



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 PaO ₂ /FiO ₂ 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 (\pm 1), 14 (\pm 2), 21 (\pm 2), 28 (\pm 2), 60 (\pm 2) and 90 (\pm 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 patients 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: | |
| <ul style="list-style-type: none"> - 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 (\pm 7.9) | 10.1 (\pm 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 (\pm 16.8) | 15.9 (\pm 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 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 | 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 (PaO ₂) |
| End point description: | PaO ₂ —the oxygen pressure in arterial blood. The PaO ₂ reflects how well oxygen is able to move from the lungs to the blood. It is often altered by severe illnesses, with the PaO ₂ 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 (± 0.00) | -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 PaO ₂ /FiO ₂ 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 (\pm 30.15) | 9.65 (\pm 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 occurrences (all) | 2 / 182 (1.10%) 2 | 1 / 88 (1.14%) 1 | |
| Poor venous access subjects affected / exposed occurrences (all) | 1 / 182 (0.55%) 1 | 1 / 88 (1.14%) 1 | |
| Thrombophlebitis subjects affected / exposed occurrences (all) | 2 / 182 (1.10%) 2 | 0 / 88 (0.00%) 0 | |
| Surgical and medical procedures Tracheostomy subjects affected / exposed occurrences (all) | 1 / 182 (0.55%) 1 | 0 / 88 (0.00%) 1 | |
| General disorders and administration site conditions Illness subjects affected / exposed occurrences (all) | 3 / 182 (1.65%) 4 | 1 / 88 (1.14%) 1 | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 0 / 182 (0.00%) 0 | 3 / 88 (3.41%) 4 | |
| Pyrexia subjects affected / exposed occurrences (all) | 3 / 182 (1.65%) 3 | 0 / 88 (0.00%) 0 | |
| Asthenia subjects affected / exposed occurrences (all) | 1 / 182 (0.55%) 1 | 1 / 88 (1.14%) 1 | |
| Extravasation subjects affected / exposed occurrences (all) | 1 / 182 (0.55%) 1 | 1 / 88 (1.14%) 1 | |
| Pain subjects affected / exposed occurrences (all) | 1 / 182 (0.55%) 1 | 0 / 88 (0.00%) 0 | |
| Reproductive system and breast disorders Benign prostatic hyperplasia subjects affected / exposed occurrences (all) | 0 / 182 (0.00%) 0 | 1 / 88 (1.14%) 1 | |
| Metrorrhagia | | | |

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

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

| | | | |
|--|----------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 182 (0.00%) 0 | 1 / 88 (1.14%) 1 | |
| Electrocardiogram QT prolonged subjects affected / exposed occurrences (all) | 1 / 182 (0.55%) 1 | 0 / 88 (0.00%) 0 | |
| Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) | 0 / 182 (0.00%) 0 | 1 / 88 (1.14%) 1 | |
| Vitamin D decreased subjects affected / exposed occurrences (all) | 1 / 182 (0.55%) 1 | 0 / 88 (0.00%) 0 | |
| Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) | 0 / 182 (0.00%) 0 | 1 / 88 (1.14%) 1 | |
| Cardiac disorders Tachycardia subjects affected / exposed occurrences (all) | 4 / 182 (2.20%) 5 | 3 / 88 (3.41%) 3 | |
| Atrial fibrillation subjects affected / exposed occurrences (all) | 4 / 182 (2.20%) 4 | 1 / 88 (1.14%) 1 | |
| Bradycardia subjects affected / exposed occurrences (all) | 3 / 182 (1.65%) 3 | 0 / 88 (0.00%) 0 | |
| Left ventricular failure subjects affected / exposed occurrences (all) | 0 / 182 (0.00%) 0 | 1 / 88 (1.14%) 1 | |
| Sinus tachycardia subjects affected / exposed occurrences (all) | 0 / 182 (0.00%) 0 | 1 / 88 (1.14%) 1 | |
| Supraventricular tachycardia subjects affected / exposed occurrences (all) | 1 / 182 (0.55%) 1 | 0 / 88 (0.00%) 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 occurrences (all) | 0 / 182 (0.00%) 0 | 1 / 88 (1.14%) 1 | |
| Pancytopenia subjects affected / exposed occurrences (all) | 1 / 182 (0.55%) 1 | 0 / 88 (0.00%) 0 | |
| Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all) | 1 / 182 (0.55%) 1 | 0 / 88 (0.00%) 0 | |
| Eye disorders Visual impairment subjects affected / exposed occurrences (all) | 1 / 182 (0.55%) 1 | 0 / 88 (0.00%) 0 | |
| Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) | 13 / 182 (7.14%) 14 | 10 / 88 (11.36%) 10 | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 2 / 182 (1.10%) 2 | 1 / 88 (1.14%) 1 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 1 / 182 (0.55%) 1 | 1 / 88 (1.14%) 1 | |
| Dysphagia subjects affected / exposed occurrences (all) | 1 / 182 (0.55%) 1 | 1 / 88 (1.14%) 1 | |
| Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) | 2 / 182 (1.10%) 2 | 0 / 88 (0.00%) 0 | |
| Vomiting subjects affected / exposed occurrences (all) | 1 / 182 (0.55%) 1 | 1 / 88 (1.14%) 1 | |
| Diverticulum intestinal haemorrhagic subjects affected / exposed occurrences (all) | 1 / 182 (0.55%) 1 | 0 / 88 (0.00%) 0 | |
| Hepatobiliary disorders | | | |

| | | | |
|---|----------------------|---------------------|--|
| Hypertransaminasaemia subjects affected / exposed occurrences (all) | 3 / 182 (1.65%) 3 | 2 / 88 (2.27%) 2 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash subjects affected / exposed occurrences (all) | 1 / 182 (0.55%) 1 | 1 / 88 (1.14%) 1 | |
| Decubitus ulcer subjects affected / exposed occurrences (all) | 1 / 182 (0.55%) 1 | 0 / 88 (0.00%) 0 | |
| Hyperhidrosis subjects affected / exposed occurrences (all) | 1 / 182 (0.55%) 1 | 0 / 88 (0.00%) 0 | |
| Rash macular subjects affected / exposed occurrences (all) | 1 / 182 (0.55%) 1 | 0 / 88 (0.00%) 0 | |
| Skin lesion subjects affected / exposed occurrences (all) | 1 / 182 (0.55%) 1 | 0 / 88 (0.00%) 0 | |
| Renal and urinary disorders | | | |
| Oliguria subjects affected / exposed occurrences (all) | 3 / 182 (1.65%) 3 | 2 / 88 (2.27%) 2 | |
| Acute kidney injury subjects affected / exposed occurrences (all) | 2 / 182 (1.10%) 2 | 1 / 88 (1.14%) 1 | |
| Endocrine disorders | | | |
| Hyperparathyroidism secondary subjects affected / exposed occurrences (all) | 2 / 182 (1.10%) 2 | 0 / 88 (0.00%) 0 | |
| Euthyroid sick syndrome subjects affected / exposed occurrences (all) | 0 / 182 (0.00%) 0 | 1 / 88 (1.14%) 1 | |
| Hypothyroidism subjects affected / exposed occurrences (all) | 1 / 182 (0.55%) 1 | 0 / 88 (0.00%) 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 occurrences (all) | 0 / 182 (0.00%) 0 | 1 / 88 (1.14%) 1 | |
| Moraxella infection subjects affected / exposed occurrences (all) | 1 / 182 (0.55%) 1 | 0 / 88 (0.00%) 0 | |
| Oral fungal infection subjects affected / exposed occurrences (all) | 1 / 182 (0.55%) 1 | 0 / 88 (0.00%) 0 | |
| Phlebitis infective subjects affected / exposed occurrences (all) | 1 / 182 (0.55%) 1 | 0 / 88 (0.00%) 0 | |
| Staphylococcal infection subjects affected / exposed occurrences (all) | 1 / 182 (0.55%) 1 | 0 / 88 (0.00%) 0 | |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus subjects affected / exposed occurrences (all) | 4 / 182 (2.20%) 4 | 1 / 88 (1.14%) 1 | |
| Hyperkalaemia subjects affected / exposed occurrences (all) | 2 / 182 (1.10%) 2 | 2 / 88 (2.27%) 2 | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 3 / 182 (1.65%) 3 | 1 / 88 (1.14%) 1 | |
| Vitamin D deficiency subjects affected / exposed occurrences (all) | 1 / 182 (0.55%) 1 | 3 / 88 (3.41%) 3 | |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 2 / 182 (1.10%) 2 | 1 / 88 (1.14%) 1 | |
| Eating disorder subjects affected / exposed occurrences (all) | 2 / 182 (1.10%) 2 | 0 / 88 (0.00%) 0 | |
| Dehydration subjects affected / exposed occurrences (all) | 1 / 182 (0.55%) 1 | 0 / 88 (0.00%) 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: