EU Clinical Trials Register

Clinical trial results:
A Multicenter, Randomized, Open-label, Parallel Group Pilot Study to Evaluate the Safety and Efficacy of Prolastin® plus Standard Medical Treatment (SMT) versus SMT alone in Hospitalized Subjects with COVID-19.

Summary

EudraCT number	2020-001953-36
Trial protocol	ES
Global end of trial date	11 June 2021

Results information

Result version number	v1 (current)
This version publication date	11 January 2022
First version publication date	11 January 2022

Trial information

Trial identification

Sponsor protocol code	GC2005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04495101
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Instituto Grifols, S.A.
Sponsor organisation address	Can Guasch, 2, Parets del Vallès, , Barcelona, Spain, 08150
Public contact	Department of Clinical Trials, Instituto Grifols, S.A., 34 935712000, IGregulatory.affairs@grifols.com
Scientific contact	Department of Clinical Trials, Instituto Grifols, S.A., 34 935712000, IGregulatory.affairs@grifols.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	18 August 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 June 2021
Global end of trial reached?	Yes
Global end of trial date	11 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine if Prolastin plus SMT can reduce the proportion of subjects dying or requiring intensive care unit (ICU) admission on or before Day 15 or who are dependent on invasive mechanical ventilation on Day 15 versus SMT alone in hospitalized subjects with COVID-19.

Protection of trial subjects:

Investigators ensured that the study was conducted in full conformance with GCP, appropriate local laws and regulations, and the Declaration of Helsinki. The protocol and protocol amendments for this study were prepared in accordance with ICH Guidelines (and any other relevant regulations). The protocol dated 05 May 2020, two subsequent protocol amendments, and the Informed Consent Form (ICF) were reviewed and approved by the IRB/EC of each participating research study center prior to implementation. Regulatory Authority approvals/authorizations/ notifications, where required, were in place, and fully documented prior to study start. The IRBs/ECs had to supply to the Sponsor, upon request, a list of members involved in the review and approval of the protocol, protocol amendments, consent form and a statement to confirm that the IRB/EC was organized and operating according to GCP Guidelines and applicable laws and regulations. Modifications to the study protocol and protocol amendments were only implemented following agreement by the Sponsor and Investigator. Any deviations from the protocol required full documentation and explanation by the Investigator.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	29 July 2020
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	Spain: 100
Worldwide total number of subjects	100
EEA total number of subjects	100

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)	67
From 65 to 84 years	32
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 8 centers in Spain; however, 2 of the 8 centers did not enroll any subjects. The first patient was enrolled 29 Jul 2020, the last patient was enrolled 12 Apr 2021. The last subject completed their last visit 10 Jun 2021.

Pre-assignment

Screening details:

Subjects were assessed for trial eligibility during the screening period. All of the inclusion criteria and none of the exclusion criteria had to be met for subject to be eligible for study enrollment. A total of 103 subjects were screened, 100 subjects were included in the ITT population and randomized.

Pre-assignment period milestones

Number of subjects started	100
Number of subjects completed	100

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Prolastin + Standard Medical Treatment

Arm description:

Subjects in the Prolastin + Standard Medical Treatment (SMT) arm received two IV doses of Prolastin at 120 mg/kg body weight, 1 week apart (at Day 1 and, an optional dose, at Day 8, for those still hospitalized).

Arm type	Experimental
Investigational medicinal product name	Prolastin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Subjects in the Prolastin + SMT arm were given an IV dose of 120 mg/kg (body weight) on Day 1 and Day 8. For those who had been discharged from the hospital, the second infusion was not mandatory and was at the discretion of the Principal Investigator and subject. Once reconstituted, Prolastin had a concentration of Alpha 1-Proteinase Inhibitor of 25 mg/mL. The infusion rate was at the Principal Investigator's discretion depending on the patient's condition and need to avoid fluid overload. Preparation of the solution for infusion from the lyophilized product was performed by a healthcare professional under aseptic conditions. Prolastin was infused using a separate line by itself, without mixing with other intravenous fluids or medications. Prolastin in Type I glass vials. Each original pack contained 1 powder vial (1000 mg alpha1-PI, human), 1 solvent vial (40 mL water for injections), and 1 Mix2Vial transfer device for reconstitution.

Arm title	Standard Medical Treatment

Arm description:

Subjects in the Standard Medical Treatment (SMT) received medical care based on their research study center's standard practices for the management of COVID-19 patients.

Arm type	Standard Medical Treatment

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Prolastin + Standard Medical Treatment	Standard Medical Treatment
Started	50	50
Completed	41	44
Not completed	9	6
Consent withdrawn by subject	4	1
Death	3	4
Subject transferred to another center 15Apr2021	1	-
Patient refused Day 29 to avoid trip to hospital	-	1
No treatment in pharmacy to administer prolastin	1	-

Baseline characteristics

Reporting groups

Reporting group title	Prolastin + Standard Medical Treatment
Reporting group description:	

Subjects in the Prolastin + Standard Medical Treatment (SMT) arm received two IV doses of Prolastin at 120 mg/kg body weight, 1 week apart (at Day 1 and, an optional dose, at Day 8, for those still hospitalized).

Reporting group title	Standard Medical Treatment
Reporting group description:	

Subjects in the Standard Medical Treatment (SMT) received medical care based on their research study center's standard practices for the management of COVID-19 patients.

Reporting group values	Prolastin + Standard Medical Treatment	Standard Medical Treatment	Total
Number of subjects	50	50	100
Age categorical			
Units: Subjects			
Adults (18-64 years)	31	36	67
From 65-84 years	19	13	32
85 years and over	0	1	1
Age continuous			
Units: years			
median	60.5	55.5	
full range (min-max)	30 to 83	29 to 89	-
Gender categorical			
Units: Subjects			
Female	21	19	40
Male	29	31	60
Race			
Units: Subjects			
White	44	48	92
Black or African American	1	0	1
Asian	1	0	1
American Indian or Alaska Native	1	2	3
Native Hawaiian or Other Pacific Islander	1	0	1
Other	2	0	2
Ethnicity			
Units: Subjects			
Hispanic or Latino	36	43	79
Not Hispanic or Latino	14	7	21
Weight			
Units: Kilograms			
median	80.0	80.0	
full range (min-max)	53.6 to 120.0	53.3 to 130.0	-
BMI			
Units: kg/m^2			
median	27.35	28.15	
full range (min-max)	19.6 to 47.9	20.4 to 53.4	-
Height			

Units: centimeter			
median	167.5	165.0	
full range (min-max)	148 to 194	152 to 185	-
Duration of potential COVID-19 exposure			
The SD value "9.9999" for reporting group 1 should read as "Not applicable".			
Units: day			
arithmetic mean	16.0	13.4	
standard deviation	± 9.9999	± 4.28	-
Duration of first COVID-19 symptoms			
Units: day			
arithmetic mean	9.3	8.9	
standard deviation	± 4.31	± 3.08	-
Duration of first positive PCR (RT-PCR)/NAT or other commercial or public health assay result			
Units: day			
arithmetic mean	3.5	4.0	
standard deviation	± 2.79	± 3.10	-
7-Point Ordinal Scale			
Ordinal scale measure of clinical status: 1) Death; 2) Hospitalized, on invasive mechanical ventilation or ECMO; 3) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen; 6) Not hospitalized, limitation on activities; 7) Not hospitalized, no limitations on activities			
Units: Point			
arithmetic mean	3.9	3.8	
standard deviation	± 0.61	± 0.49	-
National Early Warning Score (NEWS)			
This metric is used to assess clinical status. Data were only collected in 33 subjects from the Prolastin + SMT arm and 32 subjects in the SMT arm.			
Units: Point			
arithmetic mean	3.3	3.3	
standard deviation	± 1.73	± 1.41	-

End points

End points reporting groups

Reporting group title	Prolastin + Standard Medical Treatment
Reporting group description:	
Subjects in the Prolastin + Standard Medical Treatment (SMT) arm received two IV doses of Prolastin at 120 mg/kg body weight, 1 week apart (at Day 1 and, an optional dose, at Day 8, for those still hospitalized).	
Reporting group title	Standard Medical Treatment
Reporting group description:	
Subjects in the Standard Medical Treatment (SMT) received medical care based on their research study center's standard practices for the management of COVID-19 patients.	

Primary: Primary: Number of subjects dying, requiring ICU admission, or dependent on high flow oxygen devices on or before Day 15

End point title	Primary: Number of subjects dying, requiring ICU admission, or dependent on high flow oxygen devices on or before Day 15
End point description:	
This primary efficacy variable was defined as the proportion of subjects dying or requiring ICU admission on or before Day 15 or who were dependent on invasive mechanical ventilation on Day 15.	
End point type	Primary
End point timeframe:	
Day 1 through Day 15	

End point values	Prolastin + Standard Medical Treatment	Standard Medical Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	50		
Units: Subjects				
Dying on or Before Day 15	3	4		
Requiring ICU Admission on or Before Day 15	4	7		
Dependent on IMV on Day 15	3	2		
Meeting Primary Endpoint	7	11		

Statistical analyses

Statistical analysis title	(Prolastin+SMT)-SMT
Statistical analysis description:	
The difference in the proportions of subjects meeting the primary efficacy endpoint between the treatment groups.	
Comparison groups	Prolastin + Standard Medical Treatment v Standard Medical Treatment

Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.4356
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	-8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.2
upper limit	7.6

Secondary: Secondary: Assessment of Clinical Severity: Change in NEWS from Baseline through Day 29

End point title	Secondary: Assessment of Clinical Severity: Change in NEWS from Baseline through Day 29

End point description:

The NEWS was calculated based on 7 clinical parameters (respiration rate, oxygen saturation, any supplemental oxygen, temperature, systolic blood pressure, heart rate, level of consciousness).

Average across all post-baseline visits was not estimable for the SMT arm hence added value "9.9999" to avoid a validation error.

End point type	Secondary

End point timeframe:

Day 1 through Day 29.

End point values	Prolastin + Standard Medical Treatment	Standard Medical Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	50		
Units: Score				
least squares mean (confidence interval 95%)				
Day 15	-2.62 (-3.21 to -2.03)	-2.39 (-2.96 to -1.82)		
Day 29	-2.80 (-3.40 to -2.20)	-2.80 (-3.37 to -2.23)		
Average across all post-baseline visits	-1.24 (-1.78 to -0.71)	9.9999 (9.9999 to 9.9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Time to clinical response: NEWS <= 2 maintained for 24 hours

End point title	Secondary: Time to clinical response: NEWS <= 2 maintained for 24 hours

End point description:

Clinical response is defined as the NEWS score <=2 maintained for 24 hours from Day 1 through Day 29. The time to the first occurrence of clinical response was estimated using the Kaplan-Meier (KM) method.

End point type	Secondary

End point timeframe:

Day 1 through Day 29.

End point values	Prolastin + Standard Medical Treatment	Standard Medical Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	50		
Units: Days				
arithmetic mean (confidence interval 95%)				
25th Percentile	3 (2 to 4)	4 (2 to 5)		
50th Percentile (Median)	6 (4 to 8)	7 (5 to 8)		
75th Percentile	8 (7 to 16)	12 (8 to 15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Time to hospital discharge: Defined as duration of hospitalization

End point title	Secondary: Time to hospital discharge: Defined as duration of hospitalization

End point description:

Time to hospital discharge is defined as duration of hospitalization from Day 1 through Day 29. The proportion of subjects who were discharged from the hospital was estimated using the Cumulative Incidence Function. Deaths that occurred prior to discharge from the hospital was treated as a competing risk.

End point type	Secondary

End point timeframe:

Post-randomization through Day 29.

End point values	Prolastin + Standard Medical Treatment	Standard Medical Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	50		
Units: Days				
arithmetic mean (standard deviation)	11.68 (± 8.43)	11.88 (± 8.35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: If admitted to ICU: Duration of ICU stay

End point title	Secondary: If admitted to ICU: Duration of ICU stay

End point description:

The duration of ICU stay from post-randomization through Day 29 was calculated based on ICU admission and discharge dates. Number of days in the ICU was compared between treatment groups using an ANOVA model, including number of days in the ICU as a dependent variable and treatment group as a fixed effect.

End point type	Secondary

End point timeframe:

Post-randomization through Day 29.

End point values	Prolastin + Standard Medical Treatment	Standard Medical Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	50		
Units: Days				
arithmetic mean (standard deviation)	1.62 (± 6.18)	2.0 (± 5.93)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Duration of any oxygen use

End point title	Secondary: Duration of any oxygen use

End point description:

The duration of any oxygen use from Day 1 through Day 29 was calculated based on the start/stop date of using oxygen supplementation. Number of days on oxygen was compared between treatment groups using an analysis of variance (ANOVA) model, including number of days on oxygen as a dependent variable and treatment group as a fixed effect.

End point type	Secondary

End point timeframe:

Day 1 through Day 29

End point values	Prolastin + Standard Medical Treatment	Standard Medical Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	50		
Units: Days				
arithmetic mean (standard deviation)	10.02 (± 9.15)	10.56 (± 9.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: If requiring mechanical ventilation: Duration mechanical ventilation

End point title	Secondary: If requiring mechanical ventilation: Duration mechanical ventilation
End point description:	

The duration on mechanical ventilation from post randomization through Day 29 was calculated based on the start/stop dates of mechanical ventilation. Number of days on mechanical ventilation was compared between treatment groups using an ANOVA model, including number of days on mechanical ventilation as a dependent variable and treatment group as a fixed effect.

End point type	Secondary
End point timeframe:	

Post-randomization through Day 29

End point values	Prolastin + Standard Medical Treatment	Standard Medical Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	50		
Units: Days				
arithmetic mean (standard deviation)	1.44 (± 5.47)	0.74 (± 3.77)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Clinical Status: Absolute value and mean change from baseline in the Ordinal scale

End point title	Secondary: Clinical Status: Absolute value and mean change from baseline in the Ordinal scale

End point description:

The absolute value and change from baseline in the Ordinal scale from Day 1 through Day 29 were summarized by treatment group and visit using descriptive statistics.
The 7-point Ordinal scale is as follows:
1) Death;
2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);
3) Hospitalized, on non-invasive ventilation or high flow oxygen devices;
4) Hospitalized, requiring supplemental oxygen;
5) Hospitalized, not requiring supplemental oxygen;
6) Not hospitalized, limitation on activities;
7) Not hospitalized, no limitations on activities.

End point type	Secondary

End point timeframe:

Day 1 through Day 29

End point values	Prolastin + Standard Medical Treatment	Standard Medical Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	50		
Units: Scale				
least squares mean (confidence interval 95%)				
Day 15	1.74 (1.40 to 2.07)	1.89 (1.57 to 2.21)		
Day 29	2.05 (1.71 to 2.39)	2.18 (1.86 to 2.50)		
Average across all post-baseline visits	0.37 (0.11 to 0.64)	0.62 (0.36 to 0.88)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Proportion (percentage) of subjects in each severity category of the 7- point Ordinal scale

End point title	Secondary: Proportion (percentage) of subjects in each severity category of the 7- point Ordinal scale

End point description:

The proportion of subjects in each severity category of the 7-point Ordinal scale at Day 15 and Day 29 was tabulated. The difference in severity category distribution between treatment groups at Day 15 and Day 29 was examined using proportional-odds cumulative logit model.
The 7- point Ordinal scale is as follows:
1) Death;
2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO);
3) Hospitalized, on non-invasive ventilation or high flow oxygen devices;
4) Hospitalized, requiring supplemental oxygen;
5) Hospitalized, not requiring supplemental oxygen;
6) Not hospitalized, limitation on activities;
7) Not hospitalized, no limitations on activities.

End point type	Secondary

End point timeframe:

At Day 15 and Day 29

End point values	Prolastin + Standard Medical Treatment	Standard Medical Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	50		
Units: Percentage of subjects				
Day 15: Scale 1	3	3		
Day 15: Scale 2	3	1		
Day 15: Scale 3	1	3		
Day 15: Scale 4	2	4		
Day 15: Scale 5	4	4		
Day 15: Scale 6	4	4		
Day 15: Scale 7	26	29		
Day 29: Scale 1	3	4		
Day 29: Scale 2	3	1		
Day 29: Scale 3	0	1		
Day 29: Scale 4	0	2		
Day 29: Scale 5	1	0		
Day 29: Scale 6	8	6		
Day 29: Scale 7	29	34		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Time to sustained normalization of temperature and proportion of patients with normalization of fever at all time points, defined as temperature < 36.6 °C armpit, < 37.2 °C oral, or < 37.8 °C rectal sustained for at least 24 hours

End point title	Secondary: Time to sustained normalization of temperature and proportion of patients with normalization of fever at all time points, defined as temperature < 36.6 °C armpit, < 37.2 °C oral, or < 37.8 °C rectal sustained for at least 24 hours

End point description:

Sustained normalization of temperature is defined as the temperature <36.6 ºC armpit (axillary), <37.2 ºC oral, or <37.8 ºC rectal sustained for at least 24 hours through Day 29. These values represent the time to first occurrence of sustained normalization of temperature (Days).

End point type	Secondary

End point timeframe:

Day 1 through Day 29

End point values	Prolastin + Standard Medical Treatment	Standard Medical Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	50		
Units: Days				
arithmetic mean (confidence interval 95%)				
25th Percentile	2 (2 to 3)	2 (2 to 3)		
50th Percentile (Median)	3 (2 to 5)	4 (3 to 4)		
75th Percentile	6 (5 to 8)	5 (4 to 6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Number of subjects who develop Acute Respiratory Distress Syndrome (ARDS)

End point title	Secondary: Number of subjects who develop Acute Respiratory Distress Syndrome (ARDS)

End point description:

Berlin criteria for ARDS was assessed on Day 1, 5, 15, and 29. The presence of ARDS and the degree of ARDS by Berlin criteria (Mild, Moderate, Severe) was tabulated by treatment group at each visit.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 5, Day 15, and Day 29.

End point values	Prolastin + Standard Medical Treatment	Standard Medical Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	50		
Units: Number of subjects				
Baseline	19	18		
Day 5	16	15		
Day 15	6	5		
Day 29	3	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Proportion of subjects without clinical progression (defined as death, start of mechanical ventilation, or ICU admission) at Day 15 and Day 29

End point title	Secondary: Proportion of subjects without clinical progression

	(defined as death, start of mechanical ventilation, or ICU admission) at Day 15 and Day 29

End point description:

Proportion of subjects without clinical progression (defined as death, start of mechanical ventilation, or ICU admission) at Day 15 and Day 29.

No statistically significant difference in proportion of subjects without clinical progression was observed between treatment groups (p=0.3328)
Overall Kaplan-Meier Analysis: Prolastin+SMT arm (N=50): 43 were censored and 7 experienced clinical progression. SMT arm (N=50): 39 were censored and 11 experienced clinical progression.

End point type	Secondary

End point timeframe:

Day 15 and Day 29

End point values	Prolastin + Standard Medical Treatment	Standard Medical Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	50		
Units: Percentage of subjects				
number (confidence interval 95%)				
Day 15: % of subjects without clinical progression	84.8 (70.8 to 92.5)	77.9 (63.6 to 87.1)		
Day 29: % of subjects without clinical progression	84.8 (70.8 to 92.5)	77.9 (63.6 to 87.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Summary and analysis of all-cause mortality through Day 29.

End point title	Secondary: Summary and analysis of all-cause mortality through Day 29.

End point description:

Summary and analysis of all-cause mortality through Day 29.

End point type	Secondary

End point timeframe:

Day 1 through Day 29

End point values	Prolastin + Standard Medical Treatment	Standard Medical Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	50		
Units: Subjects				

Alive at Day 29	47	46		
Dead at Day 29	3	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:	
Up to Day 29	
Adverse event reporting additional description:	
Safety population included subjects who received any amount of Prolastin in addition to SMT. For the SMT alone arm, the Safety population included all subjects randomized to this arm.	
Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Prolastin+SMT
Reporting group description: -	
Reporting group title	SMT1

Reporting group description: -

Serious adverse events	Prolastin+SMT	SMT1	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 46 (15.22%)	12 / 50 (24.00%)	
number of deaths (all causes)	23	18	
number of deaths resulting from adverse events	4	6	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	2 / 46 (4.35%)	0 / 50 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 46 (2.17%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 46 (0.00%)	1 / 50 (2.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

	Prolastin+SMT	SMT1	
subjects affected / exposed	0 / 46 (0.00%)	4 / 50 (8.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	4 / 46 (8.70%)	6 / 50 (12.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 4	0 / 6	
Superinfection bacterial			
subjects affected / exposed	1 / 46 (2.17%)	0 / 50 (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: 0 %

Non-serious adverse events	Prolastin+SMT	SMT1	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 46 (43.48%)	12 / 50 (24.00%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 46 (2.17%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Catheter site phlebitis			
subjects affected / exposed	1 / 46 (2.17%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	1 / 46 (2.17%)	2 / 50 (4.00%)	
occurrences (all)	1	2	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	2 / 46 (4.35%)	0 / 50 (0.00%)	
occurrences (all)	2	0	
Acute respiratory failure			

subjects affected / exposed	1 / 46 (2.17%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
Nasal congestion			
subjects affected / exposed	1 / 46 (2.17%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Pneumothorax			
subjects affected / exposed	1 / 46 (2.17%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Pulmonary alveolar haemorrhage			
subjects affected / exposed	1 / 46 (2.17%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Pulmonary embolism			
subjects affected / exposed	0 / 46 (0.00%)	2 / 50 (4.00%)	
occurrences (all)	0	2	
Respiratory failure			
subjects affected / exposed	0 / 46 (0.00%)	4 / 50 (8.00%)	
occurrences (all)	0	4	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 46 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	
Anxiety			
subjects affected / exposed	1 / 46 (2.17%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Initial insomnia			
subjects affected / exposed	1 / 46 (2.17%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Middle insomnia			
subjects affected / exposed	1 / 46 (2.17%)	0 / 50 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 46 (2.17%)	1 / 50 (2.00%)	
occurrences (all)	1	1	
C-reactive protein increased			

subjects affected / exposed	0 / 46 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	1
Fibrin D dimer increased		
subjects affected / exposed	2 / 46 (4.35%)	1 / 50 (2.00%)
occurrences (all)	3	1
Serum ferritin increased		
subjects affected / exposed	1 / 46 (2.17%)	1 / 50 (2.00%)
occurrences (all)	1	1
Transaminases increased		
subjects affected / exposed	0 / 46 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	1
Injury, poisoning and procedural complications		
Tongue injury		
subjects affected / exposed	0 / 46 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	1
Cardiac disorders		
Atrial fibrillation		
subjects affected / exposed	0 / 46 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	1
Myocardial infarction		
subjects affected / exposed	0 / 46 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	1
Supraventricular extrasystoles		
subjects affected / exposed	0 / 46 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	1
Tachycardia		
subjects affected / exposed	0 / 46 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	1
Nervous system disorders		
Dizziness		
subjects affected / exposed	1 / 46 (2.17%)	0 / 50 (0.00%)
occurrences (all)	1	0
Blood and lymphatic system disorders		
Anaemia		
subjects affected / exposed	1 / 46 (2.17%)	2 / 50 (4.00%)
occurrences (all)	1	2

Bicytopenia		
subjects affected / exposed	0 / 46 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	1
Iron deficiency anaemia		
subjects affected / exposed	1 / 46 (2.17%)	0 / 50 (0.00%)
occurrences (all)	1	0
Gastrointestinal disorders		
Constipation		
subjects affected / exposed	2 / 46 (4.35%)	0 / 50 (0.00%)
occurrences (all)	2	0
Diarrhoea		
subjects affected / exposed	1 / 46 (2.17%)	0 / 50 (0.00%)
occurrences (all)	1	0
Haemorrhagic necrotic pancreatitis		
subjects affected / exposed	0 / 46 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	1
Rectal haemorrhage		
subjects affected / exposed	0 / 46 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	1
Upper gastrointestinal haemorrhage		
subjects affected / exposed	1 / 46 (2.17%)	0 / 50 (0.00%)
occurrences (all)	1	0
Hepatobiliary disorders		
Hypertransaminasaemia		
subjects affected / exposed	0 / 46 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	1
Skin and subcutaneous tissue disorders		
Decubitus ulcer		
subjects affected / exposed	0 / 46 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	1
Pigmentation disorder		
subjects affected / exposed	1 / 46 (2.17%)	0 / 50 (0.00%)
occurrences (all)	1	0
Rash pruritic		
subjects affected / exposed	1 / 46 (2.17%)	0 / 50 (0.00%)
occurrences (all)	1	0
Subcutaneous emphysema		

subjects affected / exposed	1 / 46 (2.17%)	0 / 50 (0.00%)	
occurrences (all)	1	0	

Renal and urinary disorders

Acute kidney injury

subjects affected / exposed	0 / 46 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	

Haematuria

subjects affected / exposed	1 / 46 (2.17%)	1 / 50 (2.00%)	
occurrences (all)	1	1	

Renal failure

subjects affected / exposed	0 / 46 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	

Musculoskeletal and connective tissue disorders

Muscle spasms

subjects affected / exposed	1 / 46 (2.17%)	1 / 50 (2.00%)	
occurrences (all)	1	1	

Pain in extremity

subjects affected / exposed	0 / 46 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	

Synovial cyst

subjects affected / exposed	1 / 46 (2.17%)	0 / 50 (0.00%)	
occurrences (all)	1	0	

Infections and infestations

COVID-19 pneumonia

subjects affected / exposed	4 / 46 (8.70%)	6 / 50 (12.00%)	
occurrences (all)	4	6	

Pneumonia bacterial

subjects affected / exposed	0 / 46 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	

Pneumonia necrotising

subjects affected / exposed	0 / 46 (0.00%)	1 / 50 (2.00%)	
occurrences (all)	0	1	

Superinfection bacterial

subjects affected / exposed	1 / 46 (2.17%)	1 / 50 (2.00%)	
occurrences (all)	1	1	

Vascular device infection

subjects affected / exposed	0 / 46 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	1

Metabolism and nutrition disorders		
Hyperglycaemia		
subjects affected / exposed	2 / 46 (4.35%)	1 / 50 (2.00%)
occurrences (all)	2	1
Vitamin D deficiency		
subjects affected / exposed	1 / 46 (2.17%)	0 / 50 (0.00%)
occurrences (all)	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 May 2020	Protocol Amendment 4: Version 5.0 Sections 5.2.1, 7.2.2, and Appendix 1: Inclusion criterion number 2 was changed to include that laboratory-confirmed novel coronavirus infection was performed during the hospital admission and not less than 72 hours prior to randomization. This change aimed to expand the window for documented positive test results and avoid limitations due to the timing of test procedures.
08 October 2020	Protocol Amendment 5 :Version 6.0 Sections 4.2, 7.2.3: Clarified that all samples were mandatory at all time points regardless of hospital discharge status and that Day 5 ±1 day assessments were mandatory for all subjects, to emphasize that planned laboratory testing remained mandatory regardless of study subjects' discharge status. Sections 4.2, 4.4.1, 6.1, 7.2.3. and Appendix 1: Clarified that if the subject was discharged from the hospital before Day 8, the second infusion of Prolastin was not mandatory and was at the discretion of the Principal Investigator and the subject. Sections 4.2., 7.2.3, and Appendix 1: The note "for Day 6 through Day 10, this stipulation is for as long as subjects are hospitalized" was added to indicate that daily assessments through Day 10 were required as long as the subjects remained hospitalized. Section 4.2: Figure 4-1 was replaced to include the new study schema and requirements. Section 7.2.2, Appendix 1: Added specific parameters for collection of demographic data (including age [year of birth], gender, race, and ethnicity), to ensure completeness and consistency. Sections 7.2.3, 7.2.4: Changed study schedule and assessments for subjects who could be discharged from the hospital early into the study. Section 7.2.4.1: New Section added to clarify subject visit schedule, and conditions for Day 8 and second infusion of Prolastin.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported