



## Clinical trial results:

### Phase 2 Study of PTG-300 in Non-Transfusion Dependent (NTD) and Transfusion-Dependent (TD) Beta-Thalassemia Subjects with Chronic Anemia

#### Summary

EudraCT number	2018-001984-21
Trial protocol	GB GR 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-300-02
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03802201
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 evaluate the safety and tolerability of PTG-300 in subjects with NTD and TD  $\beta$ -thalassemia.
2. To obtain preliminary evidence of PTG-300's efficacy for treating chronic anemia in subjects with  $\beta$ -thalassemia.
3. To identify the optimal starting dose, titration algorithm, dose range and dose regimen to be used in Phase 3 studies.

Protection of trial subjects:

The study was conducted in accordance with the protocol, the Declaration of Helsinki and the International Conference on Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP). A Safety Monitoring Board monitored subject safety in a regularly scheduled and completely unblinded manner throughout the study. All patients and legal guardians (in the case of minors) gave written informed consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 November 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

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	Tunisia: 5
Country: Number of subjects enrolled	Thailand: 18
Country: Number of subjects enrolled	Malaysia: 12
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Greece: 12
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.

### Pre-assignment

Screening details:

133 subjects aged 12 to 65 years, with transfusion dependent (TD) and non-transfusion dependent (NTD)  $\beta$ -thalassemia screened during screening period (Day -28 to Day -1). General & disease-specific medical history recorded, independent of  $\beta$ -thalassemia subpopulation. Transfusion required during the screening period for TD patients.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	TD adult and adolescent participants: PTG-300

Arm description:

Adult and adolescent patients with transfusion dependent (TD)  $\beta$ -thalassemia, who received repeated doses of PTG-300

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 schedule. 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  $\pm 2$  days. Dosing window for twice weekly administration was  $\pm 1$  day.

<b>Arm title</b>	NTD adult and adolescent participants: PTG-300
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Arm description:

Adult and adolescent patients with non-transfusion dependent (NTD)  $\beta$ -thalassemia, who received repeated doses of PTG-300

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 schedule. 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  $\pm 2$  days. Dosing window for twice weekly administration was  $\pm 1$  day.

<b>Number of subjects in period 1</b>	TD adult and adolescent participants: PTG-300	NTD adult and adolescent participants: PTG-300
Started	39	24
Completed	32	18
Not completed	7	6
Consent withdrawn by subject	1	1
Sponsor request	6	5

## Baseline characteristics

### Reporting groups

Reporting group title	TD adult and adolescent participants: PTG-300
Reporting group description: Adult and adolescent patients with transfusion dependent (TD) $\beta$ -thalassemia, who received repeated doses of PTG-300	
Reporting group title	NTD adult and adolescent participants: PTG-300
Reporting group description: Adult and adolescent patients with non-transfusion dependent (NTD) $\beta$ -thalassemia, who received repeated doses of PTG-300	

Reporting group values	TD adult and adolescent participants: PTG-300	NTD adult and adolescent participants: PTG-300	Total
Number of subjects	39	24	63
Age categorical Units: Subjects			
Adolescents (12-17 years)	3	1	4
Adults (18-64 years)	36	23	59
Age continuous Units: years			
arithmetic mean	38	35	
standard deviation	$\pm 13.5$	$\pm 10.5$	-
Gender categorical Units: Subjects			
Female	17	9	26
Male	22	15	37
Race Units: Subjects			
White	20	10	30
Asian	17	14	31
Other	1	0	1
Not reported	1	0	1

### Subject analysis sets

Subject analysis set title	TD safety population
Subject analysis set type	Safety analysis
Subject analysis set description: $\beta$ -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: $\beta$ -Thalassemia patients belonging to the non-transfusion dependent (NTD) subpopulation, who received at least one dose of study drug	

<b>Reporting group values</b>	TD safety population	NTD safety population	
Number of subjects	39	24	
Age categorical Units: Subjects			
Adolescents (12-17 years)	3	1	
Adults (18-64 years)	36	23	
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	TD adult and adolescent participants: PTG-300
Reporting group description: Adult and adolescent patients with transfusion dependent (TD) $\beta$ -thalassemia, who received repeated doses of PTG-300	
Reporting group title	NTD adult and adolescent participants: PTG-300
Reporting group description: Adult and adolescent patients with non-transfusion dependent (NTD) $\beta$ -thalassemia, who received repeated doses of PTG-300	
Subject analysis set title	TD safety population
Subject analysis set type	Safety analysis
Subject analysis set description: $\beta$ -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: $\beta$ -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 <sup>[1][2]</sup>
End point description: Proportion of responders at each dose, where responders are defined as patients who achieve $\geq 20\%$ 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	TD adult and adolescent participants: PTG-300			
Subject group type	Reporting group			
Number of subjects analysed	37 <sup>[3]</sup>			
Units: Number of responders				
3 mg/wk	1			
10 mg/wk	2			
20 mg/wk	1			
40 mg/wk	3			
80 mg/wk	7			
40 mg 2x/wk	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: Red blood cell units required

End point title	Red blood cell units required <sup>[4][5]</sup>
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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
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End point timeframe:

8 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	TD adult and adolescent participants: PTG-300			
Subject group type	Reporting group			
Number of subjects analysed	37 <sup>[6]</sup>			
Units: Transfusion units				
arithmetic mean (standard deviation)				
3 mg/wk	0.46 (± 1.194)			
10 mg/wk	0.53 (± 1.291)			
20 mg/wk	0.49 (± 1.127)			
40 mg/wk	0.07 (± 0.953)			
80 mg/wk	-0.16 (± 1.756)			
40 mg 2x/wk	-0.00 (± 1.075)			
Any dose level	-0.21 (± 1.188)			

Notes:

[6] - 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 <sup>[7][8]</sup>
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**End point description:**

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

End point type	Primary
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**End point timeframe:**

4, 8 and 12 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	NTD adult and adolescent participants: PTG-300			
Subject group type	Reporting group			
Number of subjects analysed	23 <sup>[9]</sup>			
Units: Number of responders				
3 mg/wk	0			
10 mg/wk	0			
20 mg/wk	0			
40 mg/wk	0			
80 mg/wk	0			
40 mg 2x/wk	0			

**Notes:**

[9] - 1 patient 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 <sup>[10]</sup> <sup>[11]</sup>
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**End point description:**

Mean hemoglobin change from pre-treatment baseline at each dose level

End point type	Primary
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**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	NTD adult and adolescent participants: PTG-300			
Subject group type	Reporting group			
Number of subjects analysed	23 <sup>[12]</sup>			
Units: Hemoglobin (g/dL)				
arithmetic mean (standard deviation)				
3 mg/wk	-0.25 (± 1.184)			
10 mg/wk	-0.09 (± 0.639)			
20 mg/wk	-0.16 (± 0.638)			
40 mg/wk	-0.42 (± 0.602)			
80 mg/wk	-0.83 (± 0.682)			
40 mg 2x/wk	-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 post-dose for patients undergoing MRI evaluation	
End point type	Other pre-specified
End point timeframe:	
From baseline to last MRI performed	

End point values	TD adult and adolescent participants: PTG-300	NTD adult and adolescent participants: PTG-300		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	15		
Units: Liver iron content (mg Fe/g dry weight)				
arithmetic mean (standard deviation)				
10 mg/wk	-0.23 (± 2.499)	-0.60 (± 0)		
20 mg/wk	-0.55 (± 1.826)	-1.88 (± 4.568)		
40 mg/wk	0.94 (± 3.304)	1.93 (± 1.590)		
80 mg/wk	-9.33 (± 16.868)	-2.04 (± 7.116)		
40 mg 2x/wk	-4.20 (± 6.223)	0.60 (± 0)		

## **Statistical analyses**

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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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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### Reporting groups

Reporting group title	TD adult and adolescent participants: PTG-300
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Reporting group description:

Adult and adolescent patients with transfusion dependent (TD)  $\beta$ -thalassemia, who received repeated doses of PTG-300

Reporting group title	NTD adult and adolescent participants: PTG-300
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Reporting group description:

Adult and adolescent patients with non-transfusion dependent (NTD)  $\beta$ -thalassemia, who received repeated doses of PTG-300

Serious adverse events	TD adult and adolescent participants: PTG-300	NTD adult and adolescent participants: PTG-300	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 39 (10.26%)	2 / 24 (8.33%)	
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 / 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	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
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	

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

<b>Non-serious adverse events</b>	TD adult and adolescent participants: PTG-300	NTD adult and adolescent participants: PTG-300	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 39 (76.92%)	20 / 24 (83.33%)	
Vascular disorders			
Prehypertension			
subjects affected / exposed	2 / 39 (5.13%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Hypotension			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	6 / 39 (15.38%)	1 / 24 (4.17%)	
occurrences (all)	23	2	
Injection site pain			
subjects affected / exposed	4 / 39 (10.26%)	4 / 24 (16.67%)	
occurrences (all)	31	16	
Pyrexia			

subjects affected / exposed	3 / 39 (7.69%)	1 / 24 (4.17%)
occurrences (all)	3	1
Fatigue		
subjects affected / exposed	3 / 39 (7.69%)	2 / 24 (8.33%)
occurrences (all)	5	3
Injection site papule		
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)
occurrences (all)	1	0
Injection site urticaria		
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 macule		
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)
occurrences (all)	4	0
Injection site swelling		
subjects affected / exposed	2 / 39 (5.13%)	1 / 24 (4.17%)
occurrences (all)	2	1
Injection site reaction		
subjects affected / exposed	2 / 39 (5.13%)	3 / 24 (12.50%)
occurrences (all)	2	3
Injection site pruritus		
subjects affected / exposed	2 / 39 (5.13%)	0 / 24 (0.00%)
occurrences (all)	5	0
Chest discomfort		
subjects affected / exposed	1 / 39 (2.56%)	1 / 24 (4.17%)
occurrences (all)	2	1
Injection site atrophy		
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)
occurrences (all)	1	0
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 occurrences (all)	0 / 39 (0.00%) 0	1 / 24 (4.17%) 1	
Administration site reaction subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	1 / 24 (4.17%) 1	
Injection site hypersensitivity subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	1 / 24 (4.17%) 1	
Infusion site erythema subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 4	0 / 24 (0.00%) 0	
Injection site haematoma subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	0 / 24 (0.00%) 0	
Reproductive system and breast disorders Vaginal haemorrhage subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	0 / 24 (0.00%) 0	
Dysmenorrhoea subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 2	0 / 24 (0.00%) 0	
Menorrhagia subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	1 / 24 (4.17%) 1	
Respiratory, thoracic and mediastinal disorders Productive cough subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	0 / 24 (0.00%) 0	
Cough subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	0 / 24 (0.00%) 0	
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	1 / 24 (4.17%) 1	
Nasal discomfort			



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			
Blood folate decreased			
subjects affected / exposed	2 / 39 (5.13%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
White blood cell count decreased			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	3	0	
Haemoglobin decreased			
subjects affected / exposed	1 / 39 (2.56%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Blood creatine phosphokinase			
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 bilirubin increased			

subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	0 / 24 (0.00%) 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			
Ventricular arrhythmia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	0 / 39 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	4	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	3 / 39 (7.69%)	2 / 24 (8.33%)	
occurrences (all)	7	2	
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	
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	
Nausea			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
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	
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	
Dyspepsia			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Loose tooth			
subjects affected / exposed	0 / 39 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	1 / 39 (2.56%)	1 / 24 (4.17%)	
occurrences (all)	1	2	
Hepatobiliary disorders			

Hepatic cirrhosis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
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			
Rash			
subjects affected / exposed	2 / 39 (5.13%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Stasis dermatitis			
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	
Erythema			
subjects affected / exposed	2 / 39 (5.13%)	0 / 24 (0.00%)	
occurrences (all)	3	0	
Urticaria			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Skin hypopigmentation			
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 occurrences (all)	0 / 39 (0.00%) 0	1 / 24 (4.17%) 1	
Musculoskeletal and connective tissue disorders			
Bone infarction subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 2	0 / 24 (0.00%) 0	
Back pain subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	1 / 24 (4.17%) 1	
Bone pain subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	0 / 24 (0.00%) 0	
Myalgia subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	1 / 24 (4.17%) 1	
Neck pain subjects affected / exposed occurrences (all)	0 / 39 (0.00%) 0	1 / 24 (4.17%) 1	
Infections and infestations			
Bone abscess subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 2	0 / 24 (0.00%) 0	
Urinary tract infection subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 5	2 / 24 (8.33%) 3	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	5 / 39 (12.82%) 8	3 / 24 (12.50%) 3	
Bacterial vaginosis subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	0 / 24 (0.00%) 0	
Bronchitis subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1	0 / 24 (0.00%) 0	
Conjunctivitis			

subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Injection site infection			
subjects affected / exposed	1 / 39 (2.56%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Periodontitis			
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			
Hyperkalaemia			
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
21 February 2019	<ol style="list-style-type: none"><li>1) Added text to clarify how decisions of adding new patients would be made.</li><li>2) Section 3.3.1: Language was added to clarify how many patients could be added to each cohort.</li><li>3) Addition of text to clarify that enrollment in Cohort 6 would be based on safety experience in Cohort 5 according to the Dose Escalation Rules.</li><li>4) Removed text for Cohort Dose Reduction specifying how dose would be reduced for the cohort receiving 40 mg/week. The dose for cohort receiving 40 mg/week would be reduced to 20 mg/week which was already shown to be safe. The option of 40 mg every two weeks was removed due to lack of clear criteria to determine frequency of dose reduction.</li><li>5) Section 3.4.1.1.1: Revision of text to Safety Criteria for dose reduction to remove inconsistency in protocol and added that Hgb values of &gt;13 g/dL would be confirmed by a repeat test to align with study assessments.</li><li>6) Clarification that Hgb &gt;13 g/dL would be considered if no transfusion was performed for &gt;4 weeks as transfusion may result in Hgb values of &gt;13 g/dL for more than 7 days. This change was made to distinguish the effect of transfusion on Hgb levels from effect of PTG-300.</li><li>7) Text was added to Pregnancy Testing to include specification for negative urine pregnancy test results for NTD and TD populations as they were inadvertently omitted in original protocol.</li><li>8) Endpoints revised.</li><li>9) Inclusion and Exclusion Criteria modified to more clearly define the enrollment-eligible population.</li><li>10) Concomitant medications revised.</li><li>11) Corrected typographical error specifying Doses 5 and onward can be administered at site or home.</li><li>12) Clarification of timing of PK/PD assessments, adjusted statistical analysis sections to correspond to protocol changes.</li><li>13) Revised Physical Examination to remove ultrasound assessment.</li><li>14) Section 5.2.3: Added Treatment Compliance section to provide detail about compliance monitoring.</li><li>15) Revised definition of study completion for clarity.</li></ol>

14 June 2019	<p>1) Table 1 for Schedule of Assessments – revised footnotes to reflect scheduled assessments and clarify timing of assessments to align with other safety assessments for coagulation testing. Other changes made for clarity and to correct typographical errors.</p> <p>2) Dose Escalation Criteria revised to change description of cohort dose escalation to include the additional dose cohorts and change to Cohort 4b dose level.</p> <p>3) Dose Reduction Stopping Criteria text changed to add responsibility of Safety Monitoring Committee (SMC) flexibility in study continuation criteria.</p> <p>4) Table 4 changed to reflect requirement that dosing be suspended in cohort until SMC reviews safety data and makes recommendations.</p> <p>5) Changed Synopsis text to specify that negative urine pregnancy tests are required to proceed with dosing throughout the study.</p> <p>6) Number of patients revised to reflect changes to number of patients enrolled in the study (up to 192, minimum of 84) to account for potential cohorts and allow sponsor to treat additional patients (up to 24) to confirm safety, efficacy, and dose titration rules.</p> <p>7) Inclusion and exclusion criteria were modified.</p> <p>8) Investigational Product – Dose Level 4b in NTD and TD patients revised to add dosing option of 20 mg or 80 mg every 2 weeks and additional cohorts 7-11 to evaluate every two-week dosing and allow flexibility in dose selection.</p> <p>9) Safety Assessment added to synopsis for internal consistency</p> <p>10) Safety Assessment descriptions amended to remove specific timepoints for internal consistency with schedule of assessments and for clarity.</p> <p>11) Pregnancy Reporting revised to add that pregnancy not considered AE or SAE.</p> <p>12) Clinical Laboratory Abnormalities revised for clarity regarding what is an AE or SAE and clinical significance.</p> <p>13) Statistical Analysis section revised to remove statement regarding missing data. This was added to Statistical Analysis Plan instead. Baseline period for transfusions was changed for accuracy.</p>
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Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported