



## Clinical trial results:

**A randomized, double-blind, placebo-controlled trial to determine the safety and efficacy of estetrol (E4) for the treatment of patients with confirmed SARS-CoV-2 infection**

### Summary

EudraCT number	2020-003403-33
Trial protocol	BE HU
Global end of trial date	21 May 2021

### Results information

Result version number	v1 (current)
This version publication date	23 June 2023
First version publication date	23 June 2023

### Trial information

#### Trial identification

Sponsor protocol code	MIT-Co001-C101
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#### Additional study identifiers

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

Notes:

### Sponsors

Sponsor organisation name	NEURALIS SA
Sponsor organisation address	Rue Saint Georges 5-7, Liege, Belgium, 4000
Public contact	Clinical Study Leader, NEURALIS SA, +32 43492822, Clinical.Trials@mithra.com
Scientific contact	Clinical Study Leader, NEURALIS SA, +32 43492822, Clinical.Trials@mithra.com

Notes:

### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

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## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 September 2022
Is this the analysis of the primary completion data?	No
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Global end of trial reached?	Yes
Global end of trial date	21 May 2021
Was the trial ended prematurely?	No

Notes:

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## General information about the trial

Main objective of the trial:

Assess the ability of estetrol (E4) to improve the percentage of patients who recover by Day 28 compared with placebo, in those with confirmed SARS-CoV-2 infection who are hospitalized with moderate COVID-19 (i.e. not on high flow oxygen or mechanical ventilation).

Moderate COVID-19 was defined as described below:

- i. Positive testing by a standard nationally accepted reverse transcription polymerase chain reaction (RT PCR) assay.
- ii. Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness (including fever, cough, anosmia, dysgeusia, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms) or shortness of breath with exertion.
- iii. Clinical signs suggestive of moderate illness with COVID-19, such as respiratory rate  $\geq 20$  breaths per minute, heart rate  $\geq 90$  beats per minute.
- iv. No clinical signs indicative of severe or critical illness (i.e., need for ventilation or intensive care unit [ICU] admission)

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Protection of trial subjects:

This study was conducted in accordance with the protocol and consensus ethical principles derived from international guidelines including the Declaration of Helsinki, International Council for Harmonization Good Clinical Practice (ICH GCP), 21 CFR 50 Protection of Human Rights, Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, 21 CFR 56 Institutional Review Boards, and other applicable laws and regulations of the countries in which the study was conducted.

An independent Data Safety Monitoring Board (DSMB) was in place to review and assess the safety data at predefined meetings as required for safety reasons. The DSMB included one voting chairperson and 3 additional voting members and an unblinded statistician.

Due to the increased risk of VTE in COVID-19 infection, all patients were required to take anticoagulants as prophylaxis against VTE for the duration of the study treatment at a dose in accordance with the country's local or national guidelines.

Study MIT-Co001-C101 was designed as a two-part study (Part A and Part B). Part A addressed the primary and secondary objectives; study Part A was completed as planned. Part B was planned to be implemented after the analysis of Part A, as a separate entity and with a distinct cohort of patients. The data of Part B were to contribute to a planned Phase 3 confirmatory study. However, after the analysis of data from Part A of the current study, it was decided not to go ahead with Part B of the study -- and this was in line with the clinical study protocol.

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Background therapy:

Due to increased risk of VTE during COVID-19 infection, all subjects were required to take LMWH (or equivalent) for the duration of the study treatment (including at home after discharge). However, for patients who were already on oral anticoagulants, the addition of LMWH (or equivalent) was made at the discretion of the Investigator.

Evidence for comparator:

Evidence for comparators --- Not applicable

#### LIST OF ABBREVIATIONS IN THIS STUDY ENTRY

AE=Adverse event

AT III=Antithrombin III

CIOMS=Council for International Organizations of Medical Sciences

COVID-19=Coronavirus disease 2019

Ct=Cycle threshold

DSMB=Data Safety and Monitoring Board

E4=Estetrol

ECMO=Extracorporeal membrane oxygenation

EoT=End of treatment assessment

FiO2=Fraction of inspired oxygen

Hospt=Hospitalized

ICU=Intensive care unit

LMWH=Low molecular weight heparin

OSCI=Ordinal Scale for Clinical Improvement

PCR=Polymerase chain reaction

pO2=Partial pressure of oxygen

RNA=Ribonucleic acid

SARS-CoV-2=Severe acute respiratory syndrome coronavirus type 2

SpO2=Oxygen saturation

VTE=Venous thromboembolism

WHO=World Health Organization

Actual start date of recruitment	19 November 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	Russian Federation: 63
Country: Number of subjects enrolled	Poland: 109
Country: Number of subjects enrolled	Belgium: 3
Worldwide total number of subjects	175
EEA total number of subjects	112

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)	101
From 65 to 84 years	72
85 years and over	2

## Subject disposition

### Recruitment

Recruitment details:

Male and female subjects recruited according to the Inclusion/Exclusion Criteria. Subjects had to be hospitalized with confirmed SARS-CoV-2 infection and moderate COVID-19. Subjects were excluded from the study if they were ventilated and/or in ICU, had any unexplained vaginal bleeding, had diagnosed protein C, protein S, or AT III deficiency.

### Pre-assignment

Screening details:

Enrolled in this study were postmenopausal women who had not used hormone replacement therapy within 1 year of study start or men  $\geq 18$  years of age who used contraception from screening until 4 weeks after the last dose of study treatment, who were hospitalized with confirmed SARS-CoV-2 infection and moderate COVID-19.

### Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Estetrol (E4)

Arm description:

Subjects received Estetrol (E4) 15 mg tablets by mouth once daily for 21 consecutive days, at approximately the same time each day. Patients who were discharged from hospital during the treatment phase completed study treatment at home.

Study treatment was stopped if the patient was intubated or unable to swallow the tablets.

Arm type	Experimental
Investigational medicinal product name	Estetrol (E4)
Investigational medicinal product code	
Other name	E4
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Estetrol (E4): 15 mg tablets, taken by mouth once daily for 21 consecutive days.

<b>Arm title</b>	Placebo
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Arm description:

Subjects received placebo by mouth once daily for 21 consecutive days, at approximately the same time each day. Patients who were discharged from hospital during the Treatment Phase completed study treatment at home.

Study treatment was stopped if the patient was intubated or unable to swallow the tablets.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo: matching tablets taken by mouth once daily for 21 consecutive days.

<b>Number of subjects in period 1</b>	Estetrol (E4)	Placebo
Started	87	88
Completed	73	77
Not completed	14	11
Adverse event, serious fatal	2	2
Consent withdrawn by subject	3	3
Adverse event, non-fatal	5	2
Disease progression a prespec withdrawal criterion	4	4

## Baseline characteristics

### Reporting groups

Reporting group title	Estetrol (E4)
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Reporting group description:

Subjects received Estetrol (E4) 15 mg tablets by mouth once daily for 21 consecutive days, at approximately the same time each day. Patients who were discharged from hospital during the treatment phase completed study treatment at home.

Study treatment was stopped if the patient was intubated or unable to swallow the tablets.

Reporting group title	Placebo
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Reporting group description:

Subjects received placebo by mouth once daily for 21 consecutive days, at approximately the same time each day. Patients who were discharged from hospital during the Treatment Phase completed study treatment at home.

Study treatment was stopped if the patient was intubated or unable to swallow the tablets.

Reporting group values	Estetrol (E4)	Placebo	Total
Number of subjects	87	88	175
Age categorical			
Units: Subjects			
Adults (18-64 years)	50	51	101
From 65-84 years	36	36	72
85 years and over	1	1	2
Age continuous			
Units: years			
arithmetic mean	61.5	62.2	
standard deviation	± 12.7	± 11.6	-
Gender categorical			
Units: Subjects			
Female	33	34	67
Male	54	54	108
Sex			
Units: Subjects			
Male	54	54	108
Female	33	34	67
Race			
Units: Subjects			
White	87	88	175
Pneumonia			
Pneumonia present			
Units: Subjects			
YES	66	69	135
NO	21	18	39
Missing data	0	1	1
Antiviral medication			
Subjects receiving antiviral medication.			
Units: Subjects			
YES	35	33	68
NO	50	53	103

Missing data	2	2	4
WHO Ordinal Scale for Clinical Improvement (OSCI) score			
WHO Ordinal Scale for Clinical Improvement (OSCI) score. The OSCI score is defined in the section 'Description' for end point 1.			
Units: Subjects			
Score 4	15	14	29
Score 5	71	74	145
Score 6	1	0	1
Body Mass Index -- BMI (kg/m2)			
Units: kg/m2			
arithmetic mean	29.1	28.8	
standard deviation	± 5.3	± 5.1	-
Clinical frailty score			
Clinical Frailty Scale is a nine-point global frailty scale based on clinical evaluation in the domains of mobility, energy, physical activity, and function.  Score: 1=Very fit; 2=Well; 3=Managing well; 4=Vulnerable; 5=Mildly frail;6=Moderately frail; 7=Severely frail; 8=Very severely frail; 9=Terminally ill.			
Units: SCORE			
arithmetic mean	2.9	2.8	
standard deviation	± 1.0	± 0.9	-

## End points

### End points reporting groups

Reporting group title	Estetrol (E4)
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Reporting group description:

Subjects received Estetrol (E4) 15 mg tablets by mouth once daily for 21 consecutive days, at approximately the same time each day. Patients who were discharged from hospital during the treatment phase completed study treatment at home.

Study treatment was stopped if the patient was intubated or unable to swallow the tablets.

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Subjects received placebo by mouth once daily for 21 consecutive days, at approximately the same time each day. Patients who were discharged from hospital during the Treatment Phase completed study treatment at home.

Study treatment was stopped if the patient was intubated or unable to swallow the tablets.

### Primary: 1\_Improvement in COVID-19 -- Patients reaching a WHO OSCI score of $\leq 3$ on Day 28

End point title	1_Improvement in COVID-19 -- Patients reaching a WHO OSCI score of $\leq 3$ on Day 28
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End point description:

Improvement in COVID-19 between the placebo and Estetrol (E4) groups measured by the percentage of patients recovered on Day 28.

Recovery was defined as reaching a score of  $\leq 3$  on the OSCI WHO (0–10) scale. Patients were treated for 21 days with either E4 or placebo.

WHO OSCI scale:

Score 0=Uninfected; no viral RNA detected; 1=Asymptomatic, viral RNA detected; 2=Symptomatic, independent; 3=Symptomatic, assistance needed; 4=Hospitalized, no oxygen therapy; 5=Oxygen by mask or nasal prongs; 6=Non-invasive ventilation or high-flow oxygen; 7=Intubation and mechanical ventilation,  $pO_2/FiO_2 \geq 150$  or  $SpO_2/FiO_2 \geq 200$ ; 8=Mechanical ventilation  $pO_2/FiO_2 < 150$  ( $SpO_2/FiO_2 < 200$ ) or vasopressin; 9=Mechanical ventilation  $pO_2/FiO_2 < 150$  and vasopressin, dialysis, or ECMO; 10=Death.

Patient status score: 0=Uninfected; 1-3=Ambulatory, mild disease; 4-5=Hospt, Moderate disease; 6-9=Hospt, Severe disease; 10=Dead.

E4=Estetrol; OSCI=Ordinal Scale for Clinical Improvement; WHO=World Health Org;

End point type	Primary
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End point timeframe:

Day 28 after treatment start.

End point values	Estetrol (E4)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85 <sup>[1]</sup>	86 <sup>[2]</sup>		
Units: percent				
number (not applicable)	82.4	91.9		



Notes:

[1] - ITT population

[2] - ITT population

## Statistical analyses

<b>Statistical analysis title</b>	E4 vs Placebo
Comparison groups	Estetrol (E4) v Placebo
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority <sup>[3]</sup>
Parameter estimate	Odds ratio (OR)
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	1.07

Notes:

[3] - Odds Ratio from logistic regression model with randomized treatment included as a class factor, baseline WHO (0-10) score as class factor and age included as covariates and stratified for the randomization stratification factors of gender and antiviral treatment for COVID-19 at baseline at a given timepoint.

## Secondary: 2\_Patients with a WHO OSCI score of $\geq 6$ on Day 28

End point title	2_Patients with a WHO OSCI score of $\geq 6$ on Day 28
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End point description:

Patients with a WHO OSCI Score of  $\geq 6$  on Day 28.

Patients were treated for 21 days with either E4 or placebo.

Details of the WHO OSCI scale are shown in the description for end point 1.

E4=Estetrol; OSCI=Ordinal Scale for Clinical Improvement; WHO=World Health Organization;

End point type	Secondary
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End point timeframe:

Day 28 after treatment start.

<b>End point values</b>	Estetrol (E4)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85 <sup>[4]</sup>	86 <sup>[5]</sup>		
Units: percent				
number (not applicable)	11.8	7.0		

Notes:

[4] - ITT population

[5] - ITT population

## Statistical analyses

<b>Statistical analysis title</b>	E4 vs Placebo
Comparison groups	Estetrol (E4) v Placebo
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority <sup>[6]</sup>
Parameter estimate	Odds ratio (OR)
Point estimate	1.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	5.16

Notes:

[6] - Odds Ratio from logistic regression model with randomized treatment included as a class factor, baseline WHO (0-10) score as class factor and age included as covariates and stratified for the randomization stratification factors of gender and antiviral treatment for COVID-19 at baseline.

### Secondary: 3\_Time to recovery -- Patients reaching a WHO OSCI score of ≤3

End point title	3_Time to recovery -- Patients reaching a WHO OSCI score of ≤3
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End point description:

Time to recovery, as defined by a score of ≤3 on the WHO OSCI scale.

Patients were treated for 21 days with either E4 or placebo.

Details of the WHO OSCI scale are shown in the description of end point 1.

E4=Estetrol; OSCI=Ordinal Scale for Clinical Improvement; WHO=World Health Organization;

End point type	Secondary
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End point timeframe:

From Day 1 (start of treatment) to Day 28 (end of study).

<b>End point values</b>	Estetrol (E4)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85 <sup>[7]</sup>	86 <sup>[8]</sup>		
Units: days				
median (confidence interval 95%)	13 (12 to 14)	12 (11 to 14)		

Notes:

[7] - ITT population

[8] - ITT population

### Statistical analyses

No statistical analyses for this end point

### Secondary: 4\_Viral load

End point title	4_Viral load
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End point description:

Assess changes in SARS-CoV-2 viral load between the E4 and placebo groups.

Patients were treated for 21 days with either E4 or placebo. Assessment was made up to end of

treatment (EoT), which was defined as Day 23 or within 2 days of the last dose of study drug if treatment was stopped prior to Day 21 for reasons other than intubation or VTE. Results are presented as change from baseline. The number of patients contributing to the results is indicated under the table.

Viral load (in oropharangeal swabs) was measured by real-time PCR. This method monitors the amplification of the SARS-CoV-2 ribonucleic acid (RNA) that is performed in cycles. The cycle threshold (Ct) result represents the cycle at which the amplification product can be detected by the method; thus, the lower the Ct value the higher the amount of SARS-CoV-2 RNA that is present in the sample, representing a 'high' viral load.

End point type	Secondary
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End point timeframe:

From baseline (before treatment) to EoT (end of treatment assessment).

End point values	Estetrol (E4)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85 <sup>[9]</sup>	86 <sup>[10]</sup>		
Units: Cycle threshold (Ct)				
median (full range (min-max))				
Day 3	1.0 (-11 to 10)	2.1 (-12 to 10)		
Day 7	8.0 (-6 to 15)	3.6 (-6 to 18)		
Day 14	5.8 (1 to 16)	5.4 (-5 to 16)		
End of treatment (EoT)	6.4 (-4 to 14)	3.3 (-1 to 14)		

Notes:

[9] - ITT population

Baseline N=61

D3 N=47

D7 N=30

D14 N=8

EoT N=15

[10] - ITT population

Baseline N=63

D3 N=45

D7 N=36

D14 N=12

EoT N=11

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All AEs were followed from the first dose of study drug until 7 days ( $\pm 2$  days) after the last dose of study drug.

Adverse event reporting additional description:

Safety data are reported for Safety Population as treatment-emergent adverse events (TEAE).

The Safety Population consisted of all patients who took at least one dose of the study medication.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

### Reporting groups

Reporting group title	Estetrol (E4)
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Reporting group description:

Subjects received E4 15 mg orally once daily for 21 consecutive days, at approximately the same time each day. Patients who were discharged from hospital during the Treatment Phase completed study treatment at home.

Study treatment was stopped if the patient was intubated or unable to swallow the tablets.

Reporting group title	Placebo
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Reporting group description:

Subjects received placebo orally once daily for 21 consecutive days, at approximately the same time each day. Patients who were discharged from hospital during the Treatment Phase completed study treatment at home.

Study treatment was stopped if the patient was intubated or unable to swallow the tablets.

Serious adverse events	Estetrol (E4)	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 87 (12.64%)	7 / 88 (7.95%)	
number of deaths (all causes)	8	3	
number of deaths resulting from adverse events			
Vascular disorders			
Peripheral artery thrombosis			
subjects affected / exposed	1 / 87 (1.15%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peripheral embolism			
subjects affected / exposed	0 / 87 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 87 (1.15%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	7 / 87 (8.05%)	2 / 88 (2.27%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 5	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 87 (1.15%)	2 / 88 (2.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 87 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary tract inflammation			
subjects affected / exposed	1 / 87 (1.15%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Endotoxic shock			
subjects affected / exposed	0 / 87 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia			
subjects affected / exposed	0 / 87 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			

subjects affected / exposed	1 / 87 (1.15%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	

Frequency threshold for reporting non-serious adverse events: 3 %

<b>Non-serious adverse events</b>	Estetrol (E4)	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 87 (56.32%)	45 / 88 (51.14%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	9 / 87 (10.34%)	12 / 88 (13.64%)	
occurrences (all)	9	12	
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 87 (6.90%)	5 / 88 (5.68%)	
occurrences (all)	6	5	
Fibrin D dimer increased			
subjects affected / exposed	4 / 87 (4.60%)	5 / 88 (5.68%)	
occurrences (all)	4	5	
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 87 (2.30%)	3 / 88 (3.41%)	
occurrences (all)	2	3	
Hepatic enzyme increased			
subjects affected / exposed	5 / 87 (5.75%)	1 / 88 (1.14%)	
occurrences (all)	5	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 87 (6.90%)	8 / 88 (9.09%)	
occurrences (all)	6	9	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 87 (3.45%)	3 / 88 (3.41%)	
occurrences (all)	3	3	
Blood and lymphatic system disorders			

Anaemia subjects affected / exposed occurrences (all)	4 / 87 (4.60%) 4	1 / 88 (1.14%) 1	
Neutropenia subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0	3 / 88 (3.41%) 3	
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	3 / 87 (3.45%) 3	0 / 88 (0.00%) 0	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	2 / 87 (2.30%) 2	4 / 88 (4.55%) 4	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	2 / 87 (2.30%) 2	5 / 88 (5.68%) 5	
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	3 / 87 (3.45%) 3	0 / 88 (0.00%) 0	
Infections and infestations Clostridium difficile infection subjects affected / exposed occurrences (all)  Pneumonia subjects affected / exposed occurrences (all)	3 / 87 (3.45%) 3  0 / 87 (0.00%) 0	0 / 88 (0.00%) 0  3 / 88 (3.41%) 3	
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)  Hyperkalaemia subjects affected / exposed occurrences (all)	0 / 87 (0.00%) 0  2 / 87 (2.30%) 2	4 / 88 (4.55%) 4  3 / 88 (3.41%) 3	





## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 August 2020	<p>Global study protocol amendment:</p> <p>The inclusion criterion for postmenopausal women was amended to reduce menopausal status and HRT use from 5 years to 1 year prior to study start. Major update based on newly published data on COVID-19.</p> <p>HRT=Hormone replacement therapy</p>
20 November 2020	<p>Global study protocol amendment:</p> <p>Protocol update was made to stop treatment for patients with a positive point-of-care test but subsequent negative RT-PCR test.</p> <p>Inclusion of clinical data from male study; clarifications and updates made to exclusion criteria to exclude patients with thrombophilia or liver disease and cancer, as well as to exclude patients at risk of developing arterial or vein thrombosis/thromboembolia;</p> <p>Add criterion to exclude hypersensitivity to the active substance.</p>
18 March 2021	<p>Global study protocol amendment:</p> <p>Amendment was made regarding the sample size for the primary efficacy endpoint of Initially 300 patients; the sample size was adjusted to 162 patients.</p> <p>The study design was adjusted to be a two-part study.</p>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported