Clinical trial results:
To determine whether administration of almitrine bismesylate can ameliorate hypoxaemia in Covid-19 and augment effectiveness of supplementary oxygen therapy and respiratory support

Summary

EudraCT number	2020-002567-57
Trial protocol	GB
Global end of trial date	03 March 2023

Results information

Result version number	v1 (current)
This version publication date	27 August 2023
First version publication date	27 August 2023

Trial information

Trial identification

Sponsor protocol code	6.0

Additional study identifiers

ISRCTN number	ISRCTN11713182
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford / Clinical Trials and Research Governance
Sponsor organisation address	Joint Research Office, Boundary Brook House, Churchill Drive, Headington, Oxford, United Kingdom, OX3 7LE
Public contact	CTRG, University of Oxford / Clinical Trials and Research Governance, 00 000000, ctrg@admin.ox.ac.uk
Scientific contact	CTRG, University of Oxford / Clinical Trials and Research Governance, 00 000000, ctrg@admin.ox.ac.uk

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	16 December 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 March 2022
Global end of trial reached?	Yes
Global end of trial date	03 March 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine whether administration of almitrine bismesylate can ameliorate hypoxaemia in Covid-19 and augment the effectiveness of supplemental oxygen therapy and respiratory support.

Protection of trial subjects:

The trial was conduction in accordance with Good Clinical Practice (GCP) and with the Declaration of Helsinki, to ensure the protection of trial subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 February 2021
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	United Kingdom: 27
Worldwide total number of subjects	27
EEA total number of subjects	0

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)	17
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with severe COVID-19 pneumonia were recruited from three acute hospitals in the United Kingdom.

Pre-assignment

Screening details:

Patients admitted to hospital with confirmed or suspected COVID-19 infection were first identified by their clinical teams and then approached for their interest. Screening was then performed and eligible patients/representatives were offered participation in the trial. Given the pandemic setting, no formal screening log was kept.

Period 1

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

Blinding implementation details:

Almitrine capsules were manufactured for the trial, alongside identical placebo capsules. Packs of treatment (almitrine or placebo) were supplied with kit numbers, which were allocated by an online randomisation system (Sealed Envelope), such that both local investigators and participants remained blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Almitrine

Arm description:

Participants receiving almitrine (2 x 50 mg capsules initially, then 1 x 50 mg capsule 4-hourly for 7 days)

Arm type	Experimental
Investigational medicinal product name	Almitrine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Nasogastric use , Oral use

Dosage and administration details:

2 x 50 mg capsules initially, then 1 x 50 mg capsule 4-hourly for 7 days

Arm title	Placebo

Arm description:

Patients receiving placebo (2 capsules initially, then 1 capsule 4-hourly for 7 days)

Arm type	Placebo
Investigational medicinal product name	Placebo capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Nasogastric use , Oral use

Dosage and administration details:

2 capsules initially, then 1 capsule 4-hourly for 7 days

Number of subjects in period 1	Almitrine	Placebo
Started	13	14
Completed	11	13
Not completed	2	1
Consent withdrawn by subject	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Almitrine
Reporting group description:	
Participants receiving almitrine (2 x 50 mg capsules initially, then 1 x 50 mg capsule 4-hourly for 7 days)	
Reporting group title	Placebo
Reporting group description:	
Patients receiving placebo (2 capsules initially, then 1 capsule 4-hourly for 7 days)	

Reporting group values	Almitrine	Placebo	Total
Number of subjects	13	14	27
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			
Units: years			
arithmetic mean	61.0	56.4	
standard deviation	± 14.4	± 13.9	-
Gender categorical			
Units: Subjects			
Female	5	5	10
Male	8	9	17
Diabetic			
Patients with established diagnosis of diabetes			
Units: Subjects			
Diabetes	4	1	5
No diabetes	9	13	22
Hypertension			
Patients with established diagnosis of hypertension			
Units: Subjects			
Hypertension	5	5	10
No hypertension	8	9	17
Body mass index			
Body mass index (BMI) at point of recruitment. Note that this data was not available for 3 patients (1 in the placebo group, 2 in the almitrine group).			
Units: kg/m2			
arithmetic mean	34.4	32.7	
standard deviation	± 7.4	± 7.6	-

End points

End points reporting groups

Reporting group title	Almitrine
Reporting group description:	
Participants receiving almitrine (2 x 50 mg capsules initially, then 1 x 50 mg capsule 4-hourly for 7 days)	
Reporting group title	Placebo
Reporting group description:	
Patients receiving placebo (2 capsules initially, then 1 capsule 4-hourly for 7 days)	
Subject analysis set title	Almitrine vs. placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intention to treat analysis, based on allocation to almitrine or placebo group. Note that some participants in both group did not complete the full course of treatment, and others (two in the almitrine group and one in the placebo group) did not complete the protocol due to withdrawal of consent.	

Primary: Level of respiratory support

End point title	Level of respiratory support
End point description:	
Change in level of respiratory support over 7 days of IMP (almitrine or placebo) administration, based on COMET initiative ordinal scale (Level 0=no respiratory support; Level 1=simple inspired oxygen therapy; Level 2=non-invasive respiratory support (including CPAP, NIV, high flow nasal oxygen); Level 3=invasive respiratory support involving intubation and mechanical ventilation; Level 4=extra corporeal membrane oxygenation (ECMO); Level 5=dead). Intention to treat analysis, based on allocation to almitrine or placebo group. Note that some participants in both group did not complete the full course of treatment, and others (two in the almitrine group and one in the placebo group) did not complete the protocol due to withdrawal of consent.	
End point type	Primary
End point timeframe:	
Measured over 7 days of IMP (almitrine or placebo) administration	

End point values	Almitrine	Placebo	Almitrine vs. placebo	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	13	14	27	
Units: Level of respiratory support				
number (not applicable)	0	0	0.86	

Statistical analyses

Statistical analysis title	Ordinal logistic regression model
Statistical analysis description:	
An ordinal logistic regression model incorporating all available data was used to provide the odds of being at a higher (worse) respiratory support level in the almitrine group, compared with the placebo group. The outcome was an odds ratio of 0.86 (0.23, 3.12), i.e. the odds of being in a higher support level are slightly lower for the intervention group compared with the placebo group, but this difference was not statistically significant (p=0.8204).	
Comparison groups	Almitrine v Placebo

Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.8204
Method	Regression, Logistic

Notes:

[1] - As above.

Secondary: 30 day survival

End point title	30 day survival

End point description:

Number of patients alive or dead at 30 days. This data was not available for 3 patients, who withdrew consent for follow up (2 in the almitrine group, 1 in the placebo group. For the remaining patient, the number who died by 30 days was 7/11 in the almitrine group and 6/13 in the placebo group. There was no statical difference between groups (P=0.551).

End point type	Secondary

End point timeframe:

Survival at 30 days

End point values	Almitrine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	13		
Units: Number of patients				
Alive	4	7		
Dead	7	6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The window for adverse event reporting was from the first dose of IMP (almitrine/placebo) until 48 h after the final dose of IMP.

Adverse event reporting additional description:

Due to the pandemic setting and the high rate of adverse events in severe COVID-19 infection, only Serious Adverse Reactions were recorded/reported, as specified in the protocol. No SARs occurred. Other adverse events were not routinely recorded, but blood alanine transaminase (ALT) and lactate levels were measured daily during IMP administration.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26

Reporting groups

Reporting group title	Almitrine

Reporting group description:

Participants receiving almitrine (2 x 50 mg capsules initially, then 1 x 50 mg capsule 4-hourly for 7 days).

Due to the pandemic setting and the high rate of adverse events in severe COVID-19 infection, only Serious Adverse Reactions were recorded/reported, as specified in the protocol. No SARs occurred. Other adverse events were not routinely recorded, but blood alanine transaminase (ALT) and lactate levels were measured daily during IMP administration, so where these values became abnormal, this is listed below as an adverse event. The total number of deaths listed below relates to deaths within the adverse event reporting window (excluding those who withdrew consent for further data collection).

Reporting group title	Placebo

Reporting group description:

Patients receiving placebo (2 capsules initially, then 1 capsule 4-hourly for 7 days).

Due to the pandemic setting and the high rate of adverse events in severe COVID-19 infection, only Serious Adverse Reactions were recorded/reported, as specified in the protocol. No SARs occurred. Other adverse events were not routinely recorded, but blood alanine transaminase (ALT) and lactate levels were measured daily during IMP administration, so where these values became abnormal, this is listed below as an adverse event. The total number of deaths listed below relates to deaths within the adverse event reporting window (excluding those who withdrew consent for further data collection).

Serious adverse events	Almitrine	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	0 / 14 (0.00%)	
number of deaths (all causes)	3	2	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Almitrine	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 13 (15.38%)	5 / 14 (35.71%)	
Gastrointestinal disorders			
Deranged alanine transaminase	Additional description: Deranged alanine transaminase (ALT), defined as ALT more than three times the upper limit of normal. The ALT become deranged in 6 participants during the period of IMP administration, including 2 in the almitrine group and 4 in the placebo group		
subjects affected / exposed	2 / 13 (15.38%)	4 / 14 (28.57%)	
occurrences (all)	2	4	
Metabolism and nutrition disorders			
Elevated blood lactate	Additional description: Elevated blood lactate, defined as a value above 4 mmol/L. The lactate became abnormal in 1 participant during the period of IMP administration, who was in the placebo group.		
subjects affected / exposed	0 / 13 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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 study was terminated early, before meeting the planned recruitment target. The primary reason was the lack of eligible participants, due to the reduction in case numbers and reduced severity of disease. The study therefore lacks power.

Notes: