Clinical trial results:
An Open Label Extension Study of PTG-300 in Non-Transfusion Dependent (NTD) and Transfusion-Dependent (TD) Beta-thalassemia Subjects

Summary

EudraCT number	2018-004423-36
Trial protocol	GR GB IT
Global end of trial date	31 July 2020

Results information

Result version number	v1 (current)
This version publication date	01 April 2021
First version publication date	01 April 2021

Trial information

Trial identification

Sponsor protocol code	PTG-300-03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04054921
WHO universal trial number (UTN)	-
Other trial identifiers	IND number: 137605

Notes:

Sponsors

Sponsor organisation name	Protagonist Therapeutics Inc.
Sponsor organisation address	7707 Gateway Blvd, Suite 140, Newark, United States, CA 94560
Public contact	Clinical-Regulatory Info Group, Protagonist Therapeutics, Inc., 001 510 4740170, clinregops@ptgx-inc.com
Scientific contact	Clinical-Regulatory Info Group, Protagonist Therapeutics, Inc., 001 510 4740170, clinregops@ptgx-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	Final
Date of interim/final analysis	31 July 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2020
Global end of trial reached?	Yes
Global end of trial date	31 July 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

1.To assess the long-term safety and tolerability of PTG-300 in subjects with TD and NTD β-thalassemia

Protection of trial subjects:

The trial was conducted in compliance with the moral, ethical and scientific principles governing clinical research as set out in the current Declaration of Helsinki, and the guidelines on Good Clinical Practice (GCP). The trial was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline.

Background therapy:

-

Evidence for comparator:

-

Actual start date of recruitment	29 April 2019
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	United Kingdom: 1
Country: Number of subjects enrolled	Greece: 12
Country: Number of subjects enrolled	Lebanon: 5
Country: Number of subjects enrolled	United States: 3
Country: Number of subjects enrolled	Turkey: 7
Country: Number of subjects enrolled	Thailand: 18
Country: Number of subjects enrolled	Malaysia: 12
Country: Number of subjects enrolled	Tunisia: 5
Worldwide total number of subjects	63
EEA total number of subjects	12

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)	4
Adults (18-64 years)	59
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at a total of 35 sites, including sites in North America, Europe, Asia and the Middle East. First NTD β-Thalassemia patients enrolled 31/03/2019. First TD β-Thalassemia patients enrolled 28/04/2019.

Pre-assignment

Screening details:

11 out of 24 NTD, and 23 out of 39 TD β-Thalassemia patients successfully completed week 12 and 16 of study PTG-300-02, and met the eligibility criteria for rolling over to study PTG-300-03. 16 TD and 13 NTD subjects in study PTG-300-02 either discontinued early, or did not meet the eligibility criteria for rolling over to study PTG-300-03.

Period 1

Period 1 title	Treatment Phase (long-term extension) (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Patients with NTD β-Thalassemia

Arm description:

Patients aged 12- 65 with NTD β-Thalassemia who completed week 12 of study PTG-300-02, and met the criteria for study PTG-300-03. PTG-300-03 is an extension of Study PTG-300-02. The analysis of responders is based on the combined data from PTG-300-02 and PTG-300-03 studies. Therefore, the number of NTD β-Thalassemia patients reported for study PTG-300-03 reflects the number of NTD β-Thalassemia patients who enrolled in study PTG-300-02, and not the number of patients who enrolled in study PTG-300-03.

Arm type	Experimental
Investigational medicinal product name	PTG-300
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous administration of PTG-300 was done weekly, every 2 weeks, or twice weekly based on individual patient's dosing needs. PTG-300 was administered at the study site or at home by the patient, caregiver or home nurse, after adequate training had been imparted and documented. Dosing window for weekly administration was ±2 days. Dosing window for twice weekly administration was ±1 day.

Arm title	Patients with TD β-Thalassemia

Arm description:

Patients aged 12-65 with TD β-Thalassemia who completed week 16 of study PTG-300-02 and met the eligibility criteria for study PTG-300-03. PTG-300-03 is an extension of Study PTG-300-02. The analysis of responders is based on the combined data from PTG-300-02 and PTG-300-03 studies. Therefore, the number of TD β-Thalassemia patients reported for study PTG-300-03 reflects the number of TD β-Thalassemia patients who enrolled in study PTG-300-02, and not the number of patients who enrolled in study PTG-300-03.

Arm type	Experimental
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Number of subjects in period 1	Patients with NTD β-Thalassemia	Patients with TD β-Thalassemia
Started	24	39
Titration phase	24	39
Maintenance phase	0	0
Completed	0	0
Not completed	24	39
Study terminated prior to completion by Sponsor	24	39

Baseline characteristics

Reporting groups

Reporting group title	Patients with NTD β-Thalassemia

Reporting group description:

Patients aged 12- 65 with NTD β-Thalassemia who completed week 12 of study PTG-300-02, and met the criteria for study PTG-300-03. PTG-300-03 is an extension of Study PTG-300-02. The analysis of responders is based on the combined data from PTG-300-02 and PTG-300-03 studies. Therefore, the number of NTD β-Thalassemia patients reported for study PTG-300-03 reflects the number of NTD β-Thalassemia patients who enrolled in study PTG-300-02, and not the number of patients who enrolled in study PTG-300-03.

Reporting group title	Patients with TD β-Thalassemia

Reporting group description:

Patients aged 12-65 with TD β-Thalassemia who completed week 16 of study PTG-300-02 and met the eligibility criteria for study PTG-300-03. PTG-300-03 is an extension of Study PTG-300-02. The analysis of responders is based on the combined data from PTG-300-02 and PTG-300-03 studies. Therefore, the number of TD β-Thalassemia patients reported for study PTG-300-03 reflects the number of TD β-Thalassemia patients who enrolled in study PTG-300-02, and not the number of patients who enrolled in study PTG-300-03.

Reporting group values	Patients with NTD β-Thalassemia	Patients with TD β-Thalassemia	Total
Number of subjects	24	39	63
Age categorical Units: Subjects			
Adults aged 18-65 years	23	36	59
Adolescents aged 12-<18 years	1	3	4
Age continuous Units: years			
arithmetic mean	35	38	
standard deviation	± 10.5	± 13.5	-
Gender categorical Units: Subjects			
Female	9	17	26
Male	15	22	37
Race Units: Subjects			
White	10	20	30
Asian	14	17	31
Other	0	1	1
Not reported	0	1	1

Subject analysis sets

Subject analysis set title	TD safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

β-Thalassemia patients belonging to the transfusion dependent (TD) subpopulation, who received at least one dose of study drug.

Subject analysis set title	NTD safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

β-Thalassemia patients belonging to the non-transfusion dependent (NTD) subpopulation, who received at least one dose of study drug.

Reporting group values	TD safety population	NTD safety population	
Number of subjects	39	24	
Age categorical Units: Subjects			
Adults aged 18-65 years	36	23	
Adolescents aged 12-<18 years	3	1	
Age continuous Units: years			
arithmetic mean	38	35	
standard deviation	± 13.5	± 10.5	
Gender categorical Units: Subjects			
Female	17	9	
Male	22	15	
Race Units: Subjects			
White	20	10	
Asian	17	14	
Other	1	0	
Not reported	1	0	

End points

End points reporting groups

Reporting group title	Patients with NTD β-Thalassemia

Reporting group description:

Patients aged 12- 65 with NTD β-Thalassemia who completed week 12 of study PTG-300-02, and met the criteria for study PTG-300-03. PTG-300-03 is an extension of Study PTG-300-02. The analysis of responders is based on the combined data from PTG-300-02 and PTG-300-03 studies. Therefore, the number of NTD β-Thalassemia patients reported for study PTG-300-03 reflects the number of NTD β-Thalassemia patients who enrolled in study PTG-300-02, and not the number of patients who enrolled in study PTG-300-03.

Reporting group title	Patients with TD β-Thalassemia

Reporting group description:

Patients aged 12-65 with TD β-Thalassemia who completed week 16 of study PTG-300-02 and met the eligibility criteria for study PTG-300-03. PTG-300-03 is an extension of Study PTG-300-02. The analysis of responders is based on the combined data from PTG-300-02 and PTG-300-03 studies. Therefore, the number of TD β-Thalassemia patients reported for study PTG-300-03 reflects the number of TD β-Thalassemia patients who enrolled in study PTG-300-02, and not the number of patients who enrolled in study PTG-300-03.

Subject analysis set title	TD safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

β-Thalassemia patients belonging to the transfusion dependent (TD) subpopulation, who received at least one dose of study drug.

Subject analysis set title	NTD safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

β-Thalassemia patients belonging to the non-transfusion dependent (NTD) subpopulation, who received at least one dose of study drug.

Primary: Proportion of responders

End point title	Proportion of responders[1][2]

End point description:

Proportion of responders at each dose, where responders are defined as patients who achieve ≥ 20% reduction in the red blood cell units required over an 8-week period compared to pre-treatment baseline.

End point type	Primary

End point timeframe:

8 weeks post-dose.

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: Only descriptive statistical analyses were performed during the study.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive statistical analyses were performed during the study.

End point values	Patients with TD β-Thalassemia			
Subject group type	Reporting group			
Number of subjects analysed	37[3]			
Units: Number of responders				
3mg/week	1			
10mg/week	2			
20mg/week	1			

40mg/week	3			
80mg/week	7			
40mg 2x/week	2			
Any dose level	12			

Notes:

[3] - 2 patients removed from the efficacy analysis due to issues of site non-compliance.

Statistical analyses

No statistical analyses for this end point

Primary: Proportion of responders

End point title	Proportion of responders[4][5]

End point description:

Proportion of responders at each dose, where responders are defined as patients who achieve an increase in Hgb ≥ 1.0 g/dL from pre-treatment baseline without transfusion, (confirmed by a successive measurement at least 1 week later.)

End point type	Primary

End point timeframe:

4, 8 and 12 weeks post dose.

Notes:

[4] - 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: Only descriptive statistical analyses were performed during the study.

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive statistical analyses were performed during the study.

End point values	Patients with NTD β-Thalassemia			
Subject group type	Reporting group			
Number of subjects analysed	23[6]			
Units: Number of responders				
3mg/week	0			
10mg/week	0			
20mg/week	0			
40mg/week	0			
80mg/week	0			
40mg 2x/week	0			

Notes:

[6] - 1 patient removed from the efficacy analysis due to issues of site non-compliance.

Statistical analyses

No statistical analyses for this end point

Primary: Red blood cell units required

End point title	Red blood cell units required[7][8]

End point description:

Mean change from pre-treatment baseline in the number of red blood cell units required under each dose (standardised to 8-week period.)

End point type	Primary

End point timeframe:

8 weeks post-dose

Notes:

[7] - 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: Only descriptive statistical analyses were performed during the study.

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive statistical analyses were performed during the study.

End point values	Patients with TD β-Thalassemia			
Subject group type	Reporting group			
Number of subjects analysed	37[9]			
Units: Transfusion units				
arithmetic mean (standard deviation)				
3mg/week	0.46 (± 1.194)			
10mg/week	0.53 (± 1.291)			
20mg/week	0.49 (± 1.127)			
40mg/week	0.07 (± 0.953)			
80mg/week	-0.16 (± 1.756)			
40mg 2x/week	-0.00 (± 1.075)			
Any dose level	-0.21 (± 1.188)			

Notes:

[9] - 2 patients removed from the efficacy analysis due to issues of site non-compliance.

Statistical analyses

No statistical analyses for this end point

Primary: Hemoglobin change

End point title	Hemoglobin change[10][11]

End point description:

Mean Hemoglobin change from pre-treatment baseline at each dose level.

End point type	Primary

End point timeframe:

4, 8 and 12 weeks.

Notes:

[10] - 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: Only descriptive statistical analyses were performed during the study.

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive statistical analyses were performed during the study.

End point values	Patients with NTD β-Thalassemia			
Subject group type	Reporting group			
Number of subjects analysed	23[12]			
Units: Hemoglobin (g/dL)				
arithmetic mean (standard deviation)				
3mg/week	-0.25 (± 1.184)			
10mg/week	-0.09 (± 0.639)			
20mg/week	-0.16 (± 0.638)			
40mg/week	-0.42 (± 0.602)			
80mg/week	-0.83 (± 0.682)			
40mg 2x/week	-1.10 (± 0.212)			

Notes:

[12] - -1 patient removed from the efficacy analysis due to issues of site non-compliance

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Liver iron content

End point title	Liver iron content

End point description:

Change in mean liver iron load from baseline to the last MRI performed for TD patients undergoing MRI evaluation.

End point type	Other pre-specified

End point timeframe:

From baseline to last MRI performed.

End point values	Patients with NTD β-Thalassemia	Patients with TD β-Thalassemia		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	29		
Units: mg Fe/ g dry weight				
arithmetic mean (standard deviation)				
10mg/week	-0.60 (± 0)	-0.23 (± 2.499)		
20mg/week	-1.88 (± 4.568)	-0.55 (± 1.826)		
40mg/week	1.93 (± 1.590)	0.94 (± 3.304)		
80mg/week	-2.04 (± 7.116)	-9.33 (± 16.868)		
40mg 2x/week	0.60 (± 0)	-4.2 (± 6.223)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment related adverse events (TEAEs, including serious adverse events (SAEs)) were reported from first dose until 30 days post last PTG-300 dose.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	TD patients

Reporting group description:

All subjects treated with the study product were considered eligible for safety evaluation.

Reporting group title	NTD patients

Reporting group description:

All subjects treated with the study product were considered eligible for safety evaluation.

Serious adverse events	TD patients	NTD patients	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 39 (10.26%)	1 / 24 (4.17%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cholangiocarcinoma			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Epiploic appendagitis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic cirrhosis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal			

disorders			
Upper respiratory tract infection			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	TD patients	NTD patients	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 39 (76.92%)	20 / 24 (83.33%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Prehypertension			
subjects affected / exposed	2 / 39 (5.13%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 39 (2.56%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Fatigue			
subjects affected / exposed	3 / 39 (7.69%)	2 / 24 (8.33%)	
occurrences (all)	5	3	
Infusion site erythema			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	4	0	
Injection site hematoma			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	

Injection site atrophy			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Injection site erythema			
subjects affected / exposed	6 / 39 (15.38%)	1 / 24 (4.17%)	
occurrences (all)	23	2	
Injection site macule			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	4	0	
Injection site pain			
subjects affected / exposed	4 / 39 (10.26%)	4 / 24 (16.67%)	
occurrences (all)	31	16	
Injection site papule			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Injection site plaque			
subjects affected / exposed	2 / 39 (5.13%)	0 / 24 (0.00%)	
occurrences (all)	7	0	
Injection site pruritus			
subjects affected / exposed	2 / 39 (5.13%)	0 / 24 (0.00%)	
occurrences (all)	5	0	
Injection site reaction			
subjects affected / exposed	2 / 39 (5.13%)	4 / 24 (16.67%)	
occurrences (all)	4	6	
Injection site swelling			
subjects affected / exposed	2 / 39 (5.13%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Injection site urticaria			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	3 / 39 (7.69%)	1 / 24 (4.17%)	
occurrences (all)	3	1	
Vessel Puncture Site Thrombosis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	

Influenza like illness			
subjects affected / exposed	0 / 39 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Injection site hypersensitivity			
subjects affected / exposed	0 / 39 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Vaginal haemorrhage			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Menorrhagia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Productive cough			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Nasal discomfort			
subjects affected / exposed	0 / 39 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	0 / 39 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Pharyngeal erythema			
subjects affected / exposed	0 / 39 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Rhinitis allergic			
subjects affected / exposed	0 / 39 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Psychiatric disorders			

Depression			
subjects affected / exposed	0 / 39 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Blood bilirubin increased			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Blood creatinine increased			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Blood folate decreased			
subjects affected / exposed	2 / 39 (5.13%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Haemoglobin decreased			
subjects affected / exposed	1 / 39 (2.56%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
White blood cell count decreased			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	2 / 39 (5.13%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Contusion			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Post procedural fever			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			

Palpitations			
subjects affected / exposed	0 / 39 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	4	
Ventricular arrhythmia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 39 (12.82%)	2 / 24 (8.33%)	
occurrences (all)	8	3	
Lethargy			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Somnolence			
subjects affected / exposed	2 / 39 (5.13%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Syncope			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Migraine			
subjects affected / exposed	0 / 39 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Anaemia			
subjects affected / exposed	0 / 39 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Dental caries			

subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	1 / 39 (2.56%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Dyspepsia			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Gastroesophageal reflux disease			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 39 (2.56%)	1 / 24 (4.17%)	
occurrences (all)	1	2	
Loose tooth			
subjects affected / exposed	0 / 39 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Jaundice			
subjects affected / exposed	0 / 39 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	2 / 39 (5.13%)	0 / 24 (0.00%)	
occurrences (all)	3	0	
Rash			
subjects affected / exposed	2 / 39 (5.13%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Skin hypopigmentation			

subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Skin ulcer			
subjects affected / exposed	1 / 39 (2.56%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Stasis dermatitis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Rash papular			
subjects affected / exposed	0 / 39 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	0 / 39 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 39 (2.56%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Bone infarction			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Bone pain			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Neck pain			

subjects affected / exposed	0 / 39 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Infections and infestations			
Bacterial vaginosis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Bone abscess			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Bronchitis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Injection site infection			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	5 / 39 (12.82%)	3 / 24 (12.50%)	
occurrences (all)	7	3	
Urinary tract infection			
subjects affected / exposed	3 / 39 (7.69%)	2 / 24 (8.33%)	
occurrences (all)	5	2	
Periodontitis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Tuberculosis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hyperkalemia			

subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Decreased appetite			
subjects affected / exposed	0 / 39 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Hyperuricaemia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 February 2020	1) Study endpoints were changed to align with the PTG-300-02 study endpoints. 2) The maximum PTG-300 total dose allowed was changed from 80 mg/weekly to 40 mg/twice per week as preliminary pharmacodynamic data supported twice weekly dosing and longer corresponding reduction in serum iron levels. 3) Section 7.2: Table 4 was revised, Dose Titration was clarified, Dose Titration Algorithm table (Table B) was revised to correct errors and changes were made to specify that patients that do not meet maintenance phase criteria may start maintenance phase on Day 168 to assess effects of PTG-300 on liver and cardiac iron content to allow assessment of iron overload in patients who do not meet criteria for response. 4) Section 7.3: language was added to clarify that female patients becoming pregnant would be withdrawn from the study and clarified follow-up on Day 672 for patients who meet stopping criteria. 5) Study Procedures: Langauge revised. 6) Number of patients was changed to reflect a maximum 192 patients able to enroll in the study. 7) Hydroxyurea was removed from Prohibited Medications. 8) Dose and Mode of Administration was revised was revised to include twice weekly dosing and new dose levels and removal of every 2-week dosing regimen. 9) Efficacy Endpoint added to assess change in pre-treatment baseline of cardiac iron added due to preliminary data suggesting PTG-300 decreases iron overload. 10) Sections 7.2, 7.4, and 10.6: Assessments for cardiac iron added. 11) General changes to Schedule of Assessment Table for NTD and TD patients 12) Section 5: Text revised to reflect required participation in PTG-300-02 prior to participation in PTG-300-03 study. 13) Text added to reflect twice weekly dosing for 40 mg dose. 14) Section 10.3: Corrected CTCAE version from 4.0 to 5.0 for physical examination; Removed fasting requirement from safety laboratory tests. 15) Revised text to provide more detail and justification for sample size

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.

The analysis of responders has been combined for study PTG-300-02 and PTG-300-03. Therefore, data for study PTG-300-03 has been reported for the 63 patients who enrolled in study PTG-300-02, instead of the 34 patients who enrolled in PTG-300-03.

Notes: