Clinical trial results:
A phase 3, double-blind, randomized, placebo-controlled, multicenter study on the efficacy and safety of Reparixin in the treatment of hospitalized patients with severe COVID-19 pneumonia.

Summary

EudraCT number	2020-005919-51
Trial protocol	IT
Global end of trial date	21 September 2021

Results information

Result version number	v1 (current)
This version publication date	31 December 2022
First version publication date	31 December 2022

Trial information

Trial identification

Sponsor protocol code	REP0220

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04878055
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, Clinical Trial Transparency Manager, +39 02583831, clinops@pec.dompe.com
Scientific contact	Clinical Trial Transparency Manager, Clinical Trial Transparency Manager, +39 02583831, clinops@pec.dompe.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:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 January 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 September 2021
Global end of trial reached?	Yes
Global end of trial date	21 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to assess the efficacy and safety of Reparixin treatment as compared to placebo (both on top of standard treatment) in adult patients with severe Coronavirus disease 2019 (COVID-19) pneumonia.

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:

All patients received the standard supportive care, based on the patient’s clinical need. It could eventually include anticoagulants, corticosteroids, antibiotics, among others, as per local standard therapy and in line with international guidelines. Optimal oxygenation could be considered a SpO2 between 92% and 96%; however, no specific oxygen target was required by the protocol.

Evidence for comparator:

Please note that 287 patients were enrolled in the study, but 270 are the subjects in the FAS (8 enrolled and not randomized, 9 randomized but not treated). Results are reported for the FAS population, except where otherwise specified.

Actual start date of recruitment	14 February 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: 270
Worldwide total number of subjects	270
EEA total number of subjects	270

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)	170
From 65 to 84 years	94
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

The eligible patient population consisted of hospitalized adult patients with reverse transcriptase polymerase chain reaction (rt-PCR)-confirmed severe COVID-19. Patients were considered to have severe disease in the presence of respiratory distress and requiring supplemental oxygen. No gender and/or ethnicity restrictions applied.

Pre-assignment

Screening details:

Patients were included in the study after a variable period at home with initial symptoms of the COVID-19 infection. In case of worsening of general and pulmonary condition, the patient started the screening phase for the confirmation of the selection criteria.

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, Monitor, Data analyst, Carer

Blinding implementation details:

The realization of the double-blind design was made possible by the production of placebo tablets that were identical in appearance to the active formulation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Reparixin (randomised and treated)

Arm description:

Reparixin oral tablets, 1200 mg TID (2 tablets 600 mg each, TID) for up to 21 days or until the decision of discharge from the hospital, on top of standard supportive care.
For each administration, two tablets of Reparixin (600 mg each) or placebo were taken, for the total of three daily administrations (6 tablets daily).
Please note that patients randomized to Reparixin were 185, but the ones receiving at least one dose of IMP were 182. Three patients, hence, in this group were excluded from the primary FAS analysis of efficacy and from the safety analysis.

Arm type	Experimental
Investigational medicinal product name	Reparixin
Investigational medicinal product code	
Other name	REP
Pharmaceutical forms	Buccal tablet
Routes of administration	Buccal use, Oral use

Dosage and administration details:

Reparixin oral tablets, 1200 mg TID (2 tablets 600 mg each) for a total of three daily administrations (6 tablets daily). It was advisable to take the tablets with a glass of water to facilitate swallowing.

Arm title	Placebo (randomised and treated)

Arm description:

Placebo, 2 tablets TID (identical to Reparixin tablets) for up to 21 days or until decision of discharge from the hospital, on top of standard supportive care.
For each administration, two tablets of Reparixin (600 mg each) or placebo were taken, for the total of three daily administrations (6 tablets daily). It was advisable to take the tablets with a glass of water to facilitate swallowing.
Please note that patients randomized to placebo were 94, but the ones receiving it were 88. Six patients in this group, hence, were excluded from the primary FAS analysis of efficacy and from the safety analysis.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Buccal tablet
Routes of administration	Buccal use

Dosage and administration details:

2 tablets TID (2 tablets 600 mg each, TID) for a total of three daily administrations (6 tablets daily). It was advisable to take the tablets with a glass of water to facilitate swallowing.

Number of subjects in period 1	Reparixin (randomised and treated)	Placebo (randomised and treated)
Started	182	88
Completed	147	70
Not completed	35	18
Adverse event, serious fatal	11	7
Consent withdrawn by subject	7	3
Physician decision	1	1
unknown	5	-
Patient transferred in another department	-	2
Adverse event, non-fatal	1	-
Lost to follow-up	10	1
Day 60 visit not performed by mistake	-	4

Baseline characteristics

Reporting groups	
Reporting group title	Reparixin (randomised and treated)
Reporting group description:	
Reparixin oral tablets, 1200 mg TID (2 tablets 600 mg each, TID) for up to 21 days or until the decision of discharge from the hospital, on top of standard supportive care. For each administration, two tablets of Reparixin (600 mg each) or placebo were taken, for the total of three daily administrations (6 tablets daily). Please note that patients randomized to Reparixin were 185, but the ones receiving at least one dose of IMP were 182. Three patients, hence, in this group were excluded from the primary FAS analysis of efficacy and from the safety analysis.	
Reporting group title	Placebo (randomised and treated)
Reporting group description:	
Placebo, 2 tablets TID (identical to Reparixin tablets) for up to 21 days or until decision of discharge from the hospital, on top of standard supportive care. For each administration, two tablets of Reparixin (600 mg each) or placebo were taken, for the total of three daily administrations (6 tablets daily). It was advisable to take the tablets with a glass of water to facilitate swallowing. Please note that patients randomized to placebo were 94, but the ones receiving it were 88. Six patients in this group, hence, were excluded from the primary FAS analysis of efficacy and from the safety analysis.	

Reporting group values	Reparixin (randomised and treated)	Placebo (randomised and treated)	Total
Number of subjects	182	88	270
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	112	58	170
From 65-84 years	67	28	95
85 years and over	3	2	5
Age continuous Units: years			
arithmetic mean	61.3	60.0	
standard deviation	± 11.8	± 12.0	-
Gender categorical Units: Subjects			
Female	50	25	75
Male	132	63	195

Subject analysis sets	
Subject analysis set title	Reparixin FAS
Subject analysis set type	Full analysis

Subject analysis set description:

FAS Full Analysis Set: set which consisted of all randomized subjects who received at least one dose of the IMP. The FAS population was analyzed according to the intent-to-treat (ITT) principle, i.e. by treatment allocation regardless the occurrence of intercurrent events (treatment policy strategy). The FAS population was used for the primary analyses of the study and to present results on efficacy data.

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

Subject analysis set description:

FAS Full Analysis Set: set which consisted of all randomized subjects who received at least one dose of the IMP. The FAS population was analyzed according to the intent-to-treat (ITT) principle, i.e. by treatment allocation regardless the occurrence of intercurrent events (treatment policy strategy). The FAS population was used for the primary analyses of the study and to present results on efficacy data.

Reporting group values	Reparixin FAS	Placebo FAS	
Number of subjects	182	88	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	112	58	
From 65-84 years	66	28	
85 years and over	4	2	
Age continuous Units: years			
arithmetic mean	61.3	60.0	
standard deviation	± 11.8	± 12.0	
Gender categorical Units: Subjects			
Female	50	25	
Male	132	63	

End points

End points reporting groups

Reporting group title	Reparixin (randomised and treated)

Reporting group description:

Reparixin oral tablets, 1200 mg TID (2 tablets 600 mg each, TID) for up to 21 days or until the decision of discharge from the hospital, on top of standard supportive care.
For each administration, two tablets of Reparixin (600 mg each) or placebo were taken, for the total of three daily administrations (6 tablets daily).
Please note that patients randomized to Reparixin were 185, but the ones receiving at least one dose of IMP were 182. Three patients, hence, in this group were excluded from the primary FAS analysis of efficacy and from the safety analysis.

Reporting group title	Placebo (randomised and treated)

Reporting group description:

Placebo, 2 tablets TID (identical to Reparixin tablets) for up to 21 days or until decision of discharge from the hospital, on top of standard supportive care.
For each administration, two tablets of Reparixin (600 mg each) or placebo were taken, for the total of three daily administrations (6 tablets daily). It was advisable to take the tablets with a glass of water to facilitate swallowing.
Please note that patients randomized to placebo were 94, but the ones receiving it were 88. Six patients in this group, hence, were excluded from the primary FAS analysis of efficacy and from the safety analysis.

Subject analysis set title	Reparixin FAS
Subject analysis set type	Full analysis

Subject analysis set description:

FAS Full Analysis Set: set which consisted of all randomized subjects who received at least one dose of the IMP. The FAS population was analyzed according to the intent-to-treat (ITT) principle, i.e. by treatment allocation regardless the occurrence of intercurrent events (treatment policy strategy). The FAS population was used for the primary analyses of the study and to present results on efficacy data.

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

Subject analysis set description:

FAS Full Analysis Set: set which consisted of all randomized subjects who received at least one dose of the IMP. The FAS population was analyzed according to the intent-to-treat (ITT) principle, i.e. by treatment allocation regardless the occurrence of intercurrent events (treatment policy strategy). The FAS population was used for the primary analyses of the study and to present results on efficacy data.

Primary: Proportion of patients alive and free of respiratory failure at Day 28

End point title	Proportion of patients alive and free of respiratory failure at Day 28

End point description:

The event variable is defined as "the proportion of patients alive and free of respiratory failure at Day 28". This means no need of invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) or admission to intensive care unit (ICU) linked to worsening of respiratory parameters compared to baseline.

End point type	Primary

End point timeframe:

At day 28 (+/-2)

End point values	Reparixin FAS	Placebo FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	182	88		
Units: Patients	152	71		

Statistical analyses

Statistical analysis title	Reparixin FAS vs Placebo FAS
Comparison groups	Placebo FAS v Reparixin FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.216
Method	Two-sided regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.626
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.752
upper limit	3.514

Notes:

[1] - Analysis is based on logistic regression model with Multiple Imputation under missing not at random using retrieve dropouts with proportion of patients alive and free of respiratory failure at Day 28 as dependent variable, treatment, age group, gender and presence of concomitant disease at baseline as qualitative independent variables. Site is considered as random effects that vary randomly among patients.

Secondary: Proportion of patients alive and free of respiratory failure at Day 60

End point title	Proportion of patients alive and free of respiratory failure at Day 60

End point description:

This key secondary efficacy endpoint of the study is defined as "the proportion of patients alive and free of respiratory failure at Day 60", i.e. with no need of invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) or admission to intensive care unit (ICU) linked to worsening of respiratory parameters compared to baseline.

End point type	Secondary

End point timeframe:

At day 60

End point values	Reparixin FAS	Placebo FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	159	78		
Units: Patients	141	66		

Statistical analyses

Statistical analysis title	Reparixin FAS vs placebo FAS
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.377 [2]
Method	Chi-squared

Notes:

[2] - Comparison between treatment arms is performed by means of a Chi-squared test

Secondary: Mortality rates up to Day 28	
End point title	Mortality rates up to Day 28

End point description:

This key secondary efficacy endpoint describes number and proportion along with the 95% CI (Clopper-Pearson's formula) of patients who died was calculated up to Day 28.

End point type	Secondary

End point timeframe:

Up to day 28

End point values	Reparixin FAS	Placebo FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	168	81		
Units: Patients	10	7		

Statistical analyses

Statistical analysis title	Reparixin FAS vs placebo FAS
Comparison groups	Placebo FAS v Reparixin FAS
Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.17
Method	Two-sided regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.468
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.158
upper limit	1.386

Notes:

[3] - Analysis is based on logistic regression model with proportion of patients died up to Day 28 as dependent variable, treatment, age group, gender and presence of concomitant disease at baseline as qualitative independent variables. Site is considered as random effects that vary randomly among patients.

Secondary: Incidence of ICU admission until Day 28

End point title	Incidence of ICU admission until Day 28

End point description:

This is a key secondary efficacy endpoint. Admissions to Intensive Care Unit (ICU) had to be considered only in presence of significant worsening of respiratory status. This condition was objectively identified by means of a decrease of PaO2/FiO2 ratio of at least 40% from the baseline value or by a worsening of Investigator’s Interpretation.

End point type	Secondary

End point timeframe:

up to day 28

End point values	Reparixin FAS	Placebo FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	171	83		
Units: Patients	27	18		

Statistical analyses

Statistical analysis title	Reparixin FAS vs placebo FAS
Comparison groups	Placebo FAS v Reparixin FAS
Number of subjects included in analysis	254
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.168
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.561
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.247
upper limit	1.277

Secondary: Time to recovery until Day 28

End point title	Time to recovery until Day 28

End point description:

This is a key secondary efficacy endpoint. The event "recovery" was considered as such, if the patient has scored category 1, 2 or 3 from the 7-point WHO Ordinal Scale of clinical improvement (WHO-OS), otherwise it will be considered free of event.
Category 1: not hospitalized, with resumption of normal activities; 2: not hospitalized, but unable to resume normal activities; 3: hospitalized, not requiring supplemental oxygen; [4: hospitalized, requiring supplemental oxygen; 5: hospitalized, requiring high-flow oxygen therapy, non-invasive mechanical

ventilation, or both; 6: hospitalized, requiring ECMO, invasive mechanical ventilation, or both; 7: death].

End point type	Secondary

End point timeframe:

At day 28

End point values	Reparixin FAS	Placebo FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	182	88		
Units: Cumulative number of patients with event	141	63		

Statistical analyses

Statistical analysis title	Reparixin FAS vs placebo FAS

Statistical analysis description:

At Day 28

Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.167
Method	Gray's Test

Notes:

[4] - Estimates are calculated using a nonparametric method for cumulative incidence function with competing risks data. the cumulative incidence function was 81.6% (95% CI, 74.8 to 86.7%) in the REP group and 74.9% (95% CI, 64.0 to 83.0%) in the Placebo. Null hypothesis: the cumulative incidence functions are identical across treatment groups and estimates are calculated taking into account the following competing risks: Death, discontinuation for AEs and patient transferred to another institution.

Secondary: Proportion of patients alive and free of respiratory failure at fixed timepoints

End point title	Proportion of patients alive and free of respiratory failure at fixed timepoints

End point description:

The event variable is defined as the proportion of patients alive and free of respiratory failure at fixed timepoints. This means no need of invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) or admission to intensive care unit (ICU) linked to worsening of respiratory parameters compared to baseline. with no need of invasive mechanical ventilation or ECMO or admission to ICU linked to worsening of respiratory parameters compared to baseline.
Admissions to ICU had to be considered only in presence of significant worsening of respiratory status. This condition was objectively identified by means of a decrease of PaO2/FiO2 ratio of at least 40% from the baseline value or by a worsening of Investigator’s Interpretation.

End point type	Secondary

End point timeframe:

At days 3, 7 (± 1), 14 (± 2), 21 (± 2), 28 (± 2), 60 (±2) and 90 (±2) after randomization (randomization = day 1);

End point values	Reparixin FAS	Placebo FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	182[5]	88[6]		
Units: Patients				
Day 3	179	87		
Day 7 (+/-1)	171	79		
Day 14 (+/-2)	160	73		
Day 21 (+/-2)	155	71		
Day 28 (+/-2)	152	71		
Day 60 (+/-2)	141	66		
Day 90	15	5		

Notes:

[5] - Day 3: n=180
Day 7: n=179
Day 14: n=173
Day 21: n=172
Day 28: n=170
Day 60: n=159
D90: n=33

[6] - Day 7: n=87
Day 14: n=83
Day 21: n=83
Day 28: n=83
Day 60: n=78
Day 90: n=17

Statistical analyses

Statistical analysis title	Reparixin FAS vs placebo FAS

Statistical analysis description:

At Day 3 - please note that the number of subjects is 268 (180+88) and not 270.

Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.55 [7]
Method	Fisher exact

Notes:

[7] - Comparison between treatment arms is performed by means of a Fisher’s Exact test.

Statistical analysis title	Reparixin FAS vs placebo FAS

Statistical analysis description:

At Day 7 - Please note that the total of subjects in this analysis is not 270 but 266 (n=179 in the Reparixin group and n=87 in the placebo group).

Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.128 [8]
Method	Chi-squared

Notes:

[8] - Comparison between treatment arms is performed by means of a Chi-squared mean.

Statistical analysis title	Reparixin FAS vs placebo FAS

Statistical analysis description:

At Day 14 - Please note that the total of subjects in this analysis is not 270 but 256 (n=173 in the Reparixin group and n=83 in the placebo group).

Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.235 [9]
Method	Chi-squared

Notes:

[9] - Comparison between treatment arms is performed by means of a Chi-squared test.

Statistical analysis title	Reparixin FAS vs placebo FAS

Statistical analysis description:

At Day 21 - Please note that the total of subjects in this analysis is not 270 but 255 (n=172 in the Reparixin group and n=83 in the placebo group).

Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.281 [10]
Method	Chi-squared

Notes:

[10] - Comparison between treatment arms is performed by means of a Chi-squared test.

Statistical analysis title	Reparixin FAS vs placebo FAS

Statistical analysis description:

At Day 28 - Please note that the total of subjects in this analysis is not 270 but 253 (n=170 in the Reparixin group and n=83 in the placebo group).

Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.371 [11]
Method	Chi-squared

Notes:

[11] - Comparison between treatment arms is performed by means of a Chi-squared test.

Statistical analysis title	Reparixin FAS vs placebo FAS

Statistical analysis description:

At Day 60 - Please note that the total of subjects in this analysis is not 270 but 237 (n=159 in the Reparixin group and n=78 in the placebo group.

Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.377 [12]
Method	Chi-squared

Notes:

[12] - Comparison between treatment arms is performed by means of a Chi-squared test.

Statistical analysis title	Reparixin FAS vs placebo FAS

Statistical analysis description:

At Day 90 - Please note that the total of subjects in this analysis is not 270 but 50 (n=33 in the Reparixin group and n=17 in the placebo group).

Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.273 [13]
Method	Chi-squared

Notes:

[13] - Comparison between treatment arms is performed by means of a Chi-squared test.

Secondary: Mean changes from baseline in clinical severity score based on the 7-point WHO-OS at fixed timepoints

End point title	Mean changes from baseline in clinical severity score based on the 7-point WHO-OS at fixed timepoints

End point description:

Changes from baseline in clinical severity score are analyzed based on the 7-point WHO-OS. The 7-point WHO Ordinal Scale of clinical improvement (WHO-OS), comprises the following categories: 1: not hospitalized, with resumption of normal activities; 2: not hospitalized, but unable to resume normal activities; 3: hospitalized, not requiring supplemental oxygen; 4: hospitalized, requiring supplemental oxygen; 5: hospitalized, requiring high-flow oxygen therapy, non-invasive mechanical ventilation, or both; 6: hospitalized, requiring ECMO, invasive mechanical ventilation, or both; 7: death.

End point type	Secondary

End point timeframe:

At days 3, 7, 14, 21, 28 and EoT; days 60 and 90; at hospital discharge (HD), and at the EoS.

End point values	Reparixin FAS	Placebo FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	182[14]	88[15]		
Units: score on a scale				
arithmetic mean (standard deviation)				
Day 3	-0.1 (± 0.4)	0.0 (± 0.5)		
Day 7	-0.4 (± 1.0)	-0.3 (± 0.9)		
Day 14	-1.7 (± 1.5)	-1.5 (± 1.6)		
Day 21	-2.4 (± 1.5)	-2.3 (± 1.6)		
Day 28	-2.8 (± 1.4)	-2.6 (± 1.5)		
EoT	-0.9 (± 1.0)	-0.7 (± 1.1)		
Day 60	-3.4 (± 0.6)	-3.2 (± 0.9)		
Day 90	-3.4 (± 0.6)	-3.5 (± 0.6)		
Hospital discharge	-1.6 (± 0.9)	-1.6 (± 0.8)		
EoS	-3.0 (± 1.5)	-2.6 (± 1.8)		

Notes:

[14] - D3:n=171
D7:n=166
D14:n=142

D21:n=121
EoT:n=164
D28:n=131
HD: n=134
D60:136
D90:14
EoS:154
[15] - D3:n=84
D7:n=80
D14:n=67
D21:n=55
EoT:n=77
D28:n=59
HD=n=61
D60:n=65
D90:n=4
EOS:n=75

Statistical analyses

Statistical analysis title	Reparixin FAS vs placebo FAS
Statistical analysis description:	
At Day 3 - Please note that the number of subjects in this analysis is not 270 but 255	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.047 [16]
Method	Wilcoxon (Mann-Whitney)

Notes:
[16] - Comparison between treatment arms is performed by means of two-sample Mann-Whitney U test.

Statistical analysis title	Reparixin FAS vs placebo FAS
Statistical analysis description:	
At Day 7 - Please note that the number of subjects in this analysis is not 270 but 246	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.262 [17]
Method	Wilcoxon (Mann-Whitney)

Notes:
[17] - Comparison between treatment arms is performed by means of two-sample Mann-Whitney U test.

Statistical analysis title	Reparixin FAS vs placebo FAS
Statistical analysis description:	
At Day 14 - Please note that the number of subjects in this analysis is not 270 but 209	
Comparison groups	Reparixin FAS v Placebo FAS

Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.367 [18]
Method	Wilcoxon (Mann-Whitney)

Notes:

[18] - Comparison between treatment arms is performed by means of two-sample Mann-Whitney U test.

Statistical analysis title	Reparixin FAS vs placebo FAS

Statistical analysis description:

At Day 21 - Please note that the number of subjects in this analysis is not 270 but 176

Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.882 [19]
Method	Wilcoxon (Mann-Whitney)

Notes:

[19] - Comparison between treatment arms is performed by means of two-sample Mann-Whitney U test.

Statistical analysis title	Reparixin FAS vs placebo FAS

Statistical analysis description:

At Day 28 - Please note that the number of subjects in this analysis is not 270 but 190

Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19 [20]
Method	Wilcoxon (Mann-Whitney)

Notes:

[20] - Comparison between treatment arms is performed by means of two-sample Mann-Whitney U test.

Statistical analysis title	Reparixin FAS vs placebo FAS

Statistical analysis description:

At Day 60 - Please note that the number of subjects in this analysis is not 270 but 201

Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.161 [21]
Method	Wilcoxon (Mann-Whitney)

Notes:

[21] - Comparison between treatment arms is performed by means of two-sample Mann-Whitney U test.

Statistical analysis title	Reparixin FAS vs placebo FAS

Statistical analysis description:

At Day 90 - Please note that the number of subjects in this analysis is not 270 but 18

Comparison groups	Reparixin FAS v Placebo FAS

Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.853 [22]
Method	Wilcoxon (Mann-Whitney)

Notes:

[22] - Comparison between treatment arms is performed by means of two-sample Mann-Whitney U test.

Statistical analysis title	Reparixin FAS vs placebo FAS

Statistical analysis description:

At EOS - Please note that the number of subjects in this analysis is not 270 but 229

Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.068 [23]
Method	Wilcoxon (Mann-Whitney)

Notes:

[23] - Comparison between treatment arms is performed by means of two-sample Mann-Whitney U test.

Statistical analysis title	Reparixin FAS vs placebo FAS

Statistical analysis description:

At hospital discharge (HD) - Please note that the number of subjects in this analysis is not 270 but 195

Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.672 [24]
Method	Wilcoxon (Mann-Whitney)

Notes:

[24] - Comparison between treatment arms is performed by means of two-sample Mann-Whitney U test.

Statistical analysis title	Reparixin FAS vs placebo FAS

Statistical analysis description:

At end of treatment (EoT) - Please note that the number of subjects in this analysis is not 270 but 241

Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.153 [25]
Method	Wilcoxon (Mann-Whitney)

Notes:

[25] - Comparison between treatment arms is performed by means of two-sample Mann-Whitney U test.

Secondary: Time to clinical improvement 1 up to Day 28

End point title	Time to clinical improvement 1 up to Day 28

End point description:

Time to clinical improvement 1 is defined as the decline of 1 category in the 7-point WHO-OS) up to Day 28. Time to clinical improvement 1 up to Day 28 was analyzed as described for time to recovery: an event was considered as such, if patient declined of at least 1 category in the 7-point WHO-OS respect

to the baseline, otherwise it was be considered free of event.

End point type	Secondary

End point timeframe:

Day 1 (baseline), Days 3, 7, 14, 21, EoT, 28, HD.

End point values	Reparixin FAS	Placebo FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	182	88		
Units: number of patients with event				
Day 1	0	0		
Day3	19	6		
Day 7	56	22		
Day 14	123	50		
Day 21	146	66		
Day 28	152	68		

Statistical analyses

Statistical analysis title	Reparixin FAS vs placebo FAS

Statistical analysis description:

At day 28

Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority[26]
P-value	= 0.07
Method	Gray's Test

Notes:

[26] - Estimates are calculated using a nonparametric method for cumulative incidence function with competing risks data. The null hypothesis is that the cumulative incidence functions are identical across treatment groups and estimates are calculated taking into consideration the following competing risks: Death, reasons for discontinuation for Adverse events and patient transferred to another institution.

Secondary: Time to clinical improvement 2 up to Day 28

End point title	Time to clinical improvement 2 up to Day 28

End point description:

Time to clinical improvement 2 is defined as the decline of 2 categories in the 7-point WHO-OS) up to Day 28. Time to clinical improvement 2 up to Day 28 was analyzed as described for time to recovery. An event was considered as such, if patient declined of at least 2 categories in the 7-point WHO-OS respect to the baseline, otherwise it was considered free of event.

End point type	Secondary

End point timeframe:

Day 1 (baseline), Days 3, 7, 14, 21, 28

End point values	Reparixin FAS	Placebo FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	182	88		
Units: number of patients with event				
Day 1	0	0		
Day 3	0	0		
Day 7	19	6		
Day 14	78	35		
Day 21	105	50		
Day 28	120	56		

Statistical analyses

Statistical analysis title	Reparixin FAS vs placebo FAS
Statistical analysis description:	
At day 28	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	= 0.668
Method	Gray's Test

Notes:

[27] - Estimates are calculated using a nonparametric method for cumulative incidence function with competing risks data. The null hypothesis is that the cumulative incidence functions are identical across treatment groups and estimates are calculated taking into consideration the following competing risks: Reasons for discontinuation for Adverse events and patient transferred to another institution.

Secondary: Time to discharge from hospital up to Day 28

End point title	Time to discharge from hospital up to Day 28
End point description:	
Time to discharge from hospital up to Day 28 is analyzed as described for time to recovery.	
End point type	Secondary
End point timeframe:	
Day 1 (baseline), Days 3, 7, 14, 21, 28	

End point values	Reparixin FAS	Placebo FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	182	88		
Units: number of patients with event				
Day 1	0	0		
Day 3	2	0		
Day 7	19	10		
Day 14	100	40		
Day 21	127	58		
Day 28	143	64		

Statistical analyses

Statistical analysis title	Reparixin FAS vs placebo FAS

Statistical analysis description:

At Day 28

Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	= 0.23
Method	Gray's Test

Notes:

[28] - Estimates are calculated using a nonparametric method for cumulative incidence function with competing risks data. The null hypothesis is that the cumulative incidence functions are identical across treatment groups and estimates are calculated taking into consideration the following competing risks: Reasons for discontinuation for Adverse events and patient transferred to another institution.

Secondary: Clinical status at fixed time points either in hospital or at home (7-point WHO-OS)

End point title	Clinical status at fixed time points either in hospital or at home (7-point WHO-OS)

End point description:

Clinical status is analyzed based on the 7-point WHO-OS. The 7-point WHO Ordinal Scale of clinical improvement (WHO-OS), comprises the following categories: 1: not hospitalized, with resumption of normal activities; 2: not hospitalized, but unable to resume normal activities; 3: hospitalized, not requiring supplemental oxygen; 4: hospitalized, requiring supplemental oxygen; 5: hospitalized, requiring high-flow oxygen therapy, non-invasive mechanical ventilation, or both; 6: hospitalized, requiring ECMO, invasive mechanical ventilation, or both; 7: death.

End point type	Secondary

End point timeframe:

Days 3, 7(+/-1), 14(+/-2), 21(+/-2), 28(+/-2), 60 (+/-2), 90 (+/- 7), EOS. Hospital discharge and End of Treatment (EoT) data are attached.

End point values	Reparixin FAS	Placebo FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	182[29]	88[30]		
Units: number of patients with event				
day 3 score 1	0	0		
day 3 score 2	0	0		
day 3 score 3	5	1		
day 3 score 4	85	40		
day 3 score 5	81	42		
day 3 score 6	0	0		
day 3 score 7	0	1		
day 7 score 1	7	2		

day 7 score 2	1	0		
day 7 score 3	31	16		
day 7 score 4	66	27		
day 7 score 5	54	30		
day 7 score 6	6	5		
day 7 score 7	1	0		
day 14 score 1	52	24		
day 14 score 2	10	3		
day 14 score 3	28	12		
day 14 score 4	29	13		
day 14 score 5	17	10		
day 14 score 6	4	4		
day 14 score 7	2	1		
day 21 score 1	74	36		
day 21 score 2	8	2		
day 21 score 3	13	5		
day 21 score 4	14	5		
day 21 score 5	6	5		
day 21 score 6	5	0		
day 21 score 7	1	2		
day 28 score 1	100	40		
day 28 score 2	8	8		
day 28 score 3	7	1		
day 28 score 4	8	5		
day 28 score 5	2	2		
day 28 score 6	4	2		
day 28 score 7	2	1		
Day 60 score 1	125	56		
Day 60 score 2	9	6		
Day 60 score 3	1	0		
Day 60 score 4	0	1		
Day 60 score 5	1	2		
Day 60 score 6	0	0		
Day 60 score 7	0	0		
Day 90 score 1	14	4		
Day 90 score 2	0	0		
Day 90 score 3	0	0		
Day 90 score 4	0	0		
Day 90 score 5	0	0		
Day 90 score 6	0	0		
Day 90 score 7	0	0		
EOS score 1	132	57		
EOS score 2	7	6		
EOS score 3	1	0		
EOS score 4	2	1		
EOS score 5	3	4		
EOS score 6	1	2		
EOS score 7	8	5		

Notes:

[29] - D3:n=171
D7: n=166
D14:n=142
D21:n=121

D28:131
EoT:164
HD:134
D60:136
D90:n=14
EOS:n=154
[30] - D3: n=84
D7: n=80
D14:n=67
D21:n=55
D28:n=59
HD:n=61
EoT:n=77
D60:n=65
D90:n=4
EoS:n=75

Attachments (see zip file)	Hospital discharge and EoT data/Hospital discharge and EoT

Statistical analyses

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: day 3 - please note that the number of subjects in this analysis is not 270 but 255	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.444
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: day 7 - please note that the number of subjects in this analysis is not 270 but 246	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.357
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: day 14 - please note that the number of subjects in this analysis is not 270 but 209	
Comparison groups	Reparixin FAS v Placebo FAS

Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.484
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: day 21 - please note that the number of subjects in this analysis is not 270 but 176	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.753
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: day 28 - please note that the number of subjects in this analysis is not 270 but 190	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.26
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: day 60 - please note that the number of subjects in this analysis is not 270 but 201	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: day 90 - please note that the number of subjects in this analysis is not 270 but 18	
Comparison groups	Reparixin FAS v Placebo FAS

Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description:	
EOS - please note that the number of subjects in this analysis is not 270 but 229	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.074
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description:	
EOT - please note that the number of subjects in this analysis is not 270 but 241	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.193
Method	two-sample Mann-Whitney U test

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description:	
Hospital discharge - please note that the number of subjects in this analysis is not 270 but 195	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.131
Method	two-sample Mann-Whitney U test

Secondary: Dyspnea severity (Likert scale) at fixed timepoints

End point title	Dyspnea severity (Likert scale) at fixed timepoints

End point description:

The number of patients with Dyspnea severity Likert scale by score and treatment group is calculated for each time point.

Likert scale: grading the current experience of breathing discomfort compared to baseline (randomization) status (from -3 to 3).
-1 = minimally worse,
-2 = moderately worse,
-3 = markedly worse
0 = no change,
1 = minimally better,
2 = moderately better,
3 = markedly better,
.
Please note for the EoS timepoint, the statistical comparison IMP vs placebo was not reported because the p value is not available and the system doesn't permit to enter "NA" expression.

End point type	Secondary

End point timeframe:

Days 3, 7(+/-1), 14(+/-2), 21(+/-2), 28(+/-2), EOS, 60(+/-2). EoT and hospital discharge data are attached.

End point values	Reparixin FAS	Placebo FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	182[31]	88[32]		
Units: Number of patient with event				
day 3 score -3	1	0		
day 3 score -2	1	3		
day 3 score -1	5	1		
day 3 score 0	22	10		
day 3 score 1	37	18		
day 3 score 2	26	17		
day 3 score 3	11	3		
day 7 score -3	1	0		
day 7 score -2	0	1		
day 7 score -1	0	1		
day 7 score 0	9	6		
day 7 score 1	19	8		
day 7 score 2	31	13		
day 7 score 3	36	18		
day 14 score -3	0	0		
day 14 score -2	2	0		
day 14 score -1	0	0		
day 14 score 0	9	1		
day 14 score 1	6	6		
day 14 score 2	18	7		
day 14 score 3	41	25		
day 21 score -3	1	0		
day 21 score -2	0	0		
day 21 score -1	0	0		
day 21 score 0	6	3		
day 21 score 1	9	2		
day 21 score 2	9	7		
day 21 score 3	35	20		
day 28 score -3	0	0		
day 28 score -2	0	0		

day 28 score -1	0	0		
day 28 score 0	9	3		
day 28 score 1	7	3		
day 28 score 2	9	7		
day 28 score 3	48	20		
EOS score -3	0	0		
EOS score -2	0	0		
EOS score -1	0	0		
EOS score 0	1	0		
EOS score 1	1	0		
EOS score 2	0	0		
EOS score 3	0	0		

Notes:

[31] - D3: n= 103
D7: n= 96
D14: n= 76
D21: n=60
28: n= 73
EoT: n=77
HD: n=38
EOS: n= 2

[32] - Day3: n=52
D7: n=47
D14: n=39
D21: n=32
D28: n=33
EoT: n=38
HD:n=27
EOS:N=0

Attachments (see zip file)	HD & EoT dyspnea severity (likert scale)/Hospital discharge

Statistical analyses

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description:	
at day 3 - Please note that the number of subjects in this analysis is not 270 but 155.	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.997
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description:	
at day 7 - Please note that the number of subjects in this analysis is not 270 but 143.	
Comparison groups	Reparixin FAS v Placebo FAS

Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.712
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: at day 14 - Please note that the number of subjects in this analysis is not 270 but 115.	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.241
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: at day 21 - Please note that the number of subjects in this analysis is not 270 but 92.	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.528
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: at day 28 - Please note that the number of subjects in this analysis is not 270 but 106.	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.814
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: at EOT - Please note that the number of subjects in this analysis is not 270 but 115.	
Comparison groups	Reparixin FAS v Placebo FAS

Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.242
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Reparixin FAS vs Placebo FAS

Statistical analysis description:

at hospital discharge (HD) - Please note that the number of subjects in this analysis is not 270 but 65.

Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.722
Method	Wilcoxon (Mann-Whitney)

Secondary: Change from baseline in dyspnea severity (VAS scale) at fixed timepoints

End point title	Change from baseline in dyspnea severity (VAS scale) at fixed timepoints

End point description:

The pain VAS is a unidimensional measure of pain intensity, used to record patients' pain progression, or compare pain severity between paints with similar conditions The VAS scale is from 0 to 100. The number 0 means the worst breathing the patient has ever felt and the number 100 means the best the patient has ever felt.

End point type	Secondary

End point timeframe:

Days 3, 7(+/-1), 14(+/-2), 21(+/-2), 28(+/-2). EoT and hospital discharge data are attached.

End point values	Reparixin FAS	Placebo FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	182[33]	88[34]		
Units: score on a scale				
arithmetic mean (standard deviation)				
day 3	6.4 (± 25.3)	2.2 (± 20.6)		
day 7 (+/-1)	8.3 (± 31.1)	-0.2 (± 31.1)		
day 14(+/-2)	12.7 (± 38.5)	6.6 (± 37.4)		
day 21 (+/-2)	16.0 (± 39.5)	32.5 (± 14.3)		
day 28 (+/-2)	31.1 (± 20.3)	40.7 (± 8.3)		

Notes:

[33] - Day3: n=105
Day7: n=93
Day14:n=46
Day21:n=15
Day28:n=14
EOS:n=2

EoT: n=77
HD: n=38

[34] - Day3: n=52
Day7: n=46
Day14:n=27
Day21:n=8
Day28:n=3
EoT: n=36
HD: n=20

Attachments (see zip file)	HD & EoT dyspnea VAS scale/Hospital discharge and EoT

Statistical analyses

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: at day 3 - Please note that the number of subjects in this analysis is not 270, but it is 157	
Comparison groups	Placebo FAS v Reparixin FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.399
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: at day 7 - Please note that the number of subjects in this analysis is not 270, but it is 139	
Comparison groups	Placebo FAS v Reparixin FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: at day 14 - Please note that the number of subjects in this analysis is not 270, but it is 73	
Comparison groups	Placebo FAS v Reparixin FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: at day 21 - Please note that the number of subjects in this analysis is not 270, but it is 23	
Comparison groups	Placebo FAS v Reparixin FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.517
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: at day 28 - Please note that the number of subjects in this analysis is not 270, but it is 17	
Comparison groups	Placebo FAS v Reparixin FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.445
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: at EoT - Please note that the number of subjects in this analysis is not 270, but it is 113	
Comparison groups	Placebo FAS v Reparixin FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.324
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: at Hospital discharge - Please note that the number of subjects in this analysis is not 270, but it is 67.	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.752
Method	Wilcoxon (Mann-Whitney)

Secondary: Duration of supplemental oxygen treatment up to Day 28

End point title	Duration of supplemental oxygen treatment up to Day 28

End point description:

This endpoint is expressed as:
- The number and proportion along with the 95% CI (Clopper-Pearson’s formula) of patients using supplemental oxygen treatment by treatment group;
- The Cumulative duration of supplemental oxygen treatment in days analyzed by means of descriptive statistics by treatment. This latter is reported in the system.

End point type	Secondary

End point timeframe:

From baseline up to day 28

End point values	Reparixin FAS	Placebo FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	182[35]	88[36]		
Units: day				
arithmetic mean (standard deviation)	10.5 (± 7.3)	10.8 (± 6.8)		

Notes:

[35] - The n. of patients using supplemental oxygen was 174

[36] - The n. of patients using supplemental oxygen was 81

Statistical analyses

Statistical analysis title	Reparixin FAS vs Placebo FAS

Statistical analysis description:

Please note that the number of patients in this analysis is not 270 but 255, because patients who used supplement oxygen were 174 in the Reparixin group and 81 in the placebo group.

Comparison groups	Placebo FAS v Reparixin FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.447
Method	two-sample Mann-Whitney U test

Secondary: Number of patients requiring invasive mechanical ventilation use, or ECMO up to Day 28 and up to day 60

End point title	Number of patients requiring invasive mechanical ventilation use, or ECMO up to Day 28 and up to day 60

End point description:

Invasive mechanical ventilation is defined as the delivery of positive pressure to the lungs via an endotracheal or tracheostomy tube. During mechanical ventilation, a predetermined mixture of air (ie, oxygen and other gases) is forced into the central airways and then flows into the alveoli

End point type	Secondary

End point timeframe:

Up to day 28 and Day 60

End point values	Reparixin FAS	Placebo FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	182[37]	88[38]		
Units: Number of patient with event				
Up to day 28	9	10		
Up to day 60	9	10		

Notes:

[37] - at day 28 n=163
at day 60 n= 150
[38] - at day 28 n=82
at day 60 n= 77

Statistical analyses

Statistical analysis title	Reparixin FAS vs Placebo FAS

Statistical analysis description:

At day 28 - Please note that the number of patients in this analysis is not 270 but 245, because patients requiring IMV or ECMO were 163 in the Reparixin group and 82 in the placebo group.

Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.065 [39]
Method	Chi-squared

Notes:

[39] - Comparison between treatment arms is performed by means of a Chi-squared test

Statistical analysis title	Reparixin FAS vs Placebo FAS

Statistical analysis description:

At day 60 - Please note that the number of patients in this analysis is not 270 but 18, because patients who required IMV or ECMO were 9 in the Reparixin group and 9 in the placebo group.

Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.072 [40]
Method	Chi-squared

Notes:

[40] - Comparison between treatment arms is performed by means of a Chi-squared test

Secondary: Duration of non-invasive mechanical ventilation up to Day 60

End point title	Duration of non-invasive mechanical ventilation up to Day 60

End point description:

Non-invasive ventilation (NIV) is the delivery of oxygen (ventilation support) via a face mask and therefore eliminating the need of an endotracheal airway. NIV achieves comparative physiological benefits to conventional mechanical ventilation by reducing the work of breathing and improving gas exchange.
This endpoint is expressed as:
-Number of patients with ICU admission up to Day 60 (n=66 in Reparixin and n= 32 in the placebo group), or
-Duration of ICU admission in days up to Day 60. This latter is reported in the system.

End point type	Secondary

End point timeframe:

Up to day 60

End point values	Reparixin FAS	Placebo FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	66	32		
Units: day				
arithmetic mean (standard deviation)	9.0 (± 7.9)	10.1 (± 11.0)		

Statistical analyses

Statistical analysis title	Reparixin FAS vs Placebo FAS
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.485
Method	two-sample Mann-Whitney U test

Secondary: Duration of invasive mechanical ventilation, or ECMO up to Day 60

End point title	Duration of invasive mechanical ventilation, or ECMO up to Day 60

End point description:

Invasive mechanical ventilation is defined as the delivery of positive pressure to the lungs via an endotracheal or tracheostomy tube. During mechanical ventilation, a predetermined mixture of air (ie, oxygen and other gases) is forced into the central airways and then flows into the alveoli.
This endpoint is expressed as:
-Number of patients with ICU admission up to Day 60 (n=9 in both arms), or
-Duration of ICU admission in days up to Day 60. This latter is reported in the system.

End point type	Secondary

End point timeframe:

Up to day 60

End point values	Reparixin FAS	Placebo FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	9		
Units: days				
arithmetic mean (standard deviation)	24.8 (± 16.8)	15.9 (± 13.9)		

Statistical analyses

Statistical analysis title	Reparixin FAS vs Placebo FAS
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.267
Method	two-sample Mann-Whitney U test

Secondary: Duration of ICU admission up to Day 60

End point title	Duration of ICU admission up to Day 60

End point description:

Admission to intensive care unit or ICU is linked to worsening of respiratory parameters compared to baseline. This endpoint is expressed as:
-Number of patients with ICU admission up to Day 60 (n=12 in both arms), or
-Duration of ICU admission in days up to Day 60. This latter is reported in he system.

End point type	Secondary

End point timeframe:

Up to day 60

End point values	Reparixin FAS	Placebo FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	8		
Units: day				
arithmetic mean (standard deviation)	17.9 (± 10.1)	11.4 (± 6.7)		

Statistical analyses

Statistical analysis title	Reparixin FAS vs Placebo FAS
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.137
Method	two-sample Mann-Whitney U test

Secondary: Change from baseline to fixed timepoints of partial pressure of oxygen (PaO2)

End point title	Change from baseline to fixed timepoints of partial pressure of oxygen (PaO2)

End point description:

PaO2—the oxygen pressure in arterial blood. The PaO2 reflects how well oxygen is able to move from the lungs to the blood. It is often altered by severe illnesses, with the PaO2 test results used to guide

treatment.

End point type	Secondary

End point timeframe:

at days 3, 7, 14, 21, 28, 60, HD, EoT, and EOS.
Data on timepoints hospital discharge (HD) and end of treatment (EoT) are attached.

End point values	Reparixin FAS	Placebo FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	182[41]	88[42]		
Units: mmHg				
arithmetic mean (standard deviation)				
day 3	13.377 (± 36.568)	-5.274 (± 41.103)		
day 7	3.147 (± 33.541)	12.777 (± 81.367)		
day 14	4.002 (± 54.235)	-7.257 (± 50.645)		
day 21	3.388 (± 43.520)	-14.014 (± 54.603)		
day 28	-6.700 (± 31.896)	-52.171 (± 76.278)		
EOS	1.825 (± 20.570)	51.950 (± 215.446)		
day 60	1 (± 73.000)	0 (± 0)		

Notes:

[41] - D3:n=111
D7:n=99
D14:n=48
D21:n=24
EoT:n=87
D28:n=16
HD:n=48
D60:n=1
EoS:n=4

[42] - D3:n=57
D7:n=47
D14:n=28
D21:n=14
EoT:n=44
D28:n=7
HD:n=26
D60:n=0
EoS:n=4

Attachments (see zip file)	Pao2 HD and EoT/PAo2_EoT_HD.pdf

Statistical analyses

Statistical analysis title	Reparixin FAS vs Placebo FAS

Statistical analysis description:

at day 3 - Please note that the number of subjects in this analysis is 168

Comparison groups	Reparixin FAS v Placebo FAS

Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	two-sample Mann-Whitney U test

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: at day 7 - Please note that the number of subjects in this analysis is not 168, but it is 146	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.943
Method	two-sample Mann-Whitney U test

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: at day 14 - Please note that the number of subjects in this analysis is not 168, but it is 76	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.88
Method	two-sample Mann-Whitney U test

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: at day 21 - Please note that the number of subjects in this analysis is not 168, but it is 38	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.458
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: at day 28 - Please note that the number of subjects in this analysis is not 168, but it is 23.	
Comparison groups	Reparixin FAS v Placebo FAS

Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.285
Method	two-sample Mann-Whitney U test

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: at EOS - Please note that the number of subjects in this analysis is not 168, but it is 8	
Comparison groups	Placebo FAS v Reparixin FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.885
Method	two-sample Mann-Whitney U test

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: at HD - Please note that the number of subjects in this analysis is not 270, but it is 74	
Comparison groups	Placebo FAS v Reparixin FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.583
Method	two-sample Mann-Whitney U test

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: at End of treatment - Please note that the number of subjects in this analysis is not 270, but it is 131.	
Comparison groups	Placebo FAS v Reparixin FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5
Method	two-sample Mann-Whitney U test

Secondary: Change from baseline to fixed timepoints in Pulse oximetry by measurement of peripheral arterial oxygen saturation (SpO2)

End point title	Change from baseline to fixed timepoints in Pulse oximetry by measurement of peripheral arterial oxygen saturation (SpO2)

End point description:

Peripheral oxygen saturation (SpO2) monitoring by pulse oximetry is used to estimate the oxygen saturation of arterial blood (SaO2) and provides vital information about a patient's cardiorespiratory function

End point type	Secondary

End point timeframe:

At days 3(± 1), 7 (± 1), 14 (± 2), 21 (± 2), 28 (± 2), 60(± 2), EoT, HD, EOS. Data on HD and EoT are attached.

End point values	Reparixin FAS	Placebo FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	182[43]	88[44]		
Units: Percentage				
arithmetic mean (standard deviation)				
day 3	0.79 (± 2.88)	0.36 (± 2.78)		
day 7	0.76 (± 2.89)	0.49 (± 3.38)		
day 14	0.46 (± 2.93)	-0.83 (± 3.99)		
day 21	-0.85 (± 4.92)	-5.35 (± 11.82)		
day 28	-0.99 (± 6.15)	-1.56 (± 6.78)		
EOS	-7.57 (± 11.12)	-11.01 (± 18.49)		
day 60	-2.70 (± 000)	-2.00 (± 0.00)		

Notes:

[43] - Day 3: n=166
Day 7: n=151
Day 14: n=75
Day 21: n=35
Day 28: n=22
EOS: n=7
Day 60: n=1

[44] - Day 3: n=80
Day 7: n=74
Day 14: n=43
Day 21: n=19
Day 28: n=10
EOS: n=7
Day 60: n=2

Attachments (see zip file)	SpO2.pdf

Statistical analyses

Statistical analysis title	Reparixin FAS vs Placebo FAS

Statistical analysis description:

at day 3 - Please note that the number of subjects in this analysis is not 270, but it is 246.

Comparison groups	Reparixin FAS v Placebo FAS

Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.053
Method	two-sample Mann-Whitney U test

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: at day 7 - Please note that the number of subjects in this analysis is not 270, but it is 225.	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.245
Method	two-sample Mann-Whitney U test

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: at day 14 - Please note that the number of subjects in this analysis is not 270, but it is 118.	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.067
Method	two-sample Mann-Whitney U test

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: at day 21 - Please note that the number of subjects in this analysis is not 270, but it is 54.	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.051
Method	two-sample Mann-Whitney U test

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: at day 28 - Please note that the number of subjects in this analysis is not 270, but it is 32.	
Comparison groups	Reparixin FAS v Placebo FAS

Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.684
Method	two-sample Mann-Whitney U test

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description:	
at EOS - Please note that the number of subjects in this analysis is not 246, but it is 14.	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	two-sample Mann-Whitney U test

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description:	
at Day 60 - Please note that the number of subjects in this analysis is not 246, but it is 3.	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.48
Method	two-sample Mann-Whitney U test

Secondary: Change from baseline to fixed timepoints in PaO2/FiO2 ratio

End point title	Change from baseline to fixed timepoints in PaO2/FiO2 ratio

End point description:

The PaO2/FiO2 ratio is used to determine the severity of lung injury in mechanically ventilated patients. A normal P/F Ratio is ≥ 400 and equivalent to a PaO2 ≥ 80 mmHg on room air.
Low values of the PaO2/FIO2 ratio may be due to pathological conditions, primarily those of a respiratory nature (atelectasis, ARDS, acute pulmonary edema, pneumonia, etc.), as well as to alterations in hemodynamic status (cardiogenic shock, septic shock, etc.), or even both

End point type	Secondary

End point timeframe:

At days 3(± 1), 7 (± 1), 14 (± 2), 21 (± 2), 28 (± 2), 60(± 2), EOS. Data on HD and EoT are attached.

End point values	Reparixin FAS	Placebo FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	182[45]	88[46]		
Units: mmHg				
arithmetic mean (standard deviation)				
day 3	30.329 (± 81.291)	0.398 (± 87.607)		
day 7	77.528 (± 106.383)	65.291 (± 138.832)		
day 14	127.111 (± 135.063)	111.220 (± 171.013)		
day 21	122.746 (± 114.603)	62.520 (± 163.712)		
day 28	145.043 (± 146.515)	-22.125 (± 123.435)		
EOS	-5.333 (± 89.844)	-30.714 (± 191.669)		
day 60	200.000 (± 000)	334.000 (± 53.740)		

Notes:

[45] - Day3:n=163
Day7:n=148
Day14:n=74
Day21:n=31
Day28:n=21
Day60:n=1
HD:n=96
EoT:n=140
EOS:n=6

[46] - Day 3:n=82
D7:n=73
D14:n=43
D21:n=20
D28:n=8
HD:n=48
EoT:n=66
EOS:n=7
D60:n=2

Attachments (see zip file)	PaO2:FiO2.pdf

Statistical analyses

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: day 3 - Please note that the number of subjects in this analysis is 245	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	two-sample Mann-Whitney U test

Statistical analysis title	Reparixin FAS vs Placebo FAS

Statistical analysis description:	
day 7 - Please note that the number of subjects in this analysis is not 270, but it is 221	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.283
Method	two-sample Mann-Whitney U test

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description:	
day 14 - Please note that the number of subjects in this analysis is not 245, but it is 117	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.512
Method	two-sample Mann-Whitney U test

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description:	
day 21 - Please note that the number of subjects in this analysis is not 245, but it is 51	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.174
Method	two-sample Mann-Whitney U test

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description:	
day 28 - Please note that the number of subjects in this analysis is not 245, but it is 206	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009
Method	two-sample Mann-Whitney U test

Statistical analysis title	Reparixin FAS vs Placebo FAS

Statistical analysis description:	
EOS - Please note that the number of subjects in this analysis is not 245, but it is 13	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.224
Method	two-sample Mann-Whitney U test

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description:	
day 60 - Please note that the number of subjects in this analysis is not 270, but it is 3.	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.54
Method	two-sample Mann-Whitney U test

Secondary: Change from baseline to fixed endpoints in High-Sensitivity C Reactive Protein (hs-CRP)

End point title	Change from baseline to fixed endpoints in High-Sensitivity C Reactive Protein (hs-CRP)

End point description:

The high-sensitivity C-reactive protein (hs-CRP) test is more sensitive than the standard CRP test measuring slight increases in CRP levels even when within the normal range. Because of this greater sensitivity, the hs-CRP test can help determine your risk of cardiovascular disease (CVD).

End point type	Secondary

End point timeframe:

At days 3(± 1), 7 (± 1), 14 (± 2), 21 (± 2), 28 (± 2), HD, EoT and EoS. Data on HD and EoT are attached.

End point values	Reparixin FAS	Placebo FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	182[47]	88[48]		
Units: mg/L				
arithmetic mean (standard deviation)				
day 3	-30.07 (± 23.13)	-21.67 (± 53.33)		
day 7	-25.90 (± 95.74)	-29.62 (± 37.85)		
day 14	-25.21 (± 66.53)	-45.24 (± 62.83)		
day 21	-27.50 (± 72.23)	-47.05 (± 99.48)		

day 28	-42.60 (± 30.15)	9.65 (± 26.94)		

Notes:

[47] - Day3:n=9
Day7:n=8
Day14:n=8
Day21:n=5
Day28:n=4
HD:n=5
EoT:n=7
EOS:n=0

[48] - Day3:n=6
Day7:n=5
Day14:n=5
Day21:n=4
Day28:n=2
HD:n=3
EoT:n=6
EOS:n=1

Attachments (see zip file)	protein CRP.pdf

Statistical analyses

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: day 3 - Please note that the number of subjects in this analysis is 15, not 270.	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.68
Method	two-sample Mann-Whitney U test

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: day 7 - Please note that the number of subjects in this analysis is 13, not 270.	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.272
Method	two-sample Mann-Whitney U test

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description: day 14 - Please note that the number of subjects in this analysis is 13, not 270.	
Comparison groups	Reparixin FAS v Placebo FAS

Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	two-sample Mann-Whitney U test

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description:	
day 21 - Please note that the number of subjects in this analysis is 9, not 270.	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.903
Method	two-sample Mann-Whitney U test

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description:	
day 28 - Please note that the number of subjects in this analysis is 6, not 270.	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.105
Method	two-sample Mann-Whitney U test

Secondary: Mortality rates up to Day 60 and Day 90	
End point title	Mortality rates up to Day 60 and Day 90
End point description:	
Mortality rate, or death rate, is a measure of the number of deaths (in general, or due to a specific cause) in a particular population, scaled to the size of that population, per unit of time. The death event variable is defined as the proportion of patients died up to Day 60 and Day 90.	
End point type	Secondary
End point timeframe:	
up to day 60 (+/-2), up to day 90	

End point values	Reparixin FAS	Placebo FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	182[49]	88[50]		
Units: Patients died				
up to day 60	11	7		
up to day 90	11	7		

Notes:

[49] - Day 60: n=156
Day 90: n=27
[50] - Day 60: n=76
Day 90: n=12

Statistical analyses

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description:	
up to day 60 - Please note that the number of subjects in this analysis is 232, not 270.	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.232 [51]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.178
upper limit	1.522

Notes:

[51] - Analysis is based on logistic regression model with proportion of patients died up to Day 60 as dependent variable, treatment, age group, gender and presence of concomitant disease at baseline as qualitative independent variables. Site is considered

Statistical analysis title	Reparixin FAS vs Placebo FAS
Statistical analysis description:	
up to day 90 - Please note that the number of subjects in this analysis is 39, not 270.	
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.158 [52]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.246
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.034
upper limit	1.782

Notes:

[52] - Analysis is based on logistic regression model with proportion of patients died up to Day 90 as dependent variable, treatment, age group, gender and presence of concomitant disease at baseline as qualitative independent variables. Site is considered

Secondary: Freedom from (time to) death or respiratory failure up to Day 90

End point title	Freedom from (time to) death or respiratory failure up to Day 90

End point description:

Freedom from (time to) death or respiratory failure (need of invasive mechanical ventilation or ECMO or admission to ICU linked to worsening of respiratory parameters compared to baseline) at baseline, day 3, day 7, day 14, day 21, day 28, day 60, day 90 was performed using the same Kaplan-Meier analysis and the one-sided log-rank test that were used to test for differences between groups.

End point type	Secondary

End point timeframe:

at baseline, day 3, day 7, day 14, day 21, day 28, day 60, day 90

End point values	Reparixin FAS	Placebo FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	182	88		
Units: number of patient with event				
day 1	0	0		
day 3	2	1		
day 7	4	2		
day 14	9	5		
day 21	11	5		
day 28	16	6		
day 60	103	49		
day 90	154	72		

Statistical analyses

Statistical analysis title	Reparixin FAS vs Placebo FAS

Statistical analysis description:

Up to day 90 -

Comparison groups	Placebo FAS v Reparixin FAS
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	superiority[53]
P-value	= 0.33607
Method	Logrank

Notes:

[53] - Freedom from (time to) death or respiratory failure (need of invasive mechanical ventilation or ECMO or admission to ICU linked to worsening of respiratory parameters compared to baseline) up to Day 90 was performed using the same Kaplan-Meier analysis and the one-sided log-rank test that were used to test for differences between groups

Secondary: Time to clinical improvement 1 up to Day 28 (cumulative incidence function)

End point title	Time to clinical improvement 1 up to Day 28 (cumulative incidence function)

End point description:

Estimates are calculated using a nonparametric method for cumulative incidence function with competing risks data.

End point type	Secondary

End point timeframe:

At day 28

End point values	Reparixin FAS	Placebo FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	10		
Units: percent				
number (confidence interval 95%)	87.2 (81.2 to 91.4)	81.1 (70.6 to 88.2)		

Statistical analyses

Statistical analysis title	Reparixin vs placebo
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07
Method	Gray's test

Secondary: Time to clinical improvement 2 up to Day 28 (cumulative incidence function)

End point title	Time to clinical improvement 2 up to Day 28 (cumulative incidence function)

End point description:

Estimates are calculated using a nonparametric method for cumulative incidence function with competing risks data.

End point type	Secondary

End point timeframe:

At Day 28

End point values	Reparixin FAS	Placebo FAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	39	20		
Units: percent				
number (confidence interval 95%)	69.9 (62.3 to 76.2)	67.7 (56.3 to 76.7)		

Statistical analyses

Statistical analysis title	Reparixin vs placebo
Comparison groups	Reparixin FAS v Placebo FAS
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.668
Method	Gray's test

Other pre-specified: Number of subjects who exhibited at least 1 TEAE, at least 1 severe TEAE, at least 1 serious TEAE, at least 1 non-serious TEAE, at least 1 ADR, at least 1 serious ADR, at least 1 TEAE leading to discontinuation of IMP, etc

End point title	Number of subjects who exhibited at least 1 TEAE, at least 1 severe TEAE, at least 1 serious TEAE, at least 1 non-serious TEAE, at least 1 ADR, at least 1 serious ADR, at least 1 TEAE leading to discontinuation of IMP, etc

End point description:

AE= An adverse event is any untoward or unfavorable medical occurrence in a human. subject, including any abnormal sign (for example, abnormal physical exam or. laboratory finding), symptom, or disease, temporally associated with the subject's.
serious AE=a SAE iA serious adverse event (SAE) in human drug trials is defined as any untoward medical occurrence that at any dose
results in death
Is life-threatening
Requires inpatient hospitalization or causes prolongation of existing hospitalization
Results in persistent or significant disability/incapacity
May have caused a congenital anomaly/birth defect
Requires intervention to prevent permanent impairment or damage. The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Do note that starting from this point the safety endpoint is analysed.

End point type	Other pre-specified

End point timeframe:

Throughout the study, till Day 90 (= end of the follow-up period).

End point values	Reparixin (randomised and treated)	Placebo (randomised and treated)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182	88		
Units: number of subjects				
Number of Subjects with at least one TEAE	83	48		
Number of Subjects with at least one serious TEAE	20	13		
Number of Subjects with at least one severe TEAE	16	12		
N. sub with at least 1TEAE leading to quit IMP	19	11		
N. sub with at least 1TEAE leading to quit the stu	1	0		
Number of Subjects with TEAEs leading to death	10	7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline up to day 90 of the trial (=the end of the follow-up period).

Adverse event reporting additional description:

In the system AEs are reported for the overall period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Reparixin SAF

Reporting group description:

The Safety set (SAF) consisted of all randomized subjects who received at least one dose of the IMP. The SAF population was analyzed according to the actual treatment received and was used to present results on safety data.

Reporting group title	Placebo SAF

Reporting group description:

The Safety set (SAF) consisted of all randomized subjects who received at least one dose of the placebo. The SAF population was analyzed according to the actual treatment received and was used to present results on safety data.

Serious adverse events	Reparixin SAF	Placebo SAF	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 182 (10.99%)	13 / 88 (14.77%)	
number of deaths (all causes)	11	7	
number of deaths resulting from adverse events	10	7	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 182 (0.55%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Thrombosis			
subjects affected / exposed	0 / 182 (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	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			

subjects affected / exposed	0 / 182 (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	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	11 / 182 (6.04%)	7 / 88 (7.95%)	
occurrences causally related to treatment / all	0 / 11	0 / 7	
deaths causally related to treatment / all	0 / 8	0 / 4	
Acute respiratory failure			
subjects affected / exposed	1 / 182 (0.55%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	0 / 182 (0.00%)	2 / 88 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychotic disorder			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis			

subjects affected / exposed	1 / 182 (0.55%)	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			
Sepsis			
subjects affected / exposed	2 / 182 (1.10%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	2 / 182 (1.10%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 182 (0.55%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	0 / 182 (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	
Bacterial sepsis			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.5 %

Non-serious adverse events	Reparixin SAF	Placebo SAF	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	75 / 182 (41.21%)	42 / 88 (47.73%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 182 (1.10%)	2 / 88 (2.27%)	
occurrences (all)	2	2	
Hypotension			

subjects affected / exposed	2 / 182 (1.10%)	1 / 88 (1.14%)	
occurrences (all)	2	1	
Poor venous access			
subjects affected / exposed	1 / 182 (0.55%)	1 / 88 (1.14%)	
occurrences (all)	1	1	
Thrombophlebitis			
subjects affected / exposed	2 / 182 (1.10%)	0 / 88 (0.00%)	
occurrences (all)	2	0	
Surgical and medical procedures			
Tracheostomy			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Illness			
subjects affected / exposed	3 / 182 (1.65%)	1 / 88 (1.14%)	
occurrences (all)	4	1	
Oedema peripheral			
subjects affected / exposed	0 / 182 (0.00%)	3 / 88 (3.41%)	
occurrences (all)	0	4	
Pyrexia			
subjects affected / exposed	3 / 182 (1.65%)	0 / 88 (0.00%)	
occurrences (all)	3	0	
Asthenia			
subjects affected / exposed	1 / 182 (0.55%)	1 / 88 (1.14%)	
occurrences (all)	1	1	
Extravasation			
subjects affected / exposed	1 / 182 (0.55%)	1 / 88 (1.14%)	
occurrences (all)	1	1	
Pain			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 182 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	
Metrorrhagia			

subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 182 (0.55%)	2 / 88 (2.27%)	
occurrences (all)	1	2	
Pulmonary embolism			
subjects affected / exposed	2 / 182 (1.10%)	1 / 88 (1.14%)	
occurrences (all)	2	1	
Epistaxis			
subjects affected / exposed	2 / 182 (1.10%)	2 / 88 (2.27%)	
occurrences (all)	3	2	
Dyspnoea			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Productive cough			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Tachypnoea			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 182 (3.30%)	4 / 88 (4.55%)	
occurrences (all)	7	4	
Anxiety			
subjects affected / exposed	5 / 182 (2.75%)	4 / 88 (4.55%)	
occurrences (all)	5	4	
Agitation			
subjects affected / exposed	3 / 182 (1.65%)	1 / 88 (1.14%)	
occurrences (all)	3	1	
Mood altered			
subjects affected / exposed	3 / 182 (1.65%)	0 / 88 (0.00%)	
occurrences (all)	5	0	
Delirium			

subjects affected / exposed	1 / 182 (0.55%)	1 / 88 (1.14%)	
occurrences (all)	1	1	
Confusional state			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Hallucination			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Panic attack			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Persistent depressive disorder			
subjects affected / exposed	0 / 182 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 182 (0.55%)	2 / 88 (2.27%)	
occurrences (all)	1	2	
Transaminases increased			
subjects affected / exposed	2 / 182 (1.10%)	1 / 88 (1.14%)	
occurrences (all)	2	1	
Blood culture positive			
subjects affected / exposed	2 / 182 (1.10%)	0 / 88 (0.00%)	
occurrences (all)	2	0	
Platelet count increased			
subjects affected / exposed	1 / 182 (0.55%)	1 / 88 (1.14%)	
occurrences (all)	1	1	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Culture urine positive			

subjects affected / exposed	0 / 182 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 182 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	
Vitamin D decreased			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 182 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	4 / 182 (2.20%)	3 / 88 (3.41%)	
occurrences (all)	5	3	
Atrial fibrillation			
subjects affected / exposed	4 / 182 (2.20%)	1 / 88 (1.14%)	
occurrences (all)	4	1	
Bradycardia			
subjects affected / exposed	3 / 182 (1.65%)	0 / 88 (0.00%)	
occurrences (all)	3	0	
Left ventricular failure			
subjects affected / exposed	0 / 182 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	
Sinus tachycardia			
subjects affected / exposed	0 / 182 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	
Supraventricular tachycardia			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			

Headache			
subjects affected / exposed	1 / 182 (0.55%)	2 / 88 (2.27%)	
occurrences (all)	5	2	
Dizziness			
subjects affected / exposed	2 / 182 (1.10%)	0 / 88 (0.00%)	
occurrences (all)	2	0	
Paraesthesia			
subjects affected / exposed	1 / 182 (0.55%)	1 / 88 (1.14%)	
occurrences (all)	1	1	
Disturbance in attention			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Memory impairment			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Psychomotor hyperactivity			
subjects affected / exposed	0 / 182 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	
Syncope			
subjects affected / exposed	0 / 182 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 182 (1.10%)	0 / 88 (0.00%)	
occurrences (all)	3	0	
Thrombocytopenia			
subjects affected / exposed	2 / 182 (1.10%)	0 / 88 (0.00%)	
occurrences (all)	2	0	
Iron deficiency anaemia			
subjects affected / exposed	0 / 182 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	
Leukopenia			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	2	0	
Neutrophilia			

subjects affected / exposed	0 / 182 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	
Pancytopenia			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Visual impairment			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	13 / 182 (7.14%)	10 / 88 (11.36%)	
occurrences (all)	14	10	
Abdominal pain upper			
subjects affected / exposed	2 / 182 (1.10%)	1 / 88 (1.14%)	
occurrences (all)	2	1	
Diarrhoea			
subjects affected / exposed	1 / 182 (0.55%)	1 / 88 (1.14%)	
occurrences (all)	1	1	
Dysphagia			
subjects affected / exposed	1 / 182 (0.55%)	1 / 88 (1.14%)	
occurrences (all)	1	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 182 (1.10%)	0 / 88 (0.00%)	
occurrences (all)	2	0	
Vomiting			
subjects affected / exposed	1 / 182 (0.55%)	1 / 88 (1.14%)	
occurrences (all)	1	1	
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			

Hypertransaminasaemia			
subjects affected / exposed	3 / 182 (1.65%)	2 / 88 (2.27%)	
occurrences (all)	3	2	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 182 (0.55%)	1 / 88 (1.14%)	
occurrences (all)	1	1	
Decubitus ulcer			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Hyperhidrosis			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Rash macular			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Skin lesion			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Oliguria			
subjects affected / exposed	3 / 182 (1.65%)	2 / 88 (2.27%)	
occurrences (all)	3	2	
Acute kidney injury			
subjects affected / exposed	2 / 182 (1.10%)	1 / 88 (1.14%)	
occurrences (all)	2	1	
Endocrine disorders			
Hyperparathyroidism secondary			
subjects affected / exposed	2 / 182 (1.10%)	0 / 88 (0.00%)	
occurrences (all)	2	0	
Euthyroid sick syndrome			
subjects affected / exposed	0 / 182 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	
Hypothyroidism			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue			

disorders			
Back pain			
subjects affected / exposed	1 / 182 (0.55%)	1 / 88 (1.14%)	
occurrences (all)	1	1	
Pain in extremity			
subjects affected / exposed	1 / 182 (0.55%)	1 / 88 (1.14%)	
occurrences (all)	1	1	
Myalgia			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	3 / 182 (1.65%)	6 / 88 (6.82%)	
occurrences (all)	3	6	
Pneumonia bacterial			
subjects affected / exposed	4 / 182 (2.20%)	2 / 88 (2.27%)	
occurrences (all)	4	2	
Sepsis			
subjects affected / exposed	1 / 182 (0.55%)	4 / 88 (4.55%)	
occurrences (all)	1	4	
Clostridium difficile infection			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Oral candidiasis			
subjects affected / exposed	1 / 182 (0.55%)	2 / 88 (2.27%)	
occurrences (all)	1	2	
Bacterial sepsis			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Klebsiella infection			
subjects affected / exposed	2 / 182 (1.10%)	0 / 88 (0.00%)	
occurrences (all)	2	0	
Pneumonia			

subjects affected / exposed	2 / 182 (1.10%)	0 / 88 (0.00%)	
occurrences (all)	2	0	
Lower respiratory tract infection fungal			
subjects affected / exposed	1 / 182 (0.55%)	1 / 88 (1.14%)	
occurrences (all)	1	1	
Acquired immunodeficiency syndrome			
subjects affected / exposed	0 / 182 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	
Anal infection			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Bacteraemia			
subjects affected / exposed	0 / 182 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	
Bronchitis			
subjects affected / exposed	0 / 182 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	
Candida infection			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Cytomegalovirus syndrome			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Escherichia infection			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Fungal infection			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Hepatitis B			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Lower respiratory tract infection bacterial			

subjects affected / exposed	0 / 182 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	
Moraxella infection			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Oral fungal infection			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Phlebitis infective			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Staphylococcal infection			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	4 / 182 (2.20%)	1 / 88 (1.14%)	
occurrences (all)	4	1	
Hyperkalaemia			
subjects affected / exposed	2 / 182 (1.10%)	2 / 88 (2.27%)	
occurrences (all)	2	2	
Hypokalaemia			
subjects affected / exposed	3 / 182 (1.65%)	1 / 88 (1.14%)	
occurrences (all)	3	1	
Vitamin D deficiency			
subjects affected / exposed	1 / 182 (0.55%)	3 / 88 (3.41%)	
occurrences (all)	1	3	
Hypocalcaemia			
subjects affected / exposed	2 / 182 (1.10%)	1 / 88 (1.14%)	
occurrences (all)	2	1	
Eating disorder			
subjects affected / exposed	2 / 182 (1.10%)	0 / 88 (0.00%)	
occurrences (all)	2	0	
Dehydration			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	

Folate deficiency			
subjects affected / exposed	0 / 182 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Hypertriglyceridaemia			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Hyponatraemia			
subjects affected / exposed	1 / 182 (0.55%)	0 / 88 (0.00%)	
occurrences (all)	1	0	
Steroid diabetes			
subjects affected / exposed	0 / 182 (0.00%)	1 / 88 (1.14%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 January 2021	Protocol amendment No. 1 - The number of participating sites was increased; - Minor typographic errors were amended
14 April 2021	Protocol amendment No. 2 - According to comments received from the US FDA, the recently issued guidelines and the current updated knowledge of COVID-19 pandemic, the primary endpoint, the key secondary endpoints and (in a lesser extent) the exploratory endpoints were modified. In particular, the primary endpoint was no more defined as 'time to event' but as "the proportion of patients alive and free of respiratory failure" at a predefined time-point. - The use of a rescue therapy has been removed from secondary endpoints. - Further time-points (e.g. Day 60 and/or Day 90) were added for secondary endpoints and a safety follow-up at day 90 was added. - The sample size was recalculated, methods of analysis of the primary endpoint were changed and timelines for the interim analysis were updated based on the change of the primary endpoint. - Further specifications on contraceptive measures were added. - A clarification on the possibility of a follow-up in case of IMP discontinuation was added. - The determination of Reparixin levels was limited to sites in the US (however not performed). - Role and functions of the DMC were updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

No limitations and caveats are applicable to this summary of results.

Notes: