A phase IIa, open-label study of two doses of GLPG1837 in subjects with cystic fibrosis and the S1251N mutation

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Primary Objectives*To evaluate the safety and tolerability of multiple oral doses of GLPG1837 in subjects with CF and at least one copy of the S1251N mutation.Secondary Objectives*To assess changes in sweat chloride from baseline (Day 1) as the...

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

Summary

ID

NL-OMON43806

Source
ToetsingOnline

Brief title
Galapagos, Saphira 2

Condition

- Chromosomal abnormalities, gene alterations and gene variants

Synonym
Cystic Fibrosis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: cystic fibrosis, Phase IIa, S1251N mutation

Outcome measures

Primary outcome

Safety and tolerability will be assessed through:

•Adverse events (AEs)

•Physical examinations

•Vital signs

•12-lead ECG

•Oxygen saturation

•Safety laboratory assessments

Secondary outcome

Efficacy will be assessed through:

•sweat chloride concentration testing

•measuring pulmonary function

Study description

Background summary

GLPG1837 is a CFTR potentiator molecule in clinical development for the treatment of CF.
The compound increases the gating activity of defective CFTR, as shown in preclinical pharmacology studies in in vilro models. Clinical effectiveness of this compound administered alone can only be measured and validated in patients with potentiator-responsive mutations like S1251N. The in vilro potency of GLPG1837 exceeds that of ivacaftor when using a S1251N CFTR harboring cell line. The in vitro potency and activity of GLPG1837, as measured in S1251N/F508del patient-derived intestinal organoids, suggest that this patient group will benefit from this compound. Results from the FIH study indicate the

study drug was generally safe and well tolerated in a population of healthy subjects. As a next step in the clinical development of GLPG1837, its safety, tolerability and efficacy properties will be evaluated in this phase IIa study in CF subjects carrying the potentiator-responsive mutation S1251N.
(page 19/20 of the Protocol)

Study objective

Primary Objectives
*To evaluate the safety and tolerability of multiple oral doses of GLPG1837 in subjects with CF and at least one copy of the S1251N mutation.

Secondary Objectives
*To assess changes in sweat chloride from baseline (Day 1) as the biomarker of cystic fibrosis transmembrane conductance regulator (CFTR) ion channel function
*To explore the changes in pulmonary function (forced expiratory volume in 1 second [FEV1]) from baseline.
*To monitor the plasma concentrations of GLPG1837.

Study design

This study is a Phase IIa, open label, multi-center, ascending-dose study evaluating two oral doses of GLPG1837 in subjects with CF and the S1251N mutation.

- Screening period: up to 3 weeks.
- Length of entire treatment period: 2 consecutive periods of two weeks, without washout between the treatment periods.
- Follow-up period: 7-10 days.

Intervention

Ivacaftor is not allowed as a concomitant medication during the washout or treatment periods of the study. All subjects on a stable ivacaftor regimen for at least 2 weeks at the time of screening will have a washout period for 1 week before start of the first treatment period.
Upon the investigator*s discretion, subjects, subjects may (re-)start ivacaftor treatment following a 4-day wash-out period after the last study drug intake (to avoid interactions between study drug and ivacaftor).
Study drug administration will begin on the morning of Day 1 (at the clinic) and will end on the morning (at home) of the Day 29 visit, as follows:
Subjects will receive three different dosages administered during two consecutive periods (2 weeks 62.5 mg b.i.d. and 2 weeks 125 mg b.i.d.)
Study medication is to be taken in fed condition. Subjects will be instructed to take the study drug after consuming a fat-containing meal (breakfast or

evening meal).

Study burden and risks

patients on Ivacaftor will have to stop using that for the duration of study participation. They can restart after study has ended.
The visits require long hours, for which they are offered financial compensation (if accepted by CEC).
As it is a Phase II study, it is not sure if the patient will benefit from this drug, also if they do, they cannot continue using this drug after study ends.

Contacts

Public
Galapagos NV

Generaal De Wittelaan L11 A3
Mechelen 2800
BE
Scientific
Galapagos NV

Generaal De Wittelaan L11 A3
Mechelen 2800
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1.Male or female subjects >= 18 years of age, on the day of signing the Informed Consent Form (ICF), with a confirmed diagnosis of cystic fibrosis:
a. Clinical diagnosis of cystic fibrosis with signs/symptoms involving at least two organ systems, and
b. Medical history of elevated sweat chloride >=60 mmol/L by quantitative pilocarpine iontophoresis (documented in the subject's medical record) or 2 disease causing CFTR mutations (documented in the subject's medical record).
2.Gating S1251N CFTR mutation on at least one allele in the CFTR gene (documented in the subject's medical record or CF registry); any known or unknown mutation allowed on the 2nd allele. Subject inclusion can be performed, provided that genotype information is available in source data.
3.Subject must meet one of the following:
a. Subjects currently receiving treatment with ivacaftor must be on a stable regimen for at least 2 weeks prior to screening
Or
b. Subjects not on a treatment regimen with ivacaftor for at least 2weeks prior to screening
4.Weight >= 40.0 kg.
5.Subjects on stable concomitant treatment regimen for at least 4 weeks prior to baseline (excluding ivacaftor).
6.Pre- or post-bronchodilator FEV1 >= 40% of predicted normal for age, gender, height at screening.
7.Female subjects must have a negative blood pregnancy test. Determination of serum follicle-stimulating hormone (FSH) will be done for any suspected postmenopausal female with at least 12 months of continuous spontaneous amenorrhea, with FSH levels > 40 IU/mL being confirmative for menopause. For hysterectomy and tubal ligation, documented confirmation will be requested.
8.Subjects will have to use highly effective contraceptive methods prior to the first dose of the study drug, during the study, and for at least 12 weeks after the last dose of the study drug.
a. If the subject is a sexually active woman of childbearing potential, she and her male partner are required to simultaneously use 2 effective contraceptive methods as listed in the protocol. Hormonal contraceptives will not be considered as an effective method; however, female subjects are not required to discontinue hormonal contraceptives. Female subjects who use contraception must have done so for at least 14 days prior to the first dose of the study drug.
b. Non-vasectomized sexually active male subjects with female partners of childbearing potential must be willing to use a condom in addition to having their female partner use another form of contraception as listed

in the protocol.

Exclusion criteria

1.History of sensitivity to any component of the study drug, or a history of drug or other allergy that, in the investigator's opinion, contraindicates the subject's participation in the study.
2.On an ivacaftor-containing treatment regimen and unable or unwilling to discontinue ivacaftor for the washout and treatment periods of the study.
3.Concomitant use of antifungal drugs (e.g. itraconazole, ketoconazole, voriconazole, posaconazole) within 4 weeks of baseline.
4.A history of a clinically meaningful unstable or uncontrolled chronic disease including underlying cystic fibrosis that makes the subject unsuitable for inclusion in the study in the opinion of the investigator.
5.Liver cirrhosis and portal hypertension.
6.History of malignancy within the past 5 years (except for carcinoma in situ of the uterine cervix and basal cell carcinoma of the skin that has been treated with no evidence of recurrence).
7.Any significant change in the medical regimen (including dose and frequency) for pulmonary health within 4 weeks of baseline, including: antibiotics; corticosteroids (as defined in the protocol); inhaled bronchodilators, hypertonic saline, mannitol or dornase alfa; ibuprofen and airway clearance techniques. Individuals taking inhaled antibiotics for suppression of chronic airways infection must be on a stable regimen for at least 8 weeks prior to baseline and willing to continue the same antibiotic through Day 29.
8.Unstable pulmonary status or respiratory tract infection (including pulmonary exacerbation), based on the investigator's opinion, or changes in therapy for pulmonary disease within 4 weeks of baseline as defined in the protocol.
9.History of lung volume reduction surgery or lung transplant.
10.Use of continuous (24 hours per day) supplemental oxygen therapy.
11.Clinically significant abnormalities detected on electrocardiogram (ECG) regarding either rhythm or conduction (e.g., QTcF >= 450 ms, or aknown long QT syndrome). A first degree heart block will not be considered as a significant abnormality.
12.Use of medication known to prolong the QT interval (including herbal and naturopathic therapy).
13.History of solid organ or haematological transplantation or currently on a transplantation waiting list.
14.Abnormal liver function defined as aspartate aminotransferase (AST), alanine aminotransferase (ALT), GGT > 3 x upper limit of the normal range or bilirubin > 2 x upper limit of the normal range.
15.Abnormal renal function defined as creatinine clearance < 50mL/min

using the Cockroft-Gault equation.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-04-2016
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	GLPG1837
Generic name:	G510037

Ethics review

Approved WMO Date:	02-12-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-02-2016
Application type:	First submission
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	EUCTR2015-003292-30-NL
CCMO	NL55488.018.15