Clinical trial results:
Multicenter, adaptive, randomized, placebo-controlled, double blind, parallel-group Phase 2/3 trial, to study efficacy and safety of two doses of raloxifene in adult paucisymptomatic COVID-19 patients.

Summary

EudraCT number	2020-003936-25
Trial protocol	IT FR
Global end of trial date	12 June 2021

Results information

Result version number	v1 (current)
This version publication date	11 August 2022
First version publication date	11 August 2022

Trial information

Trial identification

Sponsor protocol code	RLX0120

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05172050
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dompé Farmaceutici S.p.A.
Sponsor organisation address	Via Santa Lucia, 6, Milano, Italy, 20122
Public contact	Clinical Trial Transparency Manager, Dompé farmaceutici S.p.A., +39 02583831, clinops@pec.dompe.it
Scientific contact	Clinical Trial Transparency Manager, Dompé farmaceutici S.p.A., +39 02583831, clinops@pec.dompe.it

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	12 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 June 2021
Global end of trial reached?	Yes
Global end of trial date	12 June 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to evaluate the efficacy and safety of two different doses of raloxifene orally administered compared to placebo in patients with early diagnosis of paucisymptomatic COVID-19. Efficacy was assessed based on the proportion of patients with undetectable SARS-CoV-2 at day 7 after randomization and the proportion of patients who required supplemental oxygen therapy and/or mechanical ventilation by day 14 after randomization. Safety was also assessed.

Protection of trial subjects:

The study was conducted under the provisions of the Declaration of Helsinki, and in accordance with the International Conference on Harmonization (ICH) Consolidated Guideline on Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 January 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 61
Worldwide total number of subjects	61
EEA total number of subjects	61

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)	47
From 65 to 84 years	14

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Actual recruitment was greatly slower than expected and this determined a significant delay in study conduction, which in turn reflected on a study completion forecast that was not in line with Sponsor's planning.

Pre-assignment

Screening details:

Due to the premature study interruption, the sample size was smaller than originally planned due to several reason that caused difficulties in patients enrollment.

Period 1

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

Blinding implementation details:

Appearance, including packaging and labelling, of the IMP (capsules, packaging) did not allow to recognize actual treatment (either raloxifene or placebo).

Arms

Are arms mutually exclusive?	Yes
Arm title	Raloxifene 60 mg

Arm description:

After an administration of two oral doses in the first day of treatment (one dose in the morning and one dose in the evening, each dose administered with 2 capsules containing 60 mg of the active substance or placebo), a single daily oral dose of raloxifene 60 mg was administered; the treatment was taken by the patients for two weeks.

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

Dosage and administration details:

Raloxifene: Raloxifene was administered as 60 mg hard gelatine capsule(s) once a day. Starting from day 2 of treatment: one single capsule (plus one of placebo to guarantee the blinding) containing 60 mg raloxifene was administered in Group 1, and 2 capsules 60 mg each for a total of 120 mg in Group 2.

Arm title	Raloxifene 120 mg

Arm description:

After an administration of two oral doses in the first day of treatment (one dose in the morning and one dose in the evening, each dose administered with 2 capsules containing 60 mg of the active substance or placebo), a single daily oral dose of raloxifene 120 mg was administered; the treatment was taken by the patients for two weeks.

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

Dosage and administration details:

Raloxifene: Raloxifene was administered as 60 mg hard gelatine capsule(s) once a day. Starting from

day 2 of treatment: one single capsule (plus one of placebo to guarantee the blinding) containing 60 mg raloxifene was administered in Group 1, and 2 capsules 60 mg each for a total of 120 mg in Group 2.

Arm title	Placebo

Arm description:

After an administration of two oral doses in the first day of treatment (one dose in the morning and one dose in the evening, each dose administered with 2 capsules containing placebo), a single daily oral dose of placebo (2 capsules guarantee the blinding design) was administered; the treatment was taken by the patients for two weeks.

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

Dosage and administration details:

Placebo: Placebo was administered orally once a day as 2 capsules (for maintaining the blinding design)

Number of subjects in period 1	Raloxifene 60 mg	Raloxifene 120 mg	Placebo
Started	22	20	19
Completed	10	9	8
Not completed	12	11	11
Negative Nasopharingeal swab	5	5	3
Development of AE or unacceptable toxicity	5	4	7
Unknown	2	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Raloxifene 60 mg
Reporting group description:	
After an administration of two oral doses in the first day of treatment (one dose in the morning and one dose in the evening, each dose administered with 2 capsules containing 60 mg of the active substance or placebo), a single daily oral dose of raloxifene 60 mg was administered; the treatment was taken by the patients for two weeks.	
Reporting group title	Raloxifene 120 mg
Reporting group description:	
After an administration of two oral doses in the first day of treatment (one dose in the morning and one dose in the evening, each dose administered with 2 capsules containing 60 mg of the active substance or placebo), a single daily oral dose of raloxifene 120 mg was administered; the treatment was taken by the patients for two weeks.	
Reporting group title	Placebo
Reporting group description:	
After an administration of two oral doses in the first day of treatment (one dose in the morning and one dose in the evening, each dose administered with 2 capsules containing placebo), a single daily oral dose of placebo (2 capsules guarantee the blinding design) was administered; the treatment was taken by the patients for two weeks.	

Reporting group values	Raloxifene 60 mg	Raloxifene 120 mg	Placebo
Number of subjects	22	20	19
Age categorical			
The Full Analysis Set (FAS) population, which included all randomized patients who received at least one dose of the study medication (either Raloxifene or Placebo). The FAS population was used for primary and secondary efficacy analyses, all the demographics and baseline characteristics. Patients were analysed according to the treatment they were randomized.			
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)	18	15	15
From 65-84 years	4	5	4
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	55.1	58.9	54.6
standard deviation	± 10.88	± 10.03	± 9.33
Gender categorical			
The Full Analysis Set (FAS) population, which included all randomized patients who received at least one dose of the study medication (either Raloxifene or Placebo). The FAS population was used for primary and secondary efficacy analyses, all the demographics and baseline characteristics. Patients were analysed according to the treatment they were randomized.			
Units: Subjects			
Female	11	8	9
Male	11	12	10

Reporting group values	Total		
Number of subjects	61		
Age categorical			
The Full Analysis Set (FAS) population, which included all randomized patients who received at least one dose of the study medication (either Raloxifene or Placebo). The FAS population was used for primary and secondary efficacy analyses, all the demographics and baseline characteristics. Patients were analysed according to the treatment they were randomized.			
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)	48		
From 65-84 years	13		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
The Full Analysis Set (FAS) population, which included all randomized patients who received at least one dose of the study medication (either Raloxifene or Placebo). The FAS population was used for primary and secondary efficacy analyses, all the demographics and baseline characteristics. Patients were analysed according to the treatment they were randomized.			
Units: Subjects			
Female	28		
Male	33		

Subject analysis sets

Subject analysis set title	Raloxifene 60 mg - FAS
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) population included all randomized patients who received at least one dose of the study medication. The FAS population was used for primary and secondary efficacy analyses.

Subject analysis set title	Raloxifene 120 mg - FAS
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) population included all randomized patients who received at least one dose of the study medication. The FAS population was used for primary and secondary efficacy analyses.

Subject analysis set title	Placebo - FAS
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) population included all randomized patients who received at least one dose of the study medication. The FAS population was used for primary and secondary efficacy analyses.

Subject analysis set title	Raloxifene 60 mg - PP
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol (PP) population included all randomized patients who received at least one dose of the study medication and did not have any Major Protocol Deviations. The PP population was used for sensitivity analyses of the efficacy endpoints.

Subject analysis set title	Raloxifene 120 mg - PP
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol (PP) population, which included all randomized patients who received at least one dose of the study medication and did not have any Major Protocol Deviations. The PP population was used for sensitivity analyses of the efficacy endpoints.

Subject analysis set title	Placebo - PP
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol (PP) population included all randomized patients who received at least one dose of the study medication and did not have any Major Protocol Deviations. The PP population was used for sensitivity analyses of the efficacy endpoints.

Reporting group values	Raloxifene 60 mg - FAS	Raloxifene 120 mg - FAS	Placebo - FAS
Number of subjects	22	20	19
Age categorical			
The Full Analysis Set (FAS) population, which included all randomized patients who received at least one dose of the study medication (either Raloxifene or Placebo). The FAS population was used for primary and secondary efficacy analyses, all the demographics and baseline characteristics. Patients were analysed according to the treatment they were randomized.			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	18	15	15
From 65-84 years	4	5	4
85 years and over			
Age continuous			
Units: years			
arithmetic mean	55.1	58.9	54.6
standard deviation	± 10.88	± 10.03	± 9.33
Gender categorical			
The Full Analysis Set (FAS) population, which included all randomized patients who received at least one dose of the study medication (either Raloxifene or Placebo). The FAS population was used for primary and secondary efficacy analyses, all the demographics and baseline characteristics. Patients were analysed according to the treatment they were randomized.			
Units: Subjects			
Female	11	8	9
Male	11	12	10

Reporting group values	Raloxifene 60 mg - PP	Raloxifene 120 mg - PP	Placebo - PP
Number of subjects	18	17	17
Age categorical			
The Full Analysis Set (FAS) population, which included all randomized patients who received at least one dose of the study medication (either Raloxifene or Placebo). The FAS population was used for primary and secondary efficacy analyses, all the demographics and baseline characteristics. Patients were analysed according to the treatment they were randomized.			
Units: Subjects			
In utero			

Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	±	±	±
Gender categorical			
The Full Analysis Set (FAS) population, which included all randomized patients who received at least one dose of the study medication (either Raloxifene or Placebo). The FAS population was used for primary and secondary efficacy analyses, all the demographics and baseline characteristics. Patients were analysed according to the treatment they were randomized.			
Units: Subjects			
Female Male			

End points

End points reporting groups

Reporting group title	Raloxifene 60 mg

Reporting group description:

After an administration of two oral doses in the first day of treatment (one dose in the morning and one dose in the evening, each dose administered with 2 capsules containing 60 mg of the active substance or placebo), a single daily oral dose of raloxifene 60 mg was administered; the treatment was taken by the patients for two weeks.

Reporting group title	Raloxifene 120 mg

Reporting group description:

After an administration of two oral doses in the first day of treatment (one dose in the morning and one dose in the evening, each dose administered with 2 capsules containing 60 mg of the active substance or placebo), a single daily oral dose of raloxifene 120 mg was administered; the treatment was taken by the patients for two weeks.

Reporting group title	Placebo

Reporting group description:

After an administration of two oral doses in the first day of treatment (one dose in the morning and one dose in the evening, each dose administered with 2 capsules containing placebo), a single daily oral dose of placebo (2 capsules guarantee the blinding design) was administered; the treatment was taken by the patients for two weeks.

Subject analysis set title	Raloxifene 60 mg - FAS
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) population included all randomized patients who received at least one dose of the study medication. The FAS population was used for primary and secondary efficacy analyses.

Subject analysis set title	Raloxifene 120 mg - FAS
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) population included all randomized patients who received at least one dose of the study medication. The FAS population was used for primary and secondary efficacy analyses.

Subject analysis set title	Placebo - FAS
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS) population included all randomized patients who received at least one dose of the study medication. The FAS population was used for primary and secondary efficacy analyses.

Subject analysis set title	Raloxifene 60 mg - PP
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol (PP) population included all randomized patients who received at least one dose of the study medication and did not have any Major Protocol Deviations. The PP population was used for sensitivity analyses of the efficacy endpoints.

Subject analysis set title	Raloxifene 120 mg - PP
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol (PP) population, which included all randomized patients who received at least one dose of the study medication and did not have any Major Protocol Deviations. The PP population was used for sensitivity analyses of the efficacy endpoints.

Subject analysis set title	Placebo - PP
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol (PP) population included all randomized patients who received at least one dose of the study medication and did not have any Major Protocol Deviations. The PP population was used for sensitivity analyses of the efficacy endpoints.

Primary: Number of Participants With Undetectable SARS-CoV-2 at PCR at Day 7 After Randomization in the FAS

End point title	Number of Participants With Undetectable SARS-CoV-2 at PCR at Day 7 After Randomization in the FAS

End point description:

Number of participants who, after an approved molecular test (PCR), were not detected as SARS-CoV2 positive. Based on Approved molecular test (PCR) result at day 7, the responses were considered as "detectable" if PCR result was "Positive" otherwise "undetectable" if PCR result was "Negative" .

End point type	Primary

End point timeframe:

At Day 7

End point values	Raloxifene 60 mg - FAS	Raloxifene 120 mg - FAS	Placebo - FAS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	19[1]	18[2]	14	
Units: count of participants	7	4	4	

Notes:

[1] - No. of patients considered in the model

[2] - No. of patients considered in the model

Statistical analyses

Statistical analysis title	Raloxifene 60 mg vs placebo[3]
Comparison groups	Raloxifene 60 mg - FAS v Placebo - FAS
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.0109 [5]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	9.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.781

Notes:

[3] - A low or upper value for the confidence interval may be missing. Values for both the lower and upper limit are expected to be provided with a 2-sided confidence interval.
Justification: The upper limit was not estimable due to the low number of events

[4] - Analysis is based on Exact Binary logistic regression model with treatment group, age group and status as main effects.
[5] - Please note that the upper limit of the IC is not estimable (NE), due to the low number of events; hence no digit was reported.

Statistical analysis title	Raloxifene 120 mg vs placebo[6]
Comparison groups	Raloxifene 120 mg - FAS v Placebo - FAS

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.0673 [8]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.414
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.858

Notes:

[6] - A low or upper value for the confidence interval may be missing. Values for both the lower and upper limit are expected to be provided with a 2-sided confidence interval.
Justification: The upper limit was not estimable due to the low number of events

[7] - Analysis is based on Exact Binary logistic regression model with treatment group, age group and status as main effects.
[8] - Please note that the upper limit of the IC is not estimable (NE), due to the low number of events; hence no digit was reported.

Primary: Number of Participants Not Requiring Oxygen Therapy and/or Mechanical Ventilation at Day 14 After Randomization in the FAS

End point title	Number of Participants Not Requiring Oxygen Therapy and/or Mechanical Ventilation at Day 14 After Randomization in the FAS

End point description:

Proportion of participants who does not require supplemental oxygen therapy (NEWS ≤ 2) and/or mechanical ventilation. NEWS is a system for scoring the physiological measurements that are routinely recorded at the patient's bedside. NEWS uses six physiological measurements. An additional two points are added if the patient is receiving oxygen therapy. The total possible score ranges from 0 to 20. If collected NEWS score > 2 or mechanical ventilation with result "Yes" then the response was considered as "Required". If collected NEWS score ≤ 2 and mechanical ventilation with result "No" then the response was considered as "Not Required" (if both NEWS score and mechanical ventilation were missing, patient was considered as missing).

End point type	Primary

End point timeframe:

At Day 14

End point values	Raloxifene 60 mg - FAS	Raloxifene 120 mg - FAS	Placebo - FAS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	18[9]	16	17	
Units: count of participants	10	8	8	

Notes:

[9] - No. of patients considered in the model

Statistical analyses

Statistical analysis title	Raloxifene 60 mg vs placebo
Comparison groups	Raloxifene 60 mg - FAS v Placebo - FAS

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.7121
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.663
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.337
upper limit	9.053

Notes:

[10] - Analysis is based on Exact Binary logistic regression model with treatment group, age group and status as main effects.

Statistical analysis title	Raloxifene 120 mg vs placebo
Comparison groups	Raloxifene 120 mg - FAS v Placebo - FAS
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	> 0.999
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.963
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.185
upper limit	4.977

Notes:

[11] - Analysis is based on Exact Binary logistic regression model with treatment group, age group and status as main effects

Primary: Number of Participants With Undetectable SARS-CoV-2 at PCR at Day 7 After Randomization in the PP population

End point title	Number of Participants With Undetectable SARS-CoV-2 at PCR at Day 7 After Randomization in the PP population

End point description:

Number of participants who, after an approved molecular test (PCR), were not detected as SARS-CoV2 positive. Based on Approved molecular test (PCR) result at day 7, the responses were considered as “detectable” if PCR result was “Positive” otherwise “undetectable” if PCR result was “Negative” .

End point type	Primary

End point timeframe:

At day 7

End point values	Raloxifene 60 mg - PP	Raloxifene 120 mg - PP	Placebo - PP	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	17[12]	17[13]	14[14]	
Units: number of subjects	9	13	14	

Notes:

[12] - No. of patients considered in the model

[13] - No. of patients considered in the model

[14] - No. of patients considered in the model

Statistical analyses

Statistical analysis title	Raloxifene 60 mg vs placebo[15]

Statistical analysis description:

This sensitivity analysis is conducted on the subjects analyzed in per protocol (PP) population.

Comparison groups	Placebo - PP v Raloxifene 60 mg - PP
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.0061 [17]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	12.186
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.147

Notes:

[15] - A low or upper value for the confidence interval may be missing. Values for both the lower and upper limit are expected to be provided with a 2-sided confidence interval.
Justification: The upper limit was not estimable due to the low number of events

[16] - Analysis is based on Exact Binary logistic regression model with treatment group, age group and status as main effects

[17] - Please note that the upper limit of the IC was not estimable due to the low number of events; hence no digit was reported.

Statistical analysis title	Raloxifene 120 mg vs placebo[18]

Statistical analysis description:

This sensitivity analysis is conducted on the subjects analyzed in per protocol (PP) population.

Comparison groups	Raloxifene 120 mg - PP v Placebo - PP
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.0567 [20]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.936
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.938

Notes:

[18] - A low or upper value for the confidence interval may be missing. Values for both the lower and upper limit are expected to be provided with a 2-sided confidence interval.

Justification: The upper limit was not estimable due to the low number of events

[19] - Analysis is based on Exact Binary logistic regression model with treatment group, age group and status as main effects.
[20] - Please note that the upper limit of the IC was not estimable due to the low number of events; hence no digit was reported.

Primary: Number of Participants Not Requiring Oxygen Therapy and/or Mechanical Ventilation at Day 14 After Randomization in the PP population

End point title	Number of Participants Not Requiring Oxygen Therapy and/or Mechanical Ventilation at Day 14 After Randomization in the PP population

End point description:

Proportion of participants who does not require supplemental oxygen therapy (NEWS ≤ 2) and/or mechanical ventilation. NEWS is a system for scoring the physiological measurements that are routinely recorded at the patient's bedside. NEWS uses six physiological measurements. An additional two points are added if the patient is receiving oxygen therapy. The total possible score ranges from 0 to 20. If collected NEWS score > 2 or mechanical ventilation with result "Yes" then the response was considered as "Required". If collected NEWS score ≤ 2 and mechanical ventilation with result "No" then the response was considered as "Not Required" (if both NEWS score and mechanical ventilation were missing, patient was considered as missing).

End point type	Primary

End point timeframe:

At Day 14

End point values	Raloxifene 60 mg - PP	Raloxifene 120 mg - PP	Placebo - PP	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	14[21]	14[22]	15[23]	
Units: number of subjects	8	8	8	

Notes:

[21] - No. of patients considered in the model

[22] - No. of patients considered in the model

[23] - No. of patients considered in the model

Statistical analyses

Statistical analysis title	Raloxifene 60 mg vs placebo

Statistical analysis description:

This sensitivity analysis is conducted on the subjects analyzed in per protocol (PP) population.

Comparison groups	Raloxifene 60 mg - PP v Placebo - PP
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	= 0.5378
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	20.153

Notes:

[24] - Analysis is based on Exact Binary logistic regression model with treatment group, age group and status as main effects

Statistical analysis title	Raloxifene 120 mg vs placebo

Statistical analysis description:

This sensitivity analysis is conducted on the subjects analyzed in per protocol (PP) population:

Comparison groups	Raloxifene 120 mg - PP v Placebo - PP
Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	> 0.999
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.209
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.185
upper limit	8.589

Notes:

[25] - Analysis is based on Exact Binary logistic regression model with treatment group, age group and status as main effects.

Secondary: Number of Participants With Undetectable SARS-CoV-2 at PCR at Days 14 and 28 After Randomization in the FAS

End point title	Number of Participants With Undetectable SARS-CoV-2 at PCR at Days 14 and 28 After Randomization in the FAS

End point description:

Number of participants with undetectable SARS-CoV-2 at PCR at day 14 after randomization, and at day 28 after randomization. Based on Approved molecular test (PCR) result at days 14 and 28 after randomization, the responses were considered as "detectable" if PCR result was "Positive" otherwise "undetectable" if PCR result was "Negative".

End point type	Secondary

End point timeframe:

At days 14 and 28 after randomization

End point values	Raloxifene 60 mg - FAS	Raloxifene 120 mg - FAS	Placebo - FAS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20[26]	18[27]	16	
Units: count of participants				
at Day 14	10	14	7	
at Day 28	17	17	12	

Notes:

[26] - No. of patients considered in the model

[27] - No. of patients considered in the model

Statistical analyses

Statistical analysis title	Raloxifene 60 mg (FAS) vs placebo (FAS)
Statistical analysis description:	
at Day 14	
Comparison groups	Raloxifene 60 mg - FAS v Placebo - FAS
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	> 0.999
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.114
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.219
upper limit	5.708

Notes:

[28] - Analysis is based on Exact Binary logistic regression model with treatment group, age group and status as main effects.

Statistical analysis title	Raloxifene 120 mg (FAS) vs placebo (FAS)
Statistical analysis description:	
at Day 14	
Comparison groups	Raloxifene 120 mg - FAS v Placebo - FAS
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	= 0.2553
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.202
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.541
upper limit	22.116

Notes:

[29] - Analysis is based on Exact Binary logistic regression model with treatment group, age group and status as main effects.

Statistical analysis title	Raloxifene 60 mg (FAS) vs placebo (FAS)
Statistical analysis description:	
at Day 28	
Comparison groups	Raloxifene 60 mg - FAS v Placebo - FAS
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority[30]
P-value	= 0.6189
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.16

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.294
upper limit	18.532

Notes:

[30] - Analysis is based on Exact Binary logistic regression model with treatment group, age group and status as main effects.

Statistical analysis title	Raloxifene 120 mg (FAS) vs placebo (FAS)

Statistical analysis description:

at Day 28

Comparison groups	Raloxifene 120 mg - FAS v Placebo - FAS
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	= 0.1662
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	7.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.586
upper limit	413.499

Notes:

[31] - Analysis is based on Exact Binary logistic regression model with treatment group, age group and status as main effects.

Secondary: Number of Participants Not Requiring Oxygen Therapy and/or Mechanical Ventilation at Day 7 an d at Day 28 in the FAS

End point title	Number of Participants Not Requiring Oxygen Therapy and/or Mechanical Ventilation at Day 7 an d at Day 28 in the FAS

End point description:

Proportion of participants who does not require supplemental oxygen therapy (NEWS ≤ 2) and/or mechanical ventilation after randomization;

End point type	Secondary

End point timeframe:

At days 7 and 28

End point values	Raloxifene 60 mg - FAS	Raloxifene 120 mg - FAS	Placebo - FAS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	22[32]	18	17[33]	
Units: count of participants				
at Day 7	12	12	11	
at Day 28	9	12	7	

Notes:

[32] - No. of patients considered in the model

[33] - No. of patients considered in the model

Statistical analyses

Statistical analysis title	Raloxifene 60 mg (FAS) vs placebo (FAS)
Statistical analysis description:	
at Day 7	
Comparison groups	Raloxifene 60 mg - FAS v Placebo - FAS
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority[34]
P-value	> 0.999
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.972
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.193
upper limit	4.906

Notes:

[34] - Analysis is based on Exact Binary logistic regression model with treatment group, age group and status as main effects

Statistical analysis title	Raloxifene 120 mg (FAS) vs placebo (FAS)
Statistical analysis description:	
at Day 7	
Comparison groups	Raloxifene 120 mg - FAS v Placebo - FAS
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority[35]
P-value	> 0.999
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.156
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	6.822

Notes:

[35] - Analysis is based on Exact Binary logistic regression model with treatment group, age group and status as main effects

Statistical analysis title	Raloxifene 60 mg (FAS) vs placebo (FAS)
Statistical analysis description:	
at Day 28	
Comparison groups	Raloxifene 60 mg - FAS v Placebo - FAS
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority[36]
P-value	> 0.999
Method	Regression, Linear
Parameter estimate	Odds ratio (OR)
Point estimate	1.066

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.208
upper limit	5.478

Notes:

[36] - Analysis is based on Exact Binary logistic regression model with treatment group, age group and status as main effects

Statistical analysis title	Raloxifene 120 mg (FAS) vs placebo (FAS)

Statistical analysis description:

at Day 28

Comparison groups	Raloxifene 120 mg - FAS v Placebo - FAS
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	superiority[37]
P-value	= 0.5465
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.068
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.369
upper limit	12.58

Notes:

[37] - Analysis is based on Exact Binary logistic regression model with treatment group, age group and status as main effects

Secondary: Number of Patients in Each National Early Warning Score (NEWS) Category in the FAS

End point title	Number of Patients in Each National Early Warning Score (NEWS) Category in the FAS

End point description:

Proportion of patients in each National Early Warning Score (NEWS) category after randomization. NEWS is a system for scoring the physiological measurements that are routinely recorded at the patient's bedside. NEWS uses six physiological measurements: respiratory rate; oxygen saturation; temperature; systolic blood pressure; heart rate and level of consciousness. Each scores 0–3 and individual scores are added together for an overall score. An additional two points are added if the patient is receiving oxygen therapy. The total possible score ranges from 0 to 20. The higher the score, the worse the outcome.

End point type	Secondary

End point timeframe:

At days 7, 14, 28

End point values	Raloxifene 60 mg - FAS	Raloxifene 120 mg - FAS	Placebo - FAS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	22	20	19	
Units: count of participants				
Day 7 - Score 0	6	5	6	
Day 7 - Score 1	3	4	5	
Day 7 - Score 2	3	3	0	

Day 7 - Score 3	1	2	0	
Day 7 - Score 4	2	0	3	
Day 7 - Score 5	1	1	0	
Day 7 - Score 7	2	1	0	
Day 7 - Missing	4	4	5	
Day 14 - Score 0	5	4	5	
Day 14 - Score 1	5	2	3	
Day 14 - Score 2	1	3	0	
Day 14 - Score 3	1	5	2	
Day 14 - Score 4	2	1	1	
Day 14 - Score 5	0	0	1	
Day 14 - Score 6	1	0	1	
Day 14 - Missing	7	5	6	
Day 28 - Score 0	5	8	5	
Day 28 - Score 1	4	5	3	
Day 28 - Score 2	1	0	1	
Day 28 - Score 3	0	0	1	
Day 28 - Score 4	2	0	1	
Day 28 - Missing	10	7	8	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Value of National Early Warning Score (NEWS) Category in the FAS

End point title	Mean Value of National Early Warning Score (NEWS) Category in the FAS

End point description:

Mean value of National Early Warning Score (NEWS) category after randomization. NEWS is a system for scoring the physiological measurements that are routinely recorded at the patient's bedside. The total possible score ranges from 0 to 20. The higher the score the greater the clinical risk. Higher scores indicate the need for escalation, medical review and possible clinical intervention and more intensive monitoring

End point type	Secondary

End point timeframe:

At days 7, 14, 28

End point values	Raloxifene 60 mg - FAS	Raloxifene 120 mg - FAS	Placebo - FAS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	22	20	19	
Units: number of patients				
arithmetic mean (standard deviation)				
Day 7	2.2 (± 2.36)	1.8 (± 1.98)	1.2 (± 1.58)	
Day 14	1.6 (± 1.84)	1.8 (± 1.37)	1.8 (± 2.12)	
Day 28	1.2 (± 1.47)	0.4 (± 0.51)	1.1 (± 1.38)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Hospitalized Participants Who at the Beginning of the Study Were at Domicile Isolation After Randomization in the FAS

End point title	Number of Hospitalized Participants Who at the Beginning of the Study Were at Domicile Isolation After Randomization in the FAS

End point description:

Proportion of hospitalized participants at Day 7, Day 14 and Day 28 after randomization among subjects who at the beginning of the study were at domicile isolation.

End point type	Secondary

End point timeframe:

At days 7, 14, 28

End point values	Raloxifene 60 mg - FAS	Raloxifene 120 mg - FAS	Placebo - FAS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	22	20	19	
Units: count of participants				
Day 7	20	18	15	
Day 14	20	18	15	
Day 28	20	18	16	

Statistical analyses

Statistical analysis title	Raloxifene 60 mg (FAS) vs placebo (FAS)

Statistical analysis description:

At Day 7

Comparison groups	Raloxifene 60 mg - FAS v Placebo - FAS
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority[38]
P-value	= 0.3899 [39]
Method	Fisher exact

Notes:

[38] - The proportion of hospitalized participants who at the beginning of the study were at domicile isolation at Day 7, Day 14 and Day 28 after randomization was analysed using comparison of proportions (i.e. comparisons of each active treatment group versus placebo at each assessment day) through Fisher’s exact test and was summarized using frequency and percent by treatment and visit.

[39] - P-Value comparing % among treatment groups Raloxifene 60mg versus Placebo using Fisher's Exact test.

Statistical analysis title	Raloxifene 120 mg (FAS) vs placebo (FAS)

Statistical analysis description:

At Day 7

Comparison groups	Raloxifene 120 mg - FAS v Placebo - FAS
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority[40]
P-value	= 0.4075 [41]
Method	Fisher exact

Notes:

[40] - The proportion of hospitalized participants who at the beginning of the study were at domicile isolation at Day 7, Day 14 and Day 28 after randomization was analysed using comparison of proportions (i.e. comparisons of each active treatment group versus placebo at each assessment day) through Fisher’s exact test and was summarized using frequency and percent by treatment and visit.
[41] - P-Value comparing % among treatment groups Raloxifene 120 mg versus Placebo using Fisher's Exact test.

Statistical analysis title	Raloxifene 60 mg (FAS) vs placebo (FAS)

Statistical analysis description:

At Day 14

Comparison groups	Raloxifene 60 mg - FAS v Placebo - FAS
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority[42]
P-value	= 0.3899 [43]
Method	Fisher exact

Notes:

[42] - The proportion of hospitalized participants who at the beginning of the study were at domicile isolation at Day 7, Day 14 and Day 28 after randomization was analysed using comparison of proportions (i.e. comparisons of each active treatment group versus placebo at each assessment day) through Fisher's exact test and was summarized using frequency and percent by treatment and visit.
[43] - P-Value comparing % among treatment groups Raloxifene 60mg versus Placebo using Fisher's Exact test.

Statistical analysis title	Raloxifene 120 mg (FAS) vs placebo (FAS)

Statistical analysis description:

At Day 14

Comparison groups	Raloxifene 120 mg - FAS v Placebo - FAS
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority[44]
P-value	= 0.4075 [45]
Method	Fisher exact

Notes:

[44] - The proportion of hospitalized participants who at the beginning of the study were at domicile isolation at Day 7, Day 14 and Day 28 after randomization was analysed using comparison of proportions (i.e. comparisons of each active treatment group versus placebo at each assessment day) through Fisher's exact test and was summarized using frequency and percent by treatment and visit.
[45] - P-Value comparing % among treatment groups Raloxifene 120mg versus Placebo using Fisher's Exact test.

Statistical analysis title	Raloxifene 60 mg (FAS) vs placebo (FAS)

Statistical analysis description:	
At Day 28	
Comparison groups	Raloxifene 60 mg - FAS v Placebo - FAS
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority[46]
P-value	= 0.6846 [47]
Method	Fisher exact

Notes:

[46] - The proportion of hospitalized participants who at the beginning of the study were at domicile isolation at Day 7, Day 14 and Day 28 after randomization was analysed using comparison of proportions (i.e. comparisons of each active treatment group versus placebo at each assessment day) through Fisher's exact test and was summarized using frequency and percent by treatment and visit.
[47] - P-Value comparing % among treatment groups Raloxifene 60mg versus Placebo using Fisher's Exact test.

Statistical analysis title	Raloxifene 120 mg (FAS) vs placebo (FAS)
Statistical analysis description:	
At Day 28	
Comparison groups	Raloxifene 120 mg - FAS v Placebo - FAS
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority[48]
P-value	= 0.6614 [49]
Method	Fisher exact

Notes:

[48] - The proportion of hospitalized participants who at the beginning of the study were at domicile isolation at Day 7, Day 14 and Day 28 after randomization was analysed using comparison of proportions (i.e. comparisons of each active treatment group versus placebo at each assessment day) through Fisher's exact test and was summarized using frequency and percent by treatment and visit.
[49] - P-Value comparing % among treatment groups Raloxifene 120mg versus Placebo using Fisher's Exact test.

Secondary: Number of Participants Admitted to Intensive Care After Randomization in the FAS

End point title	Number of Participants Admitted to Intensive Care After Randomization in the FAS

End point description:

End point type	Secondary

End point timeframe:

At days 7, 14, 28

End point values	Raloxifene 60 mg - FAS	Raloxifene 120 mg - FAS	Placebo - FAS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	22	20	19	
Units: count of participants				
Day 7	0	0	0	
Day 14	0	0	0	
Day 28	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Survivors in the FAS

End point title	Number of Survivors in the FAS

End point description:

End point type	Secondary

End point timeframe:

At days 7, 14, 28

End point values	Raloxifene 60 mg - FAS	Raloxifene 120 mg - FAS	Placebo - FAS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	22	20	19	
Units: count of participants				
Day 7	22	20	19	
Day 14	22	20	19	
Day 28	22	20	19	

Statistical analyses

Statistical analysis title	Raloxifene 60 mg (FAS) vs placebo (FAS)
Comparison groups	Raloxifene 60 mg - FAS v Placebo - FAS
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1

	Raloxifene 120 mg (FAS) vs placebo (FAS)

Statistical analysis title	
Comparison groups	Raloxifene 120 mg - FAS v Placebo - FAS
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1

Secondary: Quality of Life Questionnaire (EQ-5D-5L) at 3 Months After Randomization - EQ-5D Descriptive System

End point title	Quality of Life Questionnaire (EQ-5D-5L) at 3 Months After Randomization - EQ-5D Descriptive System

End point description:

The EQ-5D-5L consists of: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS).The EQ-5D system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the 5 dimensions can be combined into a 5-digit number describing the patient's health state.
In the EQ VAS - quantitative measure of health outcome - the patient records a self-rates health on a vertical, visual analogue scale which goes from 'Best imaginable health state' to 'Worst imaginable health state'.
Both for total and partial scores, the higher the score, the worse is the outcome.

End point type	Secondary

End point timeframe:

At month 3

End point values	Raloxifene 60 mg - FAS	Raloxifene 120 mg - FAS	Placebo - FAS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	22	20	19	
Units: count of participants				
mobility -no problems in walking about	18	12	15	
mobility - slight problems in walking abou	1	5	2	
mobility - moderate problems in walking about	0	0	1	
mobility-severe problems in walking about	0	0	0	
mobility - unable to walk about	0	0	0	
self care - no problems washing or dressing myself	18	17	18	
self care - slight problems washing or dressing my	0	0	0	

self care - moderate problems washing or dressing	1	0	0	
self care - severe problems washing or dressing my	0	0	0	
self care - unable to wash or dress myself	0	0	0	
usual activities - no problems doing my usual acti	14	14	12	
usual activities - slight problems doing my usual	3	3	5	
usual activities - moderate problems doing my usua	1	0	1	
usual activities - severe problems doing my usual	1	0	0	
usual activities - unable to do my usual activitie	0	0	0	
Pain/discomfort - no pain or discomfort	17	13	15	
Pain/discomfort - slight pain or discomfort	0	4	2	
Pain/discomfort - moderate pain or discomfort	1	0	0	
Pain/discomfort - severe pain or discomfort	1	0	1	
Pain/discomfort - extreme pain or discomfort	0	0	0	
Anxiety / Depression - I am not anxious or depress	13	10	13	
Anxiety / Depression - I am slightly anxious or de	1	5	4	
Anxiety / Depression - I am moderately anxious or	5	2	1	
Anxiety / Depression - I am severely anxious or de	0	0	0	
Anxiety / Depression - I am extremely anxious or d	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life Questionnaire (EQ-5D-5L) at 3 Months After Randomization - EQ VAS

End point title	Quality of Life Questionnaire (EQ-5D-5L) at 3 Months After Randomization - EQ VAS

End point description:

The EQ-5D-5L consists of: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS).The EQ-5D system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the 5 dimensions can be combined into a 5-digit number describing the patient's health state.
In the EQ VAS - quantitative measure of health outcome - the patient records a self-rates health on a vertical, visual analogue scale which goes from 'Best imaginable health state' to 'Worst imaginable health state'.
Both for total and partial scores, the higher the score, the worse is the outcome.

End point type	Secondary

End point timeframe:
At month 3

End point values	Raloxifene 60 mg - FAS	Raloxifene 120 mg - FAS	Placebo - FAS	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	22	20	19	
Units: score on a scale				
arithmetic mean (standard deviation)	85.6 (± 13.7)	72.5 (± 21.9)	84.1 (± 11.5)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The specific period of time over which adverse events data were collected was within Day 7, 14 and 28 after randomization.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Raloxifene 60 mg - SAF

Reporting group description:

After an administration of two oral doses in the first day of treatment (one dose in the morning and one dose in the evening, each dose administered with 2 capsules containing 60 mg of the active substance or placebo), a single daily oral dose of raloxifene 60 mg was administered; the treatment was taken by the patients for two weeks.
Raloxifene: Raloxifene was administered as 60 mg hard gelatine capsule(s) once a day. Starting from day 2 of treatment: one single capsule (plus one of placebo to guarantee the blinding) containing 60 mg raloxifene was administered in Group 1, and 2 capsules 60 mg each for a total of 120 mg in Group 2.

Reporting group title	Raloxifene 120 mg - SAF

Reporting group description:

After an administration of two oral doses in the first day of treatment (one dose in the morning and one dose in the evening, each dose administered with 2 capsules containing 60 mg of the active substance or placebo), a single daily oral dose of raloxifene 120 mg was administered; the treatment was taken by the patients for two weeks.
Raloxifene: Raloxifene was administered as 60 mg hard gelatine capsule(s) once a day. Starting from day 2 of treatment: one single capsule (plus one of placebo to guarantee the blinding) containing 60 mg raloxifene was administered in Group 1, and 2 capsules 60 mg each for a total of 120 mg in Group 2.

Reporting group title	Placebo - SAF

Reporting group description:

After an administration of two oral doses in the first day of treatment (one dose in the morning and one dose in the evening, each dose administered with 2 capsules containing placebo), a single daily oral dose of placebo (2 capsules guarantee the blinding design) was administered; the treatment was taken by the patients for two weeks.
Placebo: Placebo was administered orally once a day as 2 capsules (for maintaining the blinding design)

Serious adverse events	Raloxifene 60 mg - SAF	Raloxifene 120 mg - SAF	Placebo - SAF
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 22 (13.64%)	2 / 20 (10.00%)	5 / 19 (26.32%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma of liver			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration			

site conditions			
Pyrexia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 22 (4.55%)	0 / 20 (0.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 22 (4.55%)	1 / 20 (5.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 22 (4.55%)	1 / 20 (5.00%)	0 / 19 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 20 (0.00%)	2 / 19 (10.53%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 4.5 %

Non-serious adverse events	Raloxifene 60 mg - SAF	Raloxifene 120 mg - SAF	Placebo - SAF
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 22 (27.27%)	8 / 20 (40.00%)	6 / 19 (31.58%)
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	1 / 22 (4.55%)	0 / 20 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Peripheral swelling			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Vessel puncture site bruise			
subjects affected / exposed	0 / 22 (0.00%)	2 / 20 (10.00%)	1 / 19 (5.26%)
occurrences (all)	0	2	2
Reproductive system and breast disorders			
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 22 (4.55%)	0 / 20 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
subjects affected / exposed	1 / 22 (4.55%)	1 / 20 (5.00%)	0 / 19 (0.00%)
occurrences (all)	1	1	0
Pneumonia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 20 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Pneumonitis			

subjects affected / exposed	1 / 22 (4.55%)	0 / 20 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Respiratory failure			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 22 (4.55%)	0 / 20 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Investigations			
Fibrin D dimer increased			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Lipids increased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Transaminases increased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Chest injury			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Contusion			
subjects affected / exposed	1 / 22 (4.55%)	0 / 20 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Fall			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Paraesthesia			

subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Thrombocytosis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 22 (4.55%)	1 / 20 (5.00%)	1 / 19 (5.26%)
occurrences (all)	1	1	1
Dyspepsia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 20 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Gastric disorder			
subjects affected / exposed	1 / 22 (4.55%)	1 / 20 (5.00%)	1 / 19 (5.26%)
occurrences (all)	1	1	1
Gastrintestinal disorder			
subjects affected / exposed	2 / 22 (9.09%)	1 / 20 (5.00%)	0 / 19 (0.00%)
occurrences (all)	2	1	0
Nausea			
subjects affected / exposed	3 / 22 (13.64%)	0 / 20 (0.00%)	0 / 19 (0.00%)
occurrences (all)	3	0	0
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Hepatitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 20 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 22 (0.00%)	1 / 20 (5.00%)	1 / 19 (5.26%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Muscle spasms			

subjects affected / exposed	2 / 22 (9.09%)	1 / 20 (5.00%)	0 / 19 (0.00%)
occurrences (all)	2	1	0
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 20 (0.00%)	2 / 19 (10.53%)
occurrences (all)	1	0	2
Metabolism and nutrition disorders			
Hypertriglyceridaemia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Hypokalaemia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 20 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	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 95%IC upper limit for some endpoints was not estimable due to the low number of events

Notes: