Assessment of safety, tolerability, pharmacokinetics and pharmacodynamics of multiple oral doses of the combination of GLPG2451 and GLPG2222, with or without GLPG2737, in adult subjects with cystic fibrosis

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PRIMARY OBJECTIVESParts 1 & 2* To assess safety and tolerability of the combination of GLPG2451 and GLPG2222, with and without GLPG2737 in adult subjects with CF* To characterize the PK of GLPG2451 and GLPG2222, with and without GLPG2737 (&...

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

Summary

ID

NL-OMON46421

Source
ToetsingOnline

Brief title
Falcon

Condition

- Chromosomal abnormalities, gene alterations and gene variants

Synonym
genetic disease, thick mucus disease

Research involving

Human

Sponsors and support

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

Intervention

Keyword: Cystic Fibrosis, GLPG2737, Safety, Tolerability

Outcome measures

Primary outcome

Parts 1 & 2

* Safety and tolerability, assessed by the number of subjects with AEs

* Determine PK parameters (including Cmax, AUC0-24 on Day 14 and 28 (Part 1 only) and Ctrough through 28 days) of GLPG2737, its active metabolite G1125498 (M4), GLPG2451, its active metabolite G1171564 (M31) and GLPG2222

Part 2 only

* Change from baseline in sweat chloride concentration at Day 28

* Changes from baseline in percent predicted FEV1 at Day 28

Secondary outcome

Key secondary endpoints Part 1 only

* Change from baseline in sweat chloride concentration at Day 28

* Changes from baseline in percent predicted FEV1 at Day 28

Other secondary endpoints

* Change from baseline in sweat chloride concentration at Day 15

* Changes from baseline in percent predicted FEV1 at Day 15

* Change from baseline (pre-dose on Day 1) in the respiratory domain of the

cystic fibrosis questionnaire-revised (CFQ-R) on Day 28

Study description

Background summary

There is a high unmet medical need for subjects with CF, including subjects that are either homozygous or heterozygous for the F508del mutation (with a potentiator non-responsive mutation on the second allele). For the latter patient population, no CFTR modulator treatment options are currently available. For F508del homozygous patients, Orkambi is licensed to treat CF patients aged 12 years and above. In pivotal studies, Orkambi treatment was associated with modest improvement in pulmonary function and also led to a reduction in the number of exacerbations requiring hospital admission or antibiotic therapy. In clinical study GLPG2737-CL-105, the use of Orkambi is prohibited from 4 weeks prior to the first study drug administration until 28 days after last study drug administration. It should be noted that the decision to consider a CF patient homozygous for F508del for inclusion in this study should be weighed by the investigator against the potential benefit from treatment with Orkambi. This evaluation has to be done on a case by case basis. Furthermore, the study permits the use of Orkambi after completion of 28 days of follow-up. Beyond this follow-up period, all compounds will be essentially eliminated with the exception of M31. Based upon in vitro results, the likelihood of clinically meaningful interaction for M31 with Orkambi (or other concomitant medications) is expected to be low and is therefore not expected to have an impact on Orkambi*s PK and/or effectiveness.

Results from in vitro TransEpithelial Clamp Circuit (TECC) assays on primary human bronchial epithelial (HBE) cells derived from patients with the above described CFTR mutations indicate the potential for substantial functional improvement of CFTR activity when three CFTR modulator compounds are combined (see investigator's brochures [IB]).1,2,3
Consequently, it is expected that a triple combination therapy of a potentiator and two complementary corrector molecules can bring clinically meaningful benefit to patients with CF.

GLPG2451 is a CFTR potentiator, GLPG2222 is a CFTR corrector, and GLPG2737 is a second CFTR corrector (with a different and complementary mechanism of action to GLPG2222). It is to be noted that the pharmacological activity of these three compounds on CFTR protein is complemented by the activity of two major active metabolites; i.e., metabolite G1171564 (M31) of GLPG2451 and metabolite G1125498 (M4) of GLPG2737 (see IBs for more details).1,2,3

The main objectives of this Phase Ib clinical study are safety, tolerability, PK and pharmacodynamics (PD) of repeated doses of the combination of GLPG2451 (a CFTR potentiator) and GLPG2222 (a first CFTR corrector), before and after the addition of GLPG2737 (a second CFTR corrector), in adult CF subjects.

Study objective

PRIMARY OBJECTIVES

Parts 1 & 2
* To assess safety and tolerability of the combination of GLPG2451 and GLPG2222, with and without GLPG2737 in adult subjects with CF
* To characterize the PK of GLPG2451 and GLPG2222, with and without GLPG2737 (& active metabolites)

Part 2 only
* To assess changes in PD biomarkers of CFTR activity after administration of the combination of GLPG2451 and GLPG2222 and GLPG2737, administered to adult CF subjects

3.2. SECONDARY OBJECTIVE

Part 1 only
* To assess changes in PD biomarkers of CFTR activity after administration of the combination of GLPG2451 and GLPG2222, with or without GLPG2737, administered to adult CF subjects

Study design

This is a Phase Ib, multi-center, open-label, nonrandomized multiple cohorts study to assess the safety, tolerability, PK and pharmacodynamics of multiple doses of a combination treatment of GLPG2451 and GLPG2222, with or without GLPG2737, in adult subjects with CF.
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 24 weeks. Enrolled subjects will come to the clinical study center at screening, on Days 1 (baseline), 2/3*, 7, 14, 15, 21, and 28 and at the follow-up visits scheduled up to 24 weeks after last study drug administration. There are additional time points for PK sampling (Day 5, Day 18 and Day 29). If needed, a study nurse may collect these PK samples at the subject*s home.
* An additional Day 3 visit is foreseen for Part 2 only as the loading doses for Cohorts B and C are administered on 3 consecutive days.
Dual combination (GLPG2451 and GLPG2222) will be administered for 14 days, followed by the triple combination (GLPG2451, GLPG2222 and GLPG2737) for 14

days, without washout in between the sequential treatment periods.

Intervention

Study drugs will be taken on Days 1 to 28 in the morning, with a breakfast or snack. During the follow-up period, subjects will come to the clinical study center for PK sampling and safety assessments on pre-defined days presented in the flow charts, up to 168 days post last dose.

Study burden and risks

The most common GLPG2451 side effects that were reported in previous clinical research studies are headache, common cold, shoulder pain, lower back pain, loose stools, decreased appetite, increased energy and sore throat. No serious adverse events (SAEs) were reported.
GLPG2451 and its active metabolite G1171564 (a product that is formed during the break-down of the study drug GLPG2451 in the body) have long half-lives, meaning that after you have taken the last dose of study drug it may take approximately 5 to 6 months for the break-down product to be removed from your body.
GLPG 2451 has been studied in animals for up to 26 weeks. In these studies, some of the animals had side effects on the testes (the male sex gland that produces and stores sperm). It is not known whether humans will have the same side effects that may affect your ability to father a child. However most men with cystic fibrosis are unable to have biological children because they do not have a vas deferens (a tube in a man*s body that carry sperm away from the testes towards the penis). Furthermore, based upon the doses that will be administered, we believe the risk for you to develop adverse effects on your testes is very low.
Based on the results of 26-week rat studies and the long half-lives of GLPG2451 and its active metabolite G1171564, we believe there is a potential risk that you could develop clouding of the lens of the eye that can cause images to appear blurry (eye lens opacities) following participation in this study.
However, based upon the doses that will be administered, we believe the risk for you to develop lens opacities is very low. Furthermore, no cases of lens opacity have been observed in any of the human volunteers that have received GLPG2451 in previous clinical research studies. Yet, if you would experience any worsening of your vision, it is important to tell the study doctor, regardless of whether or not you think it has to do with the study.
Furthermore, you will be reviewed by an ophthalmologist (eye doctor) at screening to make sure that you had no pre-existing lens opacities before the study started and this examination will be repeated at the end of the dosing period and the end of the study.
Additional ophthalmological evaluations can be planned when deemed clinically relevant by your study doctor.

GLPG2222 has been tested in a limited number of human volunteers and patients with cystic fibrosis. Previous clinical studies with GLPG2222 showed that the most common side effect was headache. Other side effects reported were abnormal physical weakness or lack of energy, thirst, diarrhea, stomach pain or discomfort, inflammation of the stomach and intestine, cough, becoming markedly red in the face and often other areas of the skin, inflammation of the eyes and pruritis.

The most common GLPG2737 adverse events/side effects that were reported in previous clinical research studies in human volunteers are dry mouth or throat or skin, common cold, acne, sore throat, tiredness, skin irritation at site of ECG electrodes, cannula site reaction and headache. No serious adverse events (SAEs) were reported in these phase I studies.
Some human volunteers had mild elevations of liver enzymes (substances in the blood that measure how well your liver is functioning). These levels improved after they stopped taking GLPG2737. Some human volunteers also had a mild decrease in myeloperoxidase, a substance found in white blood cells (immune cells). It is not clear what the significance of this finding is but myeloperoxidase may play a role in fighting infections. However, this finding was not associated with any evidence of increased infection among volunteers during the study period.
GLPG2737 has been studied in animals. Some animals developed side effects on the stomach which may lead to decrease in stomach acid production that in turn may affect digestion. These findings were reversible 2- 4 weeks after stopping GLPG2737. It is not known whether GLPG2737 will lead to a decrease in stomach acid in humans.

Known side effects of the combination of GLPG2451 and GLPG2222:
The combination of GLPG2451 and GLPG2222 was considered to be well tolerated. The most common side effects of the combination of GLPG2451 and GLPG2222 that were reported in a previous clinical research study are headache, diarrhea and sore throat. No serious adverse events (SAEs) were reported.

Known side effects of the combination of GLPG2451, GLPG2222 and GLPG2737:
The combination of GLPG2451, GLPG2222 and GLPG2737 has not been given to humans before and therefore no information about adverse events in humans is known.

There is a high unmet medical need for subjects with CF, including subjects that are either homozygous or heterozygous for the F508del mutation (with a potentiator non-responsive mutation on the second allele). For the latter patient population, no CFTR modulator treatment options are currently available.

Results from in vitro TransEpithelial Clamp Circuit (TECC) assays on primary human bronchial epithelial (HBE) cells derived from patients with the above described CFTR mutations indicate the potential for substantial functional improvement of CFTR activity when three CFTR modulator compounds are combined

(see investigator's brochures [IB]).1,2,3
Consequently, it is expected that a triple combination therapy of a potentiator and two complementary corrector molecules can bring clinically meaningful benefit to patients with CF.

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

* Female or male subject *18 years of age, on the day of signing the ICF;* Confirmed clinical diagnosis of CF (documented in the subject*s medical record). ;* Eligible CFTR genotype at screening:;- Cohort A: Homozygous for the F508del CFTR mutation;- Cohort B: Heterozygous for the F508del CFTR mutation with a potentiator non-responsive mutation on the second allele;- Cohort C: Homozygous for the F508del CFTR mutation;* A body weight of *40 kg at screening. ;* Stable concomitant medication for pulmonary health for CF for at least 4 weeks

prior to the first study drug administration and planned continuation of the same concomitant medication for the duration of the dosing period of the study. Subjects with diabetes mellitus and/or pancreatic insufficiency are eligible for the study provided they are on stable treatment (e.g. medication, diet, pancreatic enzyme replacement therapy) for at least 4 weeks prior to the first study drug administration in the opinion of the investigator.;* Forced expiratory volume in 1 second (FEV1): 40% * FEV1 * 90% of predicted normal for age, sex, and height at screening (pre- or post-bronchodilator) at screening. ;* Sweat chloride concentration *60 mmol/L at screening.;* Non-smoker and non-user of any nicotine and or cannabis containing products. A non-smoker is defined as an individual who has abstained from smoking for at least 1 year prior to the screening. A non-user is defined as an individual who has abstained from any nicotine containing products for at least 1 year prior to the screening.;Reference is made to the protocol for a complete overview of the inclusion criteria.

Exclusion criteria

* History of or ongoing allergic bronchopulmonary aspergillosis.;* Medical history of cataract (or lens opacity) and/or glaucoma.;* Cataract (or lens opacity) and/or glaucoma determined by an ophthalmologist during the screening period.;* Unstable pulmonary status or respiratory tract infection (including rhinosinusitis) requiring a change in therapy within 4 weeks prior to the first study drug administration.;* 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.;* 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).;* History of malignancy within the past 5 years (except for basal cell carcinoma of the skin with no evidence of recurrence and/or carcinoma in situ of the cervix that has been treated with no evidence of recurrence).;* Use of any moderate and strong inhibitor(s) or inducer(s) of CYP3A4 within 4 weeks prior to the first study drug administration (e.g., clarithromycin, itraconazole, ketoconazole, telithromycin, rifampin, carbamazepine).;* Use of CFTR modulator therapy (e.g., lumacaftor and/or ivacaftor) within 4 weeks prior to the first study drug administration.;* Use of any oral corticosteroid within 3 months of screening; or history of oral corticosteroid use for *30 days (cumulative) within 2 years of screening.;* Abnormal liver function test at screening; defined as AST and/or ALT and/or alkaline phosphatase and/or gamma-glutamyl transferase (GGT) *3× the upper limit of normal (ULN); and/or total bilirubin *1.5× the ULN.;Reference is made to the protocol for a complete overview of the exclusion criteria.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-07-2018
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	GLPG2222
Product type:	Medicine
Brand name:	NA
Generic name:	GLPG2451
Product type:	Medicine
Brand name:	NA
Generic name:	GLPG2737

Ethics review

Approved WMO Date:	13-03-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-06-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-08-2018
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-10-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-06-2019
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	EUCTR2017-001067-20-NL
CCMO	NL64541.018.18