



Clinical trial results:

A phase IIa, open label study of multiple doses of GLPG1837 in subjects with cystic fibrosis and the G551D mutation.

Summary

EudraCT number	2015-003291-77
Trial protocol	GB DE CZ IE
Global end of trial date	06 October 2016

Results information

Result version number	v1 (current)
This version publication date	21 October 2017
First version publication date	21 October 2017

Trial information

Trial identification

Sponsor protocol code	GLPG1837-CL-201
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02707562
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	04 April 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 October 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 multiple oral doses of GLPG1837 in subjects with CF and at least one copy of the G551D 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 assess the PK profile of GLPG1837.
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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. All subjects were informed about the nature and purpose of the study, as well as of its risks and benefits. It was explained that s/he could withdraw from the study at any time for any reason and that this would not have any effect on her/his potential future medical care.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 February 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Ireland: 2
Worldwide total number of subjects	26
EEA total number of subjects	15

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)	26
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted from 23 February 2016 to 06 October 2016.
Sixteen sites across five countries (Ireland, Czech Republic, Germany, United Kingdom, Australia) participated in the study; 15 sites actively enrolled subjects in the study.

Pre-assignment

Screening details:

In total, 34 subjects were screened of which 26 were eligible and enrolled.

Period 1

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

Blinding implementation details:

This was an open label study.

Arms

Are arms mutually exclusive?	No
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Arm title	GLPG1837 - 125 mg b.i.d
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Arm description: -

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 GLPG1837 125 mg were administered as two tablets of 62.5 mg, twice daily (b.i.d) during 1 week period under fed conditions.

The study drug GLPG1837 was presented as a tablet containing 62.5 mg G510037 (G510037 is the compound code for GLPG1837).

Arm title	GLPG1837 - 250 mg b.i.d
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Arm description: -

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 GLPG1837 250 mg were administered as two tablets of 125 mg, twice daily (b.i.d) during 1 week period under fed conditions.

The study drug GLPG1837 was presented as a tablet containing 125 mg G510037.

Treatment GLPG1837 - 250 mg b.i.d succeeded treatment GLPG1837 - 125 mg b.i.d, without washout in between dosing periods.

Arm title	GLPG1837 - 500 mg b.i.d
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Arm description: -

Arm type	Experimental
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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 GLPG1837 500 mg were administered as two tablets of 250 mg, twice daily (b.i.d) during 2 week period under fed conditions.

The study drug GLPG1837 was presented as a tablet containing 250 mg G510037.

Treatment GLPG1837 - 500 mg b.i.d succeeded treatment GLPG1837 - 250 mg b.i.d, without washout in between dosing periods.

Number of subjects in period 1	GLPG1837 - 125 mg b.i.d	GLPG1837 - 250 mg b.i.d	GLPG1837 - 500 mg b.i.d
Started	26	26	26
Completed	26	26	26

Baseline characteristics

Reporting groups

Reporting group title

Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	26	26	
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)	26	26	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
median	29		
full range (min-max)	19 to 51	-	
Gender categorical			
Units: Subjects			
Female	14	14	
Male	12	12	
Race			
Units: Subjects			
White	26	26	
BMI			
Units: kg/m ²			
median	23.1		
full range (min-max)	18.9 to 33.9	-	

End points

End points reporting groups

Reporting group title	GLPG1837 - 125 mg b.i.d
Reporting group description: -	
Reporting group title	GLPG1837 - 250 mg b.i.d
Reporting group description: -	
Reporting group title	GLPG1837 - 500 mg b.i.d
Reporting group description: -	

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

End point title	Safety - TEAE (Treatment-Emergent Adverse Events) ^[1]
End point description:	The number of subjects with treatment-emergent adverse events (TEAEs). An analysis of the treatment-emergent AEs (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 last follow-up visit at multiple time points.

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 descriptive only.

End point values	GLPG1837 - 125 mg b.i.d	GLPG1837 - 250 mg b.i.d	GLPG1837 - 500 mg b.i.d	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	26	26	
Units: Subjects				
Any TEAE	14	14	20	
Severe TEAE	1	0	3	
Serious TEAE	0	0	2	
Treatment related TEAE	9	7	12	
Discontinuation due to AE	0	1	1	

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 intent-to-treat (ITT) population after sequential administration of GLPG1837 125 mg b.i.d. for 7 days (at Day 8; GLPG1837 - 125 mg b.i.d. group), GLPG1837 250 mg b.i.d. for 7 days (at Day 15; GLPG1837 - 250 mg b.i.d. group) and GLPG1837 500 mg for 14 days (at Day 29; GLPG1837 - 500 mg b.i.d. group).
End point type	Secondary

End point timeframe:

Change from baseline at Day 8, Day 15 and Day 29.

End point values	GLPG1837 - 125 mg b.i.d	GLPG1837 - 250 mg b.i.d	GLPG1837 - 500 mg b.i.d	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26	21	25	
Units: mmol/L				
arithmetic mean (confidence interval 95%)	-11.6 (-17.9 to -5.2)	-15.1 (-19.6 to -10.7)	-28.8 (-39.1 to -18.4)	

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 ITT population after sequential administration of GLPG1837 125 mg b.i.d. for 7 days (at Day 8; GLPG1837 - 125 mg b.i.d. group), GLPG1837 250 mg b.i.d. for 7 days (at Day 15; GLPG1837 - 250 mg b.i.d. group) and GLPG1837 500 mg b.i.d. for 14 days (at Day 29; GLPG1837 - 500 mg b.i.d. group).	
End point type	Secondary
End point timeframe: Change from baseline at Day 8, Day 15 and Day 29.	

End point values	GLPG1837 - 125 mg b.i.d	GLPG1837 - 250 mg b.i.d	GLPG1837 - 500 mg b.i.d	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	24	21	
Units: percent				
arithmetic mean (confidence interval 95%)	0.0 (-1.3 to 1.4)	0.6 (-1.5 to 2.6)	2.8 (0.2 to 5.3)	

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 PK population at pre-dose after sequential administration of GLPG1837 125 mg b.i.d. for 7 days (at Day 8; GLPG1837 - 125 mg b.	

i.d. group), GLPG1837 250 mg b.i.d. for 7 days (at Day 15; GLPG1837 - 250 mg b.i.d. group) and GLPG1837 500 mg b.i.d. for 14 days (at Day 29; GLPG1837 - 500 mg b.i.d. group).

End point type	Secondary
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End point timeframe:

PK blood samples were taken pre-dose at Day 8, Day 15 and Day 29

End point values	GLPG1837 - 125 mg b.i.d	GLPG1837 - 250 mg b.i.d	GLPG1837 - 500 mg b.i.d	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25	25	22	
Units: ng/mL				
geometric mean (geometric coefficient of variation)	27.3 (± 113)	47.2 (± 122)	107 (± 375)	

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:

All TEAEs are presented.

TEAEs are tabulated by System Organ Class and Preferred Term.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	GLPG1837 - 125 mg b.i.d
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Reporting group description: -

Reporting group title	GLPG1837 - 250 mg b.i.d
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Reporting group description: -

Reporting group title	GLPG1837 - 500 mg b.i.d
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Reporting group description: -

Serious adverse events	GLPG1837 - 125 mg b.i.d	GLPG1837 - 250 mg b.i.d	GLPG1837 - 500 mg b.i.d
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	2 / 26 (7.69%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Cystic fibrosis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	GLPG1837 - 125 mg b.i.d	GLPG1837 - 250 mg b.i.d	GLPG1837 - 500 mg b.i.d
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 26 (53.85%)	14 / 26 (53.85%)	20 / 26 (76.92%)
Vascular disorders			
Phlebitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	2 / 26 (7.69%)	1 / 26 (3.85%)	2 / 26 (7.69%)
occurrences (all)	2	1	2
Fatigue			
subjects affected / exposed	4 / 26 (15.38%)	5 / 26 (19.23%)	0 / 26 (0.00%)
occurrences (all)	6	5	0
Chest pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Chills			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	0 / 26 (0.00%)
occurrences (all)	2	0	0
Pyrexia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Vaginal discharge			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Sputum increased			
subjects affected / exposed	6 / 26 (23.08%)	0 / 26 (0.00%)	1 / 26 (3.85%)
occurrences (all)	6	0	2
Cough			

subjects affected / exposed	2 / 26 (7.69%)	1 / 26 (3.85%)	2 / 26 (7.69%)
occurrences (all)	2	1	2
Dyspnoea			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	1 / 26 (3.85%)
occurrences (all)	1	0	1
Haemoptysis			
subjects affected / exposed	2 / 26 (7.69%)	0 / 26 (0.00%)	0 / 26 (0.00%)
occurrences (all)	2	0	0
Nasal congestion			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Productive cough			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Wheezing			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Libido decreased			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	2 / 26 (7.69%)
occurrences (all)	1	0	2
Bacterial test			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Blood glucose increased			

subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0	1 / 26 (3.85%) 1
Blood pressure increased subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0
Blood pressure systolic increased subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0	1 / 26 (3.85%) 1
Electrocardiogram abnormal subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0	1 / 26 (3.85%) 1
Heart rate increased subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0
Urinary sediment present subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0	1 / 26 (3.85%) 1
Urine analysis abnormal subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 26 (3.85%) 1	0 / 26 (0.00%) 0
White blood cells urine subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0	1 / 26 (3.85%) 1
Injury, poisoning and procedural complications			
Arthropod bite subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 26 (3.85%) 1	0 / 26 (0.00%) 0
Concussion subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0	1 / 26 (3.85%) 1
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	4 / 26 (15.38%) 4	6 / 26 (23.08%) 9	6 / 26 (23.08%) 9
Migraine			

subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	0 / 26 (0.00%) 0	1 / 26 (3.85%) 4
Dizziness subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 26 (3.85%) 1	1 / 26 (3.85%) 1
Lethargy subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0	1 / 26 (3.85%) 1
Syncope subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0	1 / 26 (3.85%) 1
Ear and labyrinth disorders Ear discomfort subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0	1 / 26 (3.85%) 1
Tinnitus subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	1 / 26 (3.85%) 1	2 / 26 (7.69%) 4
Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	1 / 26 (3.85%) 1	2 / 26 (7.69%) 4
Abdominal pain subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 26 (3.85%) 1	2 / 26 (7.69%) 3
Diarrhoea subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	1 / 26 (3.85%) 1	0 / 26 (0.00%) 0
Constipation subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0
Eructation			

subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Gastritis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Steatorrhoea			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Glycosuria			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Urine abnormality			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 26 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Infections and infestations			
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 26 (3.85%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 26 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1

Rhinovirus infection subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0	1 / 26 (3.85%) 1
Sputum purulent subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	0 / 26 (0.00%) 0	0 / 26 (0.00%) 0
Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 26 (3.85%) 1	0 / 26 (0.00%) 0
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	1 / 26 (3.85%) 1	0 / 26 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 December 2015	<p>General Clinical Study Protocol Amendment 1, version 1.0.</p> <p>In response to recommendations and specific requests from Competent Authorities, clarifications were added to the protocol.</p> <ul style="list-style-type: none">- Revised description of contraceptive methods- Changed recommendation for spermicides- Added restrictions and recommendations related to drugs that are substrates for CYP2B6, P-gp and BRCP <p>These updates are considered substantial.</p>
14 March 2016	<p>General Clinical Study Protocol Amendment 2, version 1.0.</p> <p>Based upon a re-evaluation of 1/ the study objectives and 2/ the patient recruitment projection, the sample size of this study was increased from at least 12 to 32 subjects.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported