Clinical trial results:
Evaluation of the Efficacy and Safety of PTC299 in Hospitalized Subjects with COVID-19 (FITE19)

Summary

EudraCT number	2020-001872-13
Trial protocol	PT FR BE GR
Global end of trial date	20 July 2022

Results information

Result version number	v1 (current)
This version publication date	15 July 2023
First version publication date	15 July 2023

Trial information

Trial identification

Sponsor protocol code	PTC299-VIR-015-COV19

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04439071
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	PTC Therapeutics, Inc.
Sponsor organisation address	100 Corporate Court, South Plainfield, United States, NJ 07080
Public contact	Medical Information, PTC Therapeutics International Limited, +353 19068700, medinfo@ptcbio.com
Scientific contact	Medical Information, PTC Therapeutics, Inc., +011 44 1-866-562-4620, medinfo@ptcbio.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	20 July 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 July 2022
Global end of trial reached?	Yes
Global end of trial date	20 July 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the clinical efficacy of PTC299 compared with placebo assessed by time to respiratory improvement in adult participants hospitalized with COVID 19.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and in conformance with the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidance documents.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 July 2020
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	Australia: 3
Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	Brazil: 85
Country: Number of subjects enrolled	Mexico: 10
Country: Number of subjects enrolled	Portugal: 18
Country: Number of subjects enrolled	Spain: 50
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	189
EEA total number of subjects	86

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)	155
From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were enrolled at study sites in 7 countries (Australia, Belgium, Brazil, Mexico, Portugal, Spain, and United States.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	PTC299

Arm description:

Participants received PTC299 at 200 milligrams (mg), administered orally, twice daily (BID) on Days 1 to 7, then at 50 mg administered orally, once daily (QD) on Days 8 to 14.

Arm type	Experimental
Investigational medicinal product name	PTC299
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

PTC299 was administered per dose and schedule specified in the arm description.

Arm title	Placebo

Arm description:

Participants received PTC299-matching placebo administered orally, BID on Days 1 to 7, then administered orally, QD on Days 8 to 14.

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

Dosage and administration details:

PTC299-matching placebo was administered per schedule specified in the arm description.

Number of subjects in period 1	PTC299	Placebo
Started	94	95
Received at least 1 dose of study drug	92	95
Completed	80	77
Not completed	14	18
Adverse event, serious fatal	6	4
Consent withdrawn by subject	3	8
Randomized but not treated	2	-
Other than specified	3	3
Lost to follow-up	-	3

Baseline characteristics

Reporting groups	
Reporting group title	PTC299
Reporting group description:	
Participants received PTC299 at 200 milligrams (mg), administered orally, twice daily (BID) on Days 1 to 7, then at 50 mg administered orally, once daily (QD) on Days 8 to 14.	
Reporting group title	Placebo
Reporting group description:	
Participants received PTC299-matching placebo administered orally, BID on Days 1 to 7, then administered orally, QD on Days 8 to 14.	

Reporting group values	PTC299	Placebo	Total
Number of subjects	94	95	189
Age categorical Units: Subjects			
<65 years	78	77	155
≥65 years	16	18	34
Sex: Female, Male Units: participants			
Female	26	27	53
Male	68	68	136
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	4	6	10
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	6	1	7
White	71	69	140
More than one race	12	19	31
Unknown or Not Reported	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	55	64	119
Not Hispanic or Latino	34	26	60
Unknown or Not Reported	5	5	10

End points

End points reporting groups

Reporting group title	PTC299
Reporting group description:	
Participants received PTC299 at 200 milligrams (mg), administered orally, twice daily (BID) on Days 1 to 7, then at 50 mg administered orally, once daily (QD) on Days 8 to 14.	
Reporting group title	Placebo
Reporting group description:	
Participants received PTC299-matching placebo administered orally, BID on Days 1 to 7, then administered orally, QD on Days 8 to 14.	

Primary: Time from Randomization to Respiratory Improvement

End point title	Time from Randomization to Respiratory Improvement
End point description:	
Respiratory improvement was defined as sustained peripheral oxygen saturation (SpO2) ≥94% on room air. Median time to respiratory improvement was estimated via the Kaplan-Meier product limit method. Intent-to-treat (ITT) population included all randomized participants. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.	
End point type	Primary
End point timeframe:	
up to Day 28	

End point values	PTC299	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	76		
Units: days				
median (confidence interval 95%)	10.0 (6.0 to 15.0)	10.0 (8.0 to 13.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Time to respiratory improvement was compared between treatment groups using stratified log-rank test.	
Comparison groups	PTC299 v Placebo
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.949
Method	Logrank

Secondary: Number of Participants Requiring Invasive Ventilation

End point title	Number of Participants Requiring Invasive Ventilation

End point description:

Number of participants requiring invasive ventilation at any time during the study were reported. ITT population included all randomized participants.

End point type	Secondary

End point timeframe:

up to Day 28

End point values	PTC299	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	95		
Units: participants	16	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Requiring Supplemental Oxygen or Non-Invasive Ventilation in Participants who did not Require Supplemental Oxygen at Baseline

End point title	Number of Participants Requiring Supplemental Oxygen or Non-Invasive Ventilation in Participants who did not Require Supplemental Oxygen at Baseline

End point description:

Number of participants requiring supplemental oxygen or non-invasive ventilation at any point during the study in participants who did not require supplemental oxygen at baseline were reported. ITT population included all randomized participants. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

up to Day 28

End point values	PTC299	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	22		
Units: participants	20	19		

Statistical analyses

No statistical analyses for this end point

Secondary: Time from Randomization to Defervescence in Participants Presenting

With Fever at Enrollment (Temperature of ≥37.6 Axilla, ≥38.0 Oral, or ≥38.6°C Tympanic or Rectal)

End point title	Time from Randomization to Defervescence in Participants Presenting With Fever at Enrollment (Temperature of ≥37.6 Axilla, ≥38.0 Oral, or ≥38.6°C Tympanic or Rectal)

End point description:

Defervescence was defined as body temperature of <37.6° C axilla, <38.0° C oral, or <38.6° C tympanic or rectal without taking any antipyretic treatment and sustained until discharge or Day 28. Median time to defervescence was estimated via the Kaplan-Meier method. ITT population included all randomized participants. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint. '99999' signifies "Due to smaller number of participants with an event, upper limit of 95% confidence interval (CI) could not be calculated".

End point type	Secondary

End point timeframe:

up to Day 28

End point values	PTC299	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	22		
Units: days				
median (confidence interval 95%)	7.0 (5.0 to 28.0)	18.0 (4.0 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time from Randomization to Cough Reported as Mild or Absent

End point title	Time from Randomization to Cough Reported as Mild or Absent

End point description:

Cough was rated on a scale of severe, moderate, mild, absent, in those with cough at enrollment rated severe or moderate. Median time to cough reported as mild or absent was estimated via the Kaplan-Meier method. ITT population included all randomized participants. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

up to Day 28

End point values	PTC299	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	34		
Units: days				
median (confidence interval 95%)	3.0 (3.0 to 4.0)	5.0 (3.0 to 7.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time from Randomization to Respiratory Rate ≤ 24 Breaths per Minute on Room Air

End point title	Time from Randomization to Respiratory Rate ≤ 24 Breaths per Minute on Room Air

End point description:

Median time to respiratory rate in participants who had abnormal respiratory rate at baseline was estimated via the Kaplan-Meier method. ITT population included all randomized participants. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

up to Day 28

End point values	PTC299	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	62		
Units: days				
median (confidence interval 95%)	7.0 (5.0 to 11.0)	8.0 (6.0 to 11.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Cytokine Levels at Day 28

End point title	Change From Baseline in Cytokine Levels at Day 28

End point description:

Cytokines included Granulocyte Colony Stimulating factor; Interleukin 10, 17, 2, 6, 7; Macrophage Inflammatory Protein 1 Alpha; Monocyte Chemotactic Protein 1; and Tumor Necrosis Factor. ITT population included all randomized participants. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Day 28

End point values	PTC299	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	64		
Units: nanograms (ng)/liter (L)				
arithmetic mean (standard deviation)				
Granulocyte Colony Stimulating Factor	-0.423 (± 0.4431)	-0.467 (± 0.4750)		
Interleukin 10	-0.367 (± 0.4655)	-0.491 (± 0.4003)		
Interleukin 17	0.018 (± 0.1447)	0.002 (± 0.1425)		
Interleukin 2	0.021 (± 0.0868)	0.022 (± 0.1448)		
Interleukin 6	-0.375 (± 0.5274)	-0.442 (± 0.5062)		
Interleukin 7	-0.025 (± 0.1233)	-0.035 (± 0.1556)		
Macrophage Inflammatory Protein 1 Alpha	0.072 (± 0.2459)	0.044 (± 0.1888)		
Monocyte Chemotactic Protein 1	-0.011 (± 0.4077)	0.018 (± 0.3804)		
Tumor Necrosis Factor	-0.015 (± 0.1509)	-0.027 (± 0.1666)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time from Randomization to Dyspnea Reported as Mild or Absent

End point title	Time from Randomization to Dyspnea Reported as Mild or Absent

End point description:

Dyspnea was rated on a scale of severe, moderate, mild, absent, in those with dyspnea at enrollment rated as severe or moderate. Median time to dyspnea reported as mild or absent was estimated via the Kaplan-Meier method. ITT population included all randomized participants. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

up to Day 28

End point values	PTC299	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	35		
Units: days				
median (confidence interval 95%)	6.0 (3.0 to 9.0)	5.0 (4.0 to 7.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Level of Acute Phase Protein (Ferritin) at Day 28

End point title	Change From Baseline in Level of Acute Phase Protein (Ferritin) at Day 28

End point description:

ITT population included all randomized participants. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Day 28

End point values	PTC299	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	44		
Units: picomoles (pmol)/L				
arithmetic mean (standard deviation)	-0.410 (± 0.3096)	-0.497 (± 0.3162)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Level of Acute Phase Protein (D-Dimer) at Day 28

End point title	Change From Baseline in Level of Acute Phase Protein (D-Dimer) at Day 28

End point description:

ITT population included all randomized participants. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Day 28

End point values	PTC299	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	45		
Units: micrograms (µg)/L D-dimer units (DDU)				
arithmetic mean (standard deviation)	0.029 (± 0.9278)	-0.121 (± 0.9392)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Level of Acute Phase Protein (C Reactive Protein) at Day 28

End point title	Change From Baseline in Level of Acute Phase Protein (C Reactive Protein) at Day 28
End point description:	
End point type	Secondary
End point timeframe:	
Baseline, Day 28	

End point values	PTC299	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	46		
Units: mg/L				
arithmetic mean (standard deviation)	-1.027 (± 0.5966)	-1.111 (± 0.5633)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Level of Acute Phase Proteins (Troponin I and Troponin T) at Day 28

End point title	Change From Baseline in Level of Acute Phase Proteins (Troponin I and Troponin T) at Day 28
End point description:	
ITT population included all randomized participants. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint. 'n' = participants evaluable for specified category.	
End point type	Secondary
End point timeframe:	
Baseline, Day 28	

End point values	PTC299	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	18		
Units: µg/L				
arithmetic mean (standard deviation)				
Troponin I (n = 32, 18)	0.080 (± 1.5879)	-0.036 (± 0.2128)		
Troponin T (n = 8, 11)	0.001 (± 0.0015)	0.061 (± 0.1638)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Normalization of Complete Blood Count (CBC) who had CBC Out of Range at Baseline

End point title	Number of Participants With Normalization of Complete Blood Count (CBC) who had CBC Out of Range at Baseline

End point description:

Number of participants who returned to normal range CBC were reported. CBC included red blood cell (RBC), hemoglobin (HGB), white blood cell (WBC), and Platelets. ITT population included all randomized participants. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint. 'n' = participants evaluable for specified category.

End point type	Secondary

End point timeframe:

up to Day 28

End point values	PTC299	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	26		
Units: participants				
RBC (n = 13, 18)	7	13		
HGB (n = 13, 18)	9	13		
WBC (n = 27, 19)	22	17		
Platelets (n = 26, 26)	21	19		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Viral Load at Day 28: SARS-CoV-2 Immunoglobulin A (IgA) Antibody Ratio and SARS-CoV-2 Immunoglobulin G (IgG) Antibody Ratio

End point title	Change From Baseline in Viral Load at Day 28: SARS-CoV-2 Immunoglobulin A (IgA) Antibody Ratio and SARS-CoV-2 Immunoglobulin G (IgG) Antibody Ratio

End point description:

ITT population included all randomized participants. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint. 'n' = participants evaluable for specified category.

End point type	Secondary

End point timeframe:

Baseline, Day 28

End point values	PTC299	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	49		
Units: ratio				
arithmetic mean (standard deviation)				
SARS-CoV-2 IgA Antibody Ratio (n=49,49)	0.003 (± 0.6387)	0.165 (± 0.5122)		
SARS-CoV-2 IgG Antibody Ratio (n=50,47)	0.890 (± 0.6846)	0.874 (± 0.7604)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Viral Load at Day 28: SARS-CoV2 v2, SARS-CoV2 v2 Nasopharyngeal Swab (NPsw), and Severe Acute Resp Syndrome Coronavirus 2

End point title	Change From Baseline in Viral Load at Day 28: SARS-CoV2 v2, SARS-CoV2 v2 Nasopharyngeal Swab (NPsw), and Severe Acute Resp Syndrome Coronavirus 2

End point description:

ITT population included all randomized participants. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint. 'n' = participants evaluable for specified category. '99999' signifies "data not available since no participant was analyzed". '9999' signifies "due to single participant, standard deviation (SD) could not be calculated".

End point type	Secondary

End point timeframe:

Baseline, Day 28

End point values	PTC299	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	2		
Units: copies/mL				
arithmetic mean (standard deviation)				
SARS-CoV2 v2 (n = 0, 2)	99999 (± 99999)	-0.345 (± 0.2235)		
SARS-CoV2 v2 NPsw (n = 4, 1)	-1.201 (± 0.7503)	1.532 (± 9999)		
SARS Coronavirus 2 (n = 1, 0)	-0.432 (± 9999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Viral Load at Day 28: SARS-CoV-2 IgM Antibody Absorbance

End point title	Change From Baseline in Viral Load at Day 28: SARS-CoV-2 IgM Antibody Absorbance

End point description:

ITT population included all randomized participants. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Day 28

End point values	PTC299	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	47		
Units: absorbance (Abs)				
arithmetic mean (standard deviation)	0.000 (± 0.4691)	0.127 (± 0.4218)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Participants with Treatment-Emergent Adverse Events (TEAEs)

End point description:

An AE was as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. SAE: an AE that met at least 1 of the following criteria: resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions, congenital anomaly/birth defect, important medical event. TEAEs were defined as any AEs that occurred on or after the first study treatment through 30 days after the last dose, or any AEs occurring before the first study treatment but worsening during the treatment through 30 days after the last dose. A summary of all Serious Adverse Events and Other Adverse Events (nonserious) regardless of causality is located in the 'Reported Adverse Events' Section. Safety population included all randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

up to Day 60

End point values	PTC299	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	95		
Units: participants	52	67		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Mortalities at Day 28

End point title	Number of Mortalities at Day 28

End point description:

Mortality was defined as a death event occurring at anytime before the specific date, after the first dose has been received. Safety population included all randomized participants who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Day 28

End point values	PTC299	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	95		
Units: participants	6	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Hospitalization

End point title	Duration of Hospitalization

End point description:

ITT population included all randomized participants. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

up to Day 28

End point values	PTC299	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	83		
Units: days				
arithmetic mean (standard deviation)	8.1 (± 4.87)	9.3 (± 5.49)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time from Randomization to Respiratory Improvement Where Symptom Onset Occurred ≤5 Days

End point title	Time from Randomization to Respiratory Improvement Where Symptom Onset Occurred ≤5 Days

End point description:

Respiratory improvement was defined as SpO2 ≥94% on room air. Median time to respiratory improvement was estimated via the Kaplan-Meier product limit method. ITT population included all randomized participants. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint. '99999' signifies "Due to smaller number of participants with an event, upper limit of 95% CI could not be calculated."

End point type	Other pre-specified

End point timeframe:

up to Day 28

End point values	PTC299	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	10		
Units: days				
median (confidence interval 95%)	10.0 (4.0 to 28.0)	28.0 (7.0 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Time to respiratory improvement was compared between treatment groups using stratified log-rank test.

Comparison groups	PTC299 v Placebo

Number of subjects included in analysis	23
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.033
Method	Logrank

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
up to Day 60	
Adverse event reporting additional description:	
Safety population included all randomized participants who received at least 1 dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received PTC299-matching placebo administered orally, BID on Days 1 to 7, then administered orally, QD on Days 8 to 14.	
Reporting group title	PTC299
Reporting group description:	
Participants received PTC299 at 200 mg, administered orally, BID on Days 1 to 7, then at 50 mg administered orally, QD on Days 8 to 14.	

Serious adverse events	Placebo	PTC299	
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 95 (25.26%)	21 / 92 (22.83%)	
number of deaths (all causes)	4	9	
number of deaths resulting from adverse events			
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 95 (1.05%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	0 / 95 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 95 (1.05%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase			

increased			
subjects affected / exposed	2 / 95 (2.11%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 95 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	0 / 95 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 95 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	0 / 95 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiogenic shock			
subjects affected / exposed	0 / 95 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Right ventricular dysfunction			
subjects affected / exposed	0 / 95 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 95 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute myocardial infarction			
subjects affected / exposed	1 / 95 (1.05%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 95 (1.05%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	2 / 95 (2.11%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	2 / 95 (2.11%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	8 / 95 (8.42%)	10 / 92 (10.87%)	
occurrences causally related to treatment / all	0 / 9	0 / 12	
deaths causally related to treatment / all	0 / 1	0 / 2	
Organising pneumonia			
subjects affected / exposed	0 / 95 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	3 / 95 (3.16%)	3 / 92 (3.26%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 1	
Acute respiratory distress syndrome			

subjects affected / exposed	1 / 95 (1.05%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 95 (3.16%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	0 / 95 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 95 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 95 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 95 (2.11%)	4 / 92 (4.35%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychotic disorder			
subjects affected / exposed	0 / 95 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	1 / 95 (1.05%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint swelling			
subjects affected / exposed	1 / 95 (1.05%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Septic shock			
subjects affected / exposed	1 / 95 (1.05%)	4 / 92 (4.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 3	
Pneumonia acinetobacter			
subjects affected / exposed	0 / 95 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 95 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	1 / 95 (1.05%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bacteraemia			
subjects affected / exposed	1 / 95 (1.05%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	1 / 95 (1.05%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	1 / 95 (1.05%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	1 / 95 (1.05%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 95 (1.05%)	2 / 92 (2.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	1 / 95 (1.05%)	0 / 92 (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: 5 %

Non-serious adverse events	Placebo	PTC299	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 95 (66.32%)	50 / 92 (54.35%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	16 / 95 (16.84%)	14 / 92 (15.22%)	
occurrences (all)	25	18	
Aspartate aminotransferase increased			
subjects affected / exposed	12 / 95 (12.63%)	12 / 92 (13.04%)	
occurrences (all)	14	15	
Gamma-glutamyltransferase increased			
subjects affected / exposed	6 / 95 (6.32%)	4 / 92 (4.35%)	
occurrences (all)	9	8	
Vascular disorders			

Hypertension			
subjects affected / exposed	2 / 95 (2.11%)	7 / 92 (7.61%)	
occurrences (all)	3	8	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 95 (5.26%)	2 / 92 (2.17%)	
occurrences (all)	5	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 95 (3.16%)	8 / 92 (8.70%)	
occurrences (all)	11	10	
Lymphopenia			
subjects affected / exposed	6 / 95 (6.32%)	4 / 92 (4.35%)	
occurrences (all)	9	5	
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	9 / 95 (9.47%)	3 / 92 (3.26%)	
occurrences (all)	11	4	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	12 / 95 (12.63%)	10 / 92 (10.87%)	
occurrences (all)	13	10	
Diarrhoea			
subjects affected / exposed	5 / 95 (5.26%)	3 / 92 (3.26%)	
occurrences (all)	5	3	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 95 (5.26%)	2 / 92 (2.17%)	
occurrences (all)	5	2	
Insomnia			
subjects affected / exposed	6 / 95 (6.32%)	2 / 92 (2.17%)	
occurrences (all)	6	2	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	2 / 95 (2.11%)	6 / 92 (6.52%)	
occurrences (all)	2	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 May 2020	It included following changes: - The protocol was updated throughout to replace the standard of care (SOC) comparison arm with placebo control. - The primary objective was updated to be the time to respiratory improvement. - The primary endpoint was updated, consistent with the new primary objective. - For those secondary endpoints recording time to improvement, it was clarified that the time starts at randomization. Clarification was added on the cough severity scale. D-dimer and cardiac troponin were specified in the list of potential acute phase proteins to be assessed. - The study design was updated to reflect the change to a placebo-controlled, double blind study and to include stratification by remdesivir, prohibition of sensitive CYP2D6 substrates and investigational therapies, an increased sample size, and the addition of the Day 60 safety telephone call. - The study population size was increased. - Exclusion criterion was changed to exclude participants with ≥3 × upper limit of normal (ULN) alanine transaminase (ALT) or aspartate aminotransferase (AST) or ≥2 × ULN Tbili. - Exclusion criterion was added to exclude participants with low lymphocyte count or hemoglobin levels. - A recommendation to take PTC299 with food was added. - A safety telephone call at Day 60 was added and clarification was added around Screening and Day 1 occurring on the same day or 1 day apart. - Clarification was added that vital signs are part of safety assessments.
05 June 2020	It included following changes: - The primary endpoint was amended to the time from randomization to respiratory improvement, defined as peripheral oxygen saturation (SpO2) ≥94% on room air sustained until discharge from the hospital or the end of the study (Day 28). - The study design was amended to reflect changes made elsewhere, namely exclusion of CYP2C inducers, inclusion of the Hepatic Advisory Safety Committee (HAC), and addition of the interim analysis for futility.
23 July 2020	It included following changes: - The number of sites was increased to approximately 40. - An error in the number of study participants was corrected. - Stratification factors were amended to remove hydroxychloroquine and add dexamethasone. - Exclusion criterion was amended to clarify that participation in interventional studies is not permitted. - Exclusion criterion was amended to permit use of dexamethasone.
08 October 2020	It included following changes: - Clarification was added that the secondary endpoint of time from randomization to defervescence applies only to subjects with fever at enrollment. - Inclusion criterion, requiring participants to present with fever, was removed. - Exclusion Criterion was modified to exclude participants with lymphocyte count <500 lymphocytes/microliter (µL) and any participant with hemoglobin <11.0 grams (g)/deciliter (dL).
18 December 2020	It included following changes: - In Inclusion criterion, the window for symptom onset prior to Screening was changed from 7 to 10 days. - Clarification was added that transfer to intensive care unit (ICU), mechanical ventilation, or another medically important event (at the discretion of the investigator) as a result of disease progression would be classified as an SAE. - Text was amended to clarify that the first interim analysis would be after the first 40 participants reached Day 28 or died, withdrew consent, or were lost to follow-up and to clarify those participants who would be censored.
02 June 2021	It included following changes: - The new nonproprietary name was added. - The number of sites was increased to approximately 50. - Inclusion criterion was changed to allow symptom onset ≤14 days. - Hepatic abnormalities of Grade ≥4 will be considered unexpected adverse events.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported