Clinical trial results:
A randomized double-blind placebo-controlled, pilot trial of intravenous plasma-purified alpha-1 antitrypsin for severe COVID-19 illness.

Summary

EudraCT number	2020-001391-15
Trial protocol	IE
Global end of trial date	12 April 2021

Results information

Result version number	v1 (current)
This version publication date	26 June 2022
First version publication date	26 June 2022

Trial information

Trial identification

Sponsor protocol code	V323Oct2020

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Royal College of Surgeons Ireland
Sponsor organisation address	111 St Stephens Green, Dublin, Ireland, Dublin 2
Public contact	Mandy Jackson, Royal College of Surgeons Ireland, +353 852147569, mandyjackson@Rcsi.ie
Scientific contact	Mandy Jackson, Royal College of Surgeons Ireland, +353 852147569, mandyjackson@Rcsi.ie

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	09 September 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 April 2021
Global end of trial reached?	Yes
Global end of trial date	12 April 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of the study is to conduct a clinical trial of IV AAT as a prospective anti-inflammatory therapy for severely ill COVID-19 patients with ARDS requiring ICU admission.

The primary objective is to demonstrate a biological effect of IV Prolastin administered weekly at 120mg per kilogram of body weight in patients with severe COVID-19 illness requiring intubation and mechanical ventilation for ARDS by reducing circulating levels of IL-6 as measured by plasma ELISA. The study sample size is sufficient to demonstrate a significant difference in patients receiving Prolastin versus patients receiving placebo.

Protection of trial subjects:

Assent was provided by next of kin for those subjects unable to consent. Adequate time was always given to allow patients/patients next of kin to fully understand the study and ask any questions. In addition, attempts were always made to have subjects sign the consent form themselves if they regained capacity.

Where any participant was enrolled and did not regain capacity (due to their death or neurological impairment) the default position was that the enrolled person continued to be a participant in the trial. This was approved by the consent declaration granted by the Health Research Consent Declaration Committee.

After the 10th patient was enrolled in the trial, an interim analysis was carried out by the RCSI Statistician and data was presented to two independent physicians, following which a decision regarding whether or not to proceed was undertaken
based on (1) safety and tolerability, and (2) the status of the primary endpoint.

Regular adverse event checks at each patient visit ensured continuous safety monitoring of participants.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 April 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	Ireland: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

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)	24
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients (n=36) were enrolled between April 20, 2020, and March 18, 2021. Hospitalized patients with a working diagnosis of Acute Respiratory Distress Syndrome (ARDS) secondary to COVID-19 were screened on arrival to the ICU.

Pre-assignment

Screening details:

Eligible patients were aged ≥18 years, had a laboratory confirmed diagnosis of COVID-19, and were receiving ventilator support for moderate-to-severe ARDS with PaO2:FIO2 <200mmHg. In all patients diagnosed with COVID-19, SARS-CoV-2 infection was confirmed by RT-PCR of a nasopharyngeal swab specimen.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Designated unblinded trial personnel were used to randomise subjects and prepare the study drug. The study drug was placed into opaque infusion masking bags so that the active could not be differentiated from placebo. In addition, the giving sets used were red which masked the colour of the study drug and the infusion lines were pre-primed by unblinded personnel. These measures then allowed the infusion to be transported and administered by a blinded member of the team.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo Arm (Baseline)

Arm description:

0.9% sodium chloride

Arm type	Placebo
Investigational medicinal product name	0.9% sodium chloride
Investigational medicinal product code	ATC code: B05XX
Other name	NaCL
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Infusion

Dosage and administration details:

The placebo to be used in the study is 0.9% sodium chloride solution for infusion ("normal saline"). Composition: 9.0 g/l sodium chloride (NaCl) in sterile water for injection. Each ml contains 9 mg sodium chloride. mmol/l: Na+ : 154 Cl- : 154. pH: 4.5-7.

If randomised to Group 1, the dosing was as follows:
- Week 1: Prolastin 120mg/kg body weight IV over 60 minutes*
- Week 2: Placebo (same volume, same rate of infusion as for Prolastin)
-- Week 3: Placebo (same volume, same rate of infusion as for Prolastin)
- Week 4: Placebo (same volume, same rate of infusion as for Prolastin)

If randomised to Group 3, the dosing was as follows:
- Week 1: Placebo (same volume, same rate of infusion as for Prolastin)
- Week 2: Placebo (same volume, same rate of infusion as for Prolastin)
- Week 3: Placebo (same volume, same rate of infusion as for Prolastin)
- Week 4: Placebo (same volume, same rate of infusion as for Prolastin)

Group 2 did not contain any placebo administration.

Arm title	Plasma Purified Alpha-1 antitrypsin (Baseline)

Arm description:

The intervention used was human plasma-purified alpha-1 antitrypsin (Prolastin)

Arm type	Experimental
Investigational medicinal product name	Human plasma-purified alpha-1 antitrypsin
Investigational medicinal product code	ATCcode: B02AB02
Other name	Prolastin
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Solution for infusion

Dosage and administration details:

Group 1:
- Week 1: Prolastin 120mg/kg body weight IV over 60 minutes*
- Week 2: Placebo (same volume, same rate of infusion as for Prolastin)
- Week 3: Placebo (same volume, same rate of infusion as for Prolastin)
- Week 4: Placebo (same volume, same rate of infusion as for Prolastin)

Group 2:
- Week 1: Prolastin 120mg/kg body weight IV over 60 minutes*
- Week 2: Prolastin 120mg/kg body weight IV over 60 minutes*
- Week 3: Prolastin 120mg/kg body weight IV over 60 minutes*
- Week 4: Prolastin 120mg/kg body weight IV over 60 minutes*

Group 3 was placebo only and no Prolastin

Number of subjects in period 1	Placebo Arm (Baseline)	Plasma Purified Alpha-1 antitrypsin (Baseline)
Started	11	25
Completed	11	25

Period 2

Period 2 title	Day 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Designated unblinded trial personnel were used to randomise subjects and prepare the study drug. The study drug was placed into opaque infusion masking bags so that the active could not be differentiated from placebo. In addition, the giving sets used were red which masked the colour of the study drug and the infusion lines were pre-primed by unblinded personnel. These measures then allowed the infusion to be transported and administered by a blinded member of the team.

Arms

Are arms mutually exclusive?	Yes

Arm title	Placebo Arm (Day 2)

Arm description:

0.9% sodium chloride

Arm type	Placebo
Investigational medicinal product name	0.9% sodium chloride
Investigational medicinal product code	ATC code: B05XX
Other name	NaCL
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Infusion

Dosage and administration details:

The placebo to be used in the study is 0.9% sodium chloride solution for infusion ("normal saline"). Composition: 9.0 g/l sodium chloride (NaCl) in sterile water for injection. Each ml contains 9 mg sodium chloride. mmol/l: Na+ : 154 Cl- : 154. pH: 4.5-7.

If randomised to Group 1, the dosing was as follows:
- Week 1: Prolastin 120mg/kg body weight IV over 60 minutes*
- Week 2: Placebo (same volume, same rate of infusion as for Prolastin)
-- Week 3: Placebo (same volume, same rate of infusion as for Prolastin)
- Week 4: Placebo (same volume, same rate of infusion as for Prolastin)

If randomised to Group 3, the dosing was as follows:
- Week 1: Placebo (same volume, same rate of infusion as for Prolastin)
- Week 2: Placebo (same volume, same rate of infusion as for Prolastin)
- Week 3: Placebo (same volume, same rate of infusion as for Prolastin)
- Week 4: Placebo (same volume, same rate of infusion as for Prolastin)

Group 2 did not contain any placebo administration.

Arm title	Plasma Purified Alpha-1 antitrypsin (Day 2)

Arm description:

The intervention used was human plasma-purified alpha-1 antitrypsin (Prolastin)

Arm type	Experimental
Investigational medicinal product name	Human plasma-purified alpha-1 antitrypsin
Investigational medicinal product code	ATCcode: B02AB02
Other name	Prolastin
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Solution for infusion

Dosage and administration details:

Group 1:
- Week 1: Prolastin 120mg/kg body weight IV over 60 minutes*
- Week 2: Placebo (same volume, same rate of infusion as for Prolastin)
- Week 3: Placebo (same volume, same rate of infusion as for Prolastin)
- Week 4: Placebo (same volume, same rate of infusion as for Prolastin)

Group 2:
- Week 1: Prolastin 120mg/kg body weight IV over 60 minutes*
- Week 2: Prolastin 120mg/kg body weight IV over 60 minutes*
- Week 3: Prolastin 120mg/kg body weight IV over 60 minutes*
- Week 4: Prolastin 120mg/kg body weight IV over 60 minutes*

Group 3 was placebo only and no Prolastin

Number of subjects in period 2	Placebo Arm (Day 2)	Plasma Purified Alpha-1 antitrypsin (Day 2)
Started	11	25
Completed	11	25

Period 3

Period 3 title	Day 7 (post-infusion)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo Arm (Day 7)

Arm description:

0.9% sodium chloride

Arm type	Placebo
Investigational medicinal product name	0.9% sodium chloride
Investigational medicinal product code	ATC code: B05XX
Other name	NaCL
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Infusion

Dosage and administration details:

The placebo to be used in the study is 0.9% sodium chloride solution for infusion ("normal saline"). Composition: 9.0 g/l sodium chloride (NaCl) in sterile water for injection. Each ml contains 9 mg sodium chloride. mmol/l: Na+ : 154 Cl- : 154. pH: 4.5-7.

If randomised to Group 1, the dosing was as follows:
- Week 1: Prolastin 120mg/kg body weight IV over 60 minutes*
- Week 2: Placebo (same volume, same rate of infusion as for Prolastin)
-- Week 3: Placebo (same volume, same rate of infusion as for Prolastin)
- Week 4: Placebo (same volume, same rate of infusion as for Prolastin)

If randomised to Group 3, the dosing was as follows:
- Week 1: Placebo (same volume, same rate of infusion as for Prolastin)
- Week 2: Placebo (same volume, same rate of infusion as for Prolastin)
- Week 3: Placebo (same volume, same rate of infusion as for Prolastin)
- Week 4: Placebo (same volume, same rate of infusion as for Prolastin)

Group 2 did not contain any placebo administration.

Arm title	Plasma Purified Alpha-1 antitrypsin (Day 7)

Arm description:

The intervention used was human plasma-purified alpha-1 antitrypsin (Prolastin)

Arm type	Experimental

Investigational medicinal product name	Human plasma-purified alpha-1 antitrypsin
Investigational medicinal product code	ATCcode: B02AB02
Other name	Prolastin
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Solution for infusion

Dosage and administration details:

Group 1:
- Week 1: Prolastin 120mg/kg body weight IV over 60 minutes*
- Week 2: Placebo (same volume, same rate of infusion as for Prolastin)
- Week 3: Placebo (same volume, same rate of infusion as for Prolastin)
- Week 4: Placebo (same volume, same rate of infusion as for Prolastin)

Group 2:
- Week 1: Prolastin 120mg/kg body weight IV over 60 minutes*
- Week 2: Prolastin 120mg/kg body weight IV over 60 minutes*
- Week 3: Prolastin 120mg/kg body weight IV over 60 minutes*
- Week 4: Prolastin 120mg/kg body weight IV over 60 minutes*

Group 3 was placebo only and no Prolastin

Number of subjects in period 3	Placebo Arm (Day 7)	Plasma Purified Alpha-1 antitrypsin (Day 7)
Started	11	25
Completed	11	25

Period 4

Period 4 title	Day 28
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo Arm (Day 28)

Arm description:

0.9% sodium chloride

Arm type	Placebo
Investigational medicinal product name	0.9% sodium chloride
Investigational medicinal product code	ATC code: B05XX
Other name	NaCL
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Infusion

Dosage and administration details:

The placebo to be used in the study is 0.9% sodium chloride solution for infusion ("normal saline"). Composition: 9.0 g/l sodium chloride (NaCl) in sterile water for injection. Each ml contains 9 mg sodium chloride. mmol/l: Na+ : 154 Cl- : 154. pH: 4.5-7.

If randomised to Group 1, the dosing was as follows:
- Week 1: Prolastin 120mg/kg body weight IV over 60 minutes*
- Week 2: Placebo (same volume, same rate of infusion as for Prolastin)
-- Week 3: Placebo (same volume, same rate of infusion as for Prolastin)
- Week 4: Placebo (same volume, same rate of infusion as for Prolastin)

If randomised to Group 3, the dosing was as follows:
- Week 1: Placebo (same volume, same rate of infusion as for Prolastin)
- Week 2: Placebo (same volume, same rate of infusion as for Prolastin)
- Week 3: Placebo (same volume, same rate of infusion as for Prolastin)
- Week 4: Placebo (same volume, same rate of infusion as for Prolastin)

Group 2 did not contain any placebo administration.

Arm title	Plasma Purified Alpha-1 antitrypsin (Day 28)

Arm description:

The intervention used was human plasma-purified alpha-1 antitrypsin (Prolastin)

Arm type	Experimental
Investigational medicinal product name	Human plasma-purified alpha-1 antitrypsin
Investigational medicinal product code	ATCcode: B02AB02
Other name	Prolastin
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Solution for infusion

Dosage and administration details:

Group 1:
- Week 1: Prolastin 120mg/kg body weight IV over 60 minutes*
- Week 2: Placebo (same volume, same rate of infusion as for Prolastin)
- Week 3: Placebo (same volume, same rate of infusion as for Prolastin)
- Week 4: Placebo (same volume, same rate of infusion as for Prolastin)

Group 2:
- Week 1: Prolastin 120mg/kg body weight IV over 60 minutes*
- Week 2: Prolastin 120mg/kg body weight IV over 60 minutes*
- Week 3: Prolastin 120mg/kg body weight IV over 60 minutes*
- Week 4: Prolastin 120mg/kg body weight IV over 60 minutes*

Group 3 was placebo only and no Prolastin

Number of subjects in period 4	Placebo Arm (Day 28)	Plasma Purified Alpha-1 antitrypsin (Day 28)
Started	11	25
Completed	11	22
Not completed	0	3
Lost to follow-up	-	3

Baseline characteristics

Reporting groups	
Reporting group title	Placebo Arm (Baseline)
Reporting group description:	
0.9% sodium chloride	
Reporting group title	Plasma Purified Alpha-1 antitrypsin (Baseline)
Reporting group description:	
The intervention used was human plasma-purified alpha-1 antitrypsin (Prolastin)	

Reporting group values	Placebo Arm (Baseline)	Plasma Purified Alpha-1 antitrypsin (Baseline)	Total
Number of subjects	11	25	36
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Age was collected from the medical record for each patient at their screening visit.			
Units: years			
arithmetic mean	57	59	
standard deviation	± 13	± 11	-
Gender categorical			
Units: Subjects			
Female	2	12	14
Male	9	13	22
Body Mass Index			
Units: kg/m2			
arithmetic mean	33.4	35.2	
standard deviation	± 8.1	± 11	-

End points

End points reporting groups

Reporting group title	Placebo Arm (Baseline)
Reporting group description: 0.9% sodium chloride	
Reporting group title	Plasma Purified Alpha-1 antitrypsin (Baseline)
Reporting group description: The intervention used was human plasma-purified alpha-1 antitrypsin (Prolastin)	
Reporting group title	Placebo Arm (Day 2)
Reporting group description: 0.9% sodium chloride	
Reporting group title	Plasma Purified Alpha-1 antitrypsin (Day 2)
Reporting group description: The intervention used was human plasma-purified alpha-1 antitrypsin (Prolastin)	
Reporting group title	Placebo Arm (Day 7)
Reporting group description: 0.9% sodium chloride	
Reporting group title	Plasma Purified Alpha-1 antitrypsin (Day 7)
Reporting group description: The intervention used was human plasma-purified alpha-1 antitrypsin (Prolastin)	
Reporting group title	Placebo Arm (Day 28)
Reporting group description: 0.9% sodium chloride	
Reporting group title	Plasma Purified Alpha-1 antitrypsin (Day 28)
Reporting group description: The intervention used was human plasma-purified alpha-1 antitrypsin (Prolastin)	

Primary: Change in level of circulating IL-6 in plasma at 7 days as measured by ELISA.

End point title	Change in level of circulating IL-6 in plasma at 7 days as measured by ELISA.

End point description:

Plasma was obtained at day 0 and day 7 from patients receiving placebo (n=11) and patients receiving AAT (n=22). IL-6 levels were increased at day 7 compared to day 0 in the placebo group (day 0: 259.9 +/- 206.5 pg/ml, day 7: 348.2 +/- 264.0 pg/ml; P=0.04) and decreased at day 7 in the AAT group (day 0: 296.0 +/- 219.7 pg/ml, day 7: 217.7 +/- 168.7 pg/ml; P=0.003).

The 7-day change in plasma levels of IL-6 from baseline was +88.3 +/- 125.8 pg/ml in the placebo group compared to -78.3 +/- 112.1 pg/ml in the treatment group (P=0.002).

Patients assigned to placebo demonstrated a 37.8+/-56.6% increase in plasma IL-6 at day 7 compared to a mean reduction of 17.4+/-42.3% in those receiving IV AAT (P=0.01). IL = interleukin; AAT = alpha-1 antitrypsin.

End point type	Primary
End point timeframe: Change from Day 0 to Day 7	

End point values	Placebo Arm (Baseline)	Plasma Purified Alpha-1 antitrypsin (Baseline)	Placebo Arm (Day 7)	Plasma Purified Alpha-1 antitrypsin (Day 7)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	22	11	22
Units: pg/mL				
arithmetic mean (standard deviation)	259.9 (± 206.5)	296 (± 219.7)	348.2 (± 264)	217.7 (± 168.7)

Statistical analyses

Statistical analysis title	Statistical analysis of primary endpoint

Statistical analysis description:

Changes in the levels of inflammatory biomarkers within each patient group were analyzed using paired t-tests for normally distributed data and a nonparametric paired Wilcoxon signed-rank test in the event of data failing the test for normality.

Comparison groups	Plasma Purified Alpha-1 antitrypsin (Baseline) v Placebo Arm (Baseline)
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.05 [2]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Variability estimate	Standard deviation

Notes:

[1] - Results are reported as absolute numbers or means and standard deviations, as appropriate. Categorical variables are summarized as counts and percentages. No imputation was made for missing data. The primary efficacy analysis was on an intention to treat basis.
[2] - Changes in the levels of inflammatory biomarkers within each patient group were analyzed using paired t-tests for normally distributed data and a nonparametric paired Wilcoxon signed-rank test in the event of data failing the test for normality.

Secondary: Sequential Organ Failure Assessment (SOFA) score at day 7

End point title	Sequential Organ Failure Assessment (SOFA) score at day 7

End point description:

Sequential organ failure assessment (SOFA) score, an assessment of clinical severity incritically unwell patients

End point type	Secondary

End point timeframe:

Baseline to Day 7

End point values	Placebo Arm (Baseline)	Plasma Purified Alpha-1 antitrypsin (Baseline)	Placebo Arm (Day 7)	Plasma Purified Alpha-1 antitrypsin (Day 7)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	25	11	22
Units: Points				
arithmetic mean (standard deviation)	7.8 (± 3.3)	7.2 (± 3.4)	8.1 (± 3.5)	5.8 (± 4.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Circulating AAT levels

End point title	Circulating AAT levels

End point description:

Circulating alpha-1 antitrypsin (AAT) levels as measured by nephelometry

End point type	Secondary

End point timeframe:

Baseline to Day 7

End point values	Placebo Arm (Baseline)	Plasma Purified Alpha-1 antitrypsin (Baseline)	Placebo Arm (Day 2)	Plasma Purified Alpha-1 antitrypsin (Day 2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	22	11	22
Units: g/L				
arithmetic mean (standard deviation)	2.3 (± 0.6)	2.3 (± 0.5)	2.3 (± 0.7)	4.2 (± 0.7)

End point values	Placebo Arm (Day 7)	Plasma Purified Alpha-1 antitrypsin (Day 7)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	22		
Units: g/L				
arithmetic mean (standard deviation)	2.2 (± 0.5)	2.8 (± 0.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mortality

End point title	Mortality

End point description:

End point type	Secondary

End point timeframe:

Measured at Day 28

End point values	Placebo Arm (Day 28)	Plasma Purified Alpha-1 antitrypsin (Day 28)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	25		
Units: percent				
number (not applicable)	36	32		

Statistical analyses

No statistical analyses for this end point

Secondary: ICU Length of Stay

End point title	ICU Length of Stay

End point description:

End point type	Secondary

End point timeframe:

Measured at Day 28

End point values	Placebo Arm (Day 28)	Plasma Purified Alpha-1 antitrypsin (Day 28)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	25		
Units: day				
arithmetic mean (standard deviation)	21.4 (± 5.9)	16 (± 9.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary bacterial pneumonia

End point title	Secondary bacterial pneumonia

End point description:

End point type	Secondary

End point timeframe:

Measured at Day 28

End point values	Placebo Arm (Day 28)	Plasma Purified Alpha-1 antitrypsin (Day 28)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	25		
Units: percent				
number (not applicable)	63	44		

Statistical analyses

No statistical analyses for this end point

Secondary: Hospital Length of Stay

End point title	Hospital Length of Stay

End point description:

End point type	Secondary

End point timeframe:

measured at day 28

End point values	Placebo Arm (Day 28)	Plasma Purified Alpha-1 antitrypsin (Day 28)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	25		
Units: day				
arithmetic mean (standard deviation)	24.6 (± 6.2)	19.3 (± 8.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Ventilator Free Days

End point title	Ventilator Free Days

End point description:

End point type	Secondary

End point timeframe:

Measured at Day 28

End point values	Placebo Arm (Day 28)	Plasma Purified Alpha-1 antitrypsin (Day 28)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	25		
Units: day				
arithmetic mean (standard deviation)	3.6 (± 5.7)	8.2 (± 11.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Acute Kidney Injury

End point title	Acute Kidney Injury

End point description:

End point type	Secondary

End point timeframe:

Measured at Day 28

End point values	Placebo Arm (Day 28)	Plasma Purified Alpha-1 antitrypsin (Day 28)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	25		
Units: percent				
number (not applicable)	72	68		

Statistical analyses

No statistical analyses for this end point

Secondary: PaO2:FIO2

End point title	PaO2:FIO2

End point description:

PaO2:FIO2 – ratio of partial pressure of oxygen in arterial blood to the fraction of inspired oxygen

End point type	Secondary

End point timeframe:

Baseline to Day 7

End point values	Placebo Arm (Baseline)	Plasma Purified Alpha-1 antitrypsin (Baseline)	Placebo Arm (Day 7)	Plasma Purified Alpha-1 antitrypsin (Day 7)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	25	11	22
Units: mmHg				
arithmetic mean (standard deviation)	122.5 (± 40.5)	129.7 (± 38.2)	127.7 (± 53.7)	186.7 (± 135.1)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were checked from the screening period until the Day 28 visit (follow up)

Adverse event reporting additional description:

Adverse events were collected by the investigator team through medical chart reviews and discussion with patients at visits where possible.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	Placebo

Reporting group description: -

Reporting group title	Human alpha-1 antitrypsin (Prolastin)

Reporting group description:

A total of 4 SAEs were recorded in the treatment group, involving 2 patients. Of these, 3 SAEs were deemed not related to the study IMP by the Chief Investigator (CI). One SAE was considered to be possibly related to study IMP by the CI (hypertension persistent for >30 min post-infusion), and resolved without sequelae. None of the SAEs resulted in discontinuation of treatment.

Serious adverse events	Placebo	Human alpha-1 antitrypsin (Prolastin)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	2 / 25 (8.00%)	
number of deaths (all causes)	4	8	
number of deaths resulting from adverse events	0	0	
Investigations			
Supraventricular tachycardia	Additional description: Not related to the study drug		
subjects affected / exposed	0 / 11 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 4	0 / 8	
Vascular disorders			
Hypertension	Additional description: Determined to be possibly related to the study drug.		
subjects affected / exposed	0 / 11 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 4	0 / 8	
Cardiac disorders			
Atrial fibrillation	Additional description: not related to the study drug		

subjects affected / exposed	0 / 11 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 4	0 / 8	
Renal and urinary disorders			
Acute kidney injury	Additional description: Occurred in reporting arm 2 (Prolastin). Not determined to be related to the study drug.		
subjects affected / exposed	0 / 11 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 4	0 / 8	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Placebo	Human alpha-1 antitrypsin (Prolastin)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	5 / 25 (20.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 11 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 11 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Sinus tachycardia			
subjects affected / exposed	0 / 11 (0.00%)	3 / 25 (12.00%)	
occurrences (all)	0	3	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	0 / 11 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			

Rash subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	2 / 25 (8.00%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 October 2020	-Estimated trial duration increased to 12 months -Planned trial sites added -Addition of new Principal Investigators for this trial -Removal of wording "patients who are receiving vasopressors (0.05-0.1µg/kg/min)" when referring to the study population -Removal of wording "sex & BMI" in randomisation schedule -Medication administration time changed from 30-45 minutes to approximately 60 minutes -Inclusion criteria #2 removal of"requirement for vasopressors (0.05- 0.1 µg/kg/min) -Exclusion criteria #5 addition of wording "other than antibiotics or anti- virals" -Exclusion criteria #19 removed -Removal of mandatory Isoelectric focusing of plasma to confirm Pi*MM status at screening -Echocardiogram will be performed at screening only where possible -Additional notes added: • The screening visit and baseline visit can occur on the same day • The follow up visit after Early Discontinuation will be performed as soon as is possible. • A note added that the most recent results should be documented for assessments performed within 5 days of the screening visit -Footnote added to clarify regained capacity consent must be attempted at each visit. X indicated at Visit 1 & 2 to indicate that family member assent must be attempted before subjects are screened. -Sections deleted and wording amended to reflect that the Investigators report only serious adverse events that are possibly related to the study drug -Planned recruitment rate amended from 2 weeks to 12 months -Wording amended to interim analysis of cytokine levels taken at 7 days may be conducted.
01 December 2020	-Addition of Inclusion #4 "Patients receiving invasive mechanical ventilation or non-invasive ventilation" -Exclusion criteria #1 wording changed from "Not receiving invasive mechanical ventilation" to "Not receiving invasive mechanical ventilation or non-invasive ventilation" (i.e. patients receiving invasive mechanical ventilation or non-invasive ventilation are eligible for the trial) -Exclusion criteria #5 wording changed from "Participation in a clinical trial of an investigational medicinal product (other than antibiotics or anti-virals)" to "Participation in a clinical trial of interferon therapies, immune plasma therapies or immunoglobulin within 30 days" -Exclusion criteria #17 wording changed from "Enrolled in a concomitant clinical trial of a medicinal product (other than antibiotics or anti-virals" to "Enrolled in a concomitant clinical trial of interferon therapies, immune plasma therapies or immunoglobulin"

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The population studied was small which prevented meaningful conclusions regarding clinical outcomes from being drawn. A larger trial is needed to determine the effect of this therapy on clinical outcomes.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35291694