Clinical trial results:
Early thromboprophylaxis in COVID-19 (ETHIC trial): an open label, randomized phase IIIb trial of community-based prophylactic low-molecular-weight heparin (LMWH) versus standard of care (no enoxaparin) in COVID-19 positive patients

Summary

EudraCT number	2020-003125-39
Trial protocol	BE GB DE
Global end of trial date	30 November 2021

Results information

Result version number	v1 (current)
This version publication date	13 October 2022
First version publication date	13 October 2022
Summary attachment (see zip file)	Clinical Study Report (ETHIC Study Report.pdf)

Trial information

Trial identification

Sponsor protocol code	TRI-08892

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04492254
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	TRI
Sponsor organisation address	1b Manresa Road , London, United Kingdom, SW3 6LR
Public contact	Clinical Operations Lead, Thrombosis Research Institute, +44 02031989898, afernandez@tri-london.ac.uk
Scientific contact	Clinical Operations Lead, Thrombosis Research Institute, +44 02031989898, afernandez@tri-london.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	29 June 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 November 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of prophylactic enoxaparin compared to the current standard of care (no enoxaparin) in reducing hospital admission and/or death within 21 days of randomisation in symptomatic individuals with COVID-19 in a community setting

Protection of trial subjects:

NA

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 September 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	Spain: 10
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Belgium: 83
Country: Number of subjects enrolled	Brazil: 36
Country: Number of subjects enrolled	South Africa: 30
Country: Number of subjects enrolled	India: 57
Worldwide total number of subjects	219
EEA total number of subjects	93

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)	144
From 65 to 84 years	75
85 years and over	0

Subject disposition

Recruitment
Recruitment details: -

Pre-assignment
Screening details: In the Screening phase patients will be reviewed in order to confirm that they meet inclusion and not exclusion criteria.

Pre-assignment period milestones	
Number of subjects started	219
Number of subjects completed	219

Period 1	
Period 1 title	Enrollment until day 21 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	Clexane
Arm description: -	
Arm type	Clexane
Investigational medicinal product name	Enoxaparine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use
Dosage and administration details: 40mg once a day if IBM<100 or 40mg twice a day if IBM>100	
Arm title	Standard of Care
Arm description: -	
Arm type	Standard of Care
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Clexane	Standard of Care
Started	105	114
Completed	98	109
Not completed	7	5
Adverse event, serious fatal	1	1
Consent withdrawn by subject	4	1
Physician decision	1	3
Lost to follow-up	1	-

Baseline characteristics

End points

End points reporting groups

Reporting group title	Clexane
Reporting group description: -	
Reporting group title	Standard of Care
Reporting group description: -	

Primary: death or hospitalization to 21 days

End point title	death or hospitalization to 21 days
End point description:	
End point type	Primary
End point timeframe:	
21 days from enrolment	

End point values	Clexane	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	114		
Units: hospitalisations and deaths	105	114		

Statistical analyses

Statistical analysis title	Primary outcome of death or hospitalization to 21
Statistical analysis description:	
A log-rank test was used for statistical significance. Data were displayed using Kaplan-Meier curves by treatment. The unadjusted hazard ratio was calculated using a cox proportional hazards model.	
Comparison groups	Clexane v Standard of Care
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	other
P-value	= 219
Method	Chi-squared

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: From Day 0-enrolment until day 21	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	1

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Non Serious Adverse Events are collected in the study so because of that none has bee registered

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? Yes

Date	Interruption	Restart date
04 October 2021	This letter is to inform you that on the 30th of September the Steering Committee of the ETHIC Study decided to terminate the study following a recommendation by the study Data and Safety Monitoring Board (DSMB) after reviewing the unblinded treatment-specific endpoint data. The Steering Committee requested the DSMB review the data because the average event rate (study end point) has been much lower than expected. The observed combined event rate across the treatment and control groups was 11.6% while the study design assumed a combined event rate of approximately 21%. With an event rate of 11.6% for the rest of the study, and assuming a 25% treatment effect, the study would require an increase in the sample size from 1370 to 2,930 in order to maintain the same level of statistical power. The DSMB found no treatment signal in the observed data and the futility probability (the probability that we will not be able to state a significant treatment difference given our current data) is 96%, which is very high. Enrolment is already behind target and with the impact of vaccination on enrolment rates, it is unlikely that the study will be able to achieve the required increased sample size in a feasible time scale. We would like to note the DSMB did not identify any safety concerns with bleeding and their recommendation was exclusively based on efficacy issues. Since the DSMB met, the ACTIV-4B trial results were published (JAMA. doi:10.1001/jama.2021.17272). This trial stopped after 657 of the intended 7000 (9%) patients were enrolled because the event rate was lower than expected. Thus our experience is not unique. After the publication of the ETHIC results, we will collaborate with the OVID study investigators on a meta-analysis of all outpatient thromboprophylaxis trials. The OVID trial is very similar in design to ETHIC so the combination of these two trials alone will provide important information to the field.	-

Notes:

Limitations and caveats

None reported