



Clinical trial results:

Can Nebulised HepArin Reduce acuTE lung injury in Patients with SARS-CoV-2 Requiring Advanced Respiratory support in Ireland

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2020-003349-12 |
| Trial protocol | IE |
| Global end of trial date | 28 February 2022 |

Results information

| | |
|-----------------------------------|---|
| Result version number | v1 |
| This version publication date | 24 January 2025 |
| First version publication date | 24 January 2025 |
| Summary attachment (see zip file) | CHARTER-Ireland Summary (CHARTER-Ireland Summary.pdf) |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | NUIG-2020-003 |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|------------------------------------|
| ISRCTN number | ISRCTN12345678 |
| ClinicalTrials.gov id (NCT number) | NCT12345678 |
| WHO universal trial number (UTN) | U1234-5678-1234 |
| Other trial identifiers | NUIG sponsor number: NUIG-2020-003 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | National University of Ireland Galway |
| Sponsor organisation address | University Road, Galway, Ireland, H91 TK33 |
| Public contact | Prof John Laffey, National University of Ireland Galway, 353 91524411, jlafeey@universityofgalway.ie |
| Scientific contact | Prof John Laffey, National University of Ireland Galway, 353 91524411, jlafeey@universityofgalway.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 | 01 July 2024 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 28 February 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 February 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Effect of nebulised heparin on d-dimer profile, assessed via d-dimer AUC and via a mixed effects model, with data collected on days 1, 3, 5 and 10.

Safety of nebulised heparin delivered by Aerogun vibrating-mesh nebuliser in patients with COVID-19 induced severe respiratory failure, as measured by the incidence of severe adverse events.

Protection of trial subjects:

Trial performed to full GCP protocol. Regulatory approval received from the Health Products Regulatory Authority (HPRA) in Ireland. Ethics approval received from Galway Research Ethics Committee. Adverse event reporting requirements detailed in the protocol. Ongoing oversight of trial operations conducted by Afortiori. The DSMB met on 4 occasions, once to review and approve the DSMB charter. The remaining three reviews were study reviews, including a cumulative review of study events. The DSMB reports were prepared by Afortiori

Background therapy:

Full standard medical therapy for severe COVID-19 respiratory Failure

Evidence for comparator:

Clinical studies of nebulised heparin in patients with Acute Respiratory Distress Syndrome (ARDS) have shown it to be a safe intervention and have shown promising results in reduction of progression of lung injury and earlier hospital discharge.(1) The COVID-19 pandemic has resulted in a high volume of patients presenting to critical care with ARDS.(2) The pathophysiology of ARDS seen includes a markedly raised D-dimer level, indicative of a hypercoagulable state. (2) Previous studies have shown microvascular thrombosis as a distinct clinical feature of ARDS, leading to hyaline membrane formation and fibrosis.(3) Furthermore, patients with a raised D-dimer have areas of hypoperfusion on lung CT perfusion scans. These patients have a markedly increased mortality compared to patients with D-dimers less than the median value of enrolled patients in these studies. (2) Heparin can alter the conformation of the SARS-CoV-2 spike protein, (4) and has anti-inflammatory effects.(5)

References

1. Dixon B et al. Nebulised heparin for patients with or at risk of acute respiratory distress syndrome: a multicentre, randomised, double-blind, placebo-controlled phase 3 trial. The Lancet Respiratory Medicine. 2021;9(4):360-72.
2. Grasselli G, et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. The Lancet Respiratory Medicine. 2020.
3. Dixon B, et al. A phase 1 trial of nebulised heparin in acute lung injury. Crit Care. 2008;12(3):R64.
4. Paiardi G, et al. The binding of heparin to spike glycoprotein inhibits SARS-CoV-2 infection by three mechanisms. J Biol Chem. 2022;298(2):101507.
5. Hochart H, et al. Low-molecular weight and unfractionated heparins induce a downregulation of inflammation: decreased levels of proinflammatory cytokines and nuclear factor-kappaB in LPS-stimulated human monocytes. Br J Haematol. 2006;133(1):62-7.

| | |
|---|-----------------|
| Actual start date of recruitment | 01 October 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 | Ireland: 39 |
| Worldwide total number of subjects | 39 |
| EEA total number of subjects | 39 |

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) | 39 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants were recruited in three intensive care units across Ireland between 06/01/2021 and 28/02/2022. Recruitment was organised and supervised by intensive care research and clinical research facilities within recruiting centres and in line with national and international standards and guidelines, and local standard operating procedures.

Pre-assignment

Screening details:

The research nurses, coordinators and investigators at each site work with clinicians to identify potential candidates for enrolment. All patients with severe COVID-19 in participating Critical care units were screened daily during the study period (October 2020 to February 2022).

Period 1

| | |
|------------------------------|-------------------------|
| Period 1 title | Study Enrollment Period |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

This is an open-label trial. The standard of care group did not receive a placebo for operational reasons during COVID-19 pandemic. All patients facing study personnel were unblinded however, the statistician performing data analysis will be blinded to allocation.

Arms

| | |
|------------------------------|-----------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Heparin Therapy |

Arm description:

This group received the treatment under study

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Unfractionated Heparin |
| Investigational medicinal product code | IMP Package |
| Other name | |
| Pharmaceutical forms | Anticoagulant and preservative solution for blood |
| Routes of administration | Inhalation use |

Dosage and administration details:

Nebulised unfractionated heparin 25000 units (5ml heparin sodium 5000 IU/ml (Pinewood laboratories, Clonmel, Ireland) was administered via the Aerogen Solo® nebuliser every 6 h from enrolment to day 10, or until discontinuation of advanced respiratory support (if sooner), with the dosage and schedule based on previous work.

| | |
|------------------|---------------|
| Arm title | Standard Care |
|------------------|---------------|

Arm description:

This arm received standard medical care

| | |
|---|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 1 | Heparin Therapy | Standard Care |
|--------------------------------|-----------------|---------------|
| Started | 20 | 19 |
| Completed | 20 | 19 |

Period 2

| | |
|------------------------------|---|
| Period 2 title | Outcome |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Arms

| | |
|--|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Heparin |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | Unfractionated Heparin |
| Investigational medicinal product code | IMP Package |
| Other name | |
| Pharmaceutical forms | Anticoagulant and preservative solution for blood |
| Routes of administration | Inhalation use |

Dosage and administration details:

Nebulised unfractionated heparin 25000 units (5ml heparin sodium 5000 IU/ml (Pinewood laboratories, Clonmel, Ireland) was administered via the Aerogen Solo® nebuliser every 6 h from enrolment to day 10, or until discontinuation of advanced respiratory support (if sooner), with the dosage and schedule based on previous work.

| | |
|---|-----------------|
| Arm title | Standard Care |
| Arm description: | |
| Standard Care | |
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 2 | Heparin | Standard Care |
|--------------------------------|---------|---------------|
| Started | 20 | 19 |
| Completed | 20 | 19 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------------|
| Reporting group title | Heparin Therapy |
|-----------------------|-----------------|

Reporting group description:

This group received the treatment under study

| | |
|-----------------------|---------------|
| Reporting group title | Standard Care |
|-----------------------|---------------|

Reporting group description:

This arm received standard medical care

| Reporting group values | Heparin Therapy | Standard Care | Total |
|--|-----------------|---------------|-------|
| Number of subjects | 20 | 19 | 39 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 20 | 19 | 39 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 56.6 | 51.3 | |
| standard deviation | ± 11.5 | ± 14.9 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 7 | 8 | 15 |
| Male | 13 | 11 | 24 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Caucasian | 19 | 17 | 36 |
| Black,African,Caribbean,Ethnic Black | 0 | 2 | 2 |
| Asian, Ethnic Asian | 1 | 0 | 1 |
| COVID-19 Diagnosis | | | |
| Units: Subjects | | | |
| Confirmed | 19 | 19 | 38 |
| Suspected | 1 | 0 | 1 |
| Concomitant/Prior Steroids | | | |
| Units: Subjects | | | |
| Yes | 16 | 18 | 34 |
| No | 4 | 1 | 5 |
| Baseline Respiratory Support | | | |
| Units: Subjects | | | |
| High Flow Nasal Oxygen | 10 | 8 | 18 |

| | | | |
|--|-------------------|-----------------|----|
| Invasive Mechanical Ventilation | 7 | 6 | 13 |
| Positive Pressure Ventilator Support | 3 | 5 | 8 |
| No Advanced Respiratory Support | 0 | 0 | 0 |
| Adjunctive Therapies | | | |
| Units: Subjects | | | |
| Neuromuscular Blocking Drugs | 6 | 7 | 13 |
| Prone Position | 12 | 9 | 21 |
| None | 2 | 3 | 5 |
| Concomitant/Prior Antiviral medications | | | |
| Units: Subjects | | | |
| Yes | 1 | 0 | 1 |
| No | 19 | 19 | 38 |
| Concomitant/Prior Other Immunomodulatory Drugs | | | |
| Units: Subjects | | | |
| Yes | 3 | 4 | 7 |
| No | 17 | 15 | 32 |
| BMI | | | |
| Body Mass Index | | | |
| Units: kg/m2 | | | |
| arithmetic mean | 31.1 | 31.8 | - |
| standard deviation | ± 5.2 | ± 6.4 | - |
| First Qualifying PaO2/FiO2 Ratio | | | |
| Units: ratio | | | |
| arithmetic mean | 179.6 | 133.9 | - |
| standard deviation | ± 64.2 | ± 44.2 | - |
| Worst PaO2/FiO2 ratio (first 24 hours) | | | |
| Units: ratio | | | |
| arithmetic mean | 158.4 | 148.6 | - |
| standard deviation | ± 63.2 | ± 58.1 | - |
| Total SOFA Score | | | |
| Units: units | | | |
| median | 3 | 4 | - |
| inter-quartile range (Q1-Q3) | 3 to 8 | 3 to 9 | - |
| Lowest Mean Arterial Pressure | | | |
| Units: mmHg | | | |
| arithmetic mean | 88.5 | 84.5 | - |
| standard deviation | ± 15 | ± 15.4 | - |
| Ferritin | | | |
| Units: ng/mL | | | |
| median | 1586.5 | 1239 | - |
| inter-quartile range (Q1-Q3) | 728.25 to 2954.25 | 635.5 to 1326.0 | - |
| C-Reactive Protein | | | |
| Units: mg/L | | | |
| median | 65.6 | 43.17 | - |
| inter-quartile range (Q1-Q3) | 40.55 to 81.75 | 25.1 to 95.96 | - |
| Procalcitonin | | | |
| Units: ng/L | | | |
| median | 0.12 | 0.11 | - |
| inter-quartile range (Q1-Q3) | 0.08 to 0.18 | 0.09 to 0.27 | - |

End points

End points reporting groups

| | |
|---|-----------------|
| Reporting group title | Heparin Therapy |
| Reporting group description: This group received the treatment under study | |
| Reporting group title | Standard Care |
| Reporting group description: This arm received standard medical care | |
| Reporting group title | Heparin |
| Reporting group description: - | |
| Reporting group title | Standard Care |
| Reporting group description: Standard Care | |

Primary: Time to separation from respiratory support

| | |
|---|---|
| End point title | Time to separation from respiratory support |
| End point description: | |
| End point type | Primary |
| End point timeframe: Duration of Respiratory Support | |

| End point values | Heparin | Standard Care | | |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 19 | | |
| Units: days | | | | |
| median (inter-quartile range (Q1-Q3)) | 9 (4 to 28) | 5 (2 to 28) | | |

Statistical analyses

| | |
|---|-------------------------|
| Statistical analysis title | Survival analysis |
| Comparison groups | Heparin v Standard Care |
| Number of subjects included in analysis | 39 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.88 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.9 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.47 |
| upper limit | 1.7 |

Primary: Length of ICU stay

| | |
|---|--------------------|
| End point title | Length of ICU stay |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| Duration of Stay in Intensive Care Unit | |

| End point values | Heparin | Standard Care | | |
|---------------------------------------|---------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 19 | | |
| Units: days | | | | |
| median (inter-quartile range (Q1-Q3)) | 10.5 (5.42 to 12.4) | 7.8 (4.1 to 19.7) | | |

Statistical analyses

| | |
|---|-------------------------|
| Statistical analysis title | Survival Analysis |
| Comparison groups | Heparin v Standard Care |
| Number of subjects included in analysis | 39 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.931 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.99 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.5 |
| upper limit | 1.99 |

Primary: Length of Hospital Stay

| | |
|-----------------|-------------------------|
| End point title | Length of Hospital Stay |
|-----------------|-------------------------|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Duration of Hospital Stay

| End point values | Heparin | Standard Care | | |
|---------------------------------------|-----------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 19 | | |
| Units: days | | | | |
| median (inter-quartile range (Q1-Q3)) | 22.8 (14.35 to 32.05) | 21.6 (14.72 to 33.27) | | |

Statistical analyses

| Statistical analysis title | Survival analysis |
|---|-------------------------|
| Comparison groups | Standard Care v Heparin |
| Number of subjects included in analysis | 39 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.974 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.48 |
| upper limit | 2.13 |

Primary: 28-day mortality

| | |
|-----------------|------------------|
| End point title | 28-day mortality |
|-----------------|------------------|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

28 days from randomisation

| End point values | Heparin | Standard Care | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 19 | | |
| Units: subjects | 1 | 1 | | |

Statistical analyses

| Statistical analysis title | Relative Risk |
|---|-------------------------|
| Comparison groups | Heparin v Standard Care |
| Number of subjects included in analysis | 39 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.95 |
| Method | Relative Risk |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.95 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.06 |
| upper limit | 14.13 |

Secondary: 60-day Mortality

| | |
|----------------------------|------------------|
| End point title | 60-day Mortality |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 60 days from randomisation | |

| End point values | Heparin | Standard Care | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 19 | | |
| Units: subjects | 3 | 2 | | |

Statistical analyses

| Statistical analysis title | Relative Risk |
|----------------------------|-------------------------|
| Comparison groups | Heparin v Standard Care |

| | |
|---|-----------------|
| Number of subjects included in analysis | 39 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.712 |
| Method | Relative Risk |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.43 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.27 |
| upper limit | 7.61 |

Secondary: Any Adverse Events

| | |
|-----------------------------------|--------------------|
| End point title | Any Adverse Events |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| At any stage during participation | |

| End point values | Heparin | Standard Care | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 19 | | |
| Units: subjects | 16 | 14 | | |

Statistical analyses

| | |
|---|----------------------------|
| Statistical analysis title | Binary Logistic Regression |
| Comparison groups | Heparin v Standard Care |
| Number of subjects included in analysis | 39 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.663 |
| Method | Regression, Logistic |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.77 |
| upper limit | 1.54 |

Secondary: Any Serious Adverse Events

| | |
|-----------------|----------------------------|
| End point title | Any Serious Adverse Events |
|-----------------|----------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

During study participation

| End point values | Heparin | Standard Care | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 19 | | |
| Units: subjects | 9 | 5 | | |

Statistical analyses

| | |
|----------------------------|----------------------------|
| Statistical analysis title | Binary Logistic Regression |
|----------------------------|----------------------------|

| | |
|-------------------|-------------------------|
| Comparison groups | Heparin v Standard Care |
|-------------------|-------------------------|

| | |
|---|----|
| Number of subjects included in analysis | 39 |
|---|----|

| | |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

| | |
|---------------|-------------|
| Analysis type | superiority |
|---------------|-------------|

| | |
|---------|---------|
| P-value | = 0.249 |
|---------|---------|

| | |
|--------|----------------------|
| Method | Regression, Logistic |
|--------|----------------------|

| | |
|--------------------|-----------------|
| Parameter estimate | Risk ratio (RR) |
|--------------------|-----------------|

| | |
|----------------|------|
| Point estimate | 1.58 |
|----------------|------|

Confidence interval

| | |
|-------|------|
| level | 95 % |
|-------|------|

| | |
|-------|---------|
| sides | 2-sided |
|-------|---------|

| | |
|-------------|------|
| lower limit | 0.44 |
|-------------|------|

| | |
|-------------|------|
| upper limit | 5.73 |
|-------------|------|

Secondary: Any Haemorrhage

| | |
|-----------------|-----------------|
| End point title | Any Haemorrhage |
|-----------------|-----------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

During study participation

| End point values | Heparin | Standard Care | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 19 | | |
| Units: subjects | 5 | 3 | | |

Statistical analyses

| Statistical analysis title | Binary Logistic Regression |
|---|----------------------------|
| Comparison groups | Heparin v Standard Care |
| Number of subjects included in analysis | 39 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.512 |
| Method | Regression, Logistic |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 1.58 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.44 |
| upper limit | 5.73 |

Secondary: Requiring blood transfusion

| | |
|----------------------------|-----------------------------|
| End point title | Requiring blood transfusion |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| During study participation | |

| End point values | Heparin | Standard Care | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 19 | | |
| Units: subjects | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Thromboembolic Event

| | |
|-----------------|----------------------|
| End point title | Thromboembolic Event |
|-----------------|----------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

During study participation

| End point values | Heparin | Standard Care | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 19 | | |
| Units: subjects | 1 | 1 | | |

Statistical analyses

| | |
|---|----------------------------|
| Statistical analysis title | Binary Logistic Regression |
| Comparison groups | Heparin v Standard Care |
| Number of subjects included in analysis | 39 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.974 |
| Method | Regression, Logistic |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.974 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.06 |
| upper limit | 14.13 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During study participation

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------|
| Reporting group title | Heparin Treatment |
|-----------------------|-------------------|

Reporting group description: -

| | |
|-----------------------|---------------|
| Reporting group title | Standard Care |
|-----------------------|---------------|

Reporting group description: -

| Serious adverse events | Heparin Treatment | Standard Care | |
|---|---|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 9 / 20 (45.00%) | 5 / 19 (26.32%) | |
| number of deaths (all causes) | 3 | 2 | |
| number of deaths resulting from adverse events | 3 | 2 | |
| Investigations | | | |
| Elevated Liver Function Tests | Additional description: Elevated Liver Function Tests | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 19 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Episode of desaturation, dyspnea and altered consciousness. | Additional description: Episode of desaturation, dyspnea and altered consciousness. | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 19 (5.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Episode of desaturation, respiratory arrest call put out, readmitted to Intensive Care Unit | Additional description: Episode of desaturation, respiratory arrest call put out, readmitted to Intensive Care Unit | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 19 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Brachial Artery occlusion with arterial dissection | Additional description: Brachial Artery occlusion with arterial dissection | | |

| | | | |
|---|---|----------------|--|
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 19 (5.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | Additional description: Epistaxis | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 19 (5.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac Tamponade | Additional description: Cardiac Tamponade | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 19 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Right arm tingling and numbness | Additional description: Right arm tingling and numbness | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 19 (5.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Vomiting | Additional description: Vomiting | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 19 (5.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| acquired pneumonia | Additional description: acquired pneumonia | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 19 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Chest pain | Additional description: Chest pain | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 19 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infective Exacerbation of COPD | Additional description: Infective Exacerbation of COPD | | |

| | | | |
|---|---|----------------|--|
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 19 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Right vocal cord palsy | Additional description: Right vocal cord palsy | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 19 (5.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Severe respiratory failure | Additional description: Severe respiratory failure | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 19 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Shock Liver | Additional description: Shock Liver | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 19 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Alcohol Withdrawal | Additional description: Alcohol Withdrawal | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 19 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Worsening Acute Kidney Injury requiring renal replacement therapy | Additional description: Worsening Acute Kidney Injury requiring renal replacement therapy | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 19 (5.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Unresolved Covid-19 Pneumonitis | Additional description: Unresolved Covid-19 Pneumonitis | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 19 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Unresolved Covid-19 pneumonitis leading to Multi organ failure. | Additional description: Unresolved Covid-19 pneumonitis leading to Multi organ failure. | | |

| | | | |
|--|--|----------------|--|
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 19 (5.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Worsening Covid pneumonitis requiring Extra Corporeal Membranous Oxygenation | Additional description: Worsening Covid pneumonitis requiring Extra Corporeal Membranous Oxygenation | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 19 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Worsening of Covid pneumonitis | Additional description: Worsening of Covid pneumonitis | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 19 (5.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Metabolism and nutrition disorders | | | |
| Weight Loss | Additional description: Weight Loss | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 19 (5.26%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Heparin Treatment | Standard Care | |
|---|--|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 13 / 20 (65.00%) | 14 / 19 (73.68%) | |
| Vascular disorders | | | |
| copious blood stained secretions | Additional description: copious blood stained secretions | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Epistaxis | Additional description: Epistaxis | | |
| subjects affected / exposed | 5 / 20 (25.00%) | 3 / 19 (15.79%) | |
| occurrences (all) | 5 | 4 | |
| Haematuria | Additional description: Haematuria | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 2 / 19 (10.53%) | |
| occurrences (all) | 0 | 2 | |
| Haemoptysis | Additional description: Haemoptysis | | |

| | | | |
|---|--|----------------|--|
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypotension | Additional description: Hypotension | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 1 | 1 | |
| General disorders and administration site conditions | | | |
| Swelling to right arm | Additional description: Swelling to right arm | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Deterioration in Medical Condition | Additional description: Worsening of condition resulting in re-admission to ICU | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 1 | 1 | |
| Immune system disorders | | | |
| Allergic Reaction to betalactams | Additional description: Allergic Reaction to betalactams | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| bronchospasm | Additional description: bronchospasm | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Candida Albicans in sputum- worsening of medical history | Additional description: Candida Albicans in sputum- worsening of medical history | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Coughing episode | Additional description: Coughing episode | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Enterobacter Coloceae-Ventilator Acquired Pneumonia | Additional description: Enterobacter Coloceae-Ventilator Acquired Pneumonia | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hafnia Alvei in sputum | Additional description: Hafnia Alvei in sputum | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Hospital acquired pneumonia | Additional description: Hospital acquired pneumonia | | |

| | | | |
|--|--|-----------------|--|
| subjects affected / exposed | 0 / 20 (0.00%) | 2 / 19 (10.53%) | |
| occurrences (all) | 0 | 2 | |
| Numbness to nose | Additional description: Numbness to nose | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| patient complaining of intermitant pain to costal region | Additional description: patient complaining of intermitant pain to costal region | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pneumomediastinum | Additional description: Pneumomediastinum | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pneumothorax | Additional description: Pneumothorax | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| probable ventilator associated pneumonia | Additional description: probable ventilator associated pneumonia | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Pulmonary Embolism | Additional description: Pulmonary Embolism | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 1 | 1 | |
| query new pneumonia | Additional description: query new pneumonia | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Right sided pnemothorax | Additional description: Right sided pnemothorax | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| severe hiccups | Additional description: severe hiccups | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| severe hypoxemic respiratory failure | Additional description: severe hypoxemic respiratory failure | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| supraglottic oedema | Additional description: supraglottic oedema | | |

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|--|---|----------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| sore throat | Additional description: sore throat | | |
| subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 19 (0.00%) 0 | |
| Ventilator Aquired Pneumonia | Additional description: Ventilator Aquired Pneumonia | | |
| subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 1 / 19 (5.26%) 1 | |
| Worsening of MSSA in sputum | Additional description: Worsening of MSSA in sputum | | |
| subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| Investigations | | | |
| Abnormal Liver function test | Additional description: Abnormal Liver function test | | |
| subjects affected / exposed occurrences (all) | 3 / 20 (15.00%) 3 | 2 / 19 (10.53%) 2 | |
| Blood cultures positive for gram negative bacilli and pseudomonas aeruginosa | Additional description: Blood cultures positive for gram negative bacilli and pseudomonas aeruginosa | | |
| subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 19 (0.00%) 0 | |
| Elevated Creatinine Kinase | Additional description: Elevated Creatinine Kinase | | |
| subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| Elevated Trigylcerides | Additional description: Elevated Trigylcerides | | |
| subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 2 / 19 (10.53%) 2 | |
| Elevated Troponin | Additional description: Elevated Troponin | | |
| subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| Gram Negative Bacilli on Cultures | Additional description: Gram Negative Bacilli on Cultures | | |
| subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| T Wave Inversion | Additional description: T Wave Inversion | | |
| subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| Worsening Elevated Liver function tests | Additional description: Worsening Elevated Liver function tests | | |

| | | | |
|--|---|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| Injury, poisoning and procedural complications | | | |
| Bleeding from tracheostomy site | Additional description: Bleeding from tracheostomy site | | |
| subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| Injection site bleeding | Additional description: Injection site bleeding | | |
| subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 19 (0.00%) 0 | |
| surgical emphysema | Additional description: surgical emphysema | | |
| subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 19 (0.00%) 0 | |
| Cardiac disorders | | | |
| Atrial Fibrillation | Additional description: Atrial Fibrillation | | |
| subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 19 (0.00%) 0 | |
| Fast Atrial Fibrillation | Additional description: Fast Atrial Fibrillation | | |
| subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| Sinus tachycardia | Additional description: Sinus tachycardia | | |
| subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 19 (0.00%) 0 | |
| Symptomatic Atrial Fibrillation | Additional description: Symptomatic Atrial Fibrillation | | |
| subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 19 (0.00%) 0 | |
| Nervous system disorders | | | |
| Left Hand Numbness | Additional description: Left Hand Numbness | | |
| subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| Lockjaw sensation | Additional description: Lockjaw sensation | | |
| subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| right sided weakness | Additional description: right sided weakness | | |
| subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| Seizure like activity | Additional description: Seizure like activity | | |

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|--|--|----------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 19 (0.00%) 0 | |
| Blood and lymphatic system disorders | | | |
| anaemia | Additional description: anaemia | | |
| subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 3 / 19 (15.79%) 3 | |
| Thrombocytopenia | Additional description: Thrombocytopenia | | |
| subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 2 / 19 (10.53%) 2 | |
| Eye disorders | | | |
| papilloedema | Additional description: papilloedema | | |
| subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| Gastrointestinal disorders | | | |
| Ulceration to tongue | Additional description: Ulceration to tongue | | |
| subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 19 (0.00%) 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Left big toe mottled | Additional description: Left big toe mottled | | |
| subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| Renal and urinary disorders | | | |
| Acute Kidney Injury | Additional description: Acute Kidney Injury | | |
| subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 19 (0.00%) 0 | |
| Nephrolithiasis | Additional description: Nephrolithiasis | | |
| subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 0 / 19 (0.00%) 0 | |
| Urinary incontinence | Additional description: Urinary incontinence | | |
| subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| Worsening of acute kidney injury | Additional description: Worsening of acute kidney injury | | |
| subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 1 / 19 (5.26%) 1 | |
| Infections and infestations | | | |
| deteriorating sepsis | Additional description: deteriorating sepsis | | |

| | | | |
|---|---|-----------------|--|
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 19 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oral thrush | Additional description: Oral thrush | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Pansinusitis | Additional description: Pansinusitis | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| worsening of herpes simplex virus | Additional description: worsening of herpes simplex virus | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Metabolism and nutrition disorders | | | |
| gross Metabolism acidosis requiring re-intubation | Additional description: gross Metabolism acidosis requiring re-intubation | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| hyperkalemia | Additional description: hyperkalemia | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 19 (5.26%) | |
| occurrences (all) | 0 | 1 | |
| Hypernatremia | Additional description: Hypernatremia | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 2 / 19 (10.53%) | |
| occurrences (all) | 0 | 2 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 11 August 2020 | <ul style="list-style-type: none"> • NCT number has been added • Secondary outcomes divided into secondary and 'other' outcomes • Exclusion Criteria # 15 has been added. • Changes have been made to the IMP section 9 to make the section more explicit • Changes made to section 15.2 Auditing and Monitoring to outline the process further • Other minor changes. |
| 25 August 2020 | <p>In response to HPRA Queries:</p> <ul style="list-style-type: none"> • Exclusion criteria changed to platelet count 50 from 20 • Clarification of exclusion criteria regarding premorbid state • Clarification in Introduction Summary – our group changed to our Australian colleagues... • We have added some extra information justifying the dose selected in Introduction: "Bleeding and blood transfusion" |
| 09 September 2020 | <p>In Response to further HPRA Queries:</p> <ul style="list-style-type: none"> • Edits to introduction section on: <ul style="list-style-type: none"> • Treatment of pulmonary microvascular thrombosis and hyaline membranes • SARS-CoV-2 inactivation by heparin • Added paragraph "D-dimer as an outcome measure" • Edits to sections Safety and tolerability of nebulised heparin and Bleeding and blood transfusion • Additional exclusion criteria : Any other specific contraindication to anticoagulation including prophylactic anticoagulation not otherwise listed here |
| 25 September 2020 | <ul style="list-style-type: none"> • Amendment of Safety Outcomes to include recording of all episodes of clinically relevant non-major bleeding (CRNMB), according to the definition of the International Society on Thrombosis and Haemostasis • Amendment of Exclusion criterion #3 from 'APTT>120 seconds and this is not due to anticoagulant therapy' to read 'APTT>100 seconds and this is not due to anticoagulant therapy' |
| 01 October 2020 | <ul style="list-style-type: none"> • Amendment to exclusion criteria number 3, to remove the phrase "and this is not due to anticoagulant therapy" to just APTT > 100 seconds |
| 25 January 2021 | <ul style="list-style-type: none"> • Substantial changes were made to the protocol to extend the inclusion criteria to patients with COVID respiratory failure receiving other forms of advanced respiratory support in addition to invasive mechanical ventilation. • There are also some smaller changes such as to measurements but they are largely a reflection of the changed inclusion criteria or to correct formatting and typographical errors. • Specific exclusion criteria of systemic anticoagulation other than prophylactic anticoagulation including additional text in sections 8.8 and 8.9. |
| 22 February 2021 | <ul style="list-style-type: none"> • The title of the trial has changed from 'mechanical ventilation' to 'Advanced Respiratory support'. • Inclusion criteria altered to include patients on therapeutic anticoagulation with heparin or LMWH • Exclusion criteria updated to remove any therapeutic anticoagulation, other changes made throughout the protocol • Details of new EU MAH added to drug supplier due to Brexit • The person undertaking the role of the Vice President of Research in NUI Galway has changed personnel. This resulted in an update to the named Sponsor person. • Other minor changes have been made to the protocol. |

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.

| |
|--|
| This was an early phase study and was not powered for efficacy |
|--|

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/36104785>

<http://www.ncbi.nlm.nih.gov/pubmed/39186127>

<http://www.ncbi.nlm.nih.gov/pubmed/35106809>