



Clinical trial results:

Phase II, Randomized, Double-Blind, Placebo-Controlled, Proof-of-Concept Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of GLPG1205 in Patients with Moderate to Severe Ulcerative Colitis

Summary

EudraCT number	2014-001893-32
Trial protocol	CZ HU BE DE PL
Global end of trial date	09 November 2015

Results information

Result version number	v1 (current)
This version publication date	24 November 2016
First version publication date	24 November 2016

Trial information

Trial identification

Sponsor protocol code	GLPG1205-CL-211
-----------------------	-----------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02337608
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	01 April 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	09 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective:

- To explore the efficacy of GLPG1205 versus placebo in subjects with UC by use of the Mayo score comparing results at Week 8 to baseline.

Secondary objectives:

- To explore the efficacy of GLPG1205 versus placebo in subjects with UC by use of the partial Mayo score comparing results with baseline.
- To explore the efficacy of GLPG1205 versus placebo in subjects with UC by use of the histopathological Geboes Index comparing results at Week 8 with baseline.
- To evaluate the safety and tolerability of GLPG1205 given to subjects with moderate to severe UC for 12 weeks compared with placebo.
- To characterize the PK of GLPG1205 in subjects with UC.
- To explore the effects of GLPG1205 on selected biomarkers (e.g., fecal calprotectin, myeloperoxidase (MPO), C-reactive protein [CRP]).

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. In addition, this clinical study was conducted in compliance with all international and national laws and regulations, as well as any applicable guidelines of the countries in which the clinical study was performed.

A signed and dated informed consent was required before any screen procedures were done. The Investigators were to explain the nature, purpose, and risks of the study to each subject. Each subject was to be informed that he/she could withdraw from the study at any time and for any reason. Each subject was to be given sufficient time to consider the implications of the study before deciding whether to participate. Subjects who chose to participate had to sign an informed consent document. A copy of the signed and dated written informed consent form (ICF) was to be provided to the subject.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 December 2014
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	Poland: 21
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Czech Republic: 9
Country: Number of subjects enrolled	Germany: 7

Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Russian Federation: 16
Worldwide total number of subjects	63
EEA total number of subjects	47

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)	62
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled at study sites in Europe. The first participant was randomised on 17 December 2014. The last visit occurred on 9 November 2015.

Pre-assignment

Screening details:

102 subjects were screened.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
------------------------------	-----

Arm title	GLPG1205
------------------	----------

Arm description: -

Arm type	Experimental
Investigational medicinal product name	GLPG1205
Investigational medicinal product code	G321605
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received 100 mg GLPG1205 (2 capsules of 50 mg) qd for 12 weeks.
The GLPG1205 capsules had to be taken orally with a glass of water in the morning.

Arm title	Placebo
------------------	---------

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received 100 mg placebo (2 capsules of 50 mg) qd for 12 weeks.
The placebo capsules had to be taken orally with a glass of water in the morning.

Number of subjects in period 1	GLPG1205	Placebo
Started	42	21
Completed	31	18
Not completed	11	3
Consent withdrawn by subject	2	1
Treatment failure	3	1
Adverse event, non-fatal	6	1

Baseline characteristics

Reporting groups

Reporting group title	GLPG1205
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	GLPG1205	Placebo	Total
Number of subjects	42	21	63
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Between 18-75 years of age, inclusive	42	21	63
Age continuous			
Units: years			
arithmetic mean	38.7	41.5	
full range (min-max)	20 to 72	19 to 61	-
Gender categorical			
Units: Subjects			
Female	11	10	21
Male	31	11	42

Subject analysis sets

Subject analysis set title	GLPG1205 change vs Baseline
Subject analysis set type	Intention-to-treat
Subject analysis set description: All randomized subjects who had at least 1 dose of study drug and had at least 1 post-baseline assessment with efficacy data.	
Subject analysis set title	Placebo vs Baseline
Subject analysis set type	Intention-to-treat
Subject analysis set description: Mayo Score	

Reporting group values	GLPG1205 change vs Baseline	Placebo vs Baseline	
Number of subjects	40	21	
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)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Between 18-75 years of age, inclusive	40	21	
Age continuous Units: years arithmetic mean full range (min-max)			
Gender categorical Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	GLPG1205
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	GLPG1205 change vs Baseline
Subject analysis set type	Intention-to-treat
Subject analysis set description: All randomized subjects who had at least 1 dose of study drug and had at least 1 post-baseline assessment with efficacy data.	
Subject analysis set title	Placebo vs Baseline
Subject analysis set type	Intention-to-treat
Subject analysis set description: Mayo Score	

Primary: Efficacy: Mayo Score Week 8

End point title	Efficacy: Mayo Score Week 8
End point description: The Mayo score equals the sum of the 4 subscores (stool frequency, rectal bleeding, physician's global assessment and Mayo endoscopic subscore) and therefore ranges from 0 to 12. A score of ≤ 2 is considered remission, a score of 3 to 5 is considered mild, a score of 6 to 10 is considered moderate, and a score of 11 to 12 is considered severe.	
End point type	Primary
End point timeframe: Week 8	

End point values	GLPG1205	Placebo	GLPG1205 change vs Baseline	Placebo vs Baseline
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	40	21	40	21
Units: Score				
arithmetic mean (full range (min-max))				
Week 8	6.8 (0 to 11)	6.3 (0 to 11)	-2 (-8 to 3)	-2.4 (-9 to 1)

Statistical analyses

Statistical analysis title	Mayo score Week 8
Comparison groups	GLPG1205 v Placebo

Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.5005
Method	ANCOVA

Primary: Efficacy: Mayo Score: Derived Responses at Week 8

End point title	Efficacy: Mayo Score: Derived Responses at Week 8
End point description:	A summary of the Mayo clinical response, clinical remission, mucosal healing, and endoscopic response per treatment group at Week 8
End point type	Primary
End point timeframe:	Week 8

End point values	GLPG1205	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	21		
Units: Percentage				
number (not applicable)				
Mayo response	40	47.6		
Mayo remission	5	4.8		
Endoscopic response	10	23.8		
Mucosal healing	5	9.5		

Statistical analyses

Statistical analysis title	Mayo Score: derived responses at week 8
Comparison groups	GLPG1205 v Placebo
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.6143 ^[1]
Method	Regression, Logistic

Notes:

[1] - Mayo response (p-value=0.6143)

Mayo remission (p-value=0.9084)

Endoscopic response (p-value=0.1865)

Mucosal healing (p-value=0.5519)

There was no statistically significant difference between GLPG1205 and placebo.

Secondary: Efficacy: Partial Mayo Score

End point title	Efficacy: Partial Mayo Score
End point description:	The Partial Mayo consists of the clinical components only of the MAYO only, namely stool frequency,

rectal bleeding and physician's global assessment. Partial Mayo score ranges from 0 to 9, with higher scores indicating a more severe disease.

End point type	Secondary
End point timeframe:	
Week 4, 8, 12	

End point values	GLPG1205	Placebo	GLPG1205 change vs Baseline	Placebo vs Baseline
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	40	21	40	21
Units: Severity				
arithmetic mean (full range (min-max))				
Week 4	5.2 (1 to 8)	4.3 (0 to 8)	-1 (-6 to 2)	-1.7 (-6 to 2)
Week 8	4.3 (0 to 8)	4 (0 to 8)	-1.9 (-7 to 2)	-2 (-6 to 1)
Week 12	3.8 (0 to 8)	3.5 (0 to 9)	-2.4 (-8 to 2)	-2.5 (-6 to 2)

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy: Geboes Index

End point title	Efficacy: Geboes Index
End point description:	
The Geboes Index is the highest grade with a sub-grade above 0 and ranges from 0.0 to 5.4, with higher scores indicating a more severe disease. Scores: 0 = Structural (architectural change), 1 = Chronic inflammatory infiltrate, 2A = Lamina propria eosinophils, 2B = Lamina propria neutrophils, 3 = Neutrophils in epithelium, 4 = Crypt destruction, 5 = Erosion or ulceration.	
End point type	Secondary
End point timeframe:	
Week 8	

End point values	GLPG1205	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	21		
Units: Subjects	40	21		

Attachments (see zip file)	Table 20 Week 8 Geboes Index Shift Table.pdf
-----------------------------------	--

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics

End point title	Pharmacokinetics
-----------------	------------------

End point description:

On average, the plasma concentration of GLPG1205 in subjects with UC were within the range of the GLPG1205 plasma concentrations seen in healthy subjects who were administered GLPG1205 100 mg qd. However, some subjects showed GLPG1205 plasma concentrations that were out of the range that was observed in healthy subjects who were administered GLPG1205 at the same dose of 100 mg qd.

End point type	Secondary
----------------	-----------

End point timeframe:

A blood sample for analysis of GLPG1205 in blood plasma was collected at Week 4, 8 and 12

End point values	GLPG1205	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	0 ^[2]		
Units: Subjects	37			

Notes:

[2] - Not applicable

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamics: Fecal Calprotectin

End point title	Pharmacodynamics: Fecal Calprotectin
-----------------	--------------------------------------

End point description:

A stool sample for the assessment of fecal calprotectin levels will be assessed as a marker for intestinal inflammatory activity.

End point type	Secondary
----------------	-----------

End point timeframe:

Fecal calprotectin analysis on stool samples: Week 4, 8 and 12

End point values	GLPG1205	Placebo	GLPG1205 change vs Baseline	Placebo vs Baseline
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	40	21	40	21
Units: mg/kg				
arithmetic mean (full range (min-max))				
Week 4	748.5 (8 to 5546)	490.8 (8 to 3791)	-268.2 (-6363 to 3815)	45.9 (-881 to 2206)
Week 8	563.3 (8 to 5546)	540.3 (8 to 5063)	-453.1 (-6394 to 2455)	95.3 (-1396 to 4140)
Week 12	781 (8 to 5937)	655.2 (8 to 4582)	-235.7 (-6394 to 5590)	210.2 (-1396 to 3659)

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamics: Myeloperoxidase Week 8

End point title	Pharmacodynamics: Myeloperoxidase Week 8
End point description:	Lamina Propria MPO Positive vs. Stromal (%)
End point type	Secondary
End point timeframe:	Week 8

End point values	GLPG1205	Placebo	GLPG1205 change vs Baseline	Placebo vs Baseline
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	40	21	40	21
Units: % of MPO positive cells vs stromal cells				
arithmetic mean (full range (min-max))				
Week 8 25 cm (Distal Sigmoid)	8.9 (1 to 35)	9 (1 to 37)	0.6 (-2.2 to 3.3)	0.7 (-12 to 33)
Week 8 (Most Inflamed)	10.2 (1 to 35)	10.8 (2 to 35)	1 (-1.4 to 3.5)	0.7 (-9 to 26)

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamics: serum C-reactive Protein (CRP) Week 4, 8, 12

End point title	Pharmacodynamics: serum C-reactive Protein (CRP) Week 4, 8, 12
End point description:	
End point type	Secondary
End point timeframe:	Week 4, 8, 12

End point values	GLPG1205	Placebo	GLPG1205 change vs Baseline	Placebo vs Baseline
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	40	21	40	21
Units: mg/L				
arithmetic mean (full range (min-max))				
Week 4	10.7 (1 to 153)	5.6 (0 to 24)	2 (-55 to 140)	0.5 (-16 to 20)
Week 8	11.4 (0 to 153)	4.9 (0 to 23)	2.7 (-56 to 140)	-0.3 (-17 to 6)
Week 12	10.6 (0 to 153)	4.5 (0 to 22)	1.9 (-56 to 140)	-0.7 (-16 to 21)

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: TEAE

End point title	Safety: TEAE
-----------------	--------------

End point description:

(S)AE / TEAE: reference is made to the adverse events section.

The total number of subjects with at least one treatment-emergent adverse event (TEAE) was 9 (42.9%) subjects in the placebo group and 26 (61.9%) subjects in the GLPG1205 group.

End point type	Secondary
----------------	-----------

End point timeframe:

From screening untill follow-up visit

End point values	GLPG1205	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	21		
Units: subjects				
TEAE	26	9		
SAE	8	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: physical examination, vital signs, ECG, clinical laboratory

End point title	Safety: physical examination, vital signs, ECG, clinical laboratory
-----------------	---

End point description:

There were no clinically meaningful trends in changes from baseline for any vital signs, ECG, or physical examination variables. There were no clinically relevant abnormalities reported on laboratory

assessments. However, in the GLPG1205 group, there was a larger increase in creatinine compared to the placebo group.

End point type	Secondary
End point timeframe:	
Week 4, 8 , 12 and follow-up	
for physical exam, no week 8	

End point values	GLPG1205	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	21		
Units: Subjects	42	21		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From screening until follow-up visit

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	19.0
--------------------	------

Reporting groups

Reporting group title	GLPG1205
-----------------------	----------

Reporting group description:

The total number of subjects with at least one treatment-emergent adverse event (TEAE) was 26 (61.9%) subjects in the GLPG1205 group. In the GLPG1205 group, the highest number of subjects with TEAEs were observed the Gastrointestinal disorders SOC (11 [26.2%]), mainly with the preferred term (PT) of UC (4 [9.5%]) and nausea (3 [7.1%]).

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

The total number of subjects with at least one treatment-emergent adverse event (TEAE) was 9 (42.9%) subjects in the placebo group.

In the placebo group, the highest number of subjects with TEAEs came from the Gastrointestinal disorders SOC (3 [14.3%]) and Nervous system disorders SOC (3 [14.3%]).

Serious adverse events	GLPG1205	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 42 (19.05%)	0 / 21 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	1 / 42 (2.38%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 42 (2.38%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
anemia			

subjects affected / exposed	2 / 42 (4.76%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	4 / 42 (9.52%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash macular			
subjects affected / exposed	1 / 42 (2.38%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	GLPG1205	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 42 (61.90%)	9 / 21 (42.86%)	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 42 (9.52%)	2 / 21 (9.52%)	
occurrences (all)	4	2	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 42 (11.90%)	1 / 21 (4.76%)	
occurrences (all)	5	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 42 (11.90%)	1 / 21 (4.76%)	
occurrences (all)	5	1	
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	4 / 42 (9.52%)	0 / 21 (0.00%)	
occurrences (all)	4	0	
Nausea			

subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	0 / 21 (0.00%) 0	
Flatulence subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2	0 / 21 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	1 / 21 (4.76%) 1	
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2	0 / 21 (0.00%) 0	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2	1 / 21 (4.76%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 November 2014	The reasons for clinical study protocol amendment (CSPA) 1 were as follows: <ul style="list-style-type: none">- Updated the emergency contact email address.- In the Risk Benefit section, the interaction with several CYPs was clarified and information about drug transporters was added.- In the Removal from Subjects from Therapy Assessment section, the definition of disease worsening was added.- In the Prior and Concomitant Therapy section, guidance on possible drug-drug interactions was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported