Galápagos

CLINICAL STUDY PROTOCOL

Project Number: GLPG2222

Study Number: GLPG2222-CL-202

Study Title: A Phase IIa, randomized, double-blind, placebo-controlled study to evaluate multiple doses of GLPG2222 in subjects with Cystic Fibrosis who are homozygous for the F508del mutation.

Development Phase: IIa

Status: Final

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Sponsor: Galapagos NV
Industriepark Mechelen Noord
Generaal De Wittelaan L11 A3
2800 Mechelen, Belgium

Medical Lead: [redacted] MD MBA
Tel: [redacted]
Mobile: [redacted]

Clinical Study Lead: [redacted] MSc
Tel: [redacted]
Mobile: [redacted]

CLINICAL STUDY PROTOCOL HISTORY

CSP / Amendment #	Date	Generic / Country / Site Specific
Clinical Study Protocol v1.0: initial version (not submitted)	5-Dec-2016	Generic
Clinical Study Protocol v2.0: update to fix technical template issue (not submitted)	5-Dec-2016	Generic
Clinical Study Protocol v3.0: update to specify storage conditions of study drugs	6-Dec-2016	Generic

EMERGENCY CONTACT INFORMATION

In case of a **Serious Adverse Event (SAE)**, the investigator must fax or e-mail the Galapagos Clinical Study SAE Form within 24 hours to the [redacted] Medical Affairs Department:

[redacted] Medical Affairs SAE Fax #: [redacted]

or

e-mail: [redacted]

In case of **medical questions during the course of the study,** the investigator must contact:

- **Global and Europe:**
  [redacted], MD
  [redacted]

- **Northern America:**
  [redacted] MD
  [redacted]

- **AsiaPac:**
  [redacted] MD
  [redacted]

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

[redacted]	[redacted]
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATS/ERS	American Thoracic Society/European Respiratory Society
AUC	area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	area under the plasma concentration-time curve from time zero till 24 hours post-dose
$AUC_{(t)}$	area under the plasma concentration-time curve over the dosing interval
BCRP	breast cancer resistance protein
C_{24h}	plasma concentration observed at 24 hours post-dose
[redacted]	[redacted]
cAMP	cyclic adenosine monophosphate
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	cystic fibrosis transmembrane conductance regulator
C_{max}	maximum observed plasma concentration
CRO	Contract Research Organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	plasma concentration observed at pre-dose
CYP	cytochrome P450
DBP	diastolic blood pressure
DSMB	Data Safety Monitoring Board
EC_{50}	effective concentration providing 50% of the maximal response
ECG	electrocardiogram
eCRF	electronic Case Report Form
ED	early discontinuation
EDC	electronic Data Capture
$FEF_{25\text{-}75}$	forced expiratory flow between 25% and 75% of exhaled volume
FEV_1	forced expiratory volume in one second

[redacted]	[redacted]
FSH	follicle stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HBsAg	hepatitis B virus surface antigen
HCV	hepatitis C virus
HDPE	high-density polyethylene
hERG	human ether-a-go-go-related gene
HIV	human immunodeficiency virus
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
[redacted]	[redacted]
[redacted]	[redacted]
IRB	Institutional Review Board
IWRS	interactive web response system
LSS MA	Life Science Services Medical Affairs
NOAEL	no observed adverse effect level
OAT	organic anion transporter
OATP	organic anion-transporting polypeptide
PK	pharmacokinetic(s)
q.d.	once daily
QTc	corrected QT
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SBP	systolic blood pressure
SEM	standard error of the mean
$t_{1/2}$	terminal elimination half-life
t_{max}	time to occurrence of C_{max}
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal

WBC	white blood cell

Definition of Terms

QTcF	Fridericia's cube-root corrected QT interval: QT (ms) x $\sqrt[3]{\frac{1000}{RR(ms)}}$

STUDY SPECIFIC PROCEDURES

1. STUDY FLOW CHART

The schedule of assessments is given in the flow chart below.

EVENT	SCREENING	TREATMENT PERIOD[1]				FOLLOW-UP
Study days (D)	**D-28 till D-1**	**D1**	**D15 (±2D)**	**D29 (±2D)**	**ED**	**D43 (±3D)**
Informed consent[2]	X					
Inclusion/exclusion criteria	X	X				
CFQ-R[3]	X	X	X	X	X	X
Demographics	X					
Medical history	X					
Physical examination[4]	X	X	X	X	X	X
Weight	X	X	X	X	X	X
Vital signs[5]	X	X	X	X	X	X
Pulse oximetry[6]	X	X	X	X	X	X
12-lead ECG[7]	X	X	X	X	X	X
Sweat collection	X	X	X	X	X	X
Spirometry[8]	X	X	X	X	X	X

[1] All assessments are to be performed pre-dose. In addition, some assessments are also to be performed at defined time points post-dose when specifically mentioned.
[2] Written informed consent to be obtained before any study-related procedures and/or assessments are performed.
[3] CFQ-R to be completed prior to any other assessments scheduled for that visit.
[4] Full physical examination at screening (including height); limited physical examination (ear, nose, throat, chest and neck) at subsequent visits.
[5] Vital signs include heart rate, blood pressure (systolic and diastolic), respiratory rate and oral body temperature. Heart rate and blood pressure to be captured after 5 minutes in supine position. Vital signs must be recorded pre-dose at all visits, and additionally between 3 and 4 hours post-dose on Day 1.
[6] Pulse oximetry to determine oxygen saturation is to be captured after at least 5 minutes of rest in seated or supine position.
[7] 12-lead ECG to be measured after at least 5 minutes of rest in supine position.
[8] Spirometry must be performed pre-dose at all visits, and additionally between 1 and 2 hours post-dose on Day 1 and Day 29.

CFQ-R = Cystic Fibrosis Questionnaire - Revised; ECG = electrocardiogram; ED = early discontinuation

EVENT	SCREENING	TREATMENT PERIOD[1]				FOLLOW-UP
Study days (D)	**D-28 till D-1**	**D1**	**D15 (±2D)**	**D29 (±2D)**	**ED**	**D43 (±3D)**
Clinical safety laboratory tests[9]	X	X	X	X	X	X
Serology[10]	X					
Pregnancy test[11]	X	X		X	X	X
FSH test[12]	X					
CFTR genotyping		X				
PK blood samples[13]			X	X	X	
Exploratory biomarkers[14]		X	X	X		
Randomization		X				
Breakfast or snack to be provided[15]		X	X	X		
Study drug dosing		→	→	→		
Study drug dispensing		X	X			
Dispense subject diary	X	X	X	X		
Collect subject diary		X	X	X	X	X
AE assessment	→	→	→	→	→	
Concomitant medications	→	→	→	→	→	
Optional substudy[16]						
Nasal brushing		X	X	X		

[9] Blood and urine samples to be collected for clinical safety laboratory tests.
[10] Serology sample for hepatitis B virus surface antigen, hepatitis C virus antibody and human immunodeficiency type 1 and 2 antibodies.
[11] For female subjects of childbearing potential only; serum pregnancy test at screening, urine pregnancy test at other scheduled visits.
[12] For suspected post-menopausal female subjects only (age < 55 years and no menses for ≥ 12 months without a medical cause).
[13] PK blood samples for GLPG2222 to be taken pre-dose and 0.5, 1, 2, 3, 4, 6 and 8 hours post-dose on Day 15 (or on Day 29 if subject is not available for full PK profiling on Day 15), and pre-dose on Day 29. In case of an early discontinuation visit, one additional sample to be taken pre-dose if study drug is still taken, or at any time during the visit if study drug is no longer taken.
[14] Exploratory biomarkers include [redacted].
[15] Study drug to be taken once daily in the morning with a breakfast or snack.
[16] Only for subjects who give separate consent to participate in the optional substudy.

AE = adverse event; CFTR = cystic fibrosis transmembrane conductance regulator; FSH = follicle stimulating hormone, PK = pharmacokinetic(s)

2. INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive genetic disease caused by mutations in the gene encoding for the cystic fibrosis transmembrane conductance regulator (CFTR) protein, a cAMP-regulated anion channel expressed primarily at the apical plasma membrane of secretory epithelia. Over 2,000 mutations in the CFTR gene (*CFTR*) have been identified, which are grouped into 6 classes (class I-VI). The F508del mutation is by far the most common CFTR mutation globally, especially in the Caucasian population. Approximately 80 to 90% of CF patients in the United States and Europe have at least one copy of this mutation on one allele, with almost half of them being F508del homozygous (i.e. the mutation is present on both alleles). The F508del mutation impairs CFTR folding, stability at the endoplasmic reticulum and plasma membrane, and chloride gating. Thus, the F508del mutation results in very little to no CFTR protein in the apical membrane. CFTR dysfunction results in viscid secretions that are difficult to clear, affecting most exocrine glands, notably the pancreas, intestine, liver, and bile duct. However, most morbidity and mortality results from dehydration of the airway surface liquid and impaired airway mucociliary clearance, which leads to cycles of bacterial infection, chronic inflammation, bronchiectasis and progressive decline in pulmonary function. There is a high medical need for efficacious therapeutic approaches to treat CF subjects with the F508del mutation.

CFTR modulators are compounds designed to repair the consequences of CFTR mutations on protein expression and/or function. Overall, 2 types of small-molecule CFTR modulators are being developed: corrector molecules that are designed to restore proper protein folding and allowing for increased surface expression, and potentiator molecules targeted at improving chloride-channel gating function. In order to bring optimal clinical benefit to the F508del CF population, a combination of a potentiator and corrector(s) is needed. GLPG2222 is a CFTR corrector in development for the oral treatment of CF and represents the second component of a future potentiator/corrector(s) combination therapy targeting the F508del CF population.

2.1. PHYSICAL, CHEMICAL AND PHARMACEUTICAL PROPERTIES AND FORMULATIONS

The chemical name of GLPG2222 is 4-[(2*R*,4*R*)-4-[[[1-(2,2-difluoro-1,3-benzodioxol-5-yl)cyclopropyl]carbonyl]amino]-7-(difluoromethoxy)-3,4-dihydro-2*H*-chromen-2-yl]benzoic acid.

Two formulations are currently available for oral use: an oral suspension and a tablet.

2.2. NONCLINICAL PHARMACOLOGY

2.2.1. Primary and Secondary Pharmacology

GLPG2222 is a CFTR corrector that exhibits potent *in vitro* activity in primary patient cells harboring F508del/F508del CFTR with an effective concentration providing 50% of the maximal response [redacted] Activity of corrected F508del CFTR channel is measured in the presence of a potentiator such as GLPG1837 or GLPG2451, which is needed to obtain maximal channel opening.

On its own, GLPG2222 exhibits a modest but significant dose-dependent increase of functional F508del CFTR channel activity at the plasma membrane of primary bronchial epithelial cells (. GLPG2222 could also exhibit some clinical activity when evaluated alone in F508del homozygous patients [1].

2.2.2. Safety Pharmacology

In vitro effects on the cardiovascular system were assessed by measuring human ether-a-go-go-related gene (hERG)-related potassium currents. The concentration of about 1,000-fold the free maximum observed plasma concentration (C_{max}) extrapolated for a dose of 450 mg once daily (q.d.) in healthy subjects.

In an *in vivo* cardiovascular safety study, GLPG2222, administered orally to male and female telemetered conscious dogs at doses up to 300 mg/kg, had no significant effect on core body temperature, arterial blood pressure, PR, QRS, QT and corrected QT (QTc) intervals. There was no substantial effect on heart rate (HR), apart from a slight increase occasionally seen in some animals at 300 mg/kg. Exposure at the highest dose corresponded to a total C_{max} of in females and in males, i.e. respectively 14- and 2.6-fold the C_{max} of extrapolated for 450 mg q.d. in healthy subjects.

In the Irwin test to assess potential effects on central nervous system activity, GLPG2222 was administered orally to male rats at doses of 30, 100, and 300 mg/kg. A weak myorelaxant effect was seen at 30 and 100 mg/kg, but not at 300 mg/kg.

In a study to assess effects on the respiratory system, no effects were seen when GLPG2222 was administered orally to male rats at doses of 30, 100, and 300 mg/kg.

Based on the 4-week rat study, the C_{max} at 300 mg/kg) is expected to be approximately 6.0-fold the C_{max} of extrapolated for 450 mg q.d. in healthy subjects.

2.3. NONCLINICAL PHARMACOKINETICS AND PRODUCT METABOLISM

Absolute bioavailability of GLPG2222 was low in dog and monkey ( ), and high in rat . Plasma protein binding was high and similar between humans and animals.

The apparent terminal elimination half-life ($t_{1/2}$) ranged from in animals.

GLPG2222 exposure was similar in male and female animals. No accumulation of GLPG2222 was reported following q.d. dosing for 4 weeks in rats and dogs.

GLPG2222 was rapidly and evenly distributed throughout the body in the rat. The highest concentrations were observed in the lung and liver.

In the rat, excretion was complete at 72 hours post-dose.

The extent of GLPG2222 metabolism was low to moderate in human and animal hepatocytes. [redacted]

[redacted]

2.4. TOXICOLOGY

2.4.1. General Toxicology

Toxicology studies were performed in rats and dogs for a treatment duration up to 4 weeks, followed by a 2-week treatment-free recovery period.

In rats, GLPG2222 was given as amorphous solid dispersion at doses of 30, 100, and 300 mg/kg/day for 4 weeks. [redacted]

Based on the adverse effects seen on body weight in both sexes and testis histopathology in males at 300 mg/kg/day, the no observed adverse effect level (NOAEL) in rats was set at 100 mg/kg/day for both sexes, [redacted], which is 7.0- and 7.8-fold above the total area under the plasma concentration-time curve (AUC) [redacted]) extrapolated for 450 mg q.d. in healthy subjects.

In dogs, GLPG2222 was administered orally as nanosuspension at doses of 30, 100, and 300 mg/kg/day for 4 weeks. [redacted].

Based on the absence of adverse changes up to the highest dose, the NOAEL for GLPG2222 was established at 300 mg/kg/day, with an exposure of [redacted] in males and females, respectively, which is 1.3- and 2.1-fold above the total AUC ([redacted]) extrapolated for 450 mg q.d. in healthy subjects.

2.4.2. Genotoxicity

GLPG2222 showed no genotoxic effects *in vitro* in the Ames test, in the mouse lymphoma assay and in the *in vivo* micronucleus test included in the 4-week rat study at doses up to 300 mg/kg.

2.5. CLINICAL INVESTIGATION

2.5.1. GLPG2222-CL-101

GLPG2222 or placebo has been administered during the single ascending dose and multiple ascending dose parts of the first-in-human study GLPG2222-CL-101 in healthy male subjects. Part 1 (single ascending dose) consisted of 2 cohorts of 8 subjects (total of 16 subjects) who sequentially received a single dose of [redacted] study drug in Cohort A, and a single dose of [redacted] study drug in Cohort B in a placebo-controlled, double-blind, alternating panel manner. Subjects received the study drug in a 3:1 randomized balanced fashion so that per dose level, 6 subjects received GLPG2222 and 2 subjects received placebo. Part 2 (multiple ascending dose) consisted of 3 consecutive cohorts of 8 subjects (total of 24 subjects). Subjects in Cohort C received oral doses of [redacted] GLPG2222 or placebo q.d. for 14 days, subjects in Cohort D received oral doses of [redacted] GLPG2222 or placebo q.d. for 14 days, and subjects in Cohort E received oral doses of [redacted] GLPG2222 or placebo q.d. for 14 days. Subjects received the study drug in a 3:1 randomized balanced fashion so that per dose level, 6 subjects received GLPG2222 and 2 subjects received placebo.

Pharmacokinetics

GLPG2222 given as oral suspension in fed state was rapidly absorbed with a median time to occurrence of C_{max} (t_{max}) range of [redacted] and was eliminated with a mean [redacted] After q.d. dosing for 14 days, steady-state exposure (both C_{max} and AUC for the dosing interval) increased in proportion to the dose within the [redacted] mg dose range and more than dose-proportionally within the [redacted] dose range.

Steady state in GLPG2222 plasma concentrations was reached after 2 dosing days with a minimal accumulation (1.5). Less than 0.1% of GLPG2222 was excreted in urine.

Urinary 6-β-OH-cortisol/cortisol ratio was not impacted by q.d. repeated dosing, suggesting that GLPG2222 is not a CYP3A4 inducer.

Safety

There were no deaths or serious adverse events (SAEs) reported during the study, all treatment-emergent adverse events (TEAEs) were mild in intensity. All but one TEAE were resolved at the end of the study. One TEAE was reported as not recovered at the end of the study (600 mg q.d., nasopharyngitis) and was considered not related to the study drug by the investigator. Headache was the most common TEAE. There was no evidence of a dose-response relationship for any TEAE.

No clinically significant findings in physical examinations, vital signs, clinical safety laboratory tests, forced expiratory volume in one second (FEV_1), electrocardiogram (ECG) morphology, or ECG time intervals were reported up to 600 mg dosing.

2.5.2. GLPG2222-CL-102

Study GLPG2222-CL-102, a Phase I, open-label, randomized, single-dose, 3-way crossover study, was conducted to compare the bioavailability of GLPG2222 given as a tablet formulation and as an oral suspension to adult male healthy subjects. Preliminary results indicated that the oral bioavailability (C_{max} and AUC) of GLPG2222 was comparable when administered in fed state as a tablet formulation or as a suspension formulation. The rate of elimination was not impacted by the formulation, while the rate of absorption was slower after administration of a tablet compared to a suspension, as shown by the shift in t_{max} [redacted]. No relevant impact of food was noted on the exposure of GLPG2222 given as tablet [redacted]), as well as on the absorption or elimination rates. No deaths, other SAEs or TEAEs leading to study drug discontinuation were reported during the study. In total, 2 TEAEs were observed, both categorized as mild. The investigator considered 1 TEAE (pain in extremity) as unlikely related to the study drug, and 1 TEAE (headache) as possibly related to the study drug. Both TEAEs were recovered at the end of the study.

2.5.3. GLPG2222-CL-104

Study GLPG2222-CL-104, a Phase I, open-label, single-center study, was conducted to evaluate the pharmacokinetics (PK) of 2 single oral doses of GLPG2222 [redacted]) in 6 adult male subjects with CF. Preliminary results indicated that GLPG2222 given as an oral solution in fed state was rapidly absorbed, with a median t_{max} of [redacted]. The dose effect on dose-normalized $AUC_{0\text{-}24h}$ and C_{max} was found to be statistically significant. However, overall, no marked deviation in dose-proportionality was observed on the PK of GLPG2222 in CF subjects, [redacted] No deaths, other SAEs or TEAEs leading to study drug discontinuation were reported during the study. In total, 3 TEAEs (in 3 subjects) were reported, 2 of which were categorized as mild (cough and productive cough) and 1 of which was categorized as moderate (headache). All 3 TEAEs were reported during the [redacted] GLPG2222 treatment period. At the time of study end, the TEAE of cough was resolving; the TEAEs productive cough and headache were resolved. The investigator considered the TEAE of cough as not related to the study drug, while the TEAEs of productive cough and headache were considered unlikely related to the study drug.

2.6. RATIONALE FOR CURRENT STUDY, STUDY DESIGN AND DOSE SELECTION

2.6.1. Rationale for the Study

GLPG2222 is a corrector that restores F508del CFTR expression to the plasma membrane of epithelial cells in a dose-dependent manner. It is one of the components of future CFTR modulator combination therapies, which are expected to bring meaningful clinical benefit. Monotherapy data from VX-809 and VX-661 clinical trials in F508del homozygous subjects have shown that a modest signal can be observed in sweat chloride concentration, a biomarker of CFTR function [2, 3, 4]. *In vitro* studies with human bronchial epithelial cells obtained from F508del homozygous donors demonstrate that GLPG2222 has higher potency compared to either VX-809 or VX-661 ([redacted] Further, GLPG2222 alone shows a small but significant activity, similar to the combination of VX-661 and VX-770, in primary bronchial

epithelial cells derived from CF subjects (If the *in vitro* effects translate to patients, the effect size may be large enough with GLPG2222 on its own to demonstrate increased biomarker activity (reduction in sweat chloride concentration and enhanced expression of F508del CFTR at the plasma membrane of epithelial cells isolated from nasal brushings [optional substudy]).

The main objective of this study is to evaluate the safety and tolerability of GLPG2222 in adult F508del homozygous subjects. Yet, in order to better understand and characterize the relationship between GLPG2222 exposure and CFTR activity, secondary and exploratory efficacy parameters will be evaluated as well. Exposure-response relationships will be explored by means of clinical (surrogate) endpoints (e.g. pulmonary function measured through spirometry and quality of life symptom scores) and biomarkers (e.g. sweat chloride concentration, and CFTR expression in nasal brushings [optional substudy]).

2.6.2. Rationale for the Study Design and Dose Selection

The randomized, double-blind study design was chosen as it is the most rigorous method to generate high quality scientific data. In addition, a placebo-controlled study contains internal evidence of assay sensitivity (i.e. when a difference is demonstrated, it is interpretable without reference to external findings), measures absolute safety and efficacy (i.e. it measures the total pharmacologically-mediated effect of treatment), is very efficient (i.e. can measure treatment effects with a smaller sample size compared with any other type of controlled study), and minimizes the effect of subject and investigator expectations [5].

This study will include 4 different doses of GLPG2222 to explore any dose-dependent activity responses. These 4 doses have been selected based on modeling of the concentration needed for activity, based on *in vitro* potencies. [redacted] Two consecutive cohorts of 25 subjects each are planned to be enrolled: Cohort A will evaluate the 2 lower dose levels of GLPG2222, while Cohort B will evaluate the 2 higher dose levels of GLPG2222. In order to allow prematurely stopping the study if an unexpected safety signal emerges, Data Safety Monitoring Board (DSMB) meetings will be planned (see Section 8 for further details).

The outcome of this study will provide insights into the activity of GLPG2222 as a single drug and will aid in dose selection for use in combination with a CFTR potentiator and a second CFTR corrector molecule.

More detailed information on GLPG2222 can be found in the Investigator's Brochure [6].

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

- To evaluate the safety and tolerability of 4 different doses of GLPG2222 administered orally and q.d. for 29 days in adult subjects with CF who are homozygous for the F508del CFTR mutation.

3.2. SECONDARY OBJECTIVES

- To assess changes in biomarkers of CFTR activity.
- To assess changes in respiratory symptoms.
- To assess the PK of GLPG2222.

4. STUDY ENDPOINTS

4.1. PRIMARY ENDPOINT

- Safety and tolerability, assessed by the incidence of adverse events (AEs), as well as changes over time in weight, vital signs, oxygen saturation by pulse oximetry, 12-lead ECG, spirometry, and clinical safety laboratory data (hematology, chemistry, coagulation and urinalysis).

4.2. SECONDARY ENDPOINTS

- Change from baseline in sweat chloride concentration through 29 days.
- Change from baseline in percent predicted FEV_1 through 29 days.
- Change from baseline in the respiratory domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) through 29 days.
- PK parameters of GLPG2222.

5. INVESTIGATIONAL PLAN

5.1. OVERALL STUDY DESIGN

This is a Phase IIa, multi-center, randomized, double-blind, placebo-controlled, parallel-group study to evaluate 4 different doses of GLPG2222 administered orally and q.d. for 29 days to adult male and female subjects with a confirmed diagnosis of CF and homozygous for the F508del CFTR mutation. Eligible subjects must be on a stable concomitant medication regimen for at least 4 weeks prior to the first study drug administration and agree to continue the same regimen for the duration of the study.

A schedule of the study design is provided in Figure 3.

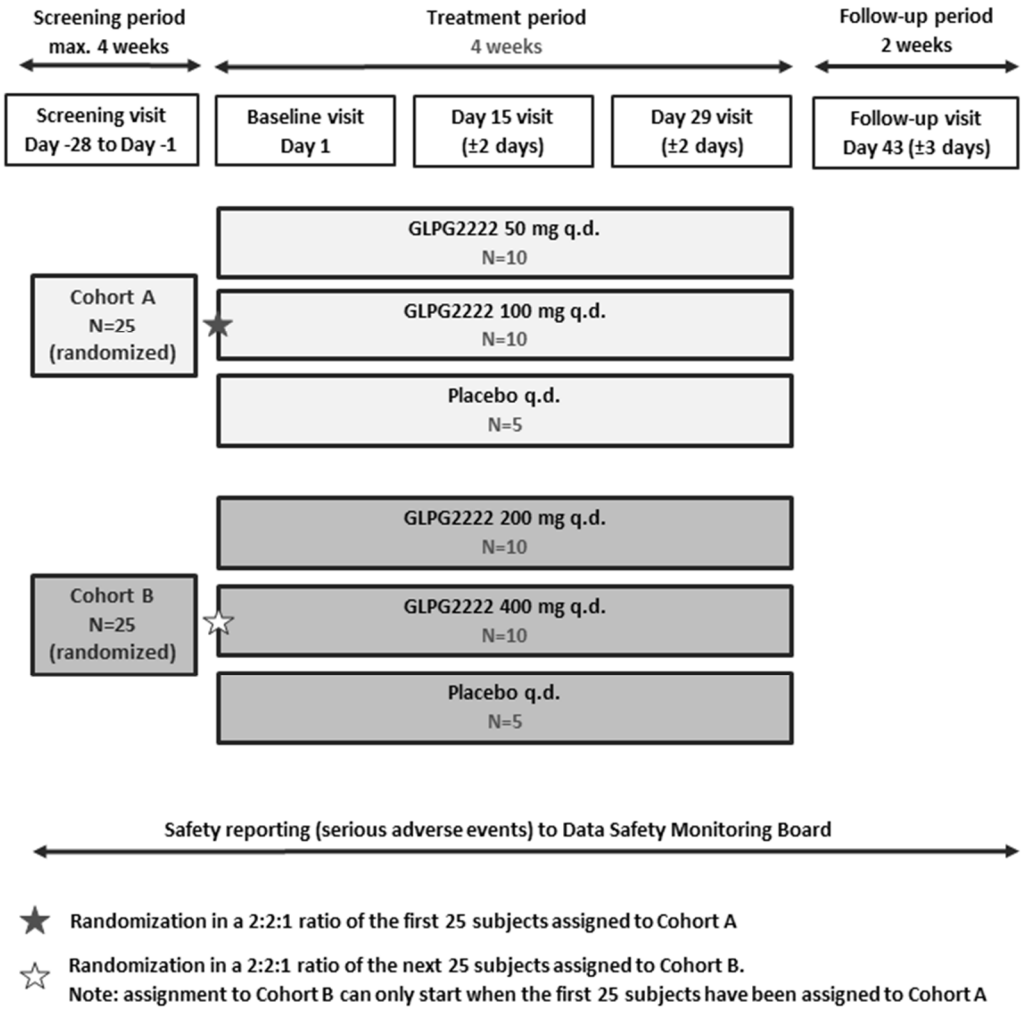

Figure 3: Study design

The study will consist of a screening period of maximum 4 weeks (starting when the subject has signed the informed consent form [ICF]), a treatment period of 4 weeks, and a follow-up period of 2 weeks. Enrolled subjects will come to the clinical study center at screening, on Day 1 (baseline), Day 15, Day 29, and at the follow-up visit (2 weeks after the last study drug administration).

Approximately 50 evaluable subjects are planned to be included sequentially in the study: the first 25 subjects will be assigned to Cohort A (i.e. subjects 1 to 25) and the next 25 subjects will be assigned to Cohort B (i.e. subjects 26 to 50). Subjects participating in Cohort A are not allowed to participate in Cohort B. In each study cohort, subjects will be randomized in a 2:2:1 ratio to receive:

- Cohort A: 50 mg GLPG2222, 100 mg GLPG2222 or placebo q.d. for 29 days.
- Cohort B: 200 mg GLPG2222, 400 mg GLPG2222 or placebo q.d. for 29 days.

Assessments for efficacy and safety will be performed during the study at the time points specified in the flow chart in Section 1.

Additionally, subjects can choose to participate in the optional substudy, in which nasal brushings will be collected (Section 6.7).

Subjects will be in the study for a duration of minimum 6 weeks and maximum 10 weeks (from screening until the follow-up visit, depending on the duration of the screening period).

The end of the study is defined as the last contact with the last subject.

5.2. STUDY POPULATION

5.2.1. Sample Size

Sufficient subjects will be screened in order to include approximately 50 evaluable CF subjects in the study (see Section 7.1).

5.2.2. Inclusion Criteria

Subjects who meet all of the following criteria are eligible for the study.

1. Male or female subject ≥ 18 years of age on the day of signing the ICF.
2. A confirmed clinical diagnosis of CF and homozygous for the F508del CFTR mutation (documented in the subject's medical record or CF registry).
3. Weight ≥ 40 kg during the screening period.
4. Stable concomitant medication regimen for at least 4 weeks prior to the first study drug administration and continuing the same regimen for the duration of the study.
5. FEV_1 ≥ 40% of predicted normal for age, gender and height at screening (pre- or post-bronchodilator). The spirometry test must meet the criteria for acceptability and repeatability as defined in the 2005 American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines on standardization of lung function testing. If screening spirometry measurements fail to meet these criteria in the first 3 efforts, up to 8 repeat spirometry efforts may be performed. If repeat values of the individual assessment(s) satisfy the eligibility criteria and are completed within the screening window, then the subject is eligible for the study (see Section 6.3.2).

6. Male and female subjects of childbearing potential must agree to use highly effective contraceptive measures as described in Section 5.2.6.2.
7. Understand and comply with protocol-specific requirements and instructions.
8. Able and willing to give voluntary written informed consent and willing to adhere to the prohibitions and restrictions (see Section 5.2.6). The ICF, as approved by the Independent Ethics Committee (IEC)/Institutional Review Board (IRB), must be signed before any study-related procedures and/or assessments are performed.

5.2.3. Exclusion Criteria

Subjects meeting one or more of the following criteria cannot be selected for this study.

1. History of serious allergic reaction to any drug as determined by the investigator (e.g. anaphylaxis requiring hospitalization) and/or known sensitivity to any component of the study drug.
2. Positive serology for human immunodeficiency virus infection (HIV-1 and/or HIV-2 antibodies), hepatitis B virus infection (hepatitis B virus surface antigen [HBsAg]) and/or hepatitis C virus (HCV) infection (HCV antibody) and/or any history of hepatitis from any cause, with the exception of hepatitis A.
3. History of immunosuppressive condition (e.g. HIV infection).
4. History of clinically meaningful unstable or uncontrolled chronic disease that makes the subject unsuitable for inclusion in the study in the opinion of the investigator.
5. Unstable pulmonary status or respiratory tract infection (including rhinosinusitis) requiring a change in therapy within 4 weeks prior to the first study drug administration.
6. Need for supplemental oxygen during the day, and > 2 L/minute while sleeping.
7. History of solid organ or hematopoietic cell transplantation.
8. History of hepatic cirrhosis with portal hypertension (e.g. signs/symptoms of splenomegaly, esophageal varices, etc.).
9. History of malignancy within the past 5 years (except for basal cell carcinoma of the skin with no evidence of recurrence or carcinoma in situ of the cervix that has been treated with no evidence of recurrence).
10. Clinically significant abnormality detected on ECG regarding rate, rhythm or conduction (e.g. QT interval corrected for heart rate using Fridericia's formula [QTcF] ≥ 450 ms for male subjects, QTcF ≥ 460 ms for female subjects).
11. Pregnant, breastfeeding or planning to become pregnant during the study or within 3 months after the last dose of study drug.
12. Clinically meaningful blood loss (including blood donation), or a transfusion of any blood product within 12 weeks prior to the first study drug administration.
13. [redacted]
14. Use of CFTR modulator therapy (e.g. lumacaftor or ivacaftor) within 4 weeks prior to the first study drug administration.
15. Concomitant use of [redacted] ithin 4 weeks prior the first study drug administration.
16. History of alcohol, medication or illicit drug abuse within one year prior to the first study drug administration.

17. Abnormal liver function test at screening; defined as aspartate aminotransferase (AST) and/or ALT and/or alkaline phosphatase and/or gamma-glutamyl transferase (GGT) ≥ 3 x the upper limit of normal (ULN); and/or total bilirubin ≥ 1.5 x the ULN.
18. Estimated creatinine clearance < 60 mL/minute using Cockcroft-Gault equation at screening.
19. Smoking or use of nicotine-containing products within 1 year prior to screening.
20. Concurrent participation in another interventional therapeutic clinical study, prior participation in an investigational drug study within 8 weeks or 5 terminal half-lives of the investigational drug (whichever is longer) prior to the first study drug administration, or prior participation in an investigational drug antibody study within 6 months prior to the first study drug administration.
21. Any condition or circumstance that, in the opinion of the investigator, makes the subject unable to comply with study procedures and requirements.
22. A history of being admitted to an institution under an administrative or court order, if applicable to national or local legislation.

5.2.4. Retesting During the Screening Period

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 can be retested once if there is clear evidence of a laboratory error (e.g. hemolyzed sample) or equipment malfunction, but only with the documented approval of the sponsor's medical lead.
- Exclusionary liver function test levels may be retested once within 14 days of the original screening date, but only with the documented approval of the sponsor's medical lead.
- Weight may be retested once within 14 days of the original screening date.

5.2.5. Rescreening

Subjects not meeting one or more inclusion or exclusion criteria will be screen failures and may only be rescreened with the documented approval of the sponsor's medical lead. If a subject is rescreened, all screening assessments will be repeated, and the screening window will begin once the first rescreening assessment has been initiated.

5.2.6. Prohibitions and Restrictions

5.2.6.1. Medication

5.2.6.1.1. Stable concomitant medication regimens

Concomitant medication regimens taken for the long-term treatment of pre-existing conditions are allowed if they are in accordance with the inclusion and exclusion criteria, and are stable for at least 4 weeks prior to the first study drug administration and continued without variation of dose or regimen during the study (see Section 5.3.8).

Subjects must remain on a stable medication regimen for pulmonary health (including dose and frequency) for at least 4 weeks prior to the first study drug administration and for the

entire study duration (i.e. until the follow-up visit). Further details are provided in Section 5.3.8.1.

Use of CFTR modulator therapy (e.g. lumacaftor or ivacaftor) is prohibited within 4 weeks prior to the first study drug administration and for the entire study duration.

[redacted]

5.2.6.2. Birth Control

Highly effective contraceptive measures for both male subjects and female subjects of childbearing potential must be documented in the source documents.

5.2.6.2.1. Female subjects of childbearing potential

For female subjects, one of the following criteria must be met for participation in the study:

- Postmenopausal, defined as:
  - Age ≥ 55 years with no menses for ≥ 12 months without a medical cause.
  - Age < 55 years with no menses for ≥ 12 months without a medical cause AND a follicle stimulating hormone (FSH) level > 40 IU/L.
- Permanently surgically sterile (bilateral oophorectomy [surgical removal of ovaries], bilateral salpingectomy or hysterectomy [surgical removal of uterus]).

If not one of the above 2 categories, a female subject is considered a woman of childbearing potential and must use one of the following highly effective methods of birth control starting on the day of signing the ICF, during the study, and for at least 3 months after the last dose of study drug:

- Combined (estrogen and progesterone containing) hormonal contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation.
- Progesterone-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation.
- Intrauterine device or intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Have a vasectomized partner, provided that the partner is the sole sexual partner of the study participant (woman of childbearing potential) and that the vasectomized partner has received medical assessment of the surgical success.
- 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, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a study, and withdrawal are not acceptable methods 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 GLPG2222 during breastfeeding is unknown. Women who are nursing are not allowed to take part in this study.

5.2.6.2.2. Male subjects with female partners of childbearing potential

Vasectomized male subjects or subjects with bilateral absence of vas deferens with female partners of childbearing potential are not required to use an additional form of contraception, provided that azoospermia has been confirmed and documented.

Non-vasectomized male subjects with female partners of childbearing potential must be willing to use a condom starting on the day of signing the ICF, during the study, and for at

least 3 months after the last dose of study drug. Their female partner should use one of the highly effective methods of birth control as defined in Section 5.2.6.2.1, or one of the following methods:

- Contraceptive diaphragm, cervical cap, or sponge plus spermicide (if available).

In case a female partner of a male subject has undergone surgical sterilization that was performed more than 1 year before screening and is documented, the subject is not required to use an additional form of contraception.

No sperm donation is allowed starting on the day of signing the ICF, during the study, and for at least 3 months after the last dose of study drug.

5.2.7. Removal of Subjects From Therapy or Assessments

The investigator will comprehensively investigate safety data (e.g. clinical laboratory parameters and AEs) to decide whether to stop dosing of individual subjects.

A subject may be discontinued from the 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.

The investigator may decide to withdraw a subject from treatment (preferably after consultation with the sponsor's medical lead) for any of the following reasons:

- Subject request.
- Use of concurrent therapy that was not permitted.
- Noncompliance with the study drug.
- Noncompliance with the study procedures.
- Lost to follow-up.
- Serious or severe AEs.
- Investigator request.
- Sponsor request.

Treatment with GLPG2222 will be discontinued and the subject will be withdrawn from the study (preferably after discussion with the sponsor's medical lead) for any of the following conditions:

- Life-threatening AE or an SAE that places the subject at immediate risk.
- Serious infection requiring parenteral antimicrobial therapy and/or hospitalization.
- Pregnancy.
- Arrhythmia or conduction abnormality, including but not limited to prolonged QTcF, where the severity is categorized as CTCAE Grade 3 or higher.
- Confirmed increase in liver function tests, defined as:
  - Two sequential AST and/or ALT elevations > 3 x ULN, with at least 1 total bilirubin value > 2 x ULN.
  - Two sequential AST and/or ALT elevations > 3 x ULN, with 2 sequential increases of alkaline phosphatase and/or GGT > 3 x ULN.
  - Two sequential AST and/or ALT elevations > 3 x ULN, accompanied by clinical signs or symptoms suggestive for hepatic injury.

- Two sequential AST and/or ALT elevations > 5 x ULN, regardless of total bilirubin value and/or alkaline phosphatase and/or GGT values and/or clinical signs or symptoms suggestive for hepatic injury.

If one of the above is detected, retesting for these laboratory parameters must be performed to determine if discontinuation criteria are confirmed. If confirmed, the sponsor's medical lead must be contacted and the subject will be withdrawn from the study. In any case, additional investigations are needed (such as: assessment of alcohol or recreational drugs intake, hepatitis infection).

- The sponsor or Regulatory Authorities close the study.
- The subject wishes to withdraw from the study.
- The subject shows a worsening of his/her medical condition (CF) which, in the investigator's opinion, requires a withdrawal from the study.

Subjects will be informed prior to study entry that they are free to withdraw from the study at any time and for any reason without jeopardizing their clinical care. If a subject is removed from the study, the investigator will immediately (at the latest within 24 hours after discontinuation) notify the sponsor. The reason for withdrawal will be documented. Discontinued subjects will not be replaced.

Subjects withdrawing from the study will be encouraged to complete the same final evaluations as subjects completing the study (completion of early discontinuation [ED] assessments and follow-up visit) according to the protocol. In particular, it is in the subject's interest that safety evaluations are performed, allowing for data to be recorded in the same way as for subjects who completed the study.

Reasonable efforts (3 attempts) will be made to contact subjects who are lost to follow-up. These efforts must be documented in the subject's file.

The sponsor has the right to terminate the study at any time in case of safety concerns or if special circumstances concerning the study drug 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 study termination.

5.3. INVESTIGATIONS MEDICINAL PRODUCTS

5.3.1. Identity of the Investigations Medicinal Products

The study drugs (GLPG2222 and placebo) will be supplied to the clinical study center pharmacist and/or investigator by or under the responsibility of the sponsor, who will also provide the pharmacist or investigator with appropriate certificates of analytical conformity and Qualified Person release documents.

GLPG2222 will be provided as tablets for oral use, containing 50, 100 or 150 mg active substance of G957389 (G957389 is the compound code for GLPG2222).

The matching placebo will be provided as a tablet for oral use.

At the clinical study center, the study drug supplies must be handled and stored safely and properly (refer to Section 5.3.6), and kept in a secured location to which only the investigator and authorized staff have access.

5.3.2. Other Medication Administered

Not applicable.

5.3.3. Dosage and Administration

Study drug administration will begin on the morning of Day 1 (at the clinic) and will end on the morning of the Day 29 visit (at the clinic).

The following GLPG2222 doses (or placebo) will be evaluated:

- Cohort A:
  - 50 mg GLPG2222 q.d.
  - 100 mg GLPG2222 q.d.
  - placebo q.d.
- Cohort B:
  - 200 mg GLPG2222 q.d.
  - 400 mg GLPG2222 q.d.
  - placebo q.d.

The study drug is to be taken q.d. in the morning with a breakfast or snack. Tablets of GLPG2222 and/or placebo will be swallowed as a whole with a glass of water. On visit days, when the study drug will be administered at the clinic after pre-dose assessments have been completed, a breakfast or snack and a glass of water will be provided by the clinical study center.

Participants are recommended to take pancreatic enzyme replacement therapy (if applicable) per guidance of the investigator.

During the study visits on Day 1 and Day 15, subjects will be provided with supply of study drug to take home.

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

5.3.4. Randomization

Approximately 50 evaluable subjects will be assigned sequentially to Cohort A (first 25 subjects) or Cohort B (next 25 subjects, i.e. subjects 26 to 50). Within each study cohort, subjects will be randomized in a 2:2:1 ratio to receive either 50 mg GLPG2222, 100 mg GLPG2222 or placebo q.d. in Cohort A, or 200 mg GLPG2222, 400 mg GLPG2222 or placebo q.d. in Cohort B for 29 days. Randomization will take place by means of a computerized interactive web response system (IWRS) according to a pre-specified randomization scheme prepared by an independent statistician at the Contract Research Organization (CRO). Subjects and study personnel will be blinded to the treatment assignment.

For each subject at each visit, the clinic will contact the IWRS to obtain the appropriate kit number to be dispensed. The kit will contain the relevant study drugs for the period until the next visit (treatment bottle for Cohort A, treatment box for Cohort B).

5.3.5. Packaging, Labeling and Distribution

The study drug packaging, labeling, Qualified Person release and distribution will be performed by [redacted] (Belgium). All manufacturing, packaging, and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements. Packaging of tablets will be performed as follows for the 2 cohorts:

Cohort A:

- Eighteen tablets of the same strength will be packaged in high-density polyethylene (HDPE) treatment bottles with a child-resistant HDPE closure. At each study drug dispensing time point, subjects in Cohort A will receive one treatment bottle to cover for 2 weeks of treatment. Hence, 2 treatment bottles will be foreseen per subject over the full study period. The bottles will be labeled according to local requirements and will have unique identifiers. The bottle label will include patient instructions for use.

Cohort B:

- Three tablets will be packaged in separate daily HDPE treatment bottles with a child-resistant HDPE closure. Nine of these daily treatment bottles will be grouped in a weekly treatment box. At each study drug dispensing time point, subjects in Cohort B will receive 2 treatment boxes to cover for 2 weeks of treatment. Hence, 4 treatment boxes will be foreseen per subject over the full study period. Both the bottles and the treatment boxes will be labeled according to local requirements and will have unique identifiers. The box label will include patient instructions for use.

The study drugs are to be dispensed according to the protocol. The distribution will only occur after the required local documentation is obtained including study approval by Competent Authorities and the IEC(s)/IRB(s).

5.3.6. Storage

The study drugs are to be stored at 15-25°C. Clinical study centers are to store their study drug supplies in a secure area until dispensed. The investigator will instruct subjects on how the study drug must be stored after it is dispensed.

5.3.7. Treatment Compliance and Drug Accountability

The investigator or designated study personnel will maintain a log of all study drugs dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study.

Subjects will return all remaining tablets and empty bottles at each study visit and/or the ED visit (if applicable). Missed doses must be discussed to try to ascertain the reason(s). Every effort must be made to ensure proper subject dosing.

All unused study drug will be returned to the drug supplier/CRO depot as applicable at the closure of the clinical study center, or will be destroyed at the clinical study center upon sponsor decision.

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 study drug. If a subject demonstrates continued noncompliance despite educational efforts, the investigator must contact the sponsor's medical lead to discuss discontinuation of the subject from the study.

Any discontinuation must be done in consultation with the sponsor's medical lead.

5.3.7.1. Subject Diary

Subjects will be given a paper diary at the screening visit to record the following (screening to follow-up):

- Any missed dose, if applicable.
- To document that study drug dose has properly been taken on a daily basis.
- The time of study drug intake, including whether food and pancreatic enzyme replacement therapy (if applicable) was taken with each dose, on the day prior to each visit to the clinic.
- From screening until the follow-up visit, changes in stable concomitant CF medication regimen, including new medicines not captured in medication history, use of inhaled antibiotics in the 24 hours prior to spirometry assessment, as well as any emerging AE.

Subjects will be instructed to bring the diary and used/unused study drug at each visit.

5.3.7.2. Subject Participation Card

On Day 1 (baseline), subjects will be provided with an emergency card containing information about their participation in the study, as well as contact details of the responsible investigator (see Section 11.3).

5.3.8. Prior and Concomitant Therapy

Concomitant therapies taken for the long-term treatment of pre-existing conditions can continue during the study provided they are in accordance with the inclusion and exclusion criteria (see Section 5.2.2 and Section 5.2.3, respectively), and with the prohibitions and restrictions (see Section 5.2.6.1). It is required that the concomitant medication regimen is stable for at least 4 weeks prior to the first study drug administration and continued without variation of dose or regimen during the study.

If additional concomitant medication needs to be administered or dose adjustments for pre-existing conditions are required during the study, this must be discussed with the sponsor's medical lead.

All concomitant therapies are to be recorded on the relevant electronic Case Report Form (eCRF) page(s), along with the reason for and details of therapy use. All surgeries will be recorded on the relevant eCRF page(s).

5.3.8.1. Stable Concomitant CF Medication Regimen

All medications in relation to the treatment of CF must be used during the study in accordance with the inclusion and exclusion criteria.

Subjects must remain on a stable medication regimen for pulmonary health (including dose and frequency) within 4 weeks prior to the first study drug administration and for the entire study duration (i.e. until the follow-up visit). Subjects who take inhaled antibiotics for suppression of chronic airway infection must be on a stable regimen for at least 8 weeks prior to the first study drug administration. Influenza vaccination cannot be administered within 4 weeks prior to the first study drug administration and for the entire study duration.

Examples of stable medication regimen for pulmonary health are: antibiotics, corticosteroids (inhaled or oral), inhaled bronchodilators, hypertonic saline, mannitol or dornase alfa; ibuprofen and airway clearance techniques.

- Subjects can be on stable treatment with chronic use of oral corticosteroids provided that the daily dose of prednisone (or equivalent) is ≤ 10 mg.
- Subjects who are using chronically inhaled antibiotics must remain on the same regimen for the duration of the study.
- Subjects who are on cycling inhaled antibiotics (including 'on/off' cycling), must continue on the same schedule. The timing of the first dose of study drug must be as close as possible to the first day of the inhaled cycling antibiotic in the cycle. This also applies to subjects who are cycling 2 different alternate inhaled antibiotics each month.

If the subject shows a worsening of his/her CF disease condition, which in the investigator's opinion needs an alternative treatment approach, treatment with study drug will be discontinued and the subject will be withdrawn from the study.

5.3.9. Blinding and Unblinding

This is a randomized, double-blind study.

The subject, the investigator, the study coordinator, the sponsor and the entire study processing team will remain blinded to treatment assignment. The blind can be broken only if the investigator deems it is necessary for the safe treatment of a subject. The investigator is encouraged to discuss considerations to break the blind with the medical monitor whenever possible and where the situation allows, and to inform the sponsor. However, the investigator is responsible for the medical care of the individual trial subject and the responsibility to break the treatment code in emergency situations resides solely with the investigator. The investigator is not required to discuss unblinding if he or she feels rapid emergency unblinding is necessary.

If the blind is broken for any reason during the course of the study, the moment at which the subject's data were unblinded and all other relevant information will be documented by the clinical study center, CRO, and other sponsor designees, as appropriate. The reason for breaking the blind will be indicated and justified in the source documentation and in the eCRF. The blind can be broken by the investigator via the IWRS.

All subjects who are unblinded while on the study will be withdrawn at the moment of unblinding, with the reason for unblinding given as the reason for discontinuation from the

study. If an AE leads to unblinding, the AE must be given as the reason for unblinding and the AE must also be recorded in the eCRF. All subjects who are unblinded must, where possible, complete the ED visit. Any AEs must be followed until resolution or until stabilization.

6. STUDY ASSESSMENTS

6.1. TIMING OF ASSESSMENTS

The study assessments described below will be performed at the time points specified in the flow chart in Section 1. All assessments should be performed pre-dose. In addition, some assessments are also to be performed at defined time points post-dose when specifically mentioned. The procedures listed below must be performed in the following order:

1. CFQ-R
2. Vital signs and pulse oximetry
3. 12-lead ECG
4. Sweat collection
5. Spirometry
6. Sampling for clinical laboratory tests and PK
7. Sampling for exploratory biomarkers
8. Nasal brushings (if applicable)

All other procedures can be performed in any order, unless otherwise stated, as long as they meet the schedule for pre- or post-dose evaluations.

6.2. INITIAL SUBJECT AND DISEASE CHARACTERISTICS

Subjects will be asked to come to the clinical study center for the screening visit, which may be scheduled between 28 days and 1 day prior to baseline (Day 1). The CFQ-R will be completed after informed consent was given by the subject, and prior to any other assessments scheduled for that visit. As part of the safety assessments, vital signs will be recorded, a pulse oximetry will be performed to measure oxygen saturation, and a 12-lead ECG will be recorded. Efficacy assessment tests will be performed, including sweat collection and spirometry. Blood and urine samples will be collected for clinical safety laboratory tests, serology, pregnancy test, and FSH test (if applicable). In addition, the following assessments will be done during screening: a complete check of inclusion and exclusion criteria, demographics (recording of year of birth, age and race), a general medical examination including medical and surgical history (including CF-specific medical history e.g. date of diagnosis, sweat chloride concentration prior to any treatment with a CFTR modulator, CFTR mutation, etc.) and questions about smoking habits, alcohol and drug intake, a full physical examination (including height), and weight. Finally, the subject diary will be dispensed.

All AEs (serious and non-serious) and concomitant medications will be reported continuously from the time a signed and dated ICF is obtained until the final follow-up visit.

6.3. EFFICACY ASSESSMENTS

6.3.1. Sweat Chloride Concentration

Sweat chloride concentration is a biomarker of CFTR ion channel function. It is a sensitive, standardized and non-invasive measure to assess systemic CFTR modulator effects. Chloride concentration will be measured in sweat collected by an approved collection device (Wescor Macroduct® system) according to the 2009 guidelines issued by the Clinical and Laboratory Standards Institute.

To ensure consistency and reproducibility in this multi-center study, 'trained' clinical study centers will collect sweat according to standardized operating procedures. Two sweat collections, one from each arm, will be obtained from each subject at the time points indicated in the flow chart. Sweat samples will immediately be frozen and sent to the central laboratory for testing and interpretation of results.

The clinical study center should be encouraged to select subjects for the study for which it is known that adequate quantities of sweat can be collected.

Clinical study centers and subjects should not be informed of their sweat chloride results during the entire study duration, regardless of whether the subject prematurely discontinues treatment.

6.3.2. Spirometry

Spirometry will be performed to assess pulmonary function at the time points specified in the flow chart. Spirometry must be performed pre-dose at all visits, and additionally between 1 and 2 hours post-dose on Day 1 and Day 29.

The spirometry test must meet the criteria for acceptability and repeatability as defined in the 2005 ATS/ERS guidelines on standardization of lung function testing [7].

If screening spirometry measurements fail to meet acceptability and repeatability criteria in the first 3 efforts, up to 8 repeat spirometry efforts may be performed. If repeat values of the individual assessment(s) satisfy the eligibility criteria and are completed within the screening window, then the subject is eligible for the study.

Clinical study centers will be provided with spirometers to be used for all study spirometry assessments. Pulmonary function will be measured in a standardized manner. Spirometry data will be transmitted to a centralized spirometry service for quality review. Subjects should not be informed of their study-related spirometry results during the entire study duration, regardless of whether the subject prematurely discontinues treatment.

At screening, spirometry to determine subject's eligibility should preferably be performed pre-bronchodilator. If the subject used his/her bronchodilator before the screening visit, screening spirometry is allowed to be performed post-bronchodilator. At all other study visits, spirometry should be performed pre-bronchodilator. If on Day 1, the subject forgets to withhold his/her bronchodilator, all subsequent spirometry testing should be performed post-bronchodilator, to be consistent with the conditions for the baseline measurement. If on Day 1, spirometry is collected pre-bronchodilator, but the subject forgets to withhold his/her

dose of bronchodilator at a subsequent visit, then spirometry should be collected post-bronchodilator for that visit only.

Pre-bronchodilator spirometry is defined as spirometry testing performed for a subject:

- that withheld his/her short-acting β-agonist (e.g. albuterol) or anticholinergic (e.g. ipratropium bromide) for more than 4 hours prior to the spirometry assessment, AND
- that withheld his/her long-acting bronchodilator such as salmeterol or formoterol for at least 12 hours, or longer-acting agents such as indacaterol and tiotropium for at least 24 hours prior to the spirometry assessment.

The following parameters will be measured as part of the spirometry assessment:

- FEV_1 (L) and percent predicted FEV_1 for age, gender, and height;
- Forced vital capacity (FVC) (L) and percent predicted FVC for age, gender, and height;
- FEV_1/FVC ratio;
- Forced expiratory flow between 25% and 75% of exhaled volume (FEF_{25-75}).

Predicted values will be estimated using the 2012 Global Lungs Initiative equation.

6.3.3. Cystic Fibrosis Questionnaire-Revised (CFQ-R)

Eligible subjects will be asked to complete the adult version of the CFQ-R in their native language at the time points specified in the flow chart. The CFQ-R must be completed before study drug administration and prior to the start of any assessments scheduled for that visit.

The CFQ-R questionnaire provides information about:

- Nine quality of life domains: physical, role/school, vitality, emotion, social, body image, eating, treatment burden, health perceptions.
- Three symptom scales: weight, respiratory and digestion.
- Overall health perception.

6.4. SAFETY ASSESSMENTS

The safety assessments will be based on AEs, physical examinations, vital signs, oxygen saturation by pulse oximetry, 12-lead ECG, spirometry (see efficacy assessments), and clinical safety laboratory evaluations.

6.4.1. Adverse Events

Adverse events will be recorded from the signature of the ICF until the final follow-up visit, as further described in Section 9 of this protocol.

6.4.2. Physical Examination

At each study visit, as specified in the flow chart, the physician will perform a physical examination. At screening, this will be a full physical examination including height. At subsequent visits, a limited physical examination (ear, nose, throat, chest and neck) will be performed. Weight will be measured at each visit (with shoes off).

Any clinically relevant abnormalities should be reported as AEs.

6.4.3. Vital Signs

Vital signs (i.e. HR, systolic blood pressure [SBP], diastolic blood pressure [DBP], respiratory rate and oral body temperature) will be assessed in a standardized manner at the time points specified in the flow chart. Vital signs must be recorded pre-dose at all visits, and additionally between 3 and 4 hours post-dose on Day 1. HR, SBP and DBP will be measured after 5 minutes in supine position.

Additional collection times, or changes to collection times of blood pressure, HR and body temperature will be permitted, as necessary, to ensure appropriate collection of safety data.

Normal ranges for vital signs parameters are presented in Appendix 2. Any clinically relevant abnormalities should be reported as AEs.

6.4.4. Oxygen Saturation by Pulse Oximetry

Arterial oxygen saturation by pulse oximetry will be measured at the time points specified in the flow chart. Pulse oximetry will be collected after the subject has been at rest (seated or supine) for at least 5 minutes.

Normal ranges for pulse oximetry are presented in Appendix 2. Any clinically relevant abnormalities should be reported as AEs.

6.4.5. 12-lead ECG

A resting 12-lead ECG will be recorded at the time points specified in the flow chart. Subjects should rest for at least 5 minutes in supine position prior to ECG evaluation. Parameters to be recorded include the following: HR, RR interval, PR interval, QRS, uncorrected QT interval, morphology, and rhythm analysis. QTcF will be calculated during the statistical analysis.

Normal ranges for ECG parameters are presented in Appendix 2. ECGs will be interpreted by the investigator for clinical significance. Any clinically relevant abnormalities should be reported as AEs.

6.4.6. Clinical Laboratory Evaluations

Clinical laboratory samples will be collected at the time points specified in the flow chart.

The following clinical laboratory tests will be performed:

- Hematology: hematocrit, hemoglobin, red blood cell count, WBC count, WBC differential count (absolute and relative), and platelets.
- Serum/plasma chemistry: glucose, urea, creatinine, uric acid, sodium, potassium, calcium, chloride, phosphorus, AST, ALT, GGT, total bilirubin, indirect bilirubin, alkaline phosphatase, lactate dehydrogenase, albumin, total proteins, triglycerides, cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol.
- Coagulation: activated partial thromboplastin time, prothrombin time (International Normalized Ratio).
- Urinalysis: proteins, ketones, and microscopic examination of the sediment (cylinders, erythrocytes, leukocytes), pH, leukocyte esterase, glucose.
- Serology: HBsAg, HCV antibody, HIV-1 and HIV-2 antibodies (only at screening).

- Serum pregnancy testing (β-human chorionic gonadotropin) will be performed in female subjects of childbearing potential at screening, while a urine pregnancy test will be performed at all other scheduled visits. The urine pregnancy test must be negative prior to the first study drug administration.
- FSH test for suspected post-menopausal female subjects only, defined as female subjects < 55 years with no menses for ≥ 12 months without a medical cause.
- CFTR genotyping (only at baseline).

The laboratory values outside the normal range will be flagged and clinical relevance will be assessed by the investigator. Any clinically relevant abnormalities should be reported as AEs.

6.5. PHARMACOKINETICS ASSESSMENTS

6.5.1. Blood Samples

Blood samples will be collected during the treatment period for the determination of GLPG2222 in plasma at the following time points:

- Day 15: pre-dose and 0.5, 1, 2, 3, 4, 6 and 8 hours post-dose;
  - If it is known upfront that the subject is not available for the 'full' PK profiling on Day 15, it is allowed to schedule and perform this PK profiling on Day 29.
- Day 29: pre-dose;
- ED (if applicable): one additional sample to be taken pre-dose if study drug is still taken, or at any time during the visit if study drug is no longer taken.

Plasma concentrations of GLPG2222 will be measured using a validated liquid chromatography tandem mass spectrometry method with a lower limit of quantification of 1.00 ng/mL. The details of sample handling and shipment instructions will be provided in a separate laboratory manual.

After the study is completed, any left-over samples belonging to the study subject may be stored for a period of 5 years under the control of the sponsor. These samples may be used by the sponsor or sponsor's partner, or by other companies belonging to the sponsor for additional PK investigation (i.e. metabolic profiling, which is the assessment of biochemical intermediates – metabolites - in blood in order to describe the metabolic pathway of the compound). No characterization of human genetic material will be undertaken. Specific consent for storage of samples should be obtained from the subjects. Any research outside the context described in this protocol may only be conducted after approval by the IEC(s)/IRB(s) and Regulatory Authority.

6.5.2. Sweat Samples

Remaining sweat samples (after sweat chloride concentration determination) may be used to determine the concentration of GLPG2222.

6.5.3. Pharmacokinetic Parameters

Noncompartmental PK calculations will be performed by [redacted] using Phoenix WinNonLin® (Version 6.3 or higher).

The following PK parameters will be determined for GLPG2222 from individual concentration-time profiles in plasma:

C_{max}	maximum observed plasma concentration
C_{trough}	plasma concentration observed at pre-dose
t_{max}	time to occurrence of C_{max}
$AUC_{(t)}$	area under the plasma concentration-time curve over the dosing interval calculated by the linear up - logarithmic down trapezoidal rule

On Day 15, all PK parameters will be determined (or on Day 29 if the subject is not available for full PK profiling on Day 15). On Day 29, only C_{trough} will be determined.

Additional PK parameters may be calculated as appropriate.

6.6. EXPLORATORY ASSESSMENTS

6.6.1. Exploratory Biomarkers

Blood samples for the assessment of [redacted] biomarkers and [redacted] will be collected pre-dose at the time points specified in the flow chart. The following biomarkers may be evaluated:

– [redacted]

6.7. OPTIONAL EXPLORATORY ASSESSMENT (SUBSTUDY)

6.7.1. Apical Expression of F508del CFTR Using Nasal Brushing

A corrector such as GLPG2222 will increase levels of F508del CFTR at the plasma membrane of epithelial cells. This biomarker is independent of the corrected CFTR ion channel function and solely focuses on the amount of CFTR protein present. Levels of apically located F508del CFTR can be determined in epithelial cells isolated from nasal brushings using specific CFTR antibodies.

Nasal brushings will be obtained at the time points specified in the flow chart and only from those subjects who give separate consent for this optional substudy. Details on the collection of nasal epithelial cells will be described in a separate 'Nasal Brushing Manual'.

7. STATISTICAL METHODS

All statistical calculations will be performed by the Biostatistics Department of [redacted] using the SAS (Version 9.4 or higher) and/or Phoenix WinNonlin (Version 6.3 or higher) software for statistical and PK computations. All statistical methods will be detailed in a statistical analysis plan, that will be finalized prior to the database lock. All data collected in this study will be documented using summary tables, figures and subject data listings.

7.1. DETERMINATION OF SAMPLE SIZE

The sample size calculation is based on the expected change from baseline in sweat chloride concentration after 29 days of treatment. The standard deviation of the sweat chloride concentration change is expected to be 10 mmol/L. With an 80% power, the study will be able to detect a difference between study drug doses of 14 mmol/L at a 5% 2-sided type-I error, assuming 50 subjects are included in the study in both Cohorts A and B. In case the study is only performed in Cohort A, it will be able to detect a difference between study drug doses of 16 mmol/L with 80% power. No adjustment for multiple testing (GLPG2222 doses versus placebo) has been done on the sample size calculation as this is an exploratory study.

7.2. POPULATIONS FOR ANALYSES

7.2.1. All Screened Subjects Analysis Set

All subjects who provided informed consent by signing the ICF.

7.2.2. All Enrolled Subjects Analysis Set

All subjects who were enrolled into the study.

7.2.3. Intent to Treat Analysis Set

All enrolled subjects who received at least one dose of study drug and had at least one post-baseline assessment with efficacy data.

7.2.4. Safety Analysis Set

All subjects who received at least one dose of study drug.

7.2.5. Pharmacokinetics Analysis Set

Subpopulation of the Safety Analysis Set, including all subjects who were exposed to GLPG2222 and who have available and evaluable PK data (e.g. excluding all protocol violations/deviations or AEs that may have an impact on the PK analysis).

7.3. STATISTICAL ANALYSES

7.3.1. General Statistical Considerations

Summary tabulations will display the number of observations, mean, standard error, median, minimum, and maximum for continuous variables, and the number and percent category for categorical data. Tabulated descriptive statistics and graphical data displays may be used to summarize the data. Inferential statistics will be interpreted at the 2-sided 5% level.

7.3.2. Analyses of Demographics and Baseline Characteristics

Subject disposition, protocol deviations, demographics, baseline characteristics, medical history, concomitant therapies, and exposure will be analyzed descriptively and/or listed and presented overall and by treatment group.

7.3.3. Analyses of Efficacy Parameters

Descriptive statistics of actual values, changes from baseline (pre-dose on Day 1), and percent changes from baseline will be provided.

An analysis of covariance (ANCOVA) model on the changes from baseline at each time point, with treatment as factor and baseline value as covariate, will be applied to the following parameters:

- Sweat chloride concentration;
- FEV_1;
- CFQ-R scores.

Between-group comparisons will be done for each GLPG2222 group versus the pooled placebo group (if the study is performed in both Cohorts A and B) or versus placebo in Cohort A (if the study is only performed in Cohort A).

Missing data will be imputed, also for subjects who prematurely discontinue the study. The primary imputation method will be the last-observation-carried-forward. An observed-case analysis will also be performed. Details regarding imputation method will be described in the statistical analysis plan.

A sensitivity analysis will be performed by using non-parametric tests. The GLPG2222 groups and pooled placebo group (if the study is performed in both Cohorts A and B) or the GLPG2222 groups and placebo in Cohort A (if the study is only performed in Cohort A) will be compared using a Kruskal-Wallis test (overall treatment effect) and Wilcoxon rank sum tests (pairwise comparisons versus the corresponding placebo group).

Additional exploratory analyses and graphical presentations may be performed when deemed useful to better understand the data.

7.3.4. Analyses of Safety Data

Adverse events will be fully described and coded according to the Medical Dictionary for Regulatory Activities. Physical examination, weight, vital signs, oxygen saturation by pulse oximetry, 12-lead ECG, spirometry, and clinical safety laboratory data will be analyzed descriptively. Changes from baseline (pre-dose on Day 1) and shifts according to normal ranges will be presented as well. Analysis will be done per treatment group.

7.3.5. Pharmacokinetics Analyses

Descriptive statistics will be calculated by treatment group and day for the plasma concentrations and PK parameters of GLPG2222.

Plasma concentrations of GLPG2222 will be analyzed using a population PK approach including the assessment of covariates influencing the PK in CF subjects. The relation between exposures and selected efficacy and safety endpoints will also be investigated, if relevant.

7.3.6. Exploratory Biomarkers

Exploratory biomarker data [redacted] will be analyzed using descriptive statistics of actual values, changes from baseline (pre-dose on Day 1), and percent changes from baseline.

7.3.7. Apical Expression of F508del CFTR (Optional Substudy)

For subjects who participate in the optional substudy, data on apical expression of F508del CFTR will be analyzed using descriptive statistics of actual values, changes from baseline (pre-dose on Day 1), and percent changes from baseline.

8. DATA SAFETY MONITORING BOARD

To enhance the safety and integrity of the study data, a DSMB consisting of independent experts will convene to periodically review the accumulating unblinded data for the study. The DSMB will review accumulating data and provide a recommendation on study continuation or early termination. The DSMB Charter will outline the specific responsibilities and composition of the DSMB, and will contain the details of outputs provided for the meetings, as well as the meeting schedule.

GENERAL PROCEDURES

9. ADVERSE EVENTS

9.1. DEFINITIONS

Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product.

Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose meets any of the following conditions:

- results in death;
- is life-threatening: the subject is at risk of death at the time of the event. It does not refer to an event that hypothetically might cause death if it were more severe;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect.
- is a medically significant event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definitions above.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or intensity is not consistent with the applicable product reference safety information. For a study drug, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure [6].

Associated With the Use of the Drug

An AE is considered associated with the use of the drug if the causality is possible, probable, or certain by the definitions listed in Section 9.3.

9.2. INTENSITY OF ADVERSE EVENT

Each AE must be rated on a 3-point scale of increasing intensity:

- **Mild:**
  Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.

- **Moderate:**
  Mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention/therapy required.
- **Severe:**
  Marked limitation in activity; some assistance usually required; medical intervention/therapy required, hospitalization possible.

If there is a change in intensity of an AE, it must be recorded as a separate event.

9.3. CAUSALITY ASSESSMENT

The following decision choice will be used by the investigator to describe the causality assessment between the reported event and the investigational medicinal product.

- **Unrelated:**
  No relationship between the AE and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state.
- **Unlikely:**
  Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible). Disease or other drugs provide plausible explanations.
- **Possible:**
  Event or laboratory test abnormality, with reasonable time relationship to drug intake which could also be explained by disease or other drugs. Information on drug withdrawal may be lacking or unclear.
- **Probable:**
  Event or laboratory test abnormality, with reasonable time relationship to drug intake. Event unlikely to be attributed to disease or other drugs. Response to withdrawal is clinically reasonable and rechallenge not required.
- **Certain:**
  Event or laboratory test abnormality, with plausible time relationship to drug intake which cannot be explained by 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). Rechallenge satisfactory, if necessary.

9.4. ACTION TAKEN REGARDING INVESTIGATIONAL PRODUCT (IF APPLICABLE)

The action taken must be described by choosing among:

- **Dose not changed:**
  In case no action is taken regarding the study drug.
- **Dose reduced: Not allowed in this study**
- **Drug permanently withdrawn:**
  In case a subject is permanently withdrawn from the study.
- **Drug temporarily withdrawn:**
  In case the study drug is temporarily withdrawn.
- **Not applicable:**
  Other situations (e.g. in case an AE started after the last study drug administration)

9.5. OUTCOME

Each AE outcome must be rated using one of the following terms:

- Recovered/Resolved;
- Recovered/Resolved with sequelae;
- Not recovered/Not resolved;
- Fatal;
- Recovering/Resolving;
- Unknown.

9.6. RECORDING ADVERSE EVENTS

Adverse events will be recorded from the signature of the ICF until the final follow-up visit. In case an AE is ongoing at that time, it will be followed up as much as possible by the investigator until resolution or until stabilization.

It is the responsibility of the investigator to collect all AEs (both serious and non-serious) derived by spontaneous, unsolicited reports of subjects, by observation and by routine open questioning (such as “How do you feel?”).

Any adverse or unusual event occurring during or after the clinical study (until the follow-up visit), whether observed by the investigator or investigational staff, or spontaneously reported by the subjects, will be recorded in the eCRF and medical file.

9.7. MANAGING SERIOUS ADVERSE EVENTS

Subjects experiencing an SAE or an emergency situation will be examined by a physician as soon as possible. The physician in attendance will do whatever is medically needed for the safety and well-being of the subject. 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. The subject will be followed until the SAE resolves or until the subject is medically stabilized.

9.8. REPORTING SERIOUS ADVERSE EVENTS / PREGNANCIES

9.8.1. Serious Adverse Events

All SAEs, whether or not deemed drug-related, must be recorded in the eCRF and SAE form and reported by the investigator to [redacted] Medical Affairs ([redacted] MA) within 24 hours by facsimile. Other means of transmission can be decided where facsimile is not possible. The SAE must include 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 must be reported for all subjects that experience an SAE. It is critical that the information provided on the [redacted] [redacted] SAE form matches the information recorded on the eCRF for the same event. In addition, the same information is to be recorded in the source documents.

Copies of additional laboratory tests, consultation reports, post mortem reports, hospital case reports, autopsy reports, and other documents must be sent when requested and applicable. Follow-up reports relative to the subject's subsequent course must be submitted to [redacted] MA until the event has subsided or, in case of permanent impairment, until the condition stabilizes.

9.8.2. Pregnancy

All initial reports of pregnancies in female subjects and partners of male subjects included in the study must be reported to [redacted] MA by the investigator within 24 hours of knowledge of the event, using a pregnancy form.

The investigator will contact the subject at the expected time of delivery for follow-up. Abnormal pregnancy outcomes are considered SAEs and must be reported using the SAE form.

If a subject is found to be pregnant, she must be immediately withdrawn from the study.

9.9. REPORTING SERIOUS ADVERSE EVENTS TO COMPETENT AUTHORITIES / ETHICS COMMITTEES / INSTITUTIONAL REVIEW BOARDS

[redacted] MA assumes responsibility for appropriate reporting of AEs to the Regulatory Authorities. [redacted] MA will also report to the investigator(s) all SAEs that are unlisted (unexpected) and associated with the use of the drug. The investigator(s) (or [redacted] MA where required) must report these events to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB.

Adverse events reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

After termination of the clinical study (last subject last contact in the study), any unexpected safety issue that changes the risks benefit analysis and is likely to have an impact on the subjects who have participated in it, will be reported by the sponsor/[redacted] MA as soon as possible to the Competent Authority(ies) concerned together with proposed actions.

10. STUDY CLOSURE CONSIDERATIONS

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

When the study ends, the sponsor will submit an "end of trial notification" to both the IEC/IRB and Regulatory Authorities, according to local regulations, by using the "Declaration of the End of Trial Form". The declaration will be submitted within 90 days of the end of the study.

Reasons for the closure of a clinical study center or termination of a trial by the sponsor may include but are not limited to:

- Successful completion of the trial at the clinical study center,
- The overall required number of subjects for the trial has been recruited,
- Failure of the investigator to comply with the protocol, International Council for Harmonisation-Good Clinical Practice (ICH-GCP) guidelines or local requirements,
- Safety concerns,
- Inadequate recruitment of subjects by the investigator.

11. STUDY MATERIALS

11.1. INVESTIGATIONAL MEDICAL PRODUCTS

The investigator acknowledges that the study drugs are investigational and as such must be handled strictly in accordance with the clinical study protocol and the container label. Supplies must be retained in a limited access area and under the appropriate environmental conditions as specified on delivery. Upon receipt of the study drugs, the investigator or delegate will verify whether the correct amount of study drugs are delivered and whether those are intact.

Supplies should be dispensed under the supervision of the investigator or sub-investigator, or by a hospital pharmacist. Local regulations should be adhered to. It is the investigator's or delegate's responsibility to ensure that subjects return their study drugs (including empty packages, e.g. empty bottles). Returned study drugs must not be dispensed again, even not to the same subject. Each time study drugs is dispensed to or returned by the subject, this must be documented on the Drug Accountability Form. Whenever a subject brings his/her study drug to the clinical study center for drug accountability this is not seen as a return of supplies. Unused study drug (not dispensed) and study drug returned by the subject must be available for verification by the monitor.

All used and unused study drug will be returned to the drug supplier/CRO depot or will be passed over for destruction on-site (conform local regulations) or by an authorized destruction unit after authorization by the sponsor. This will be documented on the Drug Return Form and a destruction certificate, if applicable.

11.2. STUDY DOCUMENTS

The following documents must be provided to the sponsor or representatives before shipment of study drugs to the clinical study center:

- A signed and dated protocol and amendment(s), if any.
- A copy of the signed and dated written IEC/IRB approval specifying the documents being approved: the protocol, amendments, ICF, any other written information provided to the subject and subject recruitment materials.

  This approval must clearly identify the trial by protocol title and trial number.
- Regulatory Authority approval or notification, if required.
- Documentation on which the assessment of the investigator's qualifications was based (e.g. curriculum vitae).

The following documents must be provided to the sponsor or representatives prior to enrollment of the first subject:

- The names of the current members or composition of the IEC/IRB and their position in the health-care institution or their credentials.
  In case the (sub) investigator is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the voting for the trial.
- Completed Investigator Financial Disclosure Forms from the investigator and all sub-investigators.
- Signed and dated trial agreement, if applicable.
- Signed and dated financial agreement.
- Documentation on which the assessment of the sub-investigators' qualifications was based (e.g. curriculum vitae).
- Current laboratory normal ranges for all tests required by the protocol that will be performed.
- Laboratory documentation demonstrating competence and test reliability (e.g. accreditation/license), if applicable.

11.3. PARTICIPATION CARDS

If the subjects are not under 24-hour supervision of the investigator or his/her staff (out-subjects), they must be provided with a Subject Participation Card indicating the name of the investigational product, the 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.

11.4. SOURCE DATA

The nature and location of all source documents will be discussed during the Site Initiation Visit and will be documented to ensure that all sources of original data required to complete the eCRF are known and are accessible for verification by the monitor. If electronic records are maintained, the method of verification must be discussed and agreed upon between the investigational staff and the monitor.

The required source data are discussed during the Site Initiation Visit and should include sequential notes containing at least the following information for each subject:

- Subject identification (name, year of birth, age, gender).
- Documentation that subject meets eligibility criteria, i.e. history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria).
- Participation in trial (including trial number).
- Trial discussed and date of informed consent.
- Dates of all visits.
- Documentation that protocol specific procedures were performed.
- Results of efficacy parameters, as required by the protocol.
- Start and end date (including dose regimen) of study drugs (preferably drug dispensing and return should be documented as well).
- Record of all adverse events and other safety parameters (start and end date, and preferably including causality and intensity).

- Concomitant medication (including start and end date, and dose. If relevant, dose changes should be motivated).
- Date of trial completion and reason for ED, if applicable.
- Subject Diaries.

Source data may be directly captured from devices transferred from third partners (e.g. laboratory data) or entered manually into the clinical study center's eCRF and medical file.

It is recommended that the author of an entry in the source documents is identifiable. Following ICH GCP Guidelines, direct access 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.

11.5. ELECTRONIC DATA CAPTURE

Electronic Data Capture (EDC) will be used for this study, meaning that all CRF data will be entered in eCRFs at the clinical study center. All data related to the study must be recorded in the EDC system in English.

The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or after the subject's visit. To avoid inter-observer variability, every effort must be made to ensure that all efficacy evaluations are completed by the same individual who made the initial baseline determinations. The investigator must verify that all data entries in the eCRFs are accurate and correct. If certain information is not done, not available or not applicable or unknown, the investigator must indicate this in the eCRF. The investigator will be required to electronically sign off on the clinical data.

During monitoring visits, the monitor will review the eCRFs, evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections and alterations are to be made by the responsible investigator or his/her designee. The monitor cannot enter data in the eCRFs. Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the site personnel responsible for entering the clinical data into the eCRF will be determined in advance.

If additional corrections are needed, the responsible monitor or data manager will raise a query in the EDC application. The appropriate investigational staff will answer queries sent to the investigator. This will be audit trailed by the EDC system meaning that the name of investigational staff, time and date stamp are captured.

12. ARCHIVING

The investigator maintains the study specific documents as specified in "Essential Documents for the Conduct of a Clinical Trial (ICH E6, Section 8)" and as required by the applicable regulatory requirement(s). The investigator must take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents must be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor.

It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

Under no circumstance shall the investigator re-locate or dispose of any trial 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 trial, 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 trial.

13. CONFIDENTIALITY

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 by the sponsor and must 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 trial and will not use it for other purposes.

In order to permit easy identification of the individual subject during and after the trial, 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 will remain at the clinical study center and no copy will be made.

14. REPORTING AND PUBLICATION

14.1. REPORTING

The results of the trial will be reported in a single clinical study report. A summary of the final report will be provided to the investigators, to the applicable Regulatory Authorities and IEC(s)/IRB(s) if required by the applicable regulatory requirements within one year after end of study.

One participating investigator will be appointed for review and sign off the final clinical study report. The selection of this investigator will be determined by the recruitment performance and specific expertise related to the nature and the primary objectives of the study.

14.2. PUBLICATION

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 by the sponsor and must 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 study and will not use it for other purposes without the written approval of the sponsor.

It is understood by the investigator that the sponsor will use the information developed in this clinical study in connection with the development of the compound and therefore, may disclose it as required to other clinical investigators and to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the investigator understands that he has an obligation to provide and disclose test results and all data developed during this trial to the sponsor.

The investigator may not submit for publication or presentation, the results of this study without the prior written approval of the sponsor. The investigator must understand that it is not the sponsor's intention to prevent publication of such data as is generated in the study. However, the sponsor reserves the right to control the route and rate of such publication.

The sponsor will not unreasonably withhold consent to publish the data generated in this study. However, it is the policy of the sponsor not to allow the investigators to publish their results or findings prior to the sponsor's publication of the overall study results. The investigator agrees that before he/she publishes any results of this trial, he/she shall provide the sponsor with at least 90 days for full review of the pre-publication manuscript prior to submission of the manuscript to the publisher. In accordance with generally recognized principles of scientific collaboration, co-authorship with any company personnel will be discussed and mutually agreed upon before submission of a manuscript to a publisher.

15. ETHICS

15.1. INDEPENDENT ETHICS COMMITTEE (IEC) / INSTITUTIONAL REVIEW BOARD (IRB)

This study can only be undertaken after full approval of the clinical study protocol, 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 study and the related study documents being approved, including the subject compensation programs.

During the course of study the following documents will be sent to the IEC/IRB for review:

- Changes to the Investigator's Brochure
- Reports of adverse events that are serious, unlisted and associated with the investigational drug

Substantial amendments and applicable ICF revisions 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 study subjects.

The IEC/IRB is responsible for continuous review of the study. At least once a year, the investigator will provide the IEC/IRB with a progress report to allow review of the study. Additional progress reports must be provided if required by the IEC/IRB. These requests and (re) approvals, if applicable, must be documented in writing.

15.2. REGULATORY APPROVAL / NOTIFICATION

This clinical study protocol, title and a list of clinical study centers, IEC(s)/IRB(s) approvals, as well as other relevant documentation will be submitted to the local Regulatory Authorities for review and approval prior to trial start. Upon completion, the Regulatory Authorities will be notified the study has ended. The study will only be undertaken in compliance with the local regulatory requirements.

15.3. ICH GOOD CLINICAL PRACTICE

This study will be conducted in accordance with the current ICH-GCP Guideline E6. 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 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.

This study will be conducted in compliance with the Declaration of Helsinki (1964 and successive amendments), current GCP and the applicable European and local regulatory requirements.

15.4. INFORMED CONSENT

The investigator or designated personnel must explain the study and the implications of participation (e.g. objectives, methods, anticipated benefits and possible risks) to potential subjects or their legally acceptable representatives prior to any trial related activity. Subjects will be informed that their participation is voluntary and that they may withdraw from the study at any time. They will be informed that choosing not to participate or to withdraw from the study will not have an impact on the care the subject will receive for the treatment of his/her disease. In case the subject is unable to read and write, an impartial witness must confirm the informed consent.

The subject will be given sufficient time to read the ICF and to ask additional questions. After this explanation and before entry in the study, consent must be appropriately recorded by means of the subject's personally dated signature or by the signature of an independent witness who certifies the subject's consent in writing. After having obtained the consent, a copy of the signed and dated ICF must be given to the subject.

If new information becomes available that may be relevant to the subject’s willingness to participate in the study, the subject will be informed in a timely manner by means of an updated ICF. This amended ICF will be signed and dated by the subject and the investigator to document the willingness of the subject to continue with the study.

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

16. FINANCING AND INSURANCE

16.1. FINANCIAL DISCLOSURE

The disclosed financial interest of the investigator must be collected before screening of the first subject, following study completion at the clinical study center and one year following overall study completion. The investigator must promptly update this information if any relevant changes occur during this period. Disclosable financial interests will be recorded on the Investigator Financial Disclosure Form.

Any investigator(s) added as investigational staff must complete the Investigator Financial Disclosure Form at the beginning of their participation in the study. For any investigator(s) leaving the clinical study center prior to study completion, an Investigator Financial Disclosure Form must be obtained at the end of their contribution to the study.

16.2. INDEMNIFICATION

The sponsor will indemnify the investigator and hold harmless the investigator and his or her medical staff from any claim for damages, demand or cost arising from the activities to be carried out in compliance with the clinical study protocol.

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

16.3. INSURANCE

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of clinical study. For subjects treated according to the clinical study protocol, injury possibly arising from participating in this study is covered by the liability insurance of the sponsor, unless malpractice from the investigator.

17. DATA QUALITY CONTROL / ASSURANCE

17.1. MONITORING

This clinical study will be monitored by sponsor representatives according to the current Standard Operating Procedure for the monitoring of clinical studies.

The monitor will perform on-site monitoring visits as frequently as necessary which will be documented on the monitoring log. Shortly before the study starts, the monitor will meet with the investigator and study staff involved to review the study-specific procedures on study conduct and recording the data in the eCRF. The first monitoring visit will take place as soon as possible after enrollment and the investigator shall permit the monitor to verify the progress of the study on a continues basis. The investigator shall make the eCRFs available, provide missing or corrected data and sign the eCRFs. Key data transcribed onto the eCRFs, such as the subject's sex, age, assessment dates, test results etc., will be reviewed against the available source documents. Personal information will be treated as strictly confidential and will not be made publicly available. Any inconsistency between source data and data recorded in the eCRF will be corrected.

The sponsor will ensure that appropriate QC steps are included into the different clinical study processes to guarantee adequate protection of the subjects and to guarantee the quality of the data.

17.2. AUDIT AND INSPECTION

To ensure compliance with relevant regulations, an independent Quality Assurance representative, Regulatory Authorities and/or IEC(s)/IRB(s) may review this 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 study and will have access to the data generated during the study, source documents, and subject's files. By participating in this study, investigators agree to this requirement.

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APPENDICES

Appendix 1 Study Contact Information

Role	Contact Information
Sponsor	Galapagos NV Industriepark Mechelen Noord Generaal De Wittelaan L11 A3 2800 Mechelen, Belgium
Medical Lead	[redacted] MD, MBA - Galapagos NV Generaal De Wittelaan, L11 A3 2800 Mechelen, Belgium Tel: [redacted] Mobile: [redacted] E-mail: [redacted]
Clinical Study Lead	[redacted] Galapagos NV Generaal De Wittelaan, L11 A3 2800 Mechelen, Belgium Tel: [redacted] Mobile: [redacted] E-mail: [redacted]
Head of Development Clinical Pharmacology	[redacted] – Galapagos SASU 102 Avenue Gaston Roussel 93230 Romainville, France Tel: [redacted] E-mail: [redacted]
Lead Biostatistics	[redacted] – Galapagos NV Generaal De Wittelaan, L11 A3 2800 Mechelen, Belgium Tel: [redacted] E-mail : [redacted]
Pharmacovigilance Lead	[redacted] MB ChB Generaal De Wittelaan, L11 A3 2800 Mechelen, Belgium Mobile: [redacted] Mobile: [redacted] E-mail: [redacted]

Contract Research Organization	[redacted] United Kingdom

Appendix 2 Normal Ranges for Vital Signs, Pulse Oximetry and ECG Parameters

NORMAL RANGES FOR VITAL SIGNS

Normal ranges applicable in supine position (after 5 minutes):

Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Heart rate (bpm)	Oral temperature (°C)
90 ≤ SBP ≤ 150	45 ≤ DBP ≤ 90	40 ≤ HR ≤ 100	35.5 ≤ t° ≤ 37.5

For respiratory rate, normal range for an adult person at rest: 12 to 16 breaths per minute.

NORMAL RANGES FOR PULSE OXIMETRY

Normal arterial oxygen saturation level (SpO_2): 95% to 100%.

NORMAL RANGES FOR ECG PARAMETERS

Normal ranges applicable in supine position (after 5 minutes):

PR (ms)	QRS (ms)	QTcF (ms)	Heart rate (bpm)
120 ≤ PR ≤ 220	QRS ≤ 120	QTc ≤ 450 (male subjects) QTc ≤ 460 (female subjects)	40 ≤ HR ≤ 100

SIGNATURE PAGE – SPONSOR

Title A Phase IIa, randomized, double-blind, placebo-controlled study to evaluate multiple doses of GLPG2222 in subjects with Cystic Fibrosis who are homozygous for the F508del mutation.

This Clinical Study Protocol has been reviewed and approved by the sponsor to ensure compliance with International Conference on Harmonization (ICH) guidelines for Good Clinical Practices (GCP) and applicable regulatory requirements.

Medical Lead	Signature	Date

SIGNATURE PAGE – INVESTIGATOR

Title A Phase IIa, randomized, double-blind, placebo-controlled study to evaluate multiple doses of GLPG2222 in subjects with Cystic Fibrosis who are homozygous for the F508del mutation.

I, the undersigned, have read this protocol and will conduct the study as described in compliance with the Clinical Study Protocol, in accordance with International Conference on Harmonization (ICH) guidelines for Good Clinical Practices (GCP) and applicable regulatory requirements.

Investigator Name	Signature	Date