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

Summary

EudraCT number	2015-003292-30
Trial protocol	BE NL
Global end of trial date	25 May 2016

Results information

Result version number	v1 (current)
This version publication date	09 June 2017
First version publication date	09 June 2017

Trial information

Trial identification

Sponsor protocol code	GLPG1837-CL-202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02690519
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Galapagos NV
Sponsor organisation address	Generaal De Wittelaan L11 A3, Mechelen, Belgium, 2800
Public contact	Clinical trial information desk, Galapagos NV, +32 15 342 900, rd@glpg.com
Scientific contact	Clinical trial information desk, Galapagos NV, +32 15 342 900, rd@glpg.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 April 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective:
- To evaluate the safety and tolerability of two 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 CFTR ion channel function
- To explore the changes in pulmonary function (FEV1) from baseline.
- To monitor the plasma concentrations of GLPG1837.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization (ICH) Note for Guidance on Good Clinical Practice (GCP) (CPMP/ICH/135/95) and with applicable local requirements.

Prior to the performance of any study-specific procedure, written informed consent was obtained from each subject. Each subject was informed about the nature and purpose of the study, as well as of its risks and benefits. It was explained that subjects could withdraw from the study at any time for any reason and that this would not have any effect on their potential future medical care.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 February 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Belgium: 6
Worldwide total number of subjects	7
EEA total number of subjects	7

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	7
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted from 5 Feb 2016 to 25 May 2016. Out of the 5 sites selected for participation in the study, 4 sites across two countries (Belgium, The Netherlands) actively recruited subjects.

Pre-assignment

Screening details:

In total, 7 subjects were screened and all 7 screened subjects were enrolled.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	GLPG1837 62.5 mg b.i.d.

Arm description:

Treatment 1

Arm type	Experimental
Investigational medicinal product name	GLPG1837
Investigational medicinal product code	G510037
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral doses of 62.5 mg GLPG1837 administered twice daily (b.i.d.) for 14 days in fed condition. The study drug was administered as a tablet containing 62.5 mg G510037 (G510037 is the compound code for GLPG1837).

Arm title	GLPG1837 125 mg b.i.d.

Arm description:

Treatment 2 (immediately following to treatment 1, without washout in between dosing periods)

Arm type	Experimental
Investigational medicinal product name	GLPG1837
Investigational medicinal product code	G510037
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral doses of 125 mg GLPG1837 administered twice daily (b.i.d.) for 14 days in fed condition. The study drug was administered as a tablet containing 125 mg G510037 (G510037 is the compound code for GLPG1837).

Number of subjects in period 1	GLPG1837 62.5 mg b.i.d.	GLPG1837 125 mg b.i.d.
Started	7	7
Completed	7	7

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	7	7	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	7	7	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
median	30		
full range (min-max)	18 to 51	-	
Gender categorical Units: Subjects			
Female	1	1	
Male	6	6	
Race Units: Subjects			
White	7	7	
BMI Units: kg/m2			
median	24.5		
full range (min-max)	19 to 33.8	-	

End points

End points reporting groups

Reporting group title	GLPG1837 62.5 mg b.i.d.
Reporting group description:	
Treatment 1	
Reporting group title	GLPG1837 125 mg b.i.d.
Reporting group description:	
Treatment 2 (immediately following to treatment 1, without washout in between dosing periods)	

Primary: Safety - TEAE (Treatment-Emergent Adverse Events)

End point title	Safety - TEAE (Treatment-Emergent Adverse Events)[1]

End point description:

TEAEs were reported for 5 (71.4%) subjects on 62.5 mg b.i.d. GLPG1837, 5 (71.4%) subjects on 125 mg b.i.d. GLPG1837, and 5 (71.4%) subjects during the entire GLPG1837 treatment period. All TEAEs were mild or moderate in intensity, except for one case of severe abdominal pain in the 125 mg b.i.d. GLPG1837 period.

TEAEs that were considered at least possible related to the study drug by the investigator were observed in 2 (28.6%) subjects while on 62.5 mg b.i.d. GLPG1837, one (14.3%) subject on 125 mg b.i.d. GLPG1837 and 2 (28.6%) subjects during the entire GLPG1837 treatment period. TEAEs considered at least possibly treatment-related by the investigator were: abdominal pain upper, dry mouth, gastro-oesophageal reflux disease, cough, haemoptysis and sputum increased.

An analysis of the TEAEs was performed. Laboratory assessments, 12-lead ECG, vital signs and oxygen saturation by pulse oximetry were analyzed descriptively.

End point type	Primary

End point timeframe:

From first study drug administration until the final follow-up visit at multiple timepoints.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Analysis is only descriptive

End point values	GLPG1837 62.5 mg b.i.d.	GLPG1837 125 mg b.i.d.		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	7		
Units: Subjects	5	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy - change in sweat chloride concentration

End point title	Efficacy - change in sweat chloride concentration

End point description:

The changes from baseline (Day 1 pre-dose) in sweat chloride (SwCl) concentration for the entire intent-to-treat (ITT) population and for subjects with a baseline sweat chloride ≥ 60 mmol/L after administration of GLPG1837 62.5 mg b.i.d. for 14 days (at Day 15; GLPG1837 62.5 mg b.i.d. group) and

after sequential administration of GLPG1837 62.5 mg b.i.d. for 14 days and GLPG1837 125 mg b.i.d. for 14 days (at Day 29; GLPG1837 125 mg b.i.d. group).

End point type	Secondary

End point timeframe:

Change from baseline (Day 1 pre-dose) at Day 15 and Day 29.

End point values	GLPG1837 62.5 mg b.i.d.	GLPG1837 125 mg b.i.d.		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7[2]	6[3]		
Units: Change from baseline				
arithmetic mean (confidence interval 95%)				
ITT population	-16.3 (-32.4 to -0.2)	-21.3 (-48.1 to 5.5)		
Subjects with baseline SwCl ≥ 60 mmol/L	-17.6 (-41.3 to 6.1)	-24.2 (-58.3 to 9.9)		

Notes:

[2] - N=7 for ITT population
N=5 for subjects with SwCl ≥ 60 mmol/L
[3] - N=6 for ITT population
N=5 for subjects with SwCl ≥ 60 mmol/L

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy - change in %FEV1

End point title	Efficacy - change in %FEV1

End point description:

The changes from baseline (Day 1 pre-dose) in percent predicted forced expiratory volume in 1 second (%FEV1) for the entire intent-to-treat (ITT) population after administration of GLPG1837 62.5 mg b.i.d. for 14 days (at Day 15; GLPG1837 62.5 mg b.i.d. group) and after sequential administration of GLPG1837 62.5 mg b.i.d. for 14 days and GLPG1837 125 mg b.i.d. for 14 days (at Day 29; GLPG1837 125 mg b.i.d. group).

End point type	Secondary

End point timeframe:

Change from baseline (Day 1 pre-dose) at Day 15 and Day 29.

End point values	GLPG1837 62.5 mg b.i.d.	GLPG1837 125 mg b.i.d.		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	7		
Units: Change from baseline				
arithmetic mean (confidence interval 95%)				
ITT population	-0.4 (-3.8 to 2.9)	-1.4 (-8.3 to 5.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics - plasma concentration

End point title	Pharmacokinetics - plasma concentration

End point description:

Geometric mean plasma concentrations of GLPG1837 in plasma of the entire intent-to-treat (ITT) population at pre-dose after administration of GLPG1837 62.5 mg b.i.d. for 14 days (at Day 15; GLPG1837 62.5 mg b.i.d. group) and after sequential administration of GLPG1837 62.5 mg b.i.d. for 14 days and GLPG1837 125 mg b.i.d. for 14 days (at Day 29; GLPG1837 125 mg b.i.d. group).

End point type	Secondary

End point timeframe:

at Day 15 and Day 29.

End point values	GLPG1837 62.5 mg b.i.d.	GLPG1837 125 mg b.i.d.		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	6		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
ITT population	6.64 (± 84.9)	13.7 (± 120)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs: from signing informed consent until the last follow-up visit at multiple time points.
TEAEs: from first study drug administration until the last follow-up visit at multiple time points.

Adverse event reporting additional description:

TEAEs are tabulated by System Organ Class and Preferred Term

No deaths, serious AEs (SAEs) or TEAEs leading to discontinuation of study medication were reported.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	GLPG1837 62.5 mg b.i.d.
Reporting group description:	
Treatment period 1	
Reporting group title	GLPG1837 125 mg b.i.d.
Reporting group description:	
Treatment period 2	
Reporting group title	GLPG1837 total
Reporting group description:	
Overall treatment period	

Serious adverse events	GLPG1837 62.5 mg b.i.d.	GLPG1837 125 mg b.i.d.	GLPG1837 total
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	GLPG1837 62.5 mg b.i.d.	GLPG1837 125 mg b.i.d.	GLPG1837 total
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 7 (71.43%)	5 / 7 (71.43%)	5 / 7 (71.43%)
Congenital, familial and genetic disorders			
Cystic fibrosis pancreatic			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences (all)	0	1	1

Nervous system disorders			
Headache			
subjects affected / exposed	2 / 7 (28.57%)	2 / 7 (28.57%)	4 / 7 (57.14%)
occurrences (all)	2	4	6
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	2 / 7 (28.57%)
occurrences (all)	1	1	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences (all)	1	2	3
Abdominal pain upper			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences (all)	1	1	2
Dry mouth			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Post-tussive vomiting			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Reproductive system and breast disorders			
Menstruation delayed			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	2 / 7 (28.57%)
occurrences (all)	1	1	2
Haemoptysis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	2 / 7 (28.57%)
occurrences (all)	1	1	2
Oropharyngeal pain			

subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	2 / 7 (28.57%)
occurrences (all)	2	1	3
Sputum increased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	2 / 7 (28.57%)
occurrences (all)	1	1	2
Dyspnoea			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	2 / 7 (28.57%)
occurrences (all)	2	0	2
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	2 / 7 (28.57%)
occurrences (all)	0	2	2
Laryngitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Nasopharyngitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 7 (14.29%)
occurrences (all)	0	1	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 December 2015	In response to recommendations and specific requests from competent authorities, clarifications were added to the protocol: - Revised description of contraceptive methods. - Changed recommendation for spermicides. - Added restrictions and recommendations related to drugs that are substrates for CYP2B6, P-gp and BCRP These updates are considered substantial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported