Clinical trial results:
Adaptive phase 2/3, randomized, controlled multicenter study on the efficacy and safety of Reparixin in the treatment of hospitalized patients with COVID-19 pneumonia

Summary

EudraCT number	2020-001645-40
Trial protocol	IT
Global end of trial date	02 February 2021

Results information

Result version number	v1 (current)
This version publication date	22 May 2022
First version publication date	22 May 2022

Trial information

Trial identification

Sponsor protocol code	REPAVID-19

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04794803
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 February 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 November 2020
Global end of trial reached?	Yes
Global end of trial date	02 February 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective of the Phase 2 study was to assess the efficacy and safety of Reparixin treatment as compared to the control arm (standard of care) in adult patients with severe COVID-19 pneumonia. The objective of the Phase 3 part of the study was to assess the efficacy and safety of Reparixin treatment as compared to the control arm in adult patients with moderate or severe 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: -

Evidence for comparator: -

Actual start date of recruitment	05 May 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 4
Country: Number of subjects enrolled	Italy: 51
Worldwide total number of subjects	55
EEA total number of subjects	51

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)	27
From 65 to 84 years	27

85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 56 patients were screened and all of them were randomized to the assigned treatment group: 37 patients were randomised to receive Reparixin and 19 patients were randomised to receive standard of care.

Pre-assignment

Screening details:

56 patients were screened and randomized to the assigned treatment group: 37 patients to receive Reparixin and 19 to receive standard of care. One patient in the Reparixin group did not take at least one dose of the IMP and was excluded from both the safety set and the FAS, which comprised 55 patients overall: 36 in the Reparixin and 19 in the SoC.

Period 1

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

Blinding implementation details:

This is an open-label trial, so blinding is not applicable.

Arms

Are arms mutually exclusive?	Yes
Arm title	Reparixin

Arm description:

Reparixin oral tablets 1200 mg TID for 7 days

Reparixin: Reparixin was administered via oral tablets 1200 mg TID for 7 days. In case of improvement, treatment can be prolonged at discretion of the investigator up to a maximum of 21 days of treatment in total or live discharge from the hospital, whichever comes first.

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

Dosage and administration details:

Reparixin oral tablets 1200 mg TID for 7 days

Reparixin: Reparixin was administered via oral tablets 1200 mg TID for 7 days. In case of improvement, treatment can be prolonged at discretion of the investigator up to a maximum of 21 days of treatment in total or live discharge from the hospital, whichever comes first.

Arm title	Standard of Care

Arm description:

Standard of care. Frequently used standard of care medications were dexamethasone (or other corticosteroids), anticoagulants (low-molecular weight heparin), antibiotics, as needed.

Arm type	Active comparator
Investigational medicinal product name	Standard of care
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The standard of care is expected to change over time due to the evolving research on effective

medications for this infection and the nature of the COVID-19 longitudinal evolution and, thus, it could not be prespecified. Frequently used standard of care medications were dexamethasone (or other corticosteroids), anticoagulants (low-molecular weight heparin), antibiotics, as needed. These were recognized by the Italian Health Authorities as indicated for the treatment of the COVID-19 disease.

Number of subjects in period 1	Reparixin	Standard of Care
Started	36	19
Completed	27	11
Not completed	9	8
Patient transferred to another centre for oxygen r	4	1
Physician decision	1	1
Death	1	3
Refused to continue the treatment	1	-
Lost to follow-up	2	2
Patient admitted to ICU	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Reparixin
Reporting group description:	
Reparixin oral tablets 1200 mg TID for 7 days Reparixin: Reparixin was administered via oral tablets 1200 mg TID for 7 days. In case of improvement, treatment can be prolonged at discretion of the investigator up to a maximum of 21 days of treatment in total or live discharge from the hospital, whichever comes first.	
Reporting group title	Standard of Care
Reporting group description:	
Standard of care. Frequently used standard of care medications were dexamethasone (or other corticosteroids), anticoagulants (low-molecular weight heparin), antibiotics, as needed.	

Reporting group values	Reparixin	Standard of Care	Total
Number of subjects	36	19	55
Age categorical			
The Full Analysis Set (FAS), which consisted of all randomized subjects who received at least one dose of the IMP. The FAS population was analyzed according to intention to treat (ITT) principle, i.e. by treatment allocation regardless the occurrence of intercurrent events.			
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)	22	11	33
From 65-84 years	14	7	21
85 years and over	0	1	1
Age continuous			
The Full Analysis Set (FAS), which consisted of all randomized subjects who received at least one dose of the IMP. The FAS population was analyzed according to intention to treat (ITT) principle, i.e. by treatment allocation regardless the occurrence of intercurrent events.			
Units: years			
arithmetic mean	60.6	63.6	
standard deviation	± 13.5	± 14.2	-
Gender categorical			
The Full Analysis Set (FAS), which consisted of all randomized subjects who received at least one dose of the IMP. The FAS population was analyzed according to intention to treat (ITT) principle, i.e. by treatment allocation regardless the occurrence of intercurrent events.			
Units: Subjects			
Female	10	3	13
Male	26	16	42

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

Subject analysis set description:

The Full Analysis Set (FAS), which consisted of all randomized subjects who received at least one dose of the IMP. The FAS population was analyzed according to intention to treat (ITT) principle, i.e. by treatment allocation regardless the occurrence of intercurrent events.

Subject analysis set title	Standard of Care (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS), which consisted of all randomized subjects who received at least one dose of the IMP. The FAS population was analyzed according to intention to treat (ITT) principle, i.e. by treatment allocation regardless the occurrence of intercurrent events.

Reporting group values	Reparixin (FAS)	Standard of Care (FAS)	
Number of subjects	36	19	
Age categorical			
The Full Analysis Set (FAS), which consisted of all randomized subjects who received at least one dose of the IMP. The FAS population was analyzed according to intention to treat (ITT) principle, i.e. by treatment allocation regardless the occurrence of intercurrent events.			
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)	22	11	
From 65-84 years	14	7	
85 years and over	0	1	
Age continuous			
The Full Analysis Set (FAS), which consisted of all randomized subjects who received at least one dose of the IMP. The FAS population was analyzed according to intention to treat (ITT) principle, i.e. by treatment allocation regardless the occurrence of intercurrent events.			
Units: years			
arithmetic mean	60.6	63.6	
standard deviation	± 13.5	± 14.2	
Gender categorical			
The Full Analysis Set (FAS), which consisted of all randomized subjects who received at least one dose of the IMP. The FAS population was analyzed according to intention to treat (ITT) principle, i.e. by treatment allocation regardless the occurrence of intercurrent events.			
Units: Subjects			
Female	10	3	
Male	26	16	

End points

End points reporting groups

Reporting group title	Reparixin

Reporting group description:

Reparixin oral tablets 1200 mg TID for 7 days

Reparixin: Reparixin was administered via oral tablets 1200 mg TID for 7 days. In case of improvement, treatment can be prolonged at discretion of the investigator up to a maximum of 21 days of treatment in total or live discharge from the hospital, whichever comes first.

Reporting group title	Standard of Care

Reporting group description:

Standard of care. Frequently used standard of care medications were dexamethasone (or other corticosteroids), anticoagulants (low-molecular weight heparin), antibiotics, as needed.

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

Subject analysis set description:

The Full Analysis Set (FAS), which consisted of all randomized subjects who received at least one dose of the IMP. The FAS population was analyzed according to intention to treat (ITT) principle, i.e. by treatment allocation regardless the occurrence of intercurrent events.

Subject analysis set title	Standard of Care (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS), which consisted of all randomized subjects who received at least one dose of the IMP. The FAS population was analyzed according to intention to treat (ITT) principle, i.e. by treatment allocation regardless the occurrence of intercurrent events.

Primary: Phase 2 - Percentage of participants with Composite endpoint of clinical events

End point title	Phase 2 - Percentage of participants with Composite endpoint of clinical events

End point description:

Composite event is defined as the onset of at least one of the following events:
- supplemental oxygen requirement based on a worsening of PaO2/FiO2 ratio,
- invasive mechanical ventilation use,
- admission to Intensive Care Unit (ICU),
- use of a rescue medication for any reason.

Please note that in the measure type "number" actually is a "rate" of patients. Rate is referred to a binomial response rate while the 95% CIs are estimated by using the Clopper-Pearson's method

End point type	Primary

End point timeframe:

Up to Day 1

End point values	Reparixin (FAS)	Standard of Care (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	19		
Units: percentage				
number (confidence interval 95%)				
Composite event	16.7 (6.4 to 32.8)	42.1 (20.3 to 66.5)		
Supplemental oxygen requirement based on PaO2/FiO2	13.9 (4.7 to 29.5)	26.3 (9.1 to 51.2)		

Invasive Mechanical ventilation	2.8 (0.1 to 14.5)	5.3 (0.1 to 26.0)		
Admission to ICU	2.8 (0.1 to 14.5)	0.0 (0.0 to 17.6)		
Use of a rescue medication for any reason	0.0 (0.0 to 9.7)	26.3 (9.1 to 51.2)		

Statistical analyses

Statistical analysis title	Reparixin vs SoC
Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02164
Method	Logrank

Statistical analysis title	Reparixin vs SoC
Statistical analysis description:	
Sensitivity analysis of time to event for each single component of the primary endpoint: Supplemental oxygen requirement based on PaO2/FiO2	
Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.20043
Method	Logrank

Statistical analysis title	Reparixin vs SoC
Statistical analysis description:	
Sensitivity analysis of time to event for each single component of the primary endpoint: time to first invasive mechanical ventilation	
Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03021
Method	Logrank

Statistical analysis title	Reparixin vs SoC
Statistical analysis description:	
Sensitivity analysis of time to event for each single component of the primary endpoint: time to first admission to ICU	

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5637
Method	Logrank

Statistical analysis title	Reparixin vs SoC

Statistical analysis description:

Sensitivity analysis of time to event for each single component of the primary endpoint: time to first use of a rescue medication for any reason

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00132
Method	Logrank

Secondary: Phase 2 - Percentage of Patients With Improvement in Clinical Severity Score (as Recommended by WHO for COVID Studies) of at Least Two Points

End point title	Phase 2 - Percentage of Patients With Improvement in Clinical Severity Score (as Recommended by WHO for COVID Studies) of at Least Two Points

End point description:

Changes in clinical severity score are defined as the time to clinical improvement of two points from the time of randomization on a seven-category ordinal scale or live discharge from the hospital, whichever came first. The seven-category ordinal scale consisted of the following: 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 Extracorporeal Membrane Oxygenation (ECMO), invasive mechanical ventilation, or both; and 7) death. The higher the score, the worse the outcome. A subject is considered "improved" with a clinical severity score improvement of at least two points compared to randomization or live discharge from the hospital.

End point type	Secondary

End point timeframe:

At day 1, day 2, week 1, day 21(end of treatment, EOT), EOS (end of study, i.e. 7±3 days after EOT)

End point values	Reparixin (FAS)	Standard of Care (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	35[1]	19[2]		
Units: percentage				
number (confidence interval 95%)				
Day 1	0.0 (0.0 to 10.0)	0.0 (0.0 to 17.6)		
Day 2	0.0 (0.0 to 10.0)	0.0 (0.0 to 18.5)		

Week 1	23.5 (10.7 to 41.2)	17.6 (3.8 to 43.4)		
EOT	26.5 (12.9 to 44.4)	26.3 (9.1 to 51.2)		
EOS	61.5 (40.6 to 79.8)	55.6 (21.2 to 86.3)		

Notes:

[1] - n=35 at day 1 and 2;
n=34 at week 1 and EOT;
n=26 at EOS.

[2] - n=19 at day 1 and EOT;
n=18 at day 2;
n=17 at week 1;
n=9 at EOS.

Statistical analyses

Statistical analysis title	Reparixin vs SoC
Statistical analysis description: comparison at week 1	
Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.731
Method	Fisher exact

Statistical analysis title	Reparixin vs SoC
Statistical analysis description: at EOT. Please note that n= 53 and not 54.	
Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1
Method	Fisher exact

Statistical analysis title	Reparixin vs SoC
Statistical analysis description: at EOS. Please note that n=35 and not 54.	
Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1
Method	Fisher exact

Secondary: Phase 2 - Number of improved subjects in Dyspnea severity, assessed by Liker scale

End point title	Phase 2 - Number of improved subjects in Dyspnea severity, assessed by Liker scale

End point description:

The severity of dyspnea can be measured through the Liker scale. The Liker scale is used as follows: the patient grades his current breathing compared to when he first started the drug (from -3 to 3). "0" = no change, "1" =minimally better, "2" =moderately better, "3" =markedly better, "-1" =minimally worse, "-2" =moderately worse, "-3" =markedly worse. The higher the score, the better the outcome. N is the number of subjects for which the evaluation of the dyspnea severity scale at each time point is available. n is the number of subjects improved at each time point in comparison with the randomization.

End point type	Secondary

End point timeframe:

Baseline, day 1, day 2, week 1, day 21(end of treatment, EOT), 7±3 days after treatment period (end of study, EOS)

End point values	Reparixin (FAS)	Standard of Care (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25[3]	9[4]		
Units: count of participnts				
Baseline	0	1		
Day 1	7	2		
Day 2	12	2		
Week 1	23	6		
EOT	20	6		
EOS	16	3		

Notes:

[3] - n=11 at baseline
n=16 at Day 1 and Day 2
n=25 at week 1
n=23 at EOT
n=18 at EOS
[4] - n=6 at baseline
n=9 at Day 1 and at week 1, and EOT
n=7 at Day 2
n=3 at EOS

Statistical analyses

Statistical analysis title	Reparixin vs SoC

Statistical analysis description:

At baseline. Please note that n=... and not 34

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)

Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.353
Method	Fisher exact

Statistical analysis title	Reparixin vs SoC
Statistical analysis description: At Day 1. Please note that n=... and not 34	
Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.401
Method	Fisher exact

Statistical analysis title	Reparixin vs SoC
Statistical analysis description: At Day 2. Please note that n=... and not 34	
Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.066
Method	Fisher exact

Statistical analysis title	Reparixin vs SoC
Statistical analysis description: At week 1. Please note that n=... and not 34	
Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.102
Method	Fisher exact

Statistical analysis title	Reparixin vs SoC
Statistical analysis description: At EOT. Please note that n=... and not 34	
Comparison groups	Standard of Care (FAS) v Reparixin (FAS)

Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.314
Method	Fisher exact

Statistical analysis title	Reparixin vs SoC

Statistical analysis description:

At EOS. Please note that n=... and not 34

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact

Secondary: Phase 2 - Change From Baseline in Dyspnea severity, assessed by VAS Scale

End point title	Phase 2 - Change From Baseline in Dyspnea severity, assessed by VAS Scale

End point description:

The severity of dyspnea is measured also through the VAS scale. The VAS scale is used as follows: the patient draws a horizontal line on an axial graph (from 0 to 100) to show the degree of how he feels about breathing. The number "0" equals the worst breathing the patient has ever felt and the number "100" equals the best he has ever felt. N is the number of subjects for which the evaluation of the dyspnea severity scale at each time point is available. n is the number of subjects improved at each time point in comparison with the randomization. please note that the high number of patients with missing data in the standard of care group did not allow a reliable assessment in this group: in this case mean and SD in the EOS for SoC are missing , hence indicated as a fake "0" in the platform.

End point type	Secondary

End point timeframe:

Baseline, day 1, day 2, week 1, day 21(end of treatment, EOT), 7±3 days after treatment period (end of study, EOS)

End point values	Reparixin (FAS)	Standard of Care (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36[5]	19[6]		
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline	56.9 (± 37.3)	4.0 (± 5.5)		
to day 1	4.3 (± 8.5)	20.0 (± 40.0)		
to day 2	32.3 (± 40.3)	44.8 (± 51.7)		
week 1	29.0 (± 34.0)	86.0 (± 5.3)		
EOT	33.0 (± 41.8)	89.7 (± 0.6)		
EOS	22.5 (± 31.8)	0 (± 0)		

Notes:

[5] - n=8 Baseline
n=4 Days 1 and 2
n=5 week 1, EOT
n=2 EOS
[6] - n=5 Baseline
n=4 Days 1 and 2
n=3 wee1, EOT
n=0 EOS

Statistical analyses

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

Day 1 vs baseline

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	> 0.999 [8]
Method	Wilcoxon (Mann-Whitney)

Notes:

[7] - Please note that the total number of subjects in this analisys is not n=55 but n=8: n=4 for Reparixin and n=4 for the SoC
[8] - p-values are referred to a two-sided Wilcoxon test for differences in the change of VAS scale.

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

Day 2 vs baseline

Comparison groups	Standard of Care (FAS) v Reparixin (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	> 0.999 [10]
Method	Wilcoxon (Mann-Whitney)

Notes:

[9] - Please note that the total number of subjects in this analysis is not n=55 but n=8: n=4 for Reparixin and n=4 for the SoC
[10] - p-values are referred to a two-sided Wilcoxon test for differences in the change of VAS scale.

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

week 1 vs baseline

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.05 [12]
Method	Wilcoxon (Mann-Whitney)

Notes:

[11] - Please note that the total number of subjects in this analisys is not n=55 but n=8: n=5 for Reparixin and n=3 for the SoC
[12] - p-values are referred to a two-sided Wilcoxon test for differences in the change of VAS scale.

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:	
EOT vs baseline	
Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.0227 [14]
Method	Wilcoxon (Mann-Whitney)

Notes:

[13] - Please note that the total number of subjects in this analisys is not n=55 but n=8: n=5 for Reparixin and n=3 for the SoC
[14] - p-values are referred to a two-sided Wilcoxon test for differences in the change of VAS scale.

Secondary: Phase 2 - Changes From Baseline in Body Temperature to Any Post-baseline Timepoints

End point title	Phase 2 - Changes From Baseline in Body Temperature to Any Post-baseline Timepoints

End point description:

Variations in the mean body temperature from baseline to any post-baseline timepoint were assessed. n is the number of subjects for which the evaluation of the body temperature at each time point is available.

End point type	Secondary

End point timeframe:

Baseline, Day 1, Day 2, Week 1, EOT and EOS

End point values	Reparixin (FAS)	Standard of Care (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36[15]	19[16]		
Units: F°				
arithmetic mean (standard deviation)				
Baseline	36.4 (± 0.5)	36.5 (± 0.5)		
Day 1	-0.2 (± 0.5)	0.2 (± 0.9)		
Day 2	-0.1 (± 0.7)	-0.1 (± 0.6)		
Week 1	-0.1 (± 0.6)	-0.2 (± 0.6)		
EOT	-0.2 (± 0.6)	-0.4 (± 0.6)		
EOS	-0.1 (± 0.5)	-0.5 (± 0.6)		

Notes:

[15] - n= 34 Day 1
n=35 Day 2
n=32 Week 1 , EOT
n=10 EOS
[16] - n=18 Day 2
n=14 Week 1
n=15 EOT
n=3 EOS

Statistical analyses

Statistical analysis title	Reparixin vs Standard of care
Statistical analysis description:	
At Day 1	
Comparison groups	Reparixin (FAS) v Standard of Care (FAS)

Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.122
Method	Wilcoxon (Mann-Whitney)

Notes:

[17] - Please note that the total number of subjects in this analisys is not n=55 but n=53: n=34 for Reparixin and n=19 for the SoC

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

At Day 2

Comparison groups	Standard of Care (FAS) v Reparixin (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.985
Method	Wilcoxon (Mann-Whitney)

Notes:

[18] - Please note that the total number of subjects in this analisys is not n=55 but n=53: n=35 for Reparixin and n=18 for the SoC

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

at week 1

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.857
Method	Wilcoxon (Mann-Whitney)

Notes:

[19] - Please note that the total number of subjects in this analisys is not n=55 but n=46: n=32 for Reparixin and n=14 for the SoC

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

at EOT

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	= 0.436
Method	Wilcoxon (Mann-Whitney)

Notes:

[20] - Please note that the total number of subjects in this analisys is not n=55 but n=47: n=32 for Reparixin and n=15 for the SoC

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

At EOS

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)

Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.35
Method	Wilcoxon (Mann-Whitney)

Notes:

[21] - Please note that the total number of subjects in this analisys is not n=55 but n=13: n=10 for Reparixin and n=3 for the SoC

Secondary: Phase 2 - Percentage of Subjects Worsened, During Supplemental Oxygen Treatment, From Randomization According to PaO2/FiO2

End point title	Phase 2 - Percentage of Subjects Worsened, During Supplemental Oxygen Treatment, From Randomization According to PaO2/FiO2

End point description:

Cumulative quantity of oxygen treatment (L) = Sum of all Quantity (L) in CONCOMITANT OXYGEN TREATMENT form, from randomization to time point of interest.
According to PaO2/FiO2, the classification is 'mild' if 200 <= PaO2/FiO2 < 300 mmHg, 'moderate' if 100 <= PaO2/FiO2 < 200 mmHg, 'severe' if PaO2/FiO2 < 100 mmHg. A patient with ARDS (PaO2/FiO2<300 mmHg) is considered 'worsened' in case of a decrease of PaO2/FiO2 of at least one third (-33,3%) from the baseline PaO2/FiO2 value.
NOTE that: N is the number of subjects for which the evaluation of the PaO2/FiO2 ratio at each time point is available. While n is the number of subjects worsened at each time point in comparison with the randomization, expressed in percentage.

End point type	Secondary

End point timeframe:

At day 1, day 2, week 1, day 21(end of treatment), follow-up (FU) (7±3 days after treatment period)

End point values	Reparixin (FAS)	Standard of Care (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36[22]	19[23]		
Units: percentage				
number (confidence interval 90%)				
Day 1 - subjects worsened (%)	7.4 (0.9 to 24.3)	14.3 (1.8 to 42.8)		
Day 2 - subjects worsened (%)	12.9 (3.6 to 29.8)	20.0 (4.3 to 48.1)		
Week 1 - subjects worsened (%)	0.0 (0.0 to 13.2)	21.4 (4.7 to 50.8)		
EOT - subjects worsened (%)	0.0 (0.0 to 11.9)	8.3 (0.2 to 38.5)		
EOS - subjects worsened (%)	0.0 (0.0 to 30.8)	0.0 (0.0 to 70.8)		

Notes:

[22] - n=27 Day 1
n=31 Day 2
n=26 Week 1
n=29 EOT
n=10 EOS
[23] - n=14 Day 1, Week 1
n=15 Day 2
n=12 EOT
n=3 EOS

Statistical analyses

Statistical analysis title	Reparixin vs Standard of care
Statistical analysis description:	
Day 1	
Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	= 0.596 [25]
Method	Fisher exact

Notes:

[24] - Please note that the total number of subjects in this analisys is not n=55 but n=41: n=27 for Reparixin and n=14 for the SoC

[25] - p-values are referred to a two-sided Fisher's Exact test for worsening

Statistical analysis title	Reparixin vs Standard of care
Statistical analysis description:	
Day 2	
Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[26]
P-value	= 0.667 [27]
Method	Fisher exact

Notes:

[26] - Please note that the total number of subjects in this analisys is not n=55 but n=46: n=31 for Reparixin and n=15 for the SoC

[27] - p-values are referred to a two-sided Fisher's Exact test for worsening

Statistical analysis title	Reparixin vs Standard of care
Statistical analysis description:	
Week 1	
Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	= 0.037 [29]
Method	Fisher exact

Notes:

[28] - Please note that the total number of subjects in this analisys is not n=55 but n=40: n=26 for Reparixin and n=14 for the SoC

[29] - p-values are referred to a two-sided Fisher's Exact test for worsening

Statistical analysis title	Reparixin vs Standard of care
Statistical analysis description:	
EOT	
Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[30]
P-value	= 0.293 [31]
Method	Fisher exact

Notes:

[30] - Please note that the total number of subjects in this analisys is not n=55 but n=41: n=29 for Reparixin and n=12 for the SoC
[31] - p-values are referred to a two-sided Fisher's Exact test for worsening

Secondary: Phase 2 - Percentage of Subjects Worsened, During Supplemental Oxygen Treatment, From Randomization According to Oxygen Delivery System Classification

End point title	Phase 2 - Percentage of Subjects Worsened, During Supplemental Oxygen Treatment, From Randomization According to Oxygen Delivery System Classification

End point description:

Duration of oxygen administration (hours) = Administration end date/time - Administration start date/time / 60. N is the number of subjects for which the evaluation of the Oxygen Delivery System Classification at each time point is available. n is the number of subjects worsened at each time point, expressed in percentage, in comparison with the randomization. According to Oxygen Delivery System, the classification is 'invasive' if there is Invasive Medicinal Ventilation or ECMO, else 'high flow' if there is High Flow Nasal Cannula or BIPAP or CPAP, else 'low flow' if there is Nasal Cannula or Mask then Class=Low Flow Classification. A patient is considered 'Worsened' after baseline if there is an increase in the level of severity within the oxygen delivery system classification (Invasive > High Flow > Low Flow).

End point type	Secondary

End point timeframe:

day 1, day 2, week 1, day 21(end of treatment), follow-up (FU) (7±3 days after treatment period)

End point values	Reparixin (FAS)	Standard of Care (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36[32]	19[33]		
Units: Percentage				
number (confidence interval 95%)				
Day 1 - subjects worsened	5.6 (0.7 to 18.7)	0.0 (0.0 to 17.6)		
Day 2 - subjects worsened	5.6 (0.7 to 18.7)	5.3 (0.1 to 26.0)		
Week 1 - subjects worsened	2.9 (0.1 to 15.3)	17.6 (3.8 to 43.4)		
EOT - subjects worsened	2.9 (0.1 to 14.9)	15.8 (3.4 to 39.6)		
EOS - subjects worsened	3.6 (0.1 to 18.3)	8.3 (0.2 to 38.5)		

Notes:

[32] - n=34 Week 1
n=35 EOT
n=28 EOS
[33] - n=17 Week 1
n=12 EOS

Statistical analyses

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

Day 1

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)

Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.539 [34]
Method	Fisher exact

Notes:

[34] - p-values are referred to a two-sided Fisher’s Exact test for worsening and

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

Day 2

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [35]
Method	Fisher exact

Notes:

[35] - p-values are referred to a two-sided Fisher’s Exact test for worsening

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

Week 1

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[36]
P-value	= 0.102 [37]
Method	Fisher exact

Notes:

[36] - Please note that the total number of subjects in this analisys is not n=55 but n=51: n=34 for Reparixin and n=17 for the SoC
[37] - p-values are referred to a two-sided Fisher’s Exact test for worsening

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

EOT

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[38]
P-value	= 0.119 [39]
Method	Fisher exact

Notes:

[38] - Please note that the total number of subjects in this analisys is not n=54 but n=53: n=35 for Reparixin and n=19 for the SoC
[39] - p-values are referred to a two-sided Fisher’s Exact test for worsening

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

EOS

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[40]
P-value	= 0.515 [41]
Method	Fisher exact

Notes:

[40] - Please note that the total number of subjects in this analisys is not n=55 but n=40: n=28 for Reparixin and n=12 for the SoC

[41] - p-values are referred to a two-sided Fisher's Exact test for worsening

Secondary: Phase 2 - Oxygen Cumulative Duration During the Study

End point title	Phase 2 - Oxygen Cumulative Duration During the Study

End point description:

This outcome assesses the oxygen cumulative duration during the study.
N is the number of subjects for which the evaluation of the PaO2/FiO2 ratio or Oxygen Delivery System Classification at each time point is available. n is the number of subjects worsened at each time point in comparison with the randomization.

End point type	Secondary

End point timeframe:

Week 1, EOT, EOS

End point values	Reparixin (FAS)	Standard of Care (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36[42]	19[43]		
Units: hours				
arithmetic mean (standard deviation)				
Week 1	141.93 (± 55.68)	130.22 (± 80.89)		
EOT	151.55 (± 75.53)	134.00 (± 86.21)		
EOS	195.26 (± 198.62)	155.71 (± 135.93)		

Notes:

[42] - n=34 Week 1, EOT

[43] - n=18 Week 1. EOT, EOS

Statistical analyses

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

Week 1

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[44]
P-value	= 0.366 [45]
Method	Wilcoxon (Mann-Whitney)

Notes:

[44] - Please note that the total number of subjects in this analisys is not n=55 but n=52: n=34 for Reparixin and n=18 for the SoC

[45] - p-values are referred to a two-sided Wilcoxon test for cumulative duration.

Statistical analysis title	Reparixin vs Standard of care
Statistical analysis description: EOT	
Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[46]
P-value	= 0.489 [47]
Method	Wilcoxon (Mann-Whitney)

Notes:

[46] - Please note that the total number of subjects in this analisys is not n=55 but n=52: n=34 for Reparixin and n=18 for the SoC
[47] - p-values are referred to a two-sided Wilcoxon test for cumulative duration.

Statistical analysis title	Reparixin vs Standard of care
Statistical analysis description: EOS	
Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[48]
P-value	= 0.486 [49]
Method	Wilcoxon (Mann-Whitney)

Notes:

[48] - Please note that the total number of subjects in this analisys is not n=55 but n=54: n=36 for Reparixin and n=18 for the SoC
[49] - p-values are referred to a two-sided Wilcoxon test for cumulative duration.

Secondary: Phase 2 - Oxygen Cumulative Quantity During the Study

End point title	Phase 2 - Oxygen Cumulative Quantity During the Study

End point description:

In this endpoint is assessed the oxygen cumulative quantity needed at each single timepoint.
N is the number of subjects for which the evaluation of the PaO2/FiO2 ratio or Oxygen Delivery System Classification at each time point is available. n is the number of subjects worsened at each time point in comparison with the randomization.

End point type	Secondary

End point timeframe:

Week 1, EOT and EOS

End point values	Reparixin (FAS)	Standard of Care (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36[50]	19[51]		
Units: litre(s)				
arithmetic mean (standard deviation)				
Week 1	24.99 (± 22.22)	29.20 (± 29.51)		

EOT	25.64 (± 22.16)	29.73 (± 31.53)		
EOS	26.54 (± 22.31)	33.38 (± 31.64)		

Notes:

[50] - n=33 Week 1, EOT
n=35 EOS
[51] - n=18 Week 1, EOT, EOS

Statistical analyses

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

Week 1

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[52]
P-value	= 0.79 [53]
Method	Wilcoxon (Mann-Whitney)

Notes:

[52] - Please note that the total number of subjects in this analisys is not n=55 but n=51: n=33 for Reparixin and n=18 for the SoC
[53] - p-values are referred to a two-sided Wilcoxon test for cumulative quantity

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

EOT

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[54]
P-value	= 0.961 [55]
Method	Wilcoxon (Mann-Whitney)

Notes:

[54] - Please note that the total number of subjects in this analisys is not n=55 but n=51: n=33 for Reparixin and n=18 for the SoC
[55] - p-values are referred to a two-sided Wilcoxon test for cumulative quantity

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

EOS

Comparison groups	Standard of Care (FAS) v Reparixin (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[56]
P-value	= 0.619 [57]
Method	Wilcoxon (Mann-Whitney)

Notes:

[56] - Please note that the total number of subjects in this analisys is not n=55 but n=53: n=35 for Reparixin and n=18 for the SoC
[57] - p-values are referred to a two-sided Wilcoxon test for cumulative quantity

Secondary: Phase 2 - Percentage of Subjects Requiring Mechanical Ventilation Use, Overall

End point title	Phase 2 - Percentage of Subjects Requiring Mechanical Ventilation Use, Overall

End point description:

Percentage along with the 95% confidence interval (Clopper-Pearson's formula) of subjects requiring mechanical ventilation are calculated and compared. N is the number of subjects for which the evaluation of the use of mechanical ventilation is available. n is the number, expressed in percentage, of subjects requiring mechanical ventilation, overall.

End point type	Secondary

End point timeframe:

Baseline, day 1, day 2, week 1, day 21(end of treatment), follow-up (FU) (7±3 days after treatment period)

End point values	Reparixin (FAS)	Standard of Care (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36[58]	19[59]		
Units: percentage				
number (confidence interval 95%)				
Baseline - subjects requiring	11.1 (3.1 to 26.1)	10.5 (1.3 to 33.1)		
Day 1 - subjects requiring	11.1 (3.1 to 26.1)	10.5 (1.3 to 33.1)		
Day 2 - subjects requiring	11.4 (3.2 to 26.7)	16.7 (3.6 to 41.4)		
Week 1 - subjects requiring	8.8 (1.9 to 23.7)	11.8 (1.5 to 36.4)		
EOT - subjects requiring	8.6 (1.8 to 23.1)	5.3 (0.1 to 26.0)		
EOS - subjects requiring	0.0 (0.0 to 12.8)	0.0 (0.0 to 30.8)		

Notes:

[58] - n=35 Day 2, EOT
n=34 Week 1
n=27 EOS
[59] - n=18 Day 2
n=17 Week 1
n=10 EOS

Statistical analyses

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

Baseline

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [60]
Method	Fisher exact

Notes:

[60] - p-values are referred to a two-sided Fisher's Exact test for proportion

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

Day 1

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [61]
Method	Fisher exact

Notes:

[61] - p-values are referred to a two-sided Fisher's Exact test for proportion

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

Day 2

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[62]
P-value	= 0.678 [63]
Method	Fisher exact

Notes:

[62] - Please note that the total number of subjects in this analisys is not n=55 but n=53: n=35 for Reparixin and n=18 for the SoC

[63] - p-values are referred to a two-sided Fisher's Exact test for proportion

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

Week 1

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[64]
P-value	= 1 [65]
Method	Fisher exact

Notes:

[64] - Please note that the total number of subjects in this analisys is not n=55 but n=51: n=34 for Reparixin and n=17 for the SoC

[65] - p-values are referred to a two-sided Fisher's Exact test for proportion

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

EOT

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[66]
P-value	= 1 [67]
Method	Fisher exact

Notes:

[66] - Please note that the total number of subjects in this analisys is not n=55 but n=54: n=35 for Reparixin and n=19 for the SoC

[67] - p-values are referred to a two-sided Fisher's Exact test for proportion

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

EOS

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[68]
P-value	= 1 [69]
Method	Fisher exact

Notes:

[68] - Please note that the total number of subjects in this analisys is not n=55 but n=37: n=27 for Reparixin and n=10 for the SoC

[69] - p-values are referred to a two-sided Fisher's Exact test for proportion

Secondary: Phase 2 - Cumulative Duration of Mechanical Ventilation Use, Overall

End point title	Phase 2 - Cumulative Duration of Mechanical Ventilation Use, Overall

End point description:

Cumulative duration of mechanical ventilation (in hours) = Sum of duration of mechanical ventilation (hours) in mechanical ventilation form, from randomization to time point of interest.
Duration of mechanical ventilation (hours) = End date/time - Start date/time / 60. n is the number of subjects for which the evaluation of the use of mechanical ventilation is available

End point type	Secondary

End point timeframe:

Baseline, day 1, day 2, week 1, day 21(end of treatment), follow-up (FU) (7±3 days after treatment period)

End point values	Reparixin (FAS)	Standard of Care (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36[70]	19[71]		
Units: hour				
arithmetic mean (standard deviation)				
Week 1	162.54 (± 58.92)	142.42 (± 44.89)		
EOT	149.99 (± 52.23)	146.86 (± 43.80)		
EOS	179.51 (± 78.30)	154.86 (± 56.52)		

Notes:

[70] - n=4 Week 1, EOT, EOS

[71] - n=3 Week 1, EOT, EOS

Statistical analyses

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

Week 1

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)

Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[72]
P-value	= 0.696 [73]
Method	Wilcoxon (Mann-Whitney)

Notes:

[72] - Please note that the total number of subjects in this analisys is not n=55 but n=7: n=4 for Reparixin and n=3 for the SoC
[73] - p-values are referred to a two-sided Wilcoxon test for cumulative duration

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

EOT

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[74]
P-value	> 0.999 [75]
Method	Wilcoxon (Mann-Whitney)

Notes:

[74] - Please note that the total number of subjects in this analisys is not n=55 but n=7: n=4 for Reparixin and n=3 for the SoC
[75] - p-values are referred to a-sided Wilcoxon test for cumulative duration

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

EOS

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[76]
P-value	= 0.596 [77]
Method	Wilcoxon (Mann-Whitney)

Notes:

[76] - Please note that the total number of subjects in this analisys is not n=55 but n=7: n=4 for Reparixin and n=3 for the SoC
[77] - p-values are referred to a-sided Wilcoxon test for cumulative duration

Secondary: Phase 2 - Percentage of Subjects With Intensive Care Unit (ICU) Admission Need

End point title	Phase 2 - Percentage of Subjects With Intensive Care Unit (ICU) Admission Need

End point description:

Percentage, along with the 95% confidence interval (Clopper-Pearson’s formula), of subjects requiring ICU admission are calculated and compared.N is the number of subjects for which the evaluation of the ICU admission need is available.

End point type	Secondary

End point timeframe:

Baseline, day 1, day 2, week 1, day 21(end of treatment), follow-up (FU) (7±3 days after treatment period)

End point values	Reparixin (FAS)	Standard of Care (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36[78]	19[79]		
Units: percentage				
number (confidence interval 95%)				
Baseline - subjects admitted to ICU	2.8 (0.1 to 14.5)	5.3 (0.1 to 26.0)		
Day 1 - subjects admitted to ICU	2.8 (0.1 to 14.5)	5.3 (0.1 to 26.0)		
Day 2 - subjects admitted to ICU	5.7 (0.7 to 19.2)	5.6 (0.1 to 27.3)		
Week 1 - subjects admitted to ICU	2.9 (0.1 to 15.3)	0.0 (0.0 to 19.5)		
EOT - subjects admitted to ICU	2.9 (0.1 to 14.9)	0.0 (0.0 to 17.6)		
EOS - subjects admitted to ICU	0.0 (0.0 to 12.8)	0.0 (0.0 to 30.8)		

Notes:

[78] - n=35 Day 2 , EOT
n=34 Week 1
n=27 EOS
[79] - n=18 Day 2
n=17 Week 1
n=10 EOS

Statistical analyses

Statistical analysis title	Reparixin vs Standard of care
Statistical analysis description: Baseline	
Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [80]
Method	Fisher exact

Notes:

[80] - p-values are referred to a two-sided Fisher’s Exact test for proportion

Statistical analysis title	Reparixin vs Standard of care
Statistical analysis description: Day 1	
Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [81]
Method	Fisher exact

Notes:

[81] - p-values are referred to a two-sided Fisher’s Exact test for proportion

Statistical analysis title	Reparixin vs Standard of care
Statistical analysis description: Day 2	

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[82]
P-value	= 1 [83]
Method	Fisher exact

Notes:

[82] - Please note that the total number of subjects in this analisys is not n=55 but n=53: n=35 for Reparixin and n=18 for the SoC
[83] - p-values are referred to a two-sided Fisher’s Exact test for proportion

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

Week 1

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[84]
P-value	= 1 [85]
Method	Fisher exact

Notes:

[84] - Please note that the total number of subjects in this analisys is not n=55 but n=51: n=34 for Reparixin and n=17 for the SoC
[85] - p-values are referred to a two-sided Fisher’s Exact test for proportion

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

EOT

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[86]
P-value	= 1 [87]
Method	Fisher exact

Notes:

[86] - Please note that the total number of subjects in this analisys is not n=55 but n=54: n=35 for Reparixin and n=19 for the SoC
[87] - p-values are referred to a two-sided Fisher’s Exact test for proportion

Secondary: Phase 2 - Cumulative ICU Stay

End point title	Phase 2 - Cumulative ICU Stay

End point description:

Cumulative ICU stay was assessed at different timepoints and measured in days

End point type	Secondary

End point timeframe:

Day 1, Day 2, Week 1, EOT, EOS

End point values	Reparixin (FAS)	Standard of Care (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36[88]	19[89]		
Units: days				
median (full range (min-max))				
Day 1 - cumulative ICU stay	1.0 (1 to 1)	1.0 (1 to 1)		
Day 2 - cumulative ICU stay	2.0 (2 to 2)	2.0 (2 to 2)		
Week 1 - cumulative ICU stay	7.0 (7 to 7)	3.0 (3 to 3)		
EOT - cumulative ICU stay	6.0 (6 to 6)	3.0 (3 to 3)		
EOS - cumulative ICU stay	50.0 (50 to 50)	3.0 (3 to 3)		

Notes:

[88] - n=1 Day 1, Day 2. Week 1, EOT

[89] - n=1 Day 1, Day 2, Week 1, EOT, EOS

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2 - Lung Damage Extension by Severity and by Timepoint

End point title	Phase 2 - Lung Damage Extension by Severity and by Timepoint

End point description:

Lung damage extensions is assessed by Chest CT or Rx. This damage can be as follows: "none", "trace", "mild", "moderate", or "severe".
N is the number of subjects for which the evaluation of the lung damage extension at each time point is available.

End point type	Secondary

End point timeframe:

Baseline, day 1, day 2, week 1, day 21(end of treatment), follow-up (FU) (7±3 days after treatment period)

End point values	Reparixin (FAS)	Standard of Care (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36[90]	19[91]		
Units: partecipants				
number (not applicable)				
Baseline - none	0	0		
Baseline -trace	1	2		
Baseline - mild	9	3		
Baseline - moderate	23	11		
Baseline - severe	3	3		
Day 1 - none	0	0		
Day 1 - trace	0	0		
Day 1 - mild	0	1		
Day 1 - moderate	1	0		
Day 1 - severe	0	0		
Day 2 - none	0	0		
Day 2 - trace	0	0		
Day 2 - mild	0	1		

Day 2 - moderate	0	0		
Day 2 - severe	1	0		
Week 1 - none	0	0		
Week 1 - trace	1	0		
Week 1 - mild	6	2		
Week 1 - moderate	4	0		
Week 1 - severe	1	2		
EOT - none	1	0		
EOT - trace	3	0		
EOT - mild	8	2		
EOT - moderate	3	0		
EOT - severe	1	2		
EOS- none	0	0		
EOS - trace	0	0		
EOS - mild	1	1		
EOS - moderate	1	1		
EOS - severe	0	0		

Notes:

[90] - n=1 Day 1 (all groups) , Day 2 (all groups)
n=12 Week 1 (all groups)
n=16 EOT
n=2 EOS
[91] - n=1 Day 1 (all groups), Day 2 (all groups)
n=4 Week 1 (all groups)

Statistical analyses

Statistical analysis title	Reparixin vs Standard of care
Statistical analysis description:	
Baseline	
Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.76 [92]
Method	Wilcoxon (Mann-Whitney)

Notes:

[92] - p-values are referred to a two-sided Wilcoxon test

Statistical analysis title	Reparixin vs Standard of care
Statistical analysis description:	
Week 1	
Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[93]
P-value	= 0.394 [94]
Method	Wilcoxon (Mann-Whitney)

Notes:

[93] - Please note that the total number of subjects in this analisys is not n=55 but n=16: n=12 for Reparixin and n=4 for the SoC
[94] - p-values are referred to a two-sided Wilcoxon test

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

EOT

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[95]
P-value	= 0.141 [96]
Method	Wilcoxon (Mann-Whitney)

Notes:

[95] - Please note that the total number of subjects in this analisys is not n=55 but n=35: n=16 for Reparixin and n=19 for the SoC

[96] - p-values are referred to a two-sided Wilcoxon test

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

EOS

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[97]
P-value	> 0.999 [98]
Method	Wilcoxon (Mann-Whitney)

Notes:

[97] - Please note that the total number of subjects in this analisys is not n=55 but n=21: n=2 for Reparixin and n=19 for the SoC

[98] - p-values are referred to a two-sided Wilcoxon test

Secondary: Phase 2 - Lung Exudation by Severity and by Timepoint

End point title	Phase 2 - Lung Exudation by Severity and by Timepoint

End point description:

Lung exudation is assessed by Chest CT or Rx. This can be as follows: "none", "trace", "mild", "moderate", or "severe".
N is the number of subjects for which the evaluation of the lung damage extension at each time point is available.

End point type	Secondary

End point timeframe:

Baseline, day 1, day 2, week 1, day 21(end of treatment), follow-up (FU) (7±3 days after treatment period)

End point values	Reparixin (FAS)	Standard of Care (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36[99]	19[100]		
Units: partecipants				
number (not applicable)				
Baseline - none	32	18		
Baseline - trace	0	0		
Baseline - mild	1	0		
Baseline - moderate	3	1		
Baseline - severe	0	0		

Day 1 -none	0	0		
Day 1 - trace	0	0		
Day 1 - mild	0	0		
Day 1 - moderate	1	1		
Day 1 - severe	0	0		
Day 2 - none	0	0		
Day 2 - trace	0	0		
Day 2 - mild	0	1		
Day 2 - moderate	0	0		
Day 2 - severe	1	0		
Week 1 - none	12	3		
Week 1 - trace	0	0		
Week 1 - mild	0	0		
Week 1 - moderate	0	0		
Week 1 - severe	0	1		
EOT - none	15	3		
EOT - trace	0	0		
EOT - mild	1	0		
EOT - moderate	0	1		
EOT - severe	0	0		
EOS - none	2	2		
EOS - trace	0	0		
EOS - mild	0	0		
EOS - moderate	0	0		
EOS - severe	0	0		

Notes:

[99] - n=1 Days 1 and 2 (all groups)
n=12 Week 1 (all groups)
n=16 EOT (all groups)
n=2 EOS (all groups)
[100] - n=1 Days 1 and 2 (all groups)
n=4 Week 1 (all groups), EOT (all groups)
n=2 EOS (all groups)

Statistical analyses

Statistical analysis title	Reparixin vs Standard of care
Statistical analysis description:	
Baseline	
Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5 [101]
Method	Wilcoxon (Mann-Whitney)

Notes:

[101] - p-values are referred to a two-sided Wilcoxon test.

Statistical analysis title	Reparixin vs Standard of care
Statistical analysis description:	
Week 1	
Comparison groups	Standard of Care (FAS) v Reparixin (FAS)

Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[102]
P-value	= 0.112 [103]
Method	Wilcoxon (Mann-Whitney)

Notes:

[102] - Please note that the total number of subjects in this analisys is not n=55 but n=16: n=12 for Reparixin and n=4 for the SoC
[103] - p-values are referred to a two-sided Wilcoxon test.

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

EOT

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[104]
P-value	= 0.277 [105]
Method	Wilcoxon (Mann-Whitney)

Notes:

[104] - Please note that the total number of subjects in this analisys is not n=55 but n=20: n=16 for Reparixin and n=4 for the SoC
[105] - p-values are referred to a two-sided Wilcoxon test.

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

EOS

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[106]
P-value	> 0.999 [107]
Method	Wilcoxon (Mann-Whitney)

Notes:

[106] - Please note that the total number of subjects in this analisys is not n=55 but n=4: n=2 for Reparixin and n=2 for the SoC
[107] - p-values are referred to a two-sided Wilcoxon test.

Secondary: Phase 2 - Change From Baseline in Partial Arterial Oxygen Pressure (PaO2)

End point title	Phase 2 - Change From Baseline in Partial Arterial Oxygen Pressure (PaO2)

End point description:

PaO2 measures the pressure of oxygen dissolved in the blood and how well oxygen is able to move from the airspace of the lungs into the blood.
Normally, PaO2 is between 75 and 100 mmHg (at sea level). Lower levels indicate an unsufficient amount of oxygen flowing from the alveoli to the blood. Please note that a significant proportion of patients in both groups did not have post-baseline assessments of PaO2.
Plase note that the high number of patients with missing data in the standard of care group did not allow a reliable assessment in this group. So platform forced to insert a fake "0" values in the SD in the SoC SoC for EOT and for EOS.

End point type	Secondary

End point timeframe:

Baseline, day 1, day 2, week 1, day 21(end of treatment), follow-up (FU) (7±3 days after treatment period)

End point values	Reparixin (FAS)	Standard of Care (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36[108]	19[109]		
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline	121.69 (± 47.15)	68.64 (± 9.23)		
to Day 1	-19.61 (± 50.09)	14.20 (± 25.76)		
to Day 2	12.62 (± 60.20)	-4.68 (± 14.03)		
to Week 1	11.76 (± 25.26)	-1.13 (± 54.80)		
to EOT	8.01 (± 36.08)	-18.70 (± 0)		
to EOS	-35.76 (± 47.84)	1.80 (± 0)		

Notes:

[108] - n=17 Baseline
n=8 to Day 1 , to EOS
n=13 to Day 2
n=10 to Week 1
n=11 to EOT
[109] - n=8 Baseline
n=4 to Days 1 and 2
n=3 to Week 1
n=1 to EOT, to EOS

Statistical analyses

Statistical analysis title	Reparixin vs Standard of care
Statistical analysis description: Day 1 vs Baseline	
Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2027 [110]
Method	Wilcoxon (Mann-Whitney)

Notes:

[110] - p-values are referred to a two-sided Wilcoxon test for differences in the change

Statistical analysis title	Reparixin vs Standard of care
Statistical analysis description: Day 2 vs baseline	
Comparison groups	Reparixin (FAS) v Standard of Care (FAS)

Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[111]
P-value	= 0.3529 [112]
Method	Wilcoxon (Mann-Whitney)

Notes:

[111] - Please note that the total number of subjects in this analysis is not n=55 but n=17: n=13 for Reparixin and n=4 for the SoC
[112] - p-values are referred to a two-sided Wilcoxon test for differences in the change

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

week 1 vs baseline

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[113]
P-value	= 0.3581 [114]
Method	Wilcoxon (Mann-Whitney)

Notes:

[113] - Please note that the total number of subjects in this analysis is not n=55 but n=13: n=10 for Reparixin and n=3 for the SoC
[114] - p-values are referred to a two-sided Wilcoxon test for differences in the change.

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

EOT vs baseline

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[115]
P-value	= 0.1666 [116]
Method	Wilcoxon (Mann-Whitney)

Notes:

[115] - Please note that the total number of subjects in this analysis is not n=55 but n=12: n=11 for Reparixin and n=1 for the SoC
[116] - p-values are referred to a two-sided Wilcoxon test for differences in the change.

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

EOS vs baseline

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[117]
P-value	= 0.0851 [118]
Method	Wilcoxon (Mann-Whitney)

Notes:

[117] - Please note that the total number of subjects in this analysis is not n=55 but n=9: n=8 for Reparixin and n=1 for the SoC
[118] - p-values are referred to a two-sided Wilcoxon test for differences in the change.

Secondary: Phase 2 - Change From Baseline in Oxygen Saturation (SpO2)

End point title	Phase 2 - Change From Baseline in Oxygen Saturation (SpO2)

End point description:

SpO2 measures the amount of oxygen-carrying hemoglobin in the blood relative to the amount of hemoglobin not carrying oxygen. Acceptable normal ranges for patients without pulmonary pathology are from 95 to 99 percent.

End point type	Secondary

End point timeframe:

Baseline, day 1, day 2, week 1, day 21(end of treatment), follow-up (FU) (7±3 days after treatment period)

End point values	Reparixin (FAS)	Standard of Care (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36[119]	19[120]		
Units: percent of oxigen saturation				
arithmetic mean (standard deviation)				
Baseline	95.79 (± 3.17)	94.97 (± 2.60)		
to Day 1	0.17 (± 2.20)	-0.41 (± 3.57)		
to Day 2	0.38 (± 2.88)	-0.63 (± 3.86)		
to Week 1	1.18 (± 3.34)	0.73 (± 3.71)		
to EOT	0.88 (± 3.57)	1.19 (± 3.89)		
to EOS	0.47 (± 3.17)	-4.00 (± 1.41)		

Notes:

[119] - n=35 Baseline
n=29 Day 1, EOT
n=32 Day 2
n=30 Week 1
n=10 EOS
[120] - n=18 Baseline, Day 1
n=17 Day 2
n=13 Week 1
n=14 EOT
n=2 EOS

Statistical analyses

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

Day 1 vs baseline

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[121]
P-value	= 0.6441 [122]
Method	Wilcoxon (Mann-Whitney)

Notes:

[121] - Please note that the total number of subjects in this analisys is not n=55 but n=47: n=29 for Reparixin and n=18 for the SoC
[122] - p-values are referred to a two-sided Wilcoxon test for differences in the change.

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

Day 2 vs baseline

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)

Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[123]
P-value	= 0.3529 [124]
Method	Wilcoxon (Mann-Whitney)

Notes:

[123] - Please note that the total number of subjects in this analisys is not n=55 but n=49: n=32 for Reparixin and n=17 for the SoC
[124] - p-values are referred to a two-sided Wilcoxon test for differences in the change.

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

week 1 vs baseline

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[125]
P-value	= 0.3581 [126]
Method	Wilcoxon (Mann-Whitney)

Notes:

[125] - Please note that the total number of subjects in this analisys is not n=55 but n=43: n=30 for Reparixin and n=13 for the SoC
[126] - p-values are referred to a two-sided Wilcoxon test for differences in the change.

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

EOT vs baseline

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[127]
P-value	= 0.1666 [128]
Method	Wilcoxon (Mann-Whitney)

Notes:

[127] - Please note that the total number of subjects in this analisys is not n=55 but n=43: n=29 for Reparixin and n=14 for the SoC
[128] - p-values are referred to a two-sided Wilcoxon test for differences in the change.

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

EOS vs baseline

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[129]
P-value	= 0.0851 [130]
Method	Wilcoxon (Mann-Whitney)

Notes:

[129] - Please note that the total number of subjects in this analisys is not n=55 but n=12: n=10 for Reparixin and n=2 for the SoC
[130] - p-values are referred to a two-sided Wilcoxon test for differences in the change.

Secondary: Phase 2 - Partial Arterial Oxygen Pressure (PaO2) to Fraction of Inspiration O2 (FiO2) Ratio [PaO2/FiO2 Ratio]

End point title	Phase 2 - Partial Arterial Oxygen Pressure (PaO2) to Fraction of Inspiration O2 (FiO2) Ratio [PaO2/FiO2 Ratio]

End point description:

PaO2/FiO2 ratio is the ratio of arterial oxygen partial pressure (PaO2 in mmHg) to fractional inspired oxygen (FiO2 expressed as a fraction, not a percentage) also known as the Horowitz index, the Carrico index, and (most conveniently) the P/F ratio at sea level, the normal PaO2/FiO2 ratio is ~ 400-500 mmHg (~55-65 kPa).

End point type	Secondary

End point timeframe:

Baseline, day 1, day 2, week 1, day 21(end of treatment), follow-up (FU) (7±3 days after treatment period)

End point values	Reparixin (FAS)	Standard of Care (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36[131]	19[132]		
Units: ratio				
arithmetic mean (standard deviation)				
Baseline	186.82 (± 64.86)	196.91 (± 58.49)		
to Day 1	21.58 (± 65.81)	6.08 (± 125.00)		
to Day 2	48.29 (± 154.49)	-8.53 (± 71.74)		
to Week 1	160.80 (± 137.83)	54.28 (± 138.36)		
to EOT	171.27 (± 149.56)	74.65 (± 113.55)		
to EOS	199.26 (± 85.45)	84.87 (± 67.92)		

Notes:

[131] - n=34 Baseline
n=27 Day 1
n=31 Day 2
n=26 Week 1
n=29 EOT
n=10 EOS
[132] - n=17 Baseline
n=14 Day 1, Week 1
n=15 Day 2
n=12 EOT
n=3 EOS

Statistical analyses

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

Day 1 vs baseline

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[133]
P-value	= 0.3359 [134]
Method	Wilcoxon (Mann-Whitney)

Notes:

[133] - Please note that the total number of subjects in this analisys is not n=55 but n=41: n=27 for Reparixin and n=14 for the SoC
[134] - p-values are referred to a two-sided Wilcoxon test for differences in the change

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

Day 2 vs baseline

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[135]
P-value	= 0.3136 [136]
Method	Wilcoxon (Mann-Whitney)

Notes:

[135] - Please note that the total number of subjects in this analisys is not n=55 but n=46: n=31 for Reparixin and n=15 for the SoC
[136] - p-values are referred to a two-sided Wilcoxon test for differences in the change

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

week 1 vs baseline

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[137]
P-value	= 0.0441 [138]
Method	Wilcoxon (Mann-Whitney)

Notes:

[137] - Please note that the total number of subjects in this analisys is not n=55 but n=40: n=26 for Reparixin and n=14 for the SoC
[138] - p-values are referred to a two-sided Wilcoxon test for differences in the change

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

EOT vs baseline

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[139]
P-value	= 0.0965 [140]
Method	Wilcoxon (Mann-Whitney)

Notes:

[139] - Please note that the total number of subjects in this analisys is not n=55 but n=41: n=29 for Reparixin and n=12 for the SoC
[140] - p-values are referred to a two-sided Wilcoxon test for differences in the change

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

EOS vs baseline

Comparison groups	Standard of Care (FAS) v Reparixin (FAS)

Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[141]
P-value	= 0.0519 [142]
Method	Wilcoxon (Mann-Whitney)

Notes:

[141] - Please note that the total number of subjects in this analisys is not n=55 but n=13: n=10 for Reparixin and n=3 for the SoC
[142] - p-values are referred to a two-sided Wilcoxon test for differences in the change

Secondary: Phase 2 - Change From Baseline in Reactive Protein (CRP)

End point title	Phase 2 - Change From Baseline in Reactive Protein (CRP)

End point description:

For a standard CRP test, a normal reading is less than 10 milligram per liter (mg/L). Levels between 10 mg/L and 100 mg/L are moderately elevated and are usually due to more significant inflammation from an infectious or non-infectious cause. Inflammatory status is documented by C-reactive protein (CRP) ≥ 100mg/L.

End point type	Secondary

End point timeframe:

Baseline, day 1, day 2, week 1, day 21(end of treatment), follow-up (FU) (7±3 days after treatment period)

End point values	Reparixin (FAS)	Standard of Care (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36[143]	19[144]		
Units: mg/L				
arithmetic mean (standard deviation)				
Baseline	57.04 (± 41.44)	58.87 (± 57.25)		
to Day 1	-0.14 (± 73.28)	38.46 (± 117.19)		
to Day 2	-29.24 (± 37.66)	-2.15 (± 52.37)		
to Week 1	-39.09 (± 56.56)	0.52 (± 80.24)		
to EOT	-40.88 (± 50.27)	-25.28 (± 87.16)		
to EOS	-49.43 (± 57.65)	-45.20 (± 78.97)		

Notes:

[143] - n=35 Baseline
n=11 Day 1, EOS
n=22 Day 2
n=26 Week 1
n=24 EOT

[144] - n=9 Day 1
n=8 Day 2
n=14 Week 1
n=13 EOT
n=7 EOS

Statistical analyses

Statistical analysis title	Reparixin vs Standard of care
Statistical analysis description:	
Day 1 vs baseline	
Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[145]
P-value	= 0.47 [146]
Method	Wilcoxon (Mann-Whitney)

Notes:

[145] - Please note that the total number of subjects in this analysis is not n=55 but n=20: n=11 for Reparixin and n=9 for the SoC

[146] - p-values are referred to a two-sided Wilcoxon test for differences in the change.

Statistical analysis title	Reparixin vs Standard of care
Statistical analysis description:	
Day 2 vs baseline	
Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[147]
P-value	= 0.425 [148]
Method	Wilcoxon (Mann-Whitney)

Notes:

[147] - Please note that the total number of subjects in this analysis is not n=55 but n=30: n=22 for Reparixin and n=8 for the SoC

[148] - p-values are referred to a two-sided Wilcoxon test for differences in the change.

Statistical analysis title	Reparixin vs Standard of care
Statistical analysis description:	
week 1 vs baseline	
Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[149]
P-value	= 0.086 [150]
Method	Wilcoxon (Mann-Whitney)

Notes:

[149] - Please note that the total number of subjects in this analysis is not n=55 but n=40: n=26 for Reparixin and n=14 for the SoC

[150] - p-values are referred to a two-sided Wilcoxon test for differences in the change.

Statistical analysis title	Reparixin vs Standard of care
Statistical analysis description:	
EOT vs baseline	
Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[151]
P-value	= 0.6 [152]
Method	Wilcoxon (Mann-Whitney)

Notes:

[151] - Please note that the total number of subjects in this analysis is not n=55 but n=37: n=24 for Reparixin and n=13 for the SoC
[152] - p-values are referred to a two-sided Wilcoxon test for differences in the change.

Statistical analysis title	Reparixin vs Standard of care

Statistical analysis description:

EOS vs baseline

Comparison groups	Reparixin (FAS) v Standard of Care (FAS)
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[153]
P-value	= 0.717 [154]
Method	Wilcoxon (Mann-Whitney)

Notes:

[153] - Please note that the total number of subjects in this analysis is not n=55 but n=18: n=11 for Reparixin and n=7 for the SoC
[154] - p-values are referred to a two-sided Wilcoxon test for differences in the change.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
AE were assessed throughout the study, till day 21.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups	
Reporting group title	Reparixin SAF

Reporting group description:

Reparixin oral tablets 1200 mg TID for 7 days

Reparixin: Reparixin was administered via oral tablets 1200 mg TID for 7 days. In case of improvement, treatment can be prolonged at discretion of the investigator up to a maximum of 21 days of treatment in total or live discharge from the hospital, whichever comes first.

Reporting group title	Standard of Care SAF

Reporting group description:

Standard of care. Frequently used standard of care medications were dexamethasone (or other corticosteroids), anticoagulants (low-molecular weight heparin), antibiotics, as needed.

Serious adverse events	Reparixin SAF	Standard of Care SAF	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 36 (2.78%)	1 / 19 (5.26%)	
number of deaths (all causes)	1	3	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 36 (2.78%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Reparixin SAF	Standard of Care SAF	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 36 (2.78%)	1 / 19 (5.26%)	
Injury, poisoning and procedural complications			

Post procedural discomfort subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	1 / 19 (5.26%) 1	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	1 / 19 (5.26%) 1	
Respiratory, thoracic and mediastinal disorders Respiratory failure subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1	1 / 19 (5.26%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The low number of patients enrolled, regarded as adequate for a preliminary phase II study which was initially designed as a larger phase II/III study. The open-label study design, regarded as justified in an early phase study.

Notes: