Clinical trial results:
A PHASE 2B RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL ADAPTIVE 2-STAGE, MULTI-CENTRE STUDY TO EVALUATE THE SAFETY AND EFFICACY OF ORAL PTG-100 INDUCTION IN SUBJECTS WITH MODERATE TO SEVERE ACTIVE ULCERATIVE COLITIS

Summary

EudraCT number	2016-003452-75
Trial protocol	LV HU BE CZ NL PL HR
Global end of trial date	26 March 2018

Results information

Result version number	v1 (current)
This version publication date	11 April 2019
First version publication date	11 April 2019

Trial information

Trial identification

Sponsor protocol code	PTG-100-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02895100
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Protagonist Therapeutics, Inc
Sponsor organisation address	7707 Gateway Boulevard, Suite 140, Newark, United States, CA 94560-1160
Public contact	Clinical trials information, Protagonist Therapeutics, Inc, clinical@protagonist-inc.com
Scientific contact	Clinical trials information, Protagonist Therapeutics, Inc, clinical@protagonist-inc.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	Interim
Date of interim/final analysis	23 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 March 2018
Global end of trial reached?	Yes
Global end of trial date	26 March 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

1. To evaluate the safety and tolerability of PTG-100

2. To evaluate the efficacy of PTG-100 in the induction treatment of subjects with moderate to severe active UC compared to placebo.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trials subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 January 2017
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: 3
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Czech Republic: 3
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Latvia: 2
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Bosnia and Herzegovina: 2
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	New Zealand: 2
Country: Number of subjects enrolled	Serbia: 17
Country: Number of subjects enrolled	Korea, Republic of: 3
Country: Number of subjects enrolled	Russian Federation: 14
Country: Number of subjects enrolled	Ukraine: 13
Country: Number of subjects enrolled	United States: 21
Worldwide total number of subjects	98
EEA total number of subjects	22

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)	90
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were screened for eligibility according to the inclusion/ exclusion criteria within 42 days of dosing. Eligible subjects returned for sigmoidoscopy/ biopsy and baseline Mayo Score within 14 days of randomization. A total of 183 subjects were screened. A total of 103 subjects were randomized and 98 subjects received study drug.

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, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	PTG-100 150 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	PTG-100
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subject was administered 1 × 150mg PTG-100 capsule and 2 × placebo capsules QD

Arm title	PTG-100 300 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	PTG-100
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subject was administered 2 × 150mg PTG-100 capsules and 1 × placebo capsule QD

Arm title	PTG-100 900 mg

Arm description: -

Arm type	Experimental
Investigational medicinal product name	PTG-100
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subject was administered 3 × 300mg PTG-100 capsules QD

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:

Subject administered 3 x placebo capsules QD

Number of subjects in period 1	PTG-100 150 mg	PTG-100 300 mg	PTG-100 900 mg
Started	25	25	23
Completed	14	14	15
Not completed	11	11	8
Physician decision	2	-	-
Study terminated by Sponsor	6	5	5
Adverse event, non-fatal	1	-	1
Other	-	2	1
Lost to follow-up	1	-	-
Withdrawal by subject	1	4	1

Number of subjects in period 1	Placebo
Started	25
Completed	15
Not completed	10
Physician decision	1
Study terminated by Sponsor	7
Adverse event, non-fatal	-
Other	-
Lost to follow-up	-
Withdrawal by subject	2

Baseline characteristics

Reporting groups	
Reporting group title	PTG-100 150 mg
Reporting group description: -	
Reporting group title	PTG-100 300 mg
Reporting group description: -	
Reporting group title	PTG-100 900 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	PTG-100 150 mg	PTG-100 300 mg	PTG-100 900 mg
Number of subjects	25	25	23
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	45.2	43.8	40.6
standard deviation	± 13.8	± 17.0	± 14.1
Gender categorical Units: Subjects			
Female	7	15	14
Male	18	10	9
Race Units: Subjects			
White	19	23	22
Asian	4	1	0
Black or African American	2	0	1
Other	0	1	0
Ethnicity Units: Subjects			
Hispanic or Latino	0	2	1
Not Hispanic or Latino	25	23	22
Weight Units: kg			
arithmetic mean	77.8	70.7	72.3
standard deviation	± 16.3	± 15.4	± 19.1

Height			
Units: cm			
arithmetic mean	173.2	169.8	173.0
standard deviation	± 7.3	± 9.7	± 9.1
BMI			
Units: kg/m2			
arithmetic mean	25.7	24.5	23.9
standard deviation	± 4.7	± 5.2	± 4.5

Reporting group values	Placebo	Total	
Number of subjects	25	98	
Age categorical			
Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	42.2		
standard deviation	± 14.9	-	
Gender categorical			
Units: Subjects			
Female	10	46	
Male	15	52	
Race			
Units: Subjects			
White	23	87	
Asian	0	5	
Black or African American	2	5	
Other	0	1	
Ethnicity			
Units: Subjects			
Hispanic or Latino	1	4	
Not Hispanic or Latino	24	94	
Weight			
Units: kg			
arithmetic mean	69.5		
standard deviation	± 16.1	-	
Height			
Units: cm			
arithmetic mean	171.1		
standard deviation	± 8.3	-	
BMI			
Units: kg/m2			

arithmetic mean	23.7		
standard deviation	± 4.7	-	

End points

End points reporting groups

Reporting group title	PTG-100 150 mg
Reporting group description: -	
Reporting group title	PTG-100 300 mg
Reporting group description: -	
Reporting group title	PTG-100 900 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Efficacy: proportion of subjects receiving PTG-100 with clinical remission at Week 12

End point title	Efficacy: proportion of subjects receiving PTG-100 with clinical remission at Week 12[1]

End point description:

The primary efficacy endpoint for this study was the proportion of subjects receiving PTG-100 with clinical remission at Week 12. Clinical remission was defined using the Mayo subscores of stool frequency, rectal bleeding, and endoscopy.

End point type	Primary

End point timeframe:

Week 12

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: This trial was discontinued due to a futile outcome from the unblinded interim analysis by the independent DMC, therefore statistical analyses are not reported.

End point values	PTG-100 150 mg	PTG-100 300 mg	PTG-100 900 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	16	16	17
Units: Subjects				
Clinical Remission	1	2	3	4

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Day 0 to week 12	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21

Reporting groups	
Reporting group title	PTG-100 150 mg
Reporting group description: -	
Reporting group title	PTG-100 300 mg
Reporting group description: -	
Reporting group title	PTG-100 900 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	PTG-100 150 mg	PTG-100 300 mg	PTG-100 900 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 25 (8.00%)	2 / 25 (8.00%)	1 / 23 (4.35%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ulcerative colitis flare			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ulcerative			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exacerbation of ulcerative colitis			

subjects affected / exposed	0 / 25 (0.00%)	1 / 25 (4.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal ischaemia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Perirectal abscess			
subjects affected / exposed	1 / 25 (4.00%)	0 / 25 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 25 (4.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ulcerative colitis flare			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colitis ulcerative			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Exacerbation of ulcerative colitis			

subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intestinal ischaemia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Perirectal abscess			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	PTG-100 150 mg	PTG-100 300 mg	PTG-100 900 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 25 (28.00%)	11 / 25 (44.00%)	14 / 23 (60.87%)
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	4 / 23 (17.39%)
occurrences (all)	0	0	4
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	1 / 23 (4.35%)
occurrences (all)	0	2	1
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	3 / 23 (13.04%)
occurrences (all)	0	2	3
Abdominal pain			

subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	0 / 23 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2
Arthritis			
subjects affected / exposed	0 / 25 (0.00%)	2 / 25 (8.00%)	0 / 23 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 25 (0.00%)	3 / 25 (12.00%)	0 / 23 (0.00%)
occurrences (all)	0	3	0

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 25 (44.00%)		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			

Arthralgia subjects affected / exposed occurrences (all) Arthritis subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0 0 / 25 (0.00%) 0		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 November 2016	The Protocol (Protocol Amendment 1, dated 26 September 2016) was revised to Protocol Amendment 2, dated 01 November 2016 in response to a Food and Drug Administration (FDA) request to add measures pertinent to the progressive multifocal encephalopathy (PML) monitoring plan in the trial following review of the PTG-100 Investigational New Drug application. The revisions included: 1. Clarification that a complete neurological examination would be conducted at Screening and subjects with abnormal neurological findings would be excluded. 2. Addition of a phone follow-up 6 months after the end of study treatment to assess signs and symptoms of PML, and incorporation of features to enhance the completeness of follow up. 3. Modification of the protocol's monitoring program for PML such that it included education of site personnel and subjects about the signs and symptoms of PML and advised subjects to report to designated personnel if they experienced any of these signs or symptoms. Clarification of the conditions in which a neurologist would be consulted for the follow-up PML assessments. 4. Creation of a specific algorithm/action plan for all subjects suspected of having PML and referencing of this plan in the protocol, including details indicating which portions of the algorithm could be conducted by the Investigator or a consulting neurologist, and the conditions whereby a case would be referred to an outside panel of PML experts (with at least one neurologist) for final determination of whether or not the subject had PML. 5. Modification of Appendix D to include both a subjective and objective PML assessment checklist for screening and evaluation of suspected PML, to add further information regarding PML assessment.
16 November 2017	The Protocol Amendment 2 was revised to Protocol Amendment 3, dated 16 November 2017 in order to include the following changes: 1. Extension of the Screening window by 1 week, although sites were still encouraged to complete Screening as soon as possible. 2. Allowing for the option to have a combined Screening visit that included endoscopy. 3. Clarification of Inclusion Criteria #5d and addition of #5e, regarding contraception requirements that applied to sexual activity with a non-sterile male partner. 4. Clarification of the Exclusion Criteria #4 for Clostridium difficile to be based on the toxin result and not the PCR result. In addition, clarified that subjects with prior HCV infection who were successfully treated could be enrolled. 5. Clarification added to the synopsis that PD samples were to be collected at selected sites only (in line with the main body of the protocol). 6. Removal of the statement that all visit procedures needed to be performed prior to the final dose on Day 84. 7. Clarification of the resting time needed prior to ECG assessments. 8. Inclusion of a statement to clarify that if there was a delay to the IP shipment for Day 0 dosing, that would not be considered a protocol deviation. 9. Updating of the Sponsor's Medical Director's name and title. 10. Clarification that the 6-month phone call could occur before this date if the subject terminated early from the study. 11. Clarification for which subjects would be considered in the Interim Analysis. 12. Removal of references to dipstick in the protocol as all subjects had a macro analysis performed instead. 13. Clarification that subject numbering would be assigned by an Interactive Web Response System and not by the clinical site staff. 14. Inclusion of language to clarify how Mayo scores for rectal bleeding and stool frequency were to be calculated if the Screening visit was combined. 15. Removal of text regarding the addition of an additional dose arm (not tested in Stage 1

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Unblinded IA was performed by the DMC on 65 subjects who had completed 12 weeks dosing/terminated early. Futility was based on failure to achieve 10% conditional power for the primary efficacy endpoint. The trial was declared futile and terminated.

Notes: