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

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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 whoare homozygous for the F508del CFTR mutation.Secondary objectives:To assess changes in biomarkers of CFTR...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Interventional

Summary

ID

NL-OMON45460

Source
ToetsingOnline

Brief title
GLPG2222CL202

Condition

- Chromosomal abnormalities, gene alterations and gene variants

Synonym
mucoviscidosis, thick mucus disease

Research involving
Human

Sponsors and support

Primary sponsor: Galapagos NV
Source(s) of monetary or material Support: Galapogos NV

Intervention

Keyword: Cystic Fibrosis, GLPG2222, Safety, Tolerability

Outcome measures

Primary outcome

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.

Secondary outcome

Change from baseline in sweat chloride concentration

• Change from baseline in percent predicted FEV1

• Change from baseline in the respiratory domain of the Cystic Fibrosis

Questionnaire-Revised (CFQ-R)

• PK parameters of GLPG2222

Study description

Background summary

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.

Study 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.

Secondary objectives:
To assess changes in biomarkers of CFTR activity.
To assess changes in respiratory symptoms.
To assess the pharmacokinetics (PK) of GLPG2222.

Study design

This is a Phase IIa, multi-center, randomized, double-blind, placebo-controlled, parallel-groupstudy 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.

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.

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

Intervention

Treatment with the study drug GLPG2222/placebo:
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.

Study burden and risks

After single doses there were a total of eight TEAEs in the pooled placebo group and a total of 13 TEAEs in the combined GLPG2222 groups. Headache was the most common TEAE in both the pooled placebo group (5/8) and in the combined GLPG2222 groups (5/13). In the pooled placebo group, there were two reports of fatigue. All other TEAEs were reported only once in either treatment group, respectively. After repeated dosing, there were a total of 10 TEAEs in the pooled placebo group and 10 TEAEs in the combined GLPG2222 groups. Headache was the most common TEAE in the placebo group (4/10), all other TEAEs were reported only once in either treatment group, respectively. There was no evidence of a dose-response relationship following single or repeated dosing.
No clinically significant findings in physical examination findings, vital signs, clinical laboratory safety tests, FEV1, ECG morphology or ECG time intervals were reported up to 600 mg dosing.

GLPG2222 does not meet the criteria for a compound with high potential for risk of harm to subjects for the following reasons:
* The compound is a small molecule, not a biological.

* GLPG2222 shows a mean apparent half-life of 10 to 16h.
* The compound does not exhibit a highly species-specific action.
* GLPG2222 is not directed towards adaptive immune system targets, as confirmed by the absence of relevant hematological changes and histopathological findings in the immune organs, up to the NOAEL in the 4-week GLP toxicity studies.

There is a high medical need for efficacious therapeutic approaches to treat CF subjects with the F508del mutation.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Male or female subject >= 18 years of age on the day of signing the ICF.
• A confirmed clinical diagnosis of CF and homozygous for the F508del

CFTR mutation (documented in the subject's medical record or CF registry).
• Weight >= 40 kg during the screening period.
• 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.
• FEV1 >= 40% of predicted normal for age, gender and height at screening (pre- or ostbronchodilator).

Exclusion criteria

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.
• Unstable pulmonary status or respiratory tract infection (including rhinosinusitis) requiring a change in therapy within 4 weeks prior to the first study drug administration.
• Need for supplemental oxygen during the day, and > 2 L/minute while sleeping.
• History of hepatic cirrhosis with portal hypertension (e.g. signs/symptoms of splenomegaly, esophageal varices, etc.).
• Concomitant use of any strong inhibitor(s) or inducer(s) of CYP3A4 within 4 weeks prior to the first study drug administration.
• Use of CFTR modulator therapy (e.g. lumacaftor or ivacaftor) within 4 weeks prior to the first study drug administration.
• Concomitant use of CYP2C8 substrates within 4 weeks prior the first study drug administration.
• 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.
• Estimated creatinine clearance < 60 mL/minute using Cockcroft-Gault equation at screening.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-05-2017
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	GLPG2222

Ethics review

Approved WMO Date:	14-02-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-04-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-05-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-05-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-06-2017
Application type:	Amendment

Review commission: METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-004477-40-NL
ClinicalTrials.gov	NCTnumberpending
CCMO	NL60454.018.17