dose adjustments for pre-existing conditions need to be performed during the study, the benefit-risk to the subject should be carefully assessed and consideration given to the timing of any necessary introduction of new medications.

Use of dietary/herbal supplements including (but not limited to) St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydro-epiandrosteron, yohimbe, saw palmetto, ginseng, red yeast rice, and excessive doses of vitamins (2-fold greater than the recommended daily allowance) is prohibited within 28 days, or 5 half-lives, prior to screening and during the entire study period.

During the study, concomitant use of any moderate or strong inhibitor(s) of CYP3A4 is not allowed, as GLPG2737 (is predominantly metabolized by CYP3A4 (See Appendix 2 for a non-exhaustive list of inhibitors). If during the study, the subject's condition necessitates the use of this prohibited medication, the use of IP should be interrupted; after consultation with the CRO medical monitor (as per study contact list) and/or sponsor's study physician. Re-introduction of IP can be considered after the treatment course with the prohibited medication has been stopped.

[redacted]

[redacted]

In case of questions on concomitant medications, the CRO medical monitor (as per study contact list) and sponsor's study physician can be contacted.

3.6.4.3. Food and Beverage Restrictions

Consumption of grapefruit-containing products or Seville orange juice is prohibited. Subjects should be asked not to consume these products throughout the study period.

3.6.5. Treatment Discontinuation (Temporarily and Permanently), Subject Withdrawal, and Study Termination

A subject may be withdrawn from the clinical study at any time without the subject's consent if the investigator or sponsor determines that it is not in the best interest of the subject to continue participation. In such case, the reason for withdrawal will be documented in the source documents, and the subject will complete the early treatment discontinuation (ETD) visit and, or follow-up visit for safety assessments. The subject should complete all end of study procedures.

Permanent Discontinuation of Treatment
Treatment with IP should be discontinued by the investigator (preferably after discussion with the CRO medical monitor, who may consult and must inform the sponsor's study physician) for any of the following reasons:

- Life-threatening AE or a SAE that places the subject at immediate risk.
- Confirmed pregnancy: if a subject becomes pregnant during the study (to be confirmed by local serum pregnancy test; central measurement will also be performed), the IP has to be stopped immediately and the subject has to be followed up until birth or otherwise termination of pregnancy. The subject needs to be unblinded immediately and repeat counseling on birth defect risk must be offered in case she was on active drug.
- Arrhythmia or conduction abnormality where the severity is categorized as Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher.
- An increase for QTcF of >60 ms from baseline (Visit 2) or QTcF >500 ms at any ECG recording (any recording of triplicate ECG after Visit 2) needs to be confirmed by an ECG recording as soon as possible from the original abnormal recording at the same visit. In case of an abnormal QTcF as described above, ECG on both of these 2 recordings, the IP will be discontinued for this subject.
  After Visit 2 (Day 1), if a normal QTcF (e.g. no increase of >60 ms from baseline (i.e. Visit 2) or QTcF >500 ms) is reported during the visit, but the central cardiologist reports it as abnormal (any of the 2 criteria above), then the IP should be discontinued as soon as possible.
  At Visit 2 (Day 1, predosing), if the QTcF ≤450 ms at the local recording, and the central reading cardiology conclusion reports a QTcF >450 ms; than the subject needs to discontinue IP as soon as possible.
- Increase in LFTs
  -

- AST or ALT ≥8x ULN.
- AST or ALT elevations >3x ULN and <8x ULN: IP treatment should be withheld. If AST and/or ALT do not return to ≤3x ULN within 2 weeks then the IP should be discontinued permanently.
- AST or ALT ≥3x ULN with signs of severe liver damage (i.e. with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia [>5%], and/or total bilirubin ≥2x ULN or international normalized ratio [INR] >1.5).

For all abnormal LFTs described above a repeat sample should be taken within 48 hours to confirm the abnormality. If not possible, then the IP needs to be withheld or discontinued permanently as soon as possible as described above.

For any of the above abnormalities, close observation and follow-up is recommended, defined as:

- Repeating liver enzyme and serum bilirubin tests 2 or 3 times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases. Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis (NASH); hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function (investigator is requested to use the central lab LFT kits), as appropriate (e.g. INR, direct bilirubin).
- Considering gastroenterology or hepatology consultations (including imaging).

– Initiation of tolvaptan treatment.
– Closing of the study by the sponsor or regulatory authorities.
– Wish of the subject to stop taking IP.

Temporary Discontinuation of Treatment

For the management of AEs, the investigator can interrupt or discontinue the IP. Once the AE has stabilized or improved, IP can be reintroduced if applicable.

When the subject needs treatment based on the risk/benefit analysis with a prohibited medication (see Section 3.6.4.2 and Appendix 2), the IP can be reintroduced after end of the treatment course.

Management of Permanent or Temporary Treatment Discontinuation

Every effort should be made to keep subjects in the study and on treatment. However, the investigator can consider stopping treatment with IP, preferably after consultation with the CRO

medical monitor (as per study contact list) or sponsor's study physician (if the former is not available), in case of concerns about the subject's safety, major protocol noncompliance, serious or severe AEs or worsening of the disease condition, which in the investigator's opinion needs an alternative treatment approach not being covered in the clinical study (e.g. rescue medication).

When study treatment is discontinued, the subject will be requested to return for all visits and assessments. In case the subject is not able to return to the visits, a phone call can replace the onsite visit.

Subject Withdrawal
Subjects will be informed prior to clinical study entry that they are allowed to withdraw from the clinical study. At any time and for any reason, a subject's participation in the clinical study may terminate at his/her request without prejudice to his/her future medical care. The subject will be encouraged to share the reason(s) for withdrawal so this can be documented in the source documents. The subject will be asked to complete the ETD visit and, or follow-up visit for safety assessments, but will not be obliged to do so.

For a subject who is considered lost-to-follow-up sites should make every effort to understand whether the subject is alive, including checking the medical records and contacting general practitioner or relatives, if necessary. All attempts must be documented in the source documents.

Study Termination
The sponsor has the right to terminate the clinical study at any time in case of safety concerns or if special circumstances concerning the IP or the company itself occur, making further treatment of subjects impossible. In this event, the investigator(s) and relevant authorities will be informed of the reason for clinical study termination.

3.7. Measures to Minimize Bias

3.7.1. Randomization

At screening, subjects will be assigned a subject identification number. When a subject is confirmed to be eligible for the clinical study, the subject will be randomized. Allocation of each subject to a given treatment will be done using a centralized electronic system (interactive web response system [IWRS]). IP will be randomized in a 2:1 ratio to GLPG2737 or placebo.

3.7.2. Blinding and Unblinding

The first period of the study is a randomized, double-blind clinical study. During this double-blind period of the study the clinical study team, including the subjects, investigators, clinical study coordinators and sponsor personnel (except assigned personnel involved in unblinded procedures) are blinded to treatment assignment.

During the double-blind period of the study blinded and packaged medication will be provided to the clinical center. All IP formulations will be identical in appearance, shape, smell and taste, and packaged in the proper proportion to assure desired dosages and maintenance of the blinding. During the OLE period, unblinded packaged medication will be provided.

The blind can be broken only if the investigator deems it necessary for the safety of a subject. The investigator is encouraged to discuss considerations to break the blind with the CRO medical monitor, whenever possible and where the situation allows. However, the responsibility to break the treatment code in emergency situations resides solely with the investigator. The investigator is not required to discuss unblinding beforehand if he or she feels rapid emergency unblinding is necessary, but is required to inform the sponsor in a timely fashion after unblinding has occurred.

The blind can be broken by the investigator via IWRS. Code-breaking information (via IWRS vendor) will be provided to the bioanalytical laboratory responsible for plasma drug determination sample analysis.

4. INVESTIGATIONAL PRODUCTS

4.1. Identity of the Investigational Product(s)

The IP (GLPG2737 and placebo) will be supplied to the pharmacist of the clinical study center by and under the responsibility of the sponsor, who will also provide the investigator with appropriate certificates of analytical conformity and European Union Qualified Person release documents.

GLPG2737 will be provided as capsules for oral use, containing 75 mg [redacted] is the compound code for GLPG2737). The matching placebo will be provided as capsules for oral use.

A full list of excipients used in the capsule formulation is available in the IB for GLPG2737 (Edition 2, 20-Nov-2020) and relevant updates/addenda.

4.2. Dosage and Administration

The following dose will be used:
- 150 mg GLPG2737 q.d. (as 2 GLPG2737 capsules of 75 mg).
- Placebo q.d. (as 2 placebo capsules, only during double-blind period).

The IP has to be taken q.d. with food (i.e. breakfast or lunch, whatever is the biggest meal; as long as IP is taken approximately the same time every day). Capsules of GLPG2737 or placebo will be swallowed whole with a glass of water.

On visit days, the IP will be administered at the clinical study center after predose assessments have been completed. A breakfast and a glass of water will be provided by the clinical study center. During the visits, subjects will be provided with a supply of IP to take home (see Section 4.5 for measurement of compliance by diary).

If a subject misses a dose (e.g. because they forgot to take the IP), they must immediately take the missed dose with food and a glass of water, within 12 hours after the planned intake time. If the IP is not taken within 12 hours after the planned time, the missed dose must be skipped. Individual dose reductions will not be allowed.

Detailed information regarding the records documenting the total amount of received IP and return/destruction of the used/unused medication can be found in Section 4.5.

4.3. Packaging, Labeling and Distribution

IP packages will be labeled with clinical study-specific details.

All manufacturing, packaging and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements.

The distribution will only occur after the required local documentation is obtained, including clinical study approval by Competent Authorities and the IECs/IRBs, documentation on which the assessment of the investigator's qualifications was based (e.g. curriculum vitae), and the signed and dated study agreement and financial agreement.

GLPG2737 and placebo capsules will be packaged in high-density polyethylene (HDPE) treatment bottles with a child-resistant HDPE closure. At each IP dispensing time point, subjects will receive treatment bottles to cover for the next visit. The bottles will be labeled according to local requirements and will have unique identifiers.

4.4. Storage

Sites are to store IP supplies in a secure area below 30°C, not to be stored at refrigerated or frozen condition, until dispensed. Sites will be required to monitor the storage temperature by using at least a min-max temperature-recording device and to keep a minimum to maximum temperature log, which must be completed each working day in order to establish a record of compliance with these storage conditions. The investigator will instruct subjects on how the IP should be stored at home.

4.5. Treatment Compliance and Drug Accountability

The pharmacist or designated clinical study personnel will maintain a log of the total amount of IP received at site, amount dispensed to the subject, and the amount of IP returned by the subject to the site. IP supplies for each subject will be inventoried and accounted for throughout the clinical study. At the end of the treatment period, these records will be checked against the inventory by the study monitor. All clinical supplies will be stored in locked facilities.

Subjects will return any unused IP and empty IP packages at each visit and/or ETD Visit. Missed doses should be discussed to try to ascertain the reason(s). Every effort should be made to ensure the proper subject dose. Subjects with poor compliance will be retrained by the clinical study site. Upon sponsor approval, all unused IP and empty IP packages will be destroyed at the site. If destruction by the site is not possible or the destruction process is found unacceptable by the sponsor, the IP should be returned to the drug supplier/drug depot as appropriate.

Treatment compliance will be assessed by the investigator or designee. At each visit, site staff will review treatment compliance by assessing the number of returned IP. If a subject

demonstrates continued noncompliance despite educational efforts, the investigator must contact the sponsor's study physician to discuss discontinuation of the subject from the study.

Any discontinuation must be done in consultation with the sponsor's study physician.

4.5.1. Subject Diary

Subjects will be given a paper diary at the time points specified in the Schedule of Activities in Section 5.11 to record the following (screening until the EoS Visit 15 [Week 56] of the double-blind period):

- Any missed dose, if applicable.
- To document that IP dose has been taken properly on a daily basis, if applicable.
- The time of study drug intake, including whether food was taken with each dose.
- Changes in stable concomitant medication regimen, including new medicines not captured in medication history, as well as any emerging AEs.Subjects will be instructed to bring the diary and all remaining capsules at each visit.

5. CLINICAL STUDY ASSESSMENTS

Every effort should be made to ensure that protocol-required tests and procedures are completed as described in the Schedule of Activities (see Section 5.11). To avoid inter-observer variability, every effort should be made to ensure that all safety and efficacy evaluations are completed by the same individual who made the initial baseline determinations.

5.1. Timing of Assessments

The study assessments will be undertaken at time points and time windows as specified in the Schedule of Activities in Section 5.11. Screening and study procedures can only start after the ICF has been signed.

The preferred sequence of study assessments will be as follows:

Visit 1 (Screening):

1. In- and exclusion criteria, demographics, medical history
2. 12-lead ECG (triplicate)
3. Assessment of (S)AE(s) and prior and concomitant medication, and dispense diary
4. Physical examination, vital signs (supine heart rate, systolic and diastolic blood pressure [SBP and DBP], and body temperature), weight and height
5. Blood sampling for clinical laboratory testing FSH (if applicable), serum pregnancy test (if applicable), urine analysis (including random urine sample)
6. TKV imaging if historical imaging is older than 5 years or not available. In case MRI is performed according to study specifications and centrally read, this MRI can be used for screening and randomization. In this case, there is no need to repeat MRI at Visit 2 (Day 1).

Visit 2 (Day 1, randomization):

1. Before randomization: the below 2 criteria need to be met before proceeding to the other assessments of Visit 2:
    a. 12-lead ECG (triplicate); repeat if abnormal QTcF > 450 ms; screen failure if confirmed abnormal by the investigator (3 recordings with QTcF ≤ 450 ms need to be present)
    b. For female: urine pregnancy test; if positive a serum pregnancy test needs to be performed; screen failure if serum pregnancy test is positive

a. Only proceed to the following assessments if the subject is not screen failed by the criteria above:

2. Retrieve 24 hour urine collection from the subject upon arrival
3. Urine analysis on first morning urine
4. Assessment of (S)AE(s) and concomitant medication, and collect and dispense diary
5. Physical examination, vital signs (supine heart rate, SBP and DBP, and body temperature), and weight
6. Blood sampling for clinical laboratory tests; for genotype analysis (optional, if applicable); for [redacted]; for PK of GLPG2737 and its metabolite M4 (predose sample)
7. Optional blood sampling (1 for RNA sequencing, 1 plasma, and 1 serum sample) for future scientific research
8. IP intake
9. Blood sampling for PK analysis of GLPG2737 and M4, between 1.5 and 4 hours postdose
10. htTKV and [redacted] MRI. In case screening MRI was performed according to the study specifications and centrally read, screening MRI can be used for Day 1 and no MRI should be performed at the Day 1 visit.

Visit 3-Visit 14: *(apart from the Optional Visit and EoS Visit below)*

1. Retrieve 24 hour urine collection from the subject upon arrival (if applicable)
2. Urine analysis and urine pregnancy test (if applicable) on first morning urine
3. Assessment of (S)AE(s) and concomitant medication, and collect and dispense diary
4. 12-lead ECG (triplicate, as indicated in Schedule of Activities, Section 5.11)
5. Physical examination, vital signs (supine heart rate, SBP and DBP, and body temperature), and weight
6. Blood sampling for clinical laboratory tests; for [redacted] (on visits as indicated in Schedule of Activities, Section 5.11); for PK concentration analysis of GLPG2737 and M4 (predose sample within 30 minutes prior to IP intake at selected visits [see Section 5.6])
7. IP intake
8. htTKV and [redacted] MRI (Visit 5 [Week 4], Visit 10 [Week 26] and Visit 14 [Week 52], apart from subjects having discontinued earlier)
9. Blood sampling for postdose PK concentration analysis of GLPG2737 and M4 in parallel with htTKV / [redacted] MRI (Visit 5 [Week 4]; Refer to Section 5.6 for timing)

10. Optional blood sampling (1 for RNA sequencing, 1 plasma, and 1 serum sample) for future scientific research (Visit 14 [Week 52])

Visit 15 (EoS of double-blind period) / Roll-over visit at Week 56):

1. ICF collection for OLE period.
2. In- and exclusion criteria for OLE period.
3. Retrieve 24 hour urine collection from the subject upon arrival
4. Urine analysis and urine pregnancy test (if applicable) on first morning urine
5. 12-lead ECG (triplicate)
6. Physical examination, vital signs (supine heart rate, SBP and DBP, and body temperature), and weight
7. Assessment of (S)AE(s) and concomitant medication, and collect diary
8. htTKV and [redacted] MRI (apart from subjects with ETD)
9. Blood sampling for clinical laboratory tests and for [redacted] and optional for future scientific research
10. IP intake (only in case of participation in OLE period)

Visit 16-Visit 22 (OLE period)

1. Retrieve 24 hour urine collection from the subject upon arrival (if applicable)
2. Urine analysis and urine pregnancy test (if applicable) on first morning urine
3. Assessment of (S)AE(s) and concomitant medication
4. 12-lead ECG (single, as indicated in Schedule of Activities, Section 5.11)
5. Physical examination, vital signs (supine heart rate, SBP and DBP, and body temperature), and weight
6. Blood sampling for clinical laboratory tests-and for [redacted] (on visits as indicated in Schedule of Activities, Section 5.11) and for Visit 22 [Week 108]: optional sample for future scientific research
7. Visit 17 [Week 60] and Visit 18 [Week 66]: [redacted]
8. IP intake
9. Visit 17 [Week 60]: [redacted]
10. Visit 20 [Week 84] Visit 22 [Week 108]: [redacted]

Visit 23 (EoS) at Week 112 of the OLE Period

1. Urine analysis and urine pregnancy test (if applicable) on first morning urine
2. 12-lead ECG (single)
3. Physical examination, vital signs (supine heart rate, SBP and DBP, and body temperature), and weight
4. Assessment of (S)AE(s) and concomitant medication
5. Blood sampling for clinical laboratory tests and for [redacted]

ETD visit:
When IP is discontinued permanently, an ETD visit will be performed.

1. Urine analysis and urine pregnancy test (if applicable) on first morning urine
2. Assessment of (S)AE(s) and concomitant medication, and collect diary
3. 12-lead ECG (triplicate during double-blind period or single during OLE period)
4. Physical examination, vital signs (supine heart rate, SBP and DBP, and body temperature), and weight
5. Blood sampling for clinical laboratory tests; for [redacted] (during double-blind and OLE period) and [redacted] (only during double-blind period); for PK concentration analysis of GLPG2737 and M4
6. Optional blood sampling (1 for RNA sequencing, 1 plasma, and 1 serum sample) for future scientific research
7. In case of treatment discontinuation: ETD visit assessments 1-5 need to be done plus htTKV/[redacted] MRI depending on the time of discontinuation:
   - Between Week 0 and Week 4 (included): no MRI
   - Between Week 4 and Week 8 (included): final MRI 4 weeks after ETD visit
   - Between Week 8 and Week 26 (included): MRI at ETD visit, and final MRI 4 weeks later
   - Between Week 26 and Week 30 (included): final MRI 4 weeks after ETD visit
   - Between Week 30 and Week 56: MRI at ETD visit, and final MRI 4 weeks later
   - After Week 56: MRI htTKV to be performed if > 6 months since last MRI

Note:
In case of blood sampling via catheter, the order of assessments is less important when there is at least 30 minutes between the placement of the catheter/blood sampling via catheter and vital signs/ECG.

5.2. Unscheduled Visits

Additional visits can be performed at other time points for any assessments, if clinically indicated. These unscheduled visits and outcomes of additional assessments need to be recorded in the source and, if performed before the subject's last visit per CSP, also in the CRF.

5.3. Initial Subject and Disease Characteristics

Subjects will be asked to attend the clinical center for a screening assessment. After giving written informed consent, demographic data (age, sex and race) and a medical history will be taken, including questions regarding medication intake. A physical examination will be performed, including measurement of weight and height.

Vital signs (SBP, DBP, supine heart rate, body temperature) will be measured and a 12-lead ECG will be recorded. Subjects should rest for at least 5 minutes in the supine position before the ECG recording, blood pressure, and heart rate measurement.

The inclusion and exclusion criteria will be checked to assess eligibility for the study. All screening tests will be reviewed to confirm eligibility before randomization and the first dose.

5.4. Efficacy Assessments

5.4.1. htTKV and [redacted] by MRI

htTKV and [redacted] will be determined by MRI at time points defined in the Schedule of Activities (see Section 5.11). MRI has been shown to be accurate, reproducible and able to detect small changes in TKV over a short period of time (Chapman, Bost, & Torres, 2012). Subjects will undergo MRI using a standardized protocol.

If imaging needs to be performed for screening purposes as described in Inclusion Criterion 3, MRI can be selected as imaging method. In this case, when MRI signal acquisition procedures have been applied and centrally read, the screening MRI can be used as baseline measurement. There is no need to repeat MRI on Day 1 of the double-blind period (as long as screening MRI meets the quality criteria).

MRI signal acquisition procedures will be described in a specific laboratory manual. MRI images will be obtained at each clinical site by a trained imaging specialist. Following MRI acquisition, the images will be transferred to an Imaging Core Laboratory for centralized reading. In case the TKV MRI does not meet the quality criteria, the site is requested to perform another MRI within 10 business days of the original visit, with a maximum of 1 repetition.

Further details regarding the methodology will be provided in a separate study reference manual.

5.4.2. Estimated GFR (eGFR)

eGFR is a mathematically derived value based on a subjects serum creatinine level. The eGFR values will be based on the CKD-EPI equation, calculated from serum creatinine concentrations taken at screening and during every visit (see Schedule of Activities, Section 5.11), and will be reported by the central laboratory.

Further details regarding the methodology will be provided in a separate study reference manual and details regarding eGFR calculations will be provided in the statistical analysis plan (SAP).

5.5. Safety Assessments

This section describes methods and timing for all safety assessments and recording. Additional assessments (e.g. unscheduled clinical laboratory tests or extra vital signs recordings) are allowed to ensure appropriate collection of safety data and to assess any perceived safety concerns.

5.5.1. Adverse Events

The AEs reporting period for safety surveillance begins when the subject signs the ICF and ends at his/her last follow-up visit.

Detailed definitions, ratings and reporting requirements for AEs and SAEs are found in Section 8.

5.5.2. Clinical Laboratory Evaluations

The following clinical laboratory safety tests will be performed:

- **Hematology:**
  hematocrit, hemoglobin, red blood cell count, white blood cell count, white blood cell differential count (absolute and relative), platelets MCV, MCH, mean corpuscular hemoglobin concentration (MCHC), Vitamin B12.
- **Coagulation:**
  activated partial thromboplastin time, prothrombin time, and INR.
- **Clinical chemistry:**
  glucose, urea, creatinine, uric acid, sodium, potassium, calcium (including ionized), chloride, phosphorus, AST, ALT, GGT, total bilirubin, alkaline phosphatase, albumin, total proteins, triglycerides, cholesterol, high-density lipoprotein, low density lipoprotein, C-reactive protein, lactate dehydrogenase, amylase, lipase, Urinalysis:
  Proteins (quantitative) and ketones can be tested via standard test strip; microscopic examination of the sediment (cylinders, erythrocytes, leukocytes) if indicated (when the test strip was positive for blood and/or proteins), first morning urine for microscopy culture and sensitivity (MCS), albumin, creatinine (quantitative and ratio)
- **Serology** (only at screening):
  Hepatitis B surface antigen and hepatitis C antibody (confirmation of hepatitis C virus RNA positivity should be performed), and HIV 1 and HIV 2 antibodies only at screening. Positive hepatitis and HIV results should be reported by the investigator as required by local law.
- FSH test for females of non-childbearing potential at screening to confirm menopause, if applicable.
- **Pregnancy test for females:**
  Serum pregnancy testing (β-human chorionic gonadotropin [β-hCG]) will be performed at screening in females of childbearing potential; on the other specified days, a urine pregnancy test will be performed. The urine pregnancy test must be negative prior to the first administration of IP.

The clinical laboratory evaluations will be performed at visits specified in the Schedule of Activities in Section 5.11 (see also Section 5.1, "Timing of Assessments"). Reference ranges will be supplied by the central laboratory. Clinical laboratory values outside the normal range will be flagged and clinical relevance will be assessed by the investigator. Only laboratory test abnormalities judged as clinically significant by the principal investigator should be recorded as AEs.

The total amount of blood to be taken during the clinical study will not exceed 500 mL over a duration of 112 weeks. This includes sampling for pharmacokinetic (PK) and/or pharmacodynamic (PD) assessments.

The details of blood and urine sample handling and shipment instructions will be provided in a separate laboratory manual.

5.5.3. Physical Examination

Physical examinations will be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation at visits specified in the Schedule of Activities in Section 5.11 (see also Section 5.1, "Timing of Assessments"). The person conducting the physical examination will document this in the subject's medical records. Clinically significant abnormal findings should be recorded as AEs.

5.5.4. Vital Signs

Vital signs (SBP, DBP, supine heart rate, and body temperature) will be recorded in a standardized manner (i.e. after the subject has rested in a supine position for 5 minutes) at visits specified in the Schedule of Activities in Section 5.11 (see also Section 5.1, "Timing of Assessments"). For blood pressure, 3 measurements need to be taken within 5 minutes and the mean needs to be recorded. Vital sign parameter ranges are presented in Appendix 1. Clinically significant abnormal values should be recorded as AEs.

Height will only be assessed at screening. Weight will be assessed at screening, and on every visit as per Schedule of Activities (See Section 5.11).

5.5.5. 12-lead Electrocardiogram

During the double-blind period, at every visit (see Section 5.11) an ECG will be recorded in triplicate. During the OLE period (from Visit 16 [Week 58] onwards), ECG recording will be performed as a single measurement. Single ECG recordings during the OLE period will be read locally. The ECG must be taken after subjects rested for at least 5 minutes in the supine position.

Triplicate ECGs will be taken within preferably 15 minutes. Each ECG will be interpreted by the investigator for clinical significance at the moment of the measurement. In case of abnormal findings, even if not clinically significant, a repeat ECG will be performed as soon as possible after the original abnormal recording within the same visit and interpreted by the investigator. Central reading will be performed for all triplicate ECGs at all time points.

For Visit 2 (Day 1) of the double-blind period and Visit 15 (Week 56) of the OLE period, triplicate abnormal QTcF >450 ms (each recording of the triplicate ECG must be ≤450 ms) before IP dosing needs to be confirmed by a second recording. In case there are no 3 readings with a QTcF ≤450 ms after the second recording, then the subject cannot be randomized and will be considered a screen failure.

At Visit 2 (Day 1), if the predose QTcF recording is reported during the visit as normal by the investigator, but the overread by the cardiologist reports a QTcF >450 ms, then the subject should be discontinued as soon as possible.

At all other visits, the conclusion/evaluation of the central cardiologist reader will also overrule the reading of the ECG device.

Parameters to be recorded include the following: heart rate, PR interval, QRS interval, uncorrected QT interval, QTcF and rhythm.

QTcF will be considered as normal if ≤450 ms. After Visit 2, prolongation of QTcF to >500 ms or an increase from baseline of >60 ms will be considered a threshold of concern and the subject should be discontinued (for details, refer to Section 3.6.5). Normal ranges for ECG are provided in Appendix 1.

In case of abnormal QTcF, the investigator should adhere to clinical practice for follow-up of the subject.

ECG abnormalities will be interpreted by the investigator for clinical significance. Clinically significant abnormal values should be recorded as AEs.

In case an indwelling catheter is used, ECGs may be recorded after blood sampling, provided that there is at least 30 minutes between catheter insertion and the ECG recording. When catheter insertion would fail, the ECG needs to be taken before the venipuncture and at least 30 minutes after the failed attempt.

5.5.6. Other Safety Assessments - Control of Raised Blood Pressure

The target blood pressure for subjects with chronic renal failure should be ≤150/90 mm Hg during the study. The principles outlined in the Kidney Disease Outcomes Quality Initiative (KDOQI) hypertension guideline should be followed to ensure maintenance of blood pressure control (KDIGO_CKD_Work_Group, 2013).

5.6. Pharmacokinetic Assessments

Blood samples for the PK assessment should be collected on the time points specified below (see also Timing of Assessments in Section 5.1 and Schedule of Activities in Section 5.11).

Sparse PK sampling will be applied postdose on Visit 2 (Day 1) and Visit 5 (Week 4) to capture information on GLPG2737 and M4, absorption, distribution, and elimination.

During the course of the study, in total, 19 blood samples per subject will be collected for analysis of GLPG2737 and its metabolite M4, in plasma. Samples will be obtained by venipuncture (or indwelling cannula), preferably in the forearm.

Blood samples will be collected into vacuum tubes containing K2EDTA and will be immediately chilled (ice bath). Within 30 min after blood collection, the plasma will be separated by centrifugation at 4°C for 10 min at ca. 1500 g and transferred into storage tubes with approximately 400 µL of plasma per tube. After appropriate labeling, the plasma samples will be stored between -15 and -30°C at the clinical research center until shipment. The details of blood sample collection, handling, storage and shipment instructions will be provided in a separate laboratory manual.

The following PK sampling scheme will be applied (GLPG2737 and M4):

During double-blind period:

- **Visit 2 (Day 1):** predose and 1.5-4 hours postdose (i.e. 2 samples)
- **Visit 5 (Week 4):** predose (within 30 minutes prior to dosing), 1, 2, 3, 4 hours postdose (+/- 20 min), 5-7 hours postdose and 8-9 hours postdose (7 samples)
- **Visit 3 (Week 1), 4 (Week 2), 8 (Week 16), 10 (Week 26), 14 (Week 52):** predose sample (within 30 minutes prior to dosing)

[redacted]

[redacted]

For reliable analyses of the PK data, it is vital that the actual times of drug intake and PK sampling are recorded accurately in the CRF.

5.7. Pharmacodynamic Assessments

Double-blind period:

[redacted]

[redacted]

OLE period:

[redacted]

[redacted]

[redacted]

5.8. Other Assessments

5.8.1. Genotyping

[redacted]

[redacted]

5.8.2. Future Scientific Research

For subjects who give additional informed consent, 12 optional samples (1 for RNA sequencing, 1 plasma, and 1 serum sample each at 4 time points) will be obtained for future scientific research. These samples are scheduled to be collected before exposure (baseline, Day 1) and at the end of the double-blind treatment period (Week 52 and Week 56) and at the end of the OLE period (Week 108), or at ETD (see Schedule of Activities Section 5.11).

5.9. Sample Management

Blood and Urine Samples for Routine Safety Tests, Serology, FSH and Pregnancy Tests

All blood and urine samples for routine safety tests, serology, FSH, and pregnancy tests (if applicable) will be analyzed in a central laboratory and will be destroyed after analysis. Urinary pregnancy tests will be performed locally.

Blood and Urine Samples for PK and PD

After the end of the study (defined in Section 3.2), all biological samples obtained during the clinical study may be stored for a maximum period of 5 years (or up to 30 years for samples for future scientific or genetic research, see Section 5.10), after which the samples will be destroyed. The sample storage period will be in accordance with the IRB/EC-approved ICF and applicable laws (e.g. health authority requirements).

The stored samples shall only be used by the sponsor, sponsor partners and/or other companies contracted by the sponsor, for research related to this clinical study. Any research outside the context described in this CSP may only be conducted after approval by the IRB/IEC and Regulatory Authority and after obtaining informed consent from the subject.

[redacted]

5.10. Long Term Storage of Samples and Associated Data for Future Scientific and Genetic Research

A total of 12 additional samples will be obtained from subjects who agree to participate and provide their optional informed consent for the additional collection and use of samples for future scientific research, including long term storage of samples and associated data (see Section 5.8.2). Collection and storage of samples is detailed in a separate laboratory manual.

For subjects who agree to participate and provide their optional informed consent for long term storage of left over samples from samples already collected during the study and associated data

for future scientific and genetic research, blood and urine samples obtained during the study will be stored for 30 years or according to local legislation.

The samples and associated data collected for future scientific and genetic research will be stored in the Galapagos Biobank and may be used by the sponsor, sponsor partners and/or other companies contracted by the sponsor. The objective of biobanking is to allow the gathering of additional knowledge on the compound GLPG2737 and/or diseases it may target both investigated during this study and beyond.

Subjects are not required to consent for the collection of samples and for the long term storage of samples and associated data for future scientific and genetic research in order to participate to the study. Subjects will also be informed that consent to sample collection and storage for future research is voluntary and that they may withdraw their consent at any time. If a subject chooses to withdraw consent for the collection or storage of samples and associated data for future research then the investigator or designated personnel must inform the sponsor (withdrawal@glpg.com).

Withdrawal from the study does not, by itself, implicate withdrawal of consent for the collection or storage of samples and associated data for future research. Likewise, withdrawal of consent for the storage of samples and associated data for future research does not implicate withdrawal from the study.

In the event of subject's death or loss of competence, the already collected samples and data will continue to be used as part of the future scientific and genetic research.

The samples and associated data for future research, e.g. body fluids, solid tissue, and derivatives thereof (e.g. protein, peptides) will be destroyed no later than 30 years after the end of the study or according to local legislation. The samples and associated data storage period will be in accordance with the IRB/EC-approved ICF and applicable legislation (e.g. regulatory authority requirements).

The subject will receive additional information specific to the longterm processing of their personal data for future scientific and genetic research purposes, as required by the EU General Data Protection Regulation. This includes information about the broader scientific purposes of future research, the lawful bases of the processing activities involved, as well as the retention period of their personal data for these additional purposes. The details are included in the optional informed consent form.

5.11. Schedule of Activities

5.11.1. Double-blind Treatment Period

For detailed instructions on the clinical study procedures, please see referred sections and Section 5.1, "Timing of Assessments".

EVENT	SCREENING PERIOD	TREATMENT PERIOD							EoST / EoSA[1]		FOLLOW-UP
Study visit	**1**	**2**	**3**	**4**	**5**	**6/7/8/9**	**10/11/12/13**	**ETD[2]**	**14 EoST**	**14 EoSA**	**15 (EoS DB Period)[3]**
Study Day (D) or Week (W) (± D)	**D-28 to D-1**	**D1**	**W1 ± 3**	**W2 ± 3**	**W4 ± 3**	**W8/W12/ W16/W20 ± 4**	**W26/W34/ W42/W48 ± 4**		**W52 ± 4**	**W52 ± 4**	**W56 ± 10**
Informed consent (Section 5.3)	✓										
Inclusion/exclusion criteria (Sections 3.6 and 5.3)	✓	✓									
Demographics (Section 5.3)	✓										
Medical history (Section 5.3)	✓										
Pregnancy test[4,5] (Section 5.5.2)	✓	✓			✓	✓	✓	✓	✓		✓

[1] At Visit 14 either EoST (Treatment) or EoSA (Assessment) should be performed.
[2] Early treatment discontinuation (ETD) visit, if applicable.
[3] In case subject rolls over to the OLE period, roll-over visit in the SoA described in Open-label Treatment Period (Section 5.11.2) is also applicable.
[4] Assessment needs to be done prior to dosing, on dosing days.
[5] Serum Pregnancy test or FSH at screening. Urine pregnancy test at Day 1and subsequent visits, as indicated in the SoA.

EVENT	SCREENING PERIOD	TREATMENT PERIOD							EoST / EoSA[1]		FOLLOW-UP
Study visit	**1**	**2**	**3**	**4**	**5**	**6/7/8/9**	**10/11/12/13**	**ETD[2]**	**14 EoST**	**14 EoSA**	**15 (EoS DB Period)[3]**
Study Day (D) or Week (W) (± D)	**D-28 to D-1**	**D1**	**W1 ± 3**	**W2 ± 3**	**W4 ± 3**	**W8/W12/ W16/W20 ± 4**	**W26/W34/ W42/W48 ± 4**		**W52 ± 4**	**W52 ± 4**	**W56 ± 10**
Physical examination (Section 5.5.3)[6]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Vital signs[4] (Section 5.5.4)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Weight and Height[7]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
12-lead ECG[4,8] (Section 5.5.5)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Serology (Section 5.5.2)	✓										
Safety blood samples (Section 5.5.2)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Safety urine samples (Section 5.5.2)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

[6] Full physical examinaton should be performed at screening, randomization, Visit 5 (Week 4), Visit 10 (Week 26), and Visit 14 (Week 52). At all other visits at investigators discretion.
[7] Height only at screening.
[8] Triplicate ECG at each visit.

EVENT	SCREENING PERIOD	TREATMENT PERIOD							EoST / EoSA[1]		FOLLOW-UP
Study visit	**1**	**2**	**3**	**4**	**5**	**6/7/8/9**	**10/11/12/13**	**ETD[2]**	**14 EoST**	**14 EoSA**	**15 (EoS DB Period)[3]**
Study Day (D) or Week (W) (± D)	**D-28 to D-1**	**D1**	**W1 ± 3**	**W2 ± 3**	**W4 ± 3**	**W8/W12/ W16/W20 ± 4**	**W26/W34/ W42/W48 ± 4**		**W52 ± 4**	**W52 ± 4**	**W56 ± 10**
MRI based htTKV and [redacted] (Section 5.4.1)	(✓)[9]	✓[9]			✓		✓[10]	✓[11]	✓		✓
eGFR (Section 5.4.2)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
[redacted]											

[9] At screening TKV should be determined in case historical imaging is not available from the last 5 years (other imaging can be performed depending on local clinical practice). In case MRI is performed at screening according to study specifications and centrally read, this MRI can be used for screening and randomization. In this case, there is no need to repeat MRI at Visit 2 (Day 1).
[10] at Visit 10 (Week 26) only.
[11] For subjects discontinuing IP prematurely, the instructions of the ETD need to be followed (see Section 5.1).
[12] 24 hours urine collection to be performed 24 hours before Visit 2 (Day1), Visit 5 (Week 4), Visit 7 (Week 12), Visit 10 (Week 26), EoST Visit 14 (Week 52), and EoS Visit 15 (Week 56) – not applicable for subjects who discontinued IP.
[13] At Visit 7 (Week 12) only.
[14] PD samples directly after PK sampling (predose).

EVENT	SCREENING PERIOD	TREATMENT PERIOD							EoST / EoSA[1]		FOLLOW-UP
Study visit	**1**	**2**	**3**	**4**	**5**	**6/7/8/9**	**10/11/12/13**	**ETD[2]**	**14 EoST**	**14 EoSA**	**15 (EoS DB Period)[3]**
Study Day (D) or Week (W) (± D)	**D-28 to D-1**	**D1**	**W1 ± 3**	**W2 ± 3**	**W4 ± 3**	**W8/W12/ W16/W20 ± 4**	**W26/W34/ W42/W48 ± 4**		**W52 ± 4**	**W52 ± 4**	**W56 ± 10**
[redacted]											
First morning urine for Microscopy Culture and Sensitivity (MCS) (Section 5.5.2)	✓[17]	✓			✓			✓	✓	✓	
[redacted]											
Randomization (Section 3.7.1)		✓									
[redacted]											

[15] At Visit 6 (Week 8), Visit 7 (Week 12), Visit 8 (Week 16) only.
[16] At Visit 10 (Week 26) and Visit 11 (Week 34) only.
[17] A random urine sample can be used at the screening visit.
[18] Only in case not determined in the past.
[19] Only at Visit 8 (Week 16) and Visit 10 (Week 26).

EVENT	SCREENING PERIOD	TREATMENT PERIOD							EoST / EoSA[1]		FOLLOW-UP
Study visit	**1**	**2**	**3**	**4**	**5**	**6/7/8/9**	**10/11/12/13**	**ETD[2]**	**14 EoST**	**14 EoSA**	**15 (EoS DB Period)[3]**
Study Day (D) or Week (W) (± D)	**D-28 to D-1**	**D1**	**W1 ± 3**	**W2 ± 3**	**W4 ± 3**	**W8/W12/ W16/W20 ± 4**	**W26/W34/ W42/W48 ± 4**		**W52 ± 4**	**W52 ± 4**	**W56 ± 10**
PK blood sample, any time of the day (Section 5.6)								✓			
Optional blood samples for future scientific research (Section 5.10)		✓(pre dose)						✓	✓		✓
Dispense subject diary (Section 4.5.1)	✓	✓	✓	✓	✓	✓	✓	✓			
Collect subject diary (Section 4.5.1)		✓	✓	✓	✓	✓	✓	✓			✓
Dispense subject participation card		✓									
Randomization		✓									
Dispense IP (Section 4.3)		✓	✓	✓	✓	✓	✓				
Review IP compliance in paper diary (Section 4.5)			✓	✓	✓	✓	✓	✓	✓		
Dose IP (Section 4.2)		q.d. throughout the treatment period starting at Day 1							✓		
AE assessment (Section 5.5.1)	throughout the study										

EVENT	SCREENING PERIOD	TREATMENT PERIOD							EoST / EoSA[1]		FOLLOW-UP
Study visit	**1**	**2**	**3**	**4**	**5**	**6/7/8/9**	**10/11/12/13**	**ETD[2]**	**14 EoST**	**14 EoSA**	**15 (EoS DB Period)[3]**
Study Day (D) or Week (W) (± D)	**D-28 to D-1**	**D1**	**W1 ± 3**	**W2 ± 3**	**W4 ± 3**	**W8/W12/ W16/W20 ± 4**	**W26/W34/ W42/W48 ± 4**		**W52 ± 4**	**W52 ± 4**	**W56 ± 10**
Prior / Concomitant medication (Section 3.6.4.2)	throughout the study										

5.11.2. Open-label Treatment Period

EVENT	TREATMENT PERIOD						FOLLOW-UP
Study Visit / Phone Call	**Roll-over Visit 15** [1]	**16**	**17/18/19**	**20/21**	**22**	**ETD**[2]	**23 (EoS OLE Period)**
Week (W) (± Days)	**Week 56**	**W58 ± 3 days**	**W60/W66 / W72 ± 3 days**	**W84/W96 ± 4 days**	**W108 ± 4 days**		**W112 ± 4 days**
Informed consent (Section 5.3)	✓						
Inclusion/exclusion criteria (Sections 3.6 and 5.3)	✓						
Pregnancy test (Section 5.5.2)	✓		✓	✓	✓	✓	✓
Physical examination (Section 5.5.3)	✓	✓	✓	✓	✓	✓	✓
Vital signs (Section 5.5.4)	✓	✓	✓	✓	✓	✓	✓
Weight	✓	✓	✓	✓	✓	✓	✓
12-lead ECG (Section 5.5.5)	✓ (triplicate)	✓	✓	✓	✓	✓	✓
Safety blood samples (Section 5.5.2)	✓	✓	✓	✓	✓	✓	✓
Safety urine samples (Section 5.5.2)	✓	✓	✓	✓	✓	✓	✓
[redacted]							

EVENT	TREATMENT PERIOD						FOLLOW-UP
Study Visit / Phone Call	**Roll-over Visit 15** [1]	**16**	**17/18/19**	**20/21**	**22**	**ETD**[2]	**23 (EoS OLE Period)**
Week (W) (± Days)	**Week 56**	**W58 ± 3 days**	**W60/W66 / W72 ± 3 days**	**W84/W96 ± 4 days**	**W108 ± 4 days**		**W112 ± 4 days**
[redacted]							
First morning urine for MSC (Section 5.7)	✓[4]		✓ (W60)				
[redacted]							
Optional blood samples for future scientific research (Section 5.10)					✓	✓	
Dispense IP (Section 4.3)	✓		✓	✓			
Review IP compliance		✓	✓	✓	✓		
Dose IP (Section 4.2)	q.d. throughout the treatment period						
AE assessment (Section 5.5.1)	throughout the study						
Concomitant medication (Section 3.6.4.2)	throughout the study						

[1] Roll-over visit will take place at FU visit of the double-blind period (Week 56).
[2] Early treatment discontinuation (ETD) visit, if applicable.
[3] For subjects discontinueing IP prematurely, the instructions of the ETD need to be followed (see Section 5.1)
[4] A random urine sample can be used.

6. STATISTICAL METHODS

All statistical methods shall be detailed in a SAP that will be finalized prior to the primary analysis. All data collected in this clinical study will be documented using summary tables, figures, and subject data listings.

Any deviations from the protocol are to be justified in the SAP.

6.1. Determination of Sample Size

A total of 60 adult ADPKD subjects will be enrolled in this study. Subjects will be randomized in a 2:1 allocation ratio to GLPG2737 or placebo treatment, resulting in approximately n=40 for GLPG2737 and approximately n=20 for placebo.

The primary aim of this study is to show that GLPG2737 treatment is generally safe and well tolerated, and to show a trend in treatment difference for the active treatment versus placebo for the primary endpoint (mean percent change from baseline in htTKV over 52 weeks). Therefore, no formal sample size calculation was performed. Merely for statistical reference, the variability of the estimated treatment difference for the proposed sample size of 60 subjects is illustrated in the following paragraph:

For htTKV, prior knowledge for an existing treatment of ADPKD suggests a mean percent change from baseline to 52 weeks of 5.6% for placebo.

Assuming a common standard deviation of 4.5 for the percent change from baseline and a true mean treatment difference of 2.8% between the 2 groups, this implies a power of 83% to detect a statistically significant difference at a 2-sided significance level of 20% (using 2-sample t-test). If the dropout rate is around 10%, the power will be around 80%.

In case subjects discontinue from the study or from study treatment due to SARS-CoV-2 restrictions, additional subjects may be randomized on top of the planned sample size. The number of additional subjects randomized will not exceed the number of subjects discontinuing the study or study treatment in relation to SARS-CoV-2 restrictions. Randomization of additional subjects will ultimately be decided by the sponsor before any study lock or related unblinding has occurred.

6.2. Population for Analyses

6.2.1. All Screened Subjects

All subjects who signed and dated an ICF and underwent screening assessments to check whether or not they are eligible to participate in the clinical study.

6.2.2. All Enrolled Subjects

All subjects who were found eligible to participate in the clinical study and could be randomized.

6.2.3. All Randomized Subjects

All enrolled subjects who were randomized into the clinical study.

6.2.4. Full Analysis Set

All randomized subjects who have received/used at least one dose of IP. Subjects will be grouped according to the treatment they were randomized to.

6.2.5. Per Protocol Set

All full analysis set subjects who did not have a major protocol deviation that impacts the efficacy results (as defined in a protocol deviation plan). The determination of the per protocol population will be finalized and documented prior to database lock and unblinding.

6.2.6. Safety Analysis Set

All randomized subjects who used at least one dose of IP. Subjects will be grouped according to the treatment they received.

6.2.7. Pharmacokinetic Analysis Set

Subset of the Safety Analysis Set for which plasma concentration data are available to facilitate development of the Population PK model and for whom the time of the dose on the days of PK sampling is known.

6.2.8. Pharmacodynamic Analysis Set

Subset of the Safety Analysis Set, selecting all subjects who have a baseline and at least one post-baseline PD value excluding subjects with protocol deviations that may have an impact on PD analysis.

6.2.9. Pharmacokinetic/Pharmacodynamic Analysis Set

Intersection of the PK and PD Analysis Sets.

6.2.10. All OLE Enrolled Subjects

All randomized subjects who were found eligible to participate in OLE study period.

6.2.11. OLE Full Analysis Set

All OLE enrolled subjects who have used at least one dose of IP during the OLE study period. Subjects will be grouped according to the treatment they were randomized to (i.e. for the double-blind study period).

6.2.12. OLE Safety Analysis Set

All OLE enrolled subjects who used at least one dose of IP during the OLE period. Subjects will be grouped according to the treatment they received in the double-blind study period.

6.2.13. OLE Pharmacodynamic Analysis Set

[redacted]

6.3. Statistical Analyses

6.3.1. General Statistical Considerations

Summary tabulations will be presented and will display the number of observations, mean, standard deviations and/or standard error (as appropriate), median, minimum and maximum (for continuous variables), and the number and percentage per category (for categorical data). In addition to tabulated descriptive statistics, graphical data displays may be used to summarize the data. Unless otherwise noted, inferential statistics will be interpreted at the 2-sided 20% significance level.

All summary tabulations will be presented by treatment group and by study period (i.e. by considering double-blind treatment period and OLE period separately). Analysis will be provided by considering baseline as the last measurement before the first dose of IP.

[redacted]

The primary analysis will be performed when all subjects have reached the end of the double-blind period, or discontinued earlier. The details of the primary analysis will be described in the SAP.

6.3.2. Interim Analysis

No interim analysis is planned for this study.

6.3.3. Analyses of Demographics and Baseline Characteristics

Subject disposition (including reasons for early discontinuation), protocol deviations, demographics, baseline characteristics, medical history, and concomitant therapies will be described using summary statistics.

6.3.4. Analyses of Primary Efficacy Parameters

6.3.4.1. Analysis for Primary Efficacy Endpoint

A longitudinal analysis of the htTKV percent change from baseline until the end of the end of the double-blind period will be performed and appropriate inferential measures on the treatment difference will be obtained.

6.3.4.2. Analysis for Other Efficacy Endpoints

Combined double-blind treatment period and OLE period:

Efficacy assessments will be analyzed descriptively. Change from baseline and/or percent change from baseline will be computed as well by treatment group and by study period.

Inferential analyses may be performed on the double-blind treatment period and will be described in the SAP.

Only for the OLE period:

Efficacy assessments will be analyzed only descriptively. [redacted]

6.3.5. Analyses of Primary Safety Data

All safety analyses will be performed using the Safety Analysis Set (Section 6.2.6). Subjects will be analyzed according to the treatment they actually received. The actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration. All safety data collected on or after the first dose of IP administration up to the last contact after the last dose of IP, unless specified otherwise, will be summarized by treatment group and by study period (i.e. double-blind treatment period and OLE period) according to the IP received. Clinical safety will be addressed by assessing AEs, laboratory assessments, physical examinations, vital signs, and 12-lead ECGs.

6.3.5.1. Extent of Exposure

A subject's extent of exposure to the IP will be generated from the IP administration page of the CRF. Exposure data will be summarized by treatment group and by study period. Duration of exposure to the IP will be expressed as the number of months between the first and last dose of IP, inclusive, regardless of temporary interruptions in IP administration and summarized by treatment group.

6.3.5.2. Adverse Events

Clinical and laboratory AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities. System Organ Class (SOC), High-Level Group Term, High-Level Term, Preferred Term, and Lower-Level Term will be attached to the clinical database.

The following AEs will be considered as treatment-emergent adverse events (TEAEs):

Any AE with an onset date on or after the IP start date and no later than 30 days after last dose of IP, or any worsening of any AE on or after the IP start date.

Summaries (number and percentage of subjects) of TEAEs per subject by SOC and Preferred Term will be provided by treatment group and by study period. TEAEs will also be summarized by causal relationship to the IP and severity. In addition, TEAEs leading to premature discontinuation of the IP will be summarized and listed. Also, all SAEs, including the nontreatment-emergent SAEs, will be listed.

6.3.5.3. Clinical Laboratory Evaluations

Combined double-blind treatment period and OLE period:

Laboratory assessments will be analyzed descriptively. Changes from baseline (Day 1 predose) and shifts according to normal ranges and/or CTCAE grades will be presented as well. Analyses will be done per treatment group and per study period.

Only for the OLE period:

Laboratory assessments will be analyzed descriptively. [redacted]

6.3.5.4. Vital Signs

Combined double-blind treatment period and OLE period:

Vital signs will be analyzed descriptively. Changes from baseline (Day 1 predose) and shifts according to normal ranges will be presented as well. Analyses will be done per treatment group and per study period.

Only for the OLE period:

Vital signs will be analyzed descriptively. [redacted]

6.3.5.5. 12-Lead Electrocardiogram

Combined double-blind treatment period and OLE period:

A descriptive analysis will be done for the 12-lead ECG. Changes from baseline (Day 1 predose) and shifts according to normal ranges (Appendix 1) will be presented as well. Frequency analyses of subjects with a QTcF prolongation of >450ms, >480 ms, >500 ms and change from baseline in QTcF interval with 30 ms and 60 ms will be presented. Analyses will be done per treatment group and per study period.

Only for the OLE period:

[redacted]

6.3.6. Pharmacokinetics Analysis

Observed GLPG2737 and M4 plasma concentrations will be analyzed using a population PK approach to characterize the PK profiles of GLPG2737 and M4 in ADPKD subjects, and explore the covariates that might influence the PK in this population.

The aforementioned analysis will be described in detail in a separate pharmacometric analysis plan and will be reported separately from the clinical study report. A summary of the population PK analysis may be included in the clinical study report. Individual GLPG2737 and M4 exposure will be estimated based on the population PK model and included in the clinical study report.

Visual exploratory assessment of the relationship between exposure and response (as surrogate [redacted], efficacy and safety endpoints) will be performed to evaluate putative correlations. If applicable, the time course of the response and the effects of treatment thereupon will be described using a longitudinal model of disease progression.

The aforementioned population PK/PD analysis will be described in detail in a separate pharmacometric analysis plan and will be reported separately from the clinical study report.

Descriptive statistics will be calculated by treatment group, study period and time points for the plasma concentrations.

6.3.7. Pharmacodynamic Analyses

Combined double-blind period and OLE period:

PD data [redacted]) will be summarized using descriptive statistics of actual values, changes from baseline and percent changes from baseline by treatment group and by study period.

[redacted]

6.3.8. Analysis of Other Assessments

In case a treatment effect is observed, exploratory efficacy, safety/PK/PD analyses may be added when deemed useful to better understand the collected data. Where possible, individual and/or mean ± standard error efficacy, safety, PD, and/or GLPG2737 plasma concentrations may be plotted against one another. If performed, these analyses will be described in a separate analysis plan and reported separately from the clinical study report.

6.3.9. Additional Statistical Considerations

Not applicable.

7. DATA MONITORING

7.1. Independent Data Monitoring Committee

To monitor the safety of the subjects, an Independent Data Monitoring Committee (IDMC) consisting of an independent statistician and independent experts in the field of ADPKD will be convened to regularly review the accumulating unblinded safety data for the clinical study. The IDMC will provide a recommendation to the sponsor on clinical study continuation, suggestions for clinical study adaptation(s), or early termination. Ultimately, the final decision remains with the sponsor. The specific responsibilities, composition, meeting formats, and details of output provided for the meetings of the IDMC will be outlined in detail in the IDMC Charter.

8. SAFETY REPORTING

8.1. Definitions of Adverse Events, Serious Adverse Events and Special Situations

8.1.1. Adverse Events

An AE is any untoward medical occurrence, new or worsening of any condition, in a clinical study subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related. AEs may also include pre- or post-treatment complications that occur as a result of CSP-specified procedures, worsening of the targeted disease, overdose, drug abuse/misuse reports, or occupational exposure. Conditions that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

8.1.2. Serious Adverse Events

An SAE is defined as an AE that:

- Results in death;
- Is life-threatening (Note: The term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.);
- Requires in-patient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly / birth defect;
- Is medically significant (medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might

jeopardize the subject or might require intervention to prevent one of the other outcomes listed in the definition above).

8.1.3. Unlisted (Unexpected) Adverse Events/ Reference Safety Information

An AE is considered unlisted if the nature or intensity is not consistent with the applicable product reference safety information. For an IP, the expectedness of an AE will be determined by whether or not it is listed in the reference safety information part of the IB.

8.1.4. Adverse Events of Special Interest

Not applicable.

8.1.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance based on the investigator's judgment are not considered AEs or SAEs. However, laboratory abnormalities (e.g. clinical chemistry, hematology, and urinalysis) or other abnormal (clinical study-specific) assessments (e.g. ECG, radiography, vital signs) that require medical or surgical intervention, are associated with signs and/or symptoms, and/or lead to IP interruption, modification, or discontinuation must be recorded as an AE or SAE if they meet the definition as described in Sections 8.1.1 and 8.1.2, respectively. If the laboratory abnormality is part of a syndrome, the syndrome or diagnosis is to be reported (e.g. anemia instead of decreased hemoglobin).

The following liver enzyme elevations should be reported as SAEs: AST or ALT ≥3x ULN with signs of liver damage (total bilirubin >2x ULN OR international normalized ratio >1.5, and/or with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia [>5%]).

8.1.6. Special Situations

Special situations are situations that have a possible impact on the safe use of the IP. These situations might be or might not be associated with AEs.

- Pregnancy
- Abuse or misuse of IP
  - Abuse of IP is defined as the persistent or sporadic, intentional excessive use of the IP, which is accompanied by harmful physical or psychological effects.
  - Misuse of IP is defined as a situation where the IP is intentionally and inappropriately used not in accordance with the product information.
- Drug interaction or food interaction with IP
  - A drug interaction with IP is defined as a situation in which there is evidence or a suspicion that the IP interacts with another drug when both are administered together.
  - A food interaction with IP is defined as a situation in which there is evidence or a suspicion that the IP interacts with a food when taken together.

- Medication error with IP
  - A medication error with IP is defined as an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the subject.
- Occupational exposure to IP
  - Occupational exposure to IP is defined as an exposure to the IP as a result of one's professional or non-professional occupation.
- Overdose with IP
  - An overdose of IP is defined as the administration of a quantity of the IP given per administration or cumulatively, which is above the maximum recommended dose as per protocol (i.e. >2 tablets per day). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).
- Product complaint or quality defect of IP
  - Product complaint or quality defect of IP is defined as complaints or defects of the IP arising from potential deviations in the manufacture, packaging or distribution of the IP.

8.2. Assessment of Adverse Events and Serious Adverse Events

The investigator is responsible for assessing AEs and SAEs for causality and severity. This is the basis for the sponsor's final review and confirmation of accuracy and completeness of event information and causality assessments.

8.2.1. Assessment of Causality

The investigator is responsible for assessing the causal relationship to IP(s) administration or study procedures (e.g. invasive procedures such as venipuncture) based on her/his clinical judgment. The following decision choice will be used by the investigator to describe the causality assessment between the reported event or laboratory test abnormality and the IP.

- **Unrelated:**
  Time relationship to IP intake is improbable. Related to other etiologies such as concomitant medications or subject's clinical state.
- **Unlikely:**
  Time relationship to IP intake is improbable (but not impossible). Concomitant disease or other drugs provide plausible explanations.
- **Possible:**
  Time relationship to IP intake is reasonable. Event or laboratory test abnormality could also be explained by disease or other drugs. Information on IP withdrawal may be lacking or unclear.
- **Probable:**
  Time relationship to IP intake is reasonable. Unlikely to be attributed to concurrent disease or other drugs. Response to withdrawal is clinically reasonable and re-challenge not required.

– **Certain:**
Time relationship to IP intake is plausible. Cannot be explained by concomitant disease or other drugs. Response to withdrawal is plausible (pharmacologically, pathologically). Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon). Re-challenge satisfactory, if ethical and necessary.

It should be emphasized that ineffective treatment (worsening of the disease) should not be considered as causally related in the context of AE reporting.

8.2.2. Assessment of Severity

The severity of AEs should be graded using the CTCAE version 5.0. If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening) or Grade 5 (fatal) to describe the maximum intensity of the AE. For purposes of consistency with the CTCAE, these intensity grades are defined in the table below.

Table 1 Grading of AE Severity

Grade	Adjective	Description
Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4	Life-threatening	Urgent intervention indicated
Grade 5	Death	Death-related AE

* Instrumental activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality. This is upon the investigator's assessment.

If there is a change in intensity (worsening or improvement) of an AE, it must be recorded.

8.2.3. Outcome

Each AE must be rated by choosing among:

- Recovered/resolved;
- Recovered/resolved with sequelae;
- Recovering/resolving;
- Not recovered/not resolved;
- Fatal;
- Unknown.

8.3. Investigator Requirements and Instructions for Reporting Adverse Events, Serious Adverse Events, Pregnancies, and Other Special Situations to the Sponsor

8.3.1. Adverse Events

The AE reporting period for safety surveillance begins when the subject signs the ICF and ends at the subject's last follow-up visit (the last follow-up visit after the last dose of IP). In this period, all new AEs, regardless of cause or relationship, derived by spontaneous, unsolicited reports of subjects, by observation and by routine open questioning (such as "How do you feel?") need to be recorded in the source and in the CRF.

In case an AE is ongoing at the time of the last follow-up visit, the investigator needs to follow-up on the subject until AE resolution or reasonable stabilization and to document in the subject's source documentation. No related updates or additional data on the AE should be reported in the CRF.

If a subject is documented as lost-to-follow-up, ongoing/unknown outcome AEs will not be followed up.

If the AE meets the criteria for seriousness, the SAE form must be completed and sent to the sponsor within 24 hours (see Section 8.3.2).

8.3.2. Serious Adverse Events

Subjects experiencing an SAE or an emergency situation will be examined by a physician as soon as possible. The subject will remain under observation as long as medically indicated. Appropriate laboratory tests will be performed until all parameters return to normal or are otherwise explained or stable.

All SAEs, whether or not deemed IP-related, must be recorded in the CRF and on the SAE form. The investigator must report each SAE immediately, and under no circumstances should this exceed 24 hours following the knowledge of the SAE, as is indicated on page 2 under "Emergency Contact Information".

The SAE form should at least contain identifiers of the subject and the reporter, SAE term and statement of relatedness to the IP, and at a later stage if not yet available within 24 hours, the form needs to be completed with a clearly written narrative describing signs, symptoms, and

treatment of the event, diagnostic procedures, as well as any relevant laboratory data and any sequelae.

Follow-up and outcomes should be reported and documented in the source documents for all subjects that experience an SAE. It is important that the information provided on the SAE form matches the information recorded on the CRF for the same event.

Copies of additional laboratory tests, consultation reports, post-mortem reports, hospital case reports, autopsy reports, and other documents should be sent when requested and available. Only subject identifiers (subject number) should appear on the copies, and all names and initials should be blackened and rendered illegible. Follow-up reports relative to the subject's subsequent course must be submitted until the event has subsided or, in case of permanent impairment, until the condition stabilizes.

Any SAEs that occur after the post-treatment follow-up visit but within 30 days of the last dose of IP(s), regardless of causality, should also be reported in the source document (Emergency Contact Information on page 2). Investigators are not obligated to actively seek SAEs after the CSP-defined follow-up period. However, if the investigator is informed about an SAE that occurs at any time after the subjects' post-treatment follow-up visit and the event is deemed relevant to the use of IP(s), he/she should promptly document and report the event to the sponsor by using the SAE form.

8.3.3. Pregnancy

All initial reports of pregnancy in female subjects in the clinical study must be recorded and documented in the source documents and on the pregnancy form. The investigator must report each pregnancy immediately, and under no circumstances should this exceed 24 hours following the knowledge of the pregnancy, as is indicated on page 2 under "Emergency Contact Information".

All pregnancies should be followed up until delivery or pregnancy interruption. The investigator will contact the subject after giving consent, at the expected time of delivery for follow-up and for information regarding the outcome of the newborn. Abnormal pregnancy and/or abnormal newborn outcomes are considered SAEs and must be reported using the SAE form.

8.3.4. Reporting of Special Situations (Other Than Pregnancy) and Associated Adverse Events

In case a special situation is not associated with an AE, the special situation should be reported within 24 hours by using the Special Situations form as is indicated on page 2 under "Emergency Contact Information".

In case a special situation is associated with an AE, the special situation should be reported within 24 hours by using the Special Situations form and the associated AE should be reported as specified in Section 8.3.

In case a special situation is associated with an SAE, the special situation should be reported within 24 hours by using the SAE form (and not the Special Situations form) and the associated SAE should be reported as specified in Section 8.3.2.

8.4. Sponsor Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable United States Federal Drug Administration Code of Federal Regulations, the European Union (EU) Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, the sponsor may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions or suspected unexpected serious adverse reactions (SUSARs). The sponsor or a specified designee will notify worldwide regulatory agencies and the relevant IEC/IRB in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined using the reference safety information section in the IB or relevant local label as applicable.

All concerned investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any IP(s). The investigator should notify the IEC/IRB of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

9. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This clinical study is conducted in accordance with the current applicable regulations, ICH-GCP Guideline E6 and its updates, and local ethical and legal requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of clinical study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

The name and address of each third-party vendor (e.g. CRO) used in this study and the sponsor's study team members will be maintained in the investigator's and sponsor's files as appropriate.

9.1. Sponsor's Responsibilities

9.1.1. Regulatory Approval / Notification

Prior to clinical study start, this CSP together with all relevant documentation will be submitted to the local regulatory authorities for review and approval and/or notification in compliance with local requirements.

9.1.2. Clinical Study Closure Considerations

The sponsor reserves the right to close the investigational site or end the clinical study at any time for any reason. In case of an early termination of the clinical study or temporary halt by the sponsor, the IEC/IRB should be notified within 15 calendar days, unless otherwise specified by the IEC/IRB, including a detailed written explanation of the reasons for the termination/halt.

The end of clinical study declaration will be submitted to the regulatory authorities and IEC/IRB after the complete clinical study has ended in all participating centers, in all countries. This notification will also be submitted within 90 days of the end of the clinical study in a given country/member state or within the timelines required by the local regulations.

Reasons for the closure of an investigational site may include, but are not limited to:

- Successful completion of the clinical study at the center.
- The overall required number of subjects for the clinical study has been recruited.
- Failure of the investigator to comply with the CSP, ICH-GCP guidelines or local requirements.
- Inadequate recruitment of subjects by the investigator.

Reasons for early termination of a clinical study by the sponsor may include, but are not limited to:

- Safety concerns.
- Sufficient data suggesting lack of efficacy.

9.1.3. Indemnification

Under the conditions of a contract concluded between investigator, site and sponsor or designee, which shall prevail, the sponsor shall, except in case of gross negligence or willful misconduct, indemnify and hold harmless the investigator and his/her medical staff from any claim arising from the clinical study activities carried out in compliance with the CSP, sponsor's instructions and applicable local regulations.

The investigator must notify the sponsor immediately upon notice of any claims or lawsuits.

9.1.4. Insurance

The sponsor shall maintain insurance coverage that is sufficient to cover its obligations and that is consistent with human clinical study local regulations. Provided that the subject has been treated according to the CSP and sponsor's instructions, any injury caused to a subject which is the direct result of his/her participation to the clinical study shall be covered by the sponsor's insurance, except in case of gross negligence or willful misconduct by the investigator.

9.2. Investigator's Responsibilities

9.2.1. Source Data and Data Capture

The nature and location of all source documents need to be identified and documented to ensure that all sources of original data required to complete the eCRF are known and are accessible for verification by the monitor.

Source data may be directly captured from devices transferred from third partners (e.g. laboratory data) or entered manually into the eCRF. The eCRF completion guidelines will be provided to each investigational site.

It is recommended that the author of an entry in the source documents should be identifiable. Following ICH-GCP guidelines, direct access to sponsor's representatives to source documents must be granted for the purpose of verifying that the data recorded on the eCRF are consistent with the original source data.

9.2.2. Archiving

Unless other European Union Law require archiving for a longer period, the investigator shall archive the content of the clinical Investigator Site file (ISF) for at least 25 years after the end of the clinical study. However, the medical files of subjects shall be archived in accordance with national law.

The investigator should take measures to prevent accidental or premature destruction of these documents.

Under no circumstance shall the investigator relocate or dispose any clinical study documents before having obtained a written approval of the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this clinical study, the investigator must permit access to such reports. The subject is granting access to his/her source data by signing the ICF.

Any difficulty in storing original documents must be discussed with the monitor prior to the initiation of the clinical study.

9.2.3. Participation Cards

If the subjects are not under 24-hour supervision of the investigator or site staff, they must be provided with a subject participation card indicating the name of the IP, the clinical study number, the investigator's name, and a 24-hour emergency contact number. The subject should be advised to keep the participation card in his/her wallet at all times.

9.2.4. Reporting

Where required by IEC/IRB per local requirements, at least once a year the investigator will provide the IEC/IRB with a progress report to allow review of the clinical study (see

Section 9.4.1). At the end of the clinical study, the results of the clinical study will be reported in a clinical study report by the sponsor. A summary or full report, depending on the requirements, will be provided by the sponsor to the investigators, to the applicable regulatory authorities, and IECs/IRBs (if required by the applicable regulatory requirements) within one year, or 6 months for pediatric studies, after the end of the clinical study.

9.2.5. Publication

It is understood by the investigator that the sponsor shall be free to use the compound-related information, which is generated during the clinical study and may disclose it to other clinical investigators and to regulatory agencies. As a consequence, the investigator agrees to provide all clinical study results and data generated during this clinical study to the sponsor.

The investigator shall not be authorized to submit the results of this clinical study and any data for public disclosure (e.g. publication or presentation) without the prior written approval of the sponsor, which shall not be unreasonably withheld.

However, it is understood and agreed by the investigators that their results and/or findings shall not be authorized for publication prior to sponsor's publication of the overall clinical study results. The investigator agrees that prior to the publication of any results, he/she shall provide the sponsor with a draft copy of the intended publication. The sponsor shall have the right to review it and to make any comments. In accordance with generally accepted scientific collaboration principles, co-authorship with any staff member sponsor involved in the clinical study, will be discussed and mutually agreed upon before submission of any manuscript to a publisher.

9.3. Confidentiality

The subject will receive all information as required by the EU General Data Protection Regulation, namely the identity and contact details of the controller, the contact details of the data protection officer, the clinical research purposes, the legal basis for the processing, the recipients of the personal data, the transfer of the personal data to third countries and respective safeguards, the retention periods, the fair processing of his/her data, and all his/her data subject's rights. All details are listed in the ICF.

All information concerning the product and the sponsor's operations (such as patent applications, formulae, manufacturing processes, basic scientific data, or formulation information supplied to the investigator by the sponsor and not previously published) is considered confidential and should not be disclosed by the investigator to any third party without the sponsor's prior written approval. The investigator agrees to use this information only in accomplishing the clinical study and will not use it for other purposes.

In order to permit easy identification of the individual subject during and after the clinical study, the investigator is responsible for keeping an updated Subject Identification Code List. The monitor will review this document for completeness. However, the investigator must guarantee the subject's anonymity will be maintained. Therefore, in order to ensure subject confidentiality, the Subject Identification Code List must remain at the center and no copy will be made.

9.4. Ethical Considerations

9.4.1. Independent Ethics Committee / Institutional Review Board

This clinical study can only be undertaken after full approval of the CSP, ICF, any other written information given to subjects and subject recruitment materials has been obtained from the IEC/IRB. This approval document must be dated and clearly identify the clinical study and the related clinical study documents being approved, including the subject compensation programs, if applicable.

During the course of the clinical study, at least the following documents will be submitted to the IEC/IRB, per local requirements:

- Changes to the IB
- Reports of AEs that are serious, unlisted, and associated with the IP (in compliance with IEC/IRB, per local requirements)
- CSP amendments
- ICF amendments

CSP amendments and applicable ICF amendments must promptly be submitted to the IEC/IRB for review and approval prior to implementation of the change(s), except when necessary to eliminate an immediate hazard to the clinical study subjects, or according to local requirements.

The IEC/IRB is responsible for continuous review of the clinical study. Where required by IEC/IRB, per local requirements, at least once a year the investigator will provide the IEC/IRB with a progress report to allow review of the clinical study. Additional progress reports should be provided according to local legal requirements. These requests and (re-)approvals, if applicable, should be documented in writing.

9.4.2. Informed Consent

The investigator or designated personnel must explain the clinical study and the implications of participation (e.g. objectives, methods, anticipated benefits, possible risks) to potential subjects according to applicable regulations prior to any clinical study-related activity. Subjects will be informed that their participation is voluntary and that they may withdraw from the clinical study at any time. They will be informed that choosing not to participate or to withdraw from the clinical study will not have an impact on the care the subject will receive for the treatment of his/her disease.

The subject will be given sufficient time to read the ICF and to ask additional questions. After this explanation and before entry in the clinical study, the subject’s consent should be appropriately recorded by means of the subject's personally dated signature and by the investigator’s dated signature. In case the subject is unable to read and write, an impartial witness must certify the subject’s consent in writing on the ICF. After having obtained the consent, a copy of the signed and dated ICF must be given to the subject.

If new information becomes available relevant to the subject's willingness to participate in the clinical study, the subject will be informed in a timely manner by means of an amended ICF. This amended ICF will be signed and dated by the subject (or, if applicable, by an independent witness) and the investigator to document the willingness of the subject to continue with the clinical study.

This signed and dated amended version will be filed together with the initial signed and dated ICF.

Subjects who agree to participate in the optional genetic research assessment will sign a genetic ICF for this assessment (see Section 5.8.1). Additionally, subjects who agree on collection or long term storage of their samples for future scientific and genetic research will sign a separate ICF (see Section 5.8.2 and 5.10). The subject will be given sufficient time to read the genetic ICF and to ask additional questions. This consent should be appropriately recorded by means of the subject's personally dated signature and by the investigator's signature. After having obtained the consent, a copy of the signed and dated informed consent must be given to the subject.
Subjects are not required to consent for the genetic research assessment in order to participate to the main clinical study. Subjects will also be informed that their participation for the optional genetic research is voluntary and that they may withdraw their consent at any time. If a subject chooses to withdraw consent for the genetic assessment then the investigator or designated personnel must inform the sponsor.
Withdrawal from the main clinical study does not, by itself, constitute withdrawal of samples from the optional genetic research that were already taken before that time point. Likewise withdrawal from the optional genetic research does not constitute withdrawal from the main clinical study.

9.5. Data Quality Control/Assurance

9.5.1. Monitoring

This clinical study will be monitored by sponsor representatives according to their current Standard Operating Procedures for the monitoring of clinical studies as described in the monitoring plan.

To guarantee adequate protection of the subjects and to guarantee the quality of the data, the sponsor will ensure oversight of any clinical study-related duties and functions carried out on its behalf, including clinical study-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s).

9.5.2. Audit and Inspection

To ensure compliance with relevant regulations, an independent quality assurance representative, regulatory authorities and/or IECs/IRBs may review this clinical study. This implies that auditors/inspectors will have the right to inspect the clinical study center(s) at any time during and/or after completion of the clinical study and will have access to the data generated during the

clinical study, source documents, and subject's files. By participating in this clinical study, investigators agree to this requirement.

10. REFERENCES

Bae, K., Zhu, F., Chapman, A., Torres, V., Grantham, J., Guay-Woodford, L., . . . Miller, J. (2006). Magnetic Resonance Imaging Evaluation of Hepatic Cysts in Early Autosomal-Dominant Polycystic Kidney Disease: The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease Cohort. *Clin J Am Soc Nephrol*, 64-9.

Caroli, A., Perico, N., Perna, A., Antiga, L., Brambilla, P., Pisani, A., . . . Ruggenenti, P. (2013). Effect of longacting somatostatin analogue on kidney and cyst growth in autosomal dominant polycystic kidney disease (ALADIN): a randomised, placebo-controlled, multicentre trial. *Lancet*, 1485-95.

Chapman, A., Bost, J., & Torres, V. (2012). Kidney Volume and Functional Outcomes in Autosomal Dominant Polycystic Kidney Disease. *Clinical Journal of the American Society of Nephrology*, 479–486.

Chebib, F., Perrone, R., Chapman, A., Dahl, N., Harris, P., Mrug, M., . . . Torres, V. (2018). A Practical Guide for Treatment of Rapidly Progressive ADPKD with Tolvaptan. . *Journal of the American Society of Nephrology*, 2458-2470.

FDA. (2019). *https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table5-1.*

Fiorotto, R., & Strazzabosco, M. (2019). Pathophysiology of Cystic Fibrosis Liver Disease: A Channelopathy Leading to Alterations in Innate Immunity and in Microbiota. *Cell Mol Gastroenterol Hepatol*, 197-207.

Jouret, F., & Devuyst, O. (2020). Targeting chloride transport in autosomal dominant polycystic kidney disease. *Cellular Signalling*, 109703.

KDIGO_CKD_Work_Group. (2013). KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*, 1-150.

Orphanet. (2019). *https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=730*.

Ravine, D., Gibson, R., Walker, R., Sheffield, L., Kincaid-Smith, P., & Danks, D. (1994). Evaluation of ultrasonographic diagnostic criteria for autosomal dominant polycystic kidney disease 1. *Lancet*, 824-7.

Smith, K., Thompson, A., Baron, D., Broadbent, S., Lundstrom, G., & Perrone, R. (2018). Addressing the Need for Clinical Trial End Points in Autosomal Dominant Polycystic Kidney Disease: A Report From the Polycystic Kidney Disease Outcomes Consortium (PKDOC). *AJKD*, 533-41.

Torra, R. (2019). Recent advances in the clinical management of autosomal dominant polycystic kidney disease. *F1000Research; https://doi.org/10.12688/f1000research.17109.1*, 116.

Torres, V., Chapman, A., Devuyst, O., Gansevoort, R., Grantham, J., Higashihara, E., . . . TEMPO. (2012). Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J*, 2407-18.

Torres, V., Chapman, A., Devuyst, O., Gansevoort, R., Perrone, R., Koch, G., . . . REPRISE. (2017). Tolvaptan in Later-Stage Autosomal Dominant Polycystic Kidney Disease. *N Engl J Med*, 1930-42.

van Aerts, R., Kievit, W., D'Agnolo, H., Blijdorp, C., Casteleijn, N., Dekker, S., . . . Salih, M. (2019). Lanreotide Reduces Liver Growth In Patients With Autosomal Dominant Polycystic Liver and Kidney Disease. *Gastroenterology*, 481-491.

Wallace, D. (2011). *Cyclic AMP-mediated cyst expansion.* Biochim Biophys Acta.

Willey, C., Blais, J., Hall, A., Krasa, H., Makin, A., & Czerwiec, F. (2017). Prevalence of autosomal dominant polycystic kidney disease in the European Unio. *Nephrol Dial Transplant*, 1356-63.

Xu, N., Glockner, J., Rossetti, S., Babovich-Vuksanovic, D., Harris, P., & Torres, V. (2006). Autosomal dominant polycystic kidney disease coexisting with cystic fibrosis. *J Nephrol*, 529-34.

Yang, B., Sonawane, N., Zhao, D., Somlo, S., & Verkman, A. (2008). Small-molecule CFTR inhibitors slow cyst growth in polycystic kidney disease. *J Am Soc Nephrol*, 1300-1310.

11. APPENDICES

Appendix 1 Ranges for Vital Signs and ECG

Ranges for Vital Signs

Ranges applicable in supine position (after 5 minutes):

Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Heart rate (bpm)	Temperature (°C)
90≤ SBP ≤150	45≤ DBP ≤90	50≤ HR ≤100	35.5≤ t° ≤37.5

bpm = beats per minute; DPB = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure

Ranges for ECG Parameters

Ranges applicable in supine position (after 5 minutes):

PR (ms)	QRS (ms)	QTcF (ms)	Heart rate (bpm)
110≤ PR ≤220	QRS ≤120	QTcF ≤450	50≤ HR ≤100

bpm = beats per minute; HR = heart rate

Appendix 2 List of Moderate and Strong Inhibitor(s) of Cytochrome P450 (CYP)3A4

Non-exhaustive lists based on (FDA, 2019)

Strong CYP3A4 Inhibitors	Moderate CYP3A4 Inhibitors
Clarithromycin	Aprepritant
Cobicistat	Ciprofloxacin
Itraconazole	Crizotinib
Ketoconazole	Dronedarone
Nefazodone	Erythromycin
Ritonavir	Fluconazole
Posaconazole	Imatinib
Telithromycin	Tofisopam
Voriconazole	Verapamil
Grapefruit juice	

Appendix 3 List of Moderate and Strong Inducer(s) of Cytochrome P450 (CYP)3A4

Non-exhaustive lists based on (FDA, 2019)

Strong CYP3A4 Inducers	Moderate CYP3A4 Inducers
Carbamazepine	Bosentan
Enzalutamide	Efavirenz
Fosphenytoine	Etravirine
Lumacaftor	Modafinil
Mitotane	
Phenobarbital	
Phenytoin	
Primidone	
Rifabutin	
Rifampin	
Rifapentine	

Appendix 4 Mitigation Plan as a Consequence of SARS-CoV-2 Pandemic

In case of travel restrictions as a consequence of SARS-CoV-2 pandemic the following should be considered:

- Case-by-case evaluation between the investigator and the sponsor study physician. This may include the following:
  - The ability to guarantee the safety of the subjects and the integrity of the study based on assessment of local restrictions with respect to traveling and access to local routine healthcare
  - An assessment of the availability of resources at the investigational site
  - An assessment of the feasibility of possible alternatives to collect safety data, including telephone calls for monitoring AEs and use of local resources such as local laboratories, local measuring of vital signs, and local ECGs
  - Assessment of the individual risk of subjects based on subject characteristics and safety data collected thus far.

- Vaccination, including all COVID-19 vaccinations, is allowed prior to and during the study, according to the investigator's clinical judgment. Vaccine information should be recorded in the eCRF as prior medication if administered prior to the first dose of study drug and as concomitant medication if administered during study conduct, including administration date(s), brand name, and manufacturer.

- From Visit 10 (Week 26) onwards a visit window of >4 days could be allowed, with a maximum of 20 days of the total window.

- To ensure study subjects maintain dosing per protocol requirements during this study special delivery services through Direct to Patient (DTP) shipments of IP from the investigational site to the subject can be implemented. DTP should only be used in case of emergency where on-site IP dispensation is not possible, and if allowed per local regulations. Local guidelines must be followed and regulatory approval or notification of authorities may be required. Agreement of the subject to receive IP at home is required prior to the shipment of IP from the investigational site to the subject's home and should be documented by the investigational site staff in the medical records of the subject. The DTP process used will be reviewed and approved by the sponsor, but the DTP shipments will be coordinated by the investigational site(s) in collaboration with the local CRO without the involvement of the sponsor to ensure clinical study integrity.

- In case a randomized subject is not able to attend a scheduled study visit on site because of SARS-CoV-2 travel restrictions, a phone call or a televisit may be conducted. It is strongly recommended to conduct planned study assessments for the applicable visit as per protocol as much as possible. If possible and if local regulations allow and the subject agrees, trained study staff or trained personnel are encouraged to collect study assessments at the study subjects' home or a local facility if social distancing and hygiene rules can be applied. Only staff trained in conducting the protocol planned assessments are authorized to perform home or local facility visit assessments and the alternative arrangements need to be adequately

documented.In case there are problems with the shipment of central safety laboratory assessments the investigator is allowed to perform local safety laboratory assessments at the investigational site.

SIGNATURE PAGE – SPONSOR

Study Title:	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

CSP Version:	6.00	Date:	20-Dec-2021

This clinical study protocol has been reviewed and approved by the sponsor to ensure compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practices (GCP) and applicable regulatory requirements

An e-signature is provided at the end of this document

Study Physician	Signature	Date

SIGNATURE PAGE – INVESTIGATOR

Study Title:	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

CSP Version: 6.00 Date: 20-Dec-2021

I, the undersigned, have read this clinical study protocol and will conduct the study as described in compliance with the clinical study protocol, in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practices (GCP) and applicable regulatory requirements.

Investigator Name	Signature	Date

Signature Page for glpg2737-cl-203-protocol 11559

Approval	[redacted] 20-Dec-2021 18:07:29 GMT+0000

Signature Page for glpg2737-cl-203-protocol43952_11562_62729