



Clinical trial results:

Phase 3 randomized, double-blind, placebo-controlled, multi-center study to assess the efficacy and safety of ruxolitinib in patients with COVID-19 associated cytokine storm (RUXCOVID)

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2020-001662-11 |
| Trial protocol | DE GB FR ES IT |
| Global end of trial date | 17 October 2020 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v2 (current) |
| This version publication date | 20 June 2021 |
| First version publication date | 01 May 2021 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | CINC424J12301 |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04362137 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.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 | 17 October 2020 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 17 October 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the efficacy and safety of ruxolitinib in the treatment of patients with COVID-19 with severe respiratory disease.

The primary objective was to evaluate the efficacy (as measured by a composite endpoint of proportion of patients who die, develop respiratory failure [require mechanical ventilation], or require ICU care) of ruxolitinib + standard of care (SoC) therapy compared with placebo + SoC therapy, for the treatment of COVID-19 by Day 29.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------|
| Actual start date of recruitment | 02 May 2020 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Russian Federation: 171 |
| Country: Number of subjects enrolled | United States: 48 |
| Country: Number of subjects enrolled | Brazil: 41 |
| Country: Number of subjects enrolled | Spain: 39 |
| Country: Number of subjects enrolled | Argentina: 27 |
| Country: Number of subjects enrolled | Peru: 25 |
| Country: Number of subjects enrolled | Turkey: 20 |
| Country: Number of subjects enrolled | Mexico: 18 |
| Country: Number of subjects enrolled | United Kingdom: 14 |
| Country: Number of subjects enrolled | Colombia: 10 |
| Country: Number of subjects enrolled | France: 10 |
| Country: Number of subjects enrolled | Germany: 9 |
| Worldwide total number of subjects | 432 |
| EEA total number of subjects | 58 |

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) | 310 |
| From 65 to 84 years | 118 |
| 85 years and over | 4 |

Subject disposition

Recruitment

Recruitment details:

Participants took part in 61 investigative sites in 12 countries.

Pre-assignment

Screening details:

Patients were to be randomized on the same day as screening or up to 2 days after completing the screening procedures.

Period 1

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

Arms

| | |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Ruxolitinib 5 mg |

Arm description:

Ruxolitinib 5 mg tablets twice daily (b.i.d.) for 14 days with possible extension of treatment to 28 days

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ruxolitinib |
| Investigational medicinal product code | INC424 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Ruxolitinib 5 mg tablets twice daily (b.i.d.) for 14 days with possible extension of treatment to 28 days

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Matching-image placebo for 14 days with possible extension of treatment to 28 days

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

Dosage and administration details:

Matching-image placebo for 14 days with possible extension of treatment to 28 days

| Number of subjects in period 1 | Ruxolitinib 5 mg | Placebo |
|---------------------------------------|------------------|---------|
| Started | 287 | 145 |
| Safety Set | 281 | 143 |
| Completed | 269 | 139 |
| Not completed | 18 | 6 |
| Adverse event, serious fatal | 9 | 3 |
| Patient decision | 6 | 3 |
| Adverse event, non-fatal | 1 | - |
| Protocol deviation | 1 | - |
| Lost to follow-up | 1 | - |

Baseline characteristics

Reporting groups

| | |
|---|------------------|
| Reporting group title | Ruxolitinib 5 mg |
| Reporting group description: | |
| Ruxolitinib 5 mg tablets twice daily (b.i.d.) for 14 days with possible extension of treatment to 28 days | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Matching-image placebo for 14 days with possible extension of treatment to 28 days | |

| Reporting group values | Ruxolitinib 5 mg | Placebo | Total |
|---|------------------|---------|-------|
| Number of subjects | 287 | 145 | 432 |
| 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) | 204 | 106 | 310 |
| From 65-84 years | 79 | 39 | 118 |
| 85 years and over | 4 | 0 | 4 |
| Age Continuous Units: years | | | |
| arithmetic mean | 56.4 | 56.9 | |
| standard deviation | ± 13.7 | ± 12.5 | - |
| Sex: Female, Male Units: participants | | | |
| Female | 125 | 72 | 197 |
| Male | 162 | 73 | 235 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| White | 242 | 109 | 351 |
| American Indian Or Alaska Native | 26 | 13 | 39 |
| Black Or African American | 6 | 9 | 15 |
| Asian | 5 | 5 | 10 |
| Multiple | 3 | 2 | 5 |
| Unknown | 5 | 7 | 12 |

End points

End points reporting groups

| | |
|---|------------------|
| Reporting group title | Ruxolitinib 5 mg |
| Reporting group description: | |
| Ruxolitinib 5 mg tablets twice daily (b.i.d.) for 14 days with possible extension of treatment to 28 days | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Matching-image placebo for 14 days with possible extension of treatment to 28 days | |

Primary: Proportion of patients who die, develop respiratory failure [require mechanical ventilation] or require intensive care unit (ICU) care

| | |
|--|--|
| End point title | Proportion of patients who die, develop respiratory failure [require mechanical ventilation] or require intensive care unit (ICU) care |
| End point description: | |
| Efficacy is measured by a composite endpoint of proportion of patients who die, develop respiratory failure [require mechanical ventilation], or require intensive care unit [ICU] care for the treatment of COVID-19. Analyses are cumulative, thus analysis on Day 29 includes all events till that day. Patients who developed respiratory failure and/or required ICU at randomization are excluded from the analysis. | |
| End point type | Primary |
| End point timeframe: | |
| Day 1 - Day 29 | |

| End point values | Ruxolitinib 5 mg | Placebo | | |
|-----------------------------|------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 284 | 144 | | |
| Units: participants | 34 | 17 | | |

Statistical analyses

| | |
|---|----------------------------|
| Statistical analysis title | Ruxolitinib 5 mg/Placebo |
| Comparison groups | Placebo v Ruxolitinib 5 mg |
| Number of subjects included in analysis | 428 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.769 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.91 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.48 |
| upper limit | 1.73 |

Secondary: Clinical status

| | |
|---|-----------------|
| End point title | Clinical status |
| End point description: | |
| Clinical status is measured with the 9-point ordinal scale. | |
| The scoring is: | |
| <ul style="list-style-type: none"> - Uninfected patients have a score 0 (no clinical or virological evidence of infection). - Ambulatory patients (not in hospital or in hospital and ready for discharge) can have a score 1 (no limitation of activities) or 2 (limitation of activities). - Hospitalized patients with mild disease can have score 3 (no oxygen therapy defined as peripheral oxygen saturation (SpO2) \geq 94% on room air) or 4 (oxygen by mask or nasal prongs). - Hospitalized patients with severe disease can have score 5 (non-invasive ventilation or high-flow oxygen), 6 (intubation and mechanical ventilation) or 7 (ventilation + additional organ support - pressors, RRT (renal replacement therapy), ECMO (extracorporeal membrane oxygenation)). - Patients who die have a score 8. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Day 15, Day 29 | |

| End point values | Ruxolitinib 5 mg | Placebo | | |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 287 | 145 | | |
| Units: score on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline (n=286, 145) | 3.7 (\pm 0.56) | 3.7 (\pm 0.53) | | |
| Day 15 (n=280, 142) | 1.8 (\pm 1.54) | 1.8 (\pm 1.41) | | |
| Day 29 (n=278, 142) | 1.1 (\pm 1.61) | 1.0 (\pm 1.41) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with at least two-point improvement from baseline in clinical status

| | |
|---|---|
| End point title | Percentage of patients with at least two-point improvement from baseline in clinical status |
| End point description: | |
| Percentage of patients with at least two points improvement in clinical status on the 9-point ordinal scale. The baseline value of clinical status is defined as the last assessment prior to first dose of double-blind treatment. Patients with missing data at Day 15 and/or Day 29 are treated as non-responders. | |
| End point type | Secondary |

End point timeframe:
Baseline, Day 15, Day 29

| End point values | Ruxolitinib 5 mg | Placebo | | |
|-----------------------------|------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 286 | 145 | | |
| Units: percentage | | | | |
| number (not applicable) | | | | |
| Day 15 (n=286, 145) | 72.0 | 74.5 | | |
| Day 29 (n=286, 145) | 88.1 | 89.0 | | |

Statistical analyses

| Statistical analysis title | Ruxolitinib 5 mg/Placebo |
|---|----------------------------|
| Statistical analysis description: Day 15 | |
| Comparison groups | Ruxolitinib 5 mg v Placebo |
| Number of subjects included in analysis | 431 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.647 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.89 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.55 |
| upper limit | 1.46 |

| Statistical analysis title | Ruxolitinib 5 mg/Placebo |
|---|----------------------------|
| Statistical analysis description: Day 29 | |
| Comparison groups | Ruxolitinib 5 mg v Placebo |
| Number of subjects included in analysis | 431 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.997 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.52 |
| upper limit | 1.92 |

Secondary: Percentage of patients with at least one-point improvement from baseline in clinical status

| | |
|-----------------|---|
| End point title | Percentage of patients with at least one-point improvement from baseline in clinical status |
|-----------------|---|

End point description:

Percentage of patients with at least one point improvement in clinical status on the 9-point ordinal scale. The baseline value of clinical status is defined as the last assessment prior to first dose of double-blind treatment. Patients with missing data at Day 15 and/or Day 29 are treated as non-responders.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Day 15, Day 29

| End point values | Ruxolitinib 5 mg | Placebo | | |
|-----------------------------|------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 286 | 145 | | |
| Units: percentage | | | | |
| number (not applicable) | | | | |
| Day 15 (n=286, 145) | 87.4 | 88.3 | | |
| Day 29 (n=286, 145) | 91.3 | 93.8 | | |

Statistical analyses

| | |
|----------------------------|--------------------------|
| Statistical analysis title | Ruxolitinib 5 mg/Placebo |
|----------------------------|--------------------------|

Statistical analysis description:

Day 15

| | |
|---|----------------------------|
| Comparison groups | Ruxolitinib 5 mg v Placebo |
| Number of subjects included in analysis | 431 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.946 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.98 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.51 |
| upper limit | 1.87 |

| | |
|---|----------------------------|
| Statistical analysis title | Ruxolitinib 5 mg/Placebo |
| Statistical analysis description: | |
| Day 29 | |
| Comparison groups | Ruxolitinib 5 mg v Placebo |
| Number of subjects included in analysis | 431 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.573 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.79 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.35 |
| upper limit | 1.79 |

Secondary: Percentage of patients with at least one-point deterioration from baseline in clinical status

| | |
|--|---|
| End point title | Percentage of patients with at least one-point deterioration from baseline in clinical status |
| End point description: | |
| Percentage of patients with at least one point deterioration in clinical status on the 9-point ordinal scale. The baseline value of clinical status is defined as the last assessment prior to first dose of double-blind treatment. Patients with missing data at Day 15 and/or Day 29 are treated as non-responders. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Day 15, Day 29 | |

| End point values | Ruxolitinib 5 mg | Placebo | | |
|-----------------------------|------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 286 | 145 | | |
| Units: percentage | | | | |
| number (not applicable) | | | | |
| Day 15 (n=286, 145) | 5.6 | 6.2 | | |
| Day 29 (n=286, 145) | 4.9 | 3.4 | | |

Statistical analyses

| | |
|---|----------------------------|
| Statistical analysis title | Ruxolitinib 5 mg/Placebo |
| Statistical analysis description: | |
| Day 15 | |
| Comparison groups | Ruxolitinib 5 mg v Placebo |
| Number of subjects included in analysis | 431 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.532 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.31 |
| upper limit | 1.83 |

| | |
|---|----------------------------|
| Statistical analysis title | Ruxolitinib 5 mg/Placebo |
| Statistical analysis description: | |
| Day 29 | |
| Comparison groups | Ruxolitinib 5 mg v Placebo |
| Number of subjects included in analysis | 431 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.764 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.4 |
| upper limit | 3.49 |

Secondary: Time to improvement in clinical status

| | |
|--|--|
| End point title | Time to improvement in clinical status |
| End point description: | |
| Time to improvement in clinical status from baseline category to one less severe category of the 9-point ordinal scale. The baseline value of clinical status is defined as the last assessment prior to first dose of double-blind treatment. | |
| Median time to improvement is estimated by Kaplan-Meier method, with dead patients being censored at the maximum follow-up time in the study. Patients who did not achieve improvement and did not die are censored at their last clinical status assessment date. | |
| End point type | Secondary |
| End point timeframe: | |
| 29 days | |

| End point values | Ruxolitinib 5 mg | Placebo | | |
|----------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 286 | 145 | | |
| Units: days | | | | |
| median (confidence interval 95%) | 9.0 (8.0 to 10.0) | 9.0 (8.0 to 12.0) | | |

Statistical analyses

| Statistical analysis title | Ruxolitinib 5 mg/Placebo |
|---|----------------------------|
| Comparison groups | Ruxolitinib 5 mg v Placebo |
| Number of subjects included in analysis | 431 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.33 |
| Method | Proportional hazards model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9 |
| upper limit | 1.37 |

Secondary: Mean change from baseline in the clinical status

| | |
|---|--|
| End point title | Mean change from baseline in the clinical status |
| End point description: | |
| Mean change from baseline in the 9-point ordinal scale. The baseline value of clinical status is defined as the last assessment prior to first dose of double-blind treatment. Patients with missing data at Day 15 and/or Day 29 are excluded from the analysis. | |
| A negative change from baseline in the clinical status is a favorable outcome. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Day 15, Day 29 | |

| End point values | Ruxolitinib 5 mg | Placebo | | |
|-------------------------------------|------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 287 | 145 | | |
| Units: score on scale | | | | |
| least squares mean (standard error) | | | | |
| Day 15 (n=280, 142) | -1.96 (± 0.084) | -1.93 (± 0.118) | | |
| Day 29 (n=278, 142) | -2.61 (± 0.090) | -2.69 (± 0.126) | | |

Statistical analyses

| Statistical analysis title | Ruxolitinib 5 mg/Placebo |
|---|----------------------------|
| Statistical analysis description: | |
| Day 15 | |
| Comparison groups | Ruxolitinib 5 mg v Placebo |
| Number of subjects included in analysis | 432 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | = 0.831 |
| Method | ANCOVA |
| Parameter estimate | Least squares (LS) mean |
| Point estimate | -0.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.31 |
| upper limit | 0.25 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.144 |

Notes:

[1] - Due to EudraCT system limitations the number of subjects included in this analysis is not accurately presented in this record. The number of subjects included in this analysis is 422 instead of 432 as indicated in this record.

| Statistical analysis title | Ruxolitinib 5 mg/Placebo |
|---|----------------------------|
| Statistical analysis description: | |
| Day 29 | |
| Comparison groups | Ruxolitinib 5 mg v Placebo |
| Number of subjects included in analysis | 432 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[2] |
| P-value | = 0.624 |
| Method | ANCOVA |
| Parameter estimate | LS Mean |
| Point estimate | 0.08 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.23 |
| upper limit | 0.38 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.155 |

Notes:

[2] - Due to EudraCT system limitations the number of subjects included in this analysis is not accurately presented in this record. The number of subjects included in this analysis is 420 instead of 432 as indicated in this record.

Secondary: Mortality rate

| | |
|--|----------------|
| End point title | Mortality rate |
| End point description: | |
| Mortality rate is determined as the proportion of participants who died by study Day 15 and Day 29 | |
| End point type | Secondary |
| End point timeframe: | |
| Day 15, Day 29 | |

| End point values | Ruxolitinib 5 mg | Placebo | | |
|-----------------------------|------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 286 | 145 | | |
| Units: participants | | | | |
| Day 15 (n=286, 145) | 6 | 2 | | |
| Day 29 (n=286, 145) | 9 | 3 | | |

Statistical analyses

| | |
|---|----------------------------|
| Statistical analysis title | Ruxolitinib 5 mg/Placebo |
| Statistical analysis description: | |
| Day 15 | |
| Comparison groups | Ruxolitinib 5 mg v Placebo |
| Number of subjects included in analysis | 431 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.944 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.94 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.2 |
| upper limit | 5.57 |

| | |
|---|----------------------------|
| Statistical analysis title | Ruxolitinib 5 mg/Placebo |
| Statistical analysis description: Day 29 | |
| Comparison groups | Ruxolitinib 5 mg v Placebo |
| Number of subjects included in analysis | 431 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.775 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.35 |
| upper limit | 5.11 |

Secondary: Proportion of patients requiring mechanical ventilation

| | |
|--|---|
| End point title | Proportion of patients requiring mechanical ventilation |
| End point description: Proportion of patients requiring mechanical ventilation. Analyses are cumulative, thus analysis on Day 29 includes all events till that day. Patients who required mechanical ventilation at randomization are excluded from the analysis. | |
| End point type | Secondary |
| End point timeframe: Day 1 - Day 29 | |

| | | | | |
|-----------------------------|------------------|-----------------|--|--|
| End point values | Ruxolitinib 5 mg | Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 286 | 145 | | |
| Units: participants | 22 | 10 | | |

Statistical analyses

| | |
|-----------------------------------|----------------------------|
| Statistical analysis title | Ruxolitinib 5 mg/Placebo |
| Comparison groups | Ruxolitinib 5 mg v Placebo |

| | |
|---|----------------------|
| Number of subjects included in analysis | 431 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.987 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.99 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.45 |
| upper limit | 2.21 |

Secondary: Duration of hospitalization

| | |
|---|-----------------------------|
| End point title | Duration of hospitalization |
| End point description: | |
| Duration of hospitalization is defined as time to hospital discharge. Median time to hospital discharge is estimated by Kaplan-Meier method, with dead patients being censored at the maximum follow-up time in the study. Patients who were not discharged and did not die are censored at their last assessment date. | |
| End point type | Secondary |
| End point timeframe: | |
| 29 days | |

| End point values | Ruxolitinib 5 mg | Placebo | | |
|----------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 286 | 145 | | |
| Units: days | | | | |
| median (confidence interval 95%) | 9.0 (8.0 to 10.0) | 9.0 (8.0 to 12.0) | | |

Statistical analyses

| | |
|---|----------------------------|
| Statistical analysis title | Ruxolitinib 5 mg/Placebo |
| Comparison groups | Ruxolitinib 5 mg v Placebo |
| Number of subjects included in analysis | 431 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.738 |
| Method | Proportional hazards model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.04 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.84 |
| upper limit | 1.28 |

Secondary: Time to hospital discharge or to a NEWS2 score of ≤ 2

| | |
|--|--|
| End point title | Time to hospital discharge or to a NEWS2 score of ≤ 2 |
| End point description: | |
| <p>The time to hospital discharge or to a National Early Warning Score 2 (NEWS2) of ≤ 2 and maintained for 24 hours whichever comes first.</p> <p>The NEWS2 is based on a simple aggregate scoring system in which a score is allocated to physiological measurements, already recorded in routine practice presentation or when a patient is being monitored in hospital. The score ranges from 0 (best) to 23 (worst).</p> <p>Median time is estimated by Kaplan-Meier method, with dead patients being censored at the maximum follow-up time in the study.</p> | |
| End point type | Secondary |
| End point timeframe: | |
| 29 days | |

| End point values | Ruxolitinib 5 mg | Placebo | | |
|----------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 286 | 145 | | |
| Units: days | | | | |
| median (confidence interval 95%) | 4.0 (3.0 to 4.0) | 4.0 (3.0 to 5.0) | | |

Statistical analyses

| | |
|---|----------------------------|
| Statistical analysis title | Ruxolitinib 5 mg/Placebo |
| Comparison groups | Ruxolitinib 5 mg v Placebo |
| Number of subjects included in analysis | 431 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.869 |
| Method | Proportional hazards model |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.84 |
| upper limit | 1.23 |

Secondary: Change from baseline in NEWS2 score

| | |
|-----------------|-------------------------------------|
| End point title | Change from baseline in NEWS2 score |
|-----------------|-------------------------------------|

End point description:

The National Early Warning Score 2 (NEWS2) is based on a simple aggregate scoring system in which a score is allocated to physiological measurements, already recorded in routine practice presentation or when a patient is being monitored in hospital. The score ranges from 0 (best) to 23 (worst). At each visit, only patients with a value at both baseline and the respective visit are included.

A negative change from baseline in NEWS2 score is a favorable outcome.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Days 3, 5, 8, 11, 15, and 29

| End point values | Ruxolitinib 5 mg | Placebo | | |
|--------------------------------------|------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 287 | 145 | | |
| Units: score on scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 3 (n=264, 135) | -0.7 (± 1.91) | -0.6 (± 2.13) | | |
| Day 5 (n=230, 120) | -1.0 (± 2.02) | -0.8 (± 2.19) | | |
| Day 8 (n=175, 91) | -1.3 (± 2.25) | -1.3 (± 2.60) | | |
| Day 11 (n=113, 66) | -1.1 (± 2.70) | -1.3 (± 2.74) | | |
| Day 15 (n=257, 132) | -1.9 (± 2.34) | -2.2 (± 2.35) | | |
| Day 29 (n=234, 122) | -2.3 (± 2.37) | -2.5 (± 2.17) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in SpO2/FiO2 ratio

| | |
|-----------------|---|
| End point title | Change from baseline in SpO2/FiO2 ratio |
|-----------------|---|

End point description:

Change from baseline in peripheral oxygen saturation / fraction of inspired oxygen ratio (SpO2/FiO2 ratio). At each visit, only patients with a value at both baseline and the respective visit are included. A positive change from baseline in SpO2/FiO2 ratio is a favorable outcome.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Day 15, Day 29

| End point values | Ruxolitinib 5 mg | Placebo | | |
|--------------------------------------|---------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 287 | 145 | | |
| Units: no units | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 15 (n=260, 132) | 90.110 (± 104.4783) | 106.766 (± 100.9778) | | |
| Day 29 (n=232, 124) | 105.553 (± 98.2452) | 109.710 (± 95.4279) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients with no oxygen therapy

| | |
|---|---|
| End point title | Proportion of patients with no oxygen therapy |
| End point description: Proportion of patients with no oxygen therapy (defined as oxygen saturation \geq 94% on room air) at Days 15 and 29. Analyses are cumulative, thus analysis on each day includes all events till that day. Patients with missing data at Day 15 and/or Day 29 are excluded from the analysis. | |
| End point type | Secondary |
| End point timeframe: Day 15, Day 29 | |

| End point values | Ruxolitinib 5 mg | Placebo | | |
|-----------------------------|------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 287 | 145 | | |
| Units: participants | | | | |
| Day 15 (n= 274, 140) | 255 | 133 | | |
| Day 29 (n= 269, 139) | 262 | 136 | | |

Statistical analyses

| | |
|---|----------------------------|
| Statistical analysis title | Ruxolitinib 5 mg/Placebo |
| Statistical analysis description: Day 15 | |
| Comparison groups | Ruxolitinib 5 mg v Placebo |
| Number of subjects included in analysis | 432 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.325 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.61 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.23 |
| upper limit | 1.63 |

| | |
|---|----------------------------|
| Statistical analysis title | Ruxolitinib 5 mg/Placebo |
| Statistical analysis description: Day 29 | |
| Comparison groups | Ruxolitinib 5 mg v Placebo |
| Number of subjects included in analysis | 432 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.22 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.25 |
| upper limit | 5.4 |

Post-hoc: All Collected Deaths

| | |
|---|----------------------|
| End point title | All Collected Deaths |
| End point description: Deaths in the safety population were evaluated in all participants who received at least one dose of double-blind treatment. Total deaths were evaluated in all participants randomized. | |
| End point type | Post-hoc |
| End point timeframe: 29 days | |

| End point values | Ruxolitinib 5 mg | Placebo | | |
|--|------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 287 | 145 | | |
| Units: participants | | | | |
| Deaths in the safety population (n=281, 143) | 9 | 3 | | |
| Total deaths (n=287, 145) | 9 | 3 | | |

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of double-blind treatment and up to the last study visit (Day 29).

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 23.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Ruxolitinib 5 mg |
|-----------------------|------------------|

Reporting group description:

Ruxolitinib 5 mg tablets twice daily (b.i.d.) for 14 days with possible extension of treatment to 28 days

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

Reporting group description:

Matching-image placebo for 14 days with possible extension of treatment to 28 days

| Serious adverse events | Ruxolitinib 5 mg | Placebo | |
|---|-------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 31 / 281 (11.03%) | 15 / 143 (10.49%) | |
| number of deaths (all causes) | 9 | 3 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 281 (0.00%) | 1 / 143 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 281 (0.00%) | 1 / 143 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Endotracheal intubation complication | | | |
| subjects affected / exposed | 1 / 281 (0.36%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Fall | | | |
| subjects affected / exposed | 0 / 281 (0.00%) | 1 / 143 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 281 (0.36%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock | | | |
| subjects affected / exposed | 1 / 281 (0.36%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Adams-Stokes syndrome | | | |
| subjects affected / exposed | 1 / 281 (0.36%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 281 (0.36%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 281 (0.36%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 0 / 281 (0.00%) | 1 / 143 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Nervous system disorders | | | |
| Cerebral infarction | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 281 (0.36%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hypoglycaemic coma | | | |
| subjects affected / exposed | 1 / 281 (0.36%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 1 / 281 (0.36%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 1 / 281 (0.36%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Adverse event | | | |
| subjects affected / exposed | 1 / 281 (0.36%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 281 (0.36%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 1 / 281 (0.36%) | 1 / 143 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Performance status decreased | | | |
| subjects affected / exposed | 1 / 281 (0.36%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|---|---|--|
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 281 (0.00%) 0 / 0 0 / 0 | 1 / 143 (0.70%) 0 / 1 0 / 0 | |
| Gastrointestinal disorders Pancreatitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 281 (0.36%) 0 / 1 0 / 0 | 0 / 143 (0.00%) 0 / 0 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders Acute respiratory distress syndrome subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 281 (0.36%) 0 / 1 0 / 1 | 1 / 143 (0.70%) 0 / 1 0 / 0 | |
| Acute respiratory failure subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 4 / 281 (1.42%) 0 / 4 0 / 0 | 1 / 143 (0.70%) 0 / 1 0 / 0 | |
| Dyspnoea subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 281 (0.36%) 0 / 1 0 / 0 | 0 / 143 (0.00%) 0 / 0 0 / 0 | |
| Hypoxia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 4 / 281 (1.42%) 0 / 4 0 / 1 | 4 / 143 (2.80%) 0 / 4 0 / 0 | |
| Pneumothorax subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 281 (0.36%) 0 / 2 0 / 0 | 0 / 143 (0.00%) 0 / 0 0 / 0 | |
| Pulmonary fibrosis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 281 (0.36%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory disorder | | | |
| subjects affected / exposed | 1 / 281 (0.36%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory distress | | | |
| subjects affected / exposed | 1 / 281 (0.36%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 2 / 281 (0.71%) | 2 / 143 (1.40%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Psychiatric disorders | | | |
| Mental status changes | | | |
| subjects affected / exposed | 1 / 281 (0.36%) | 0 / 143 (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 | | | |
| Antibiotic associated colitis | | | |
| subjects affected / exposed | 1 / 281 (0.36%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 281 (0.36%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| COVID-19 | | | |
| subjects affected / exposed | 8 / 281 (2.85%) | 3 / 143 (2.10%) | |
| occurrences causally related to treatment / all | 0 / 8 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 1 | |
| COVID-19 pneumonia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 281 (0.36%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia bacteraemia | | | |
| subjects affected / exposed | 0 / 281 (0.00%) | 1 / 143 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 281 (1.07%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia fungal | | | |
| subjects affected / exposed | 1 / 281 (0.36%) | 0 / 143 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 281 (0.00%) | 1 / 143 (0.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 2 %

| Non-serious adverse events | Ruxolitinib 5 mg | Placebo | |
|---|--------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 113 / 281 (40.21%) | 62 / 143 (43.36%) | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 17 / 281 (6.05%) | 6 / 143 (4.20%) | |
| occurrences (all) | 17 | 6 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 5 / 281 (1.78%) | 3 / 143 (2.10%) | |
| occurrences (all) | 5 | 3 | |
| Transaminases increased | | | |

| | | | |
|---|--|--|--|
| subjects affected / exposed occurrences (all) | 7 / 281 (2.49%) 7 | 2 / 143 (1.40%) 2 | |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 4 / 281 (1.42%) 4 | 3 / 143 (2.10%) 3 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) | 2 / 281 (0.71%) 4 23 / 281 (8.19%) 28 | 4 / 143 (2.80%) 4 11 / 143 (7.69%) 12 | |
| Blood and lymphatic system disorders Leukocytosis subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytosis subjects affected / exposed occurrences (all) | 4 / 281 (1.42%) 4 6 / 281 (2.14%) 6 6 / 281 (2.14%) 6 | 4 / 143 (2.80%) 5 4 / 143 (2.80%) 4 3 / 143 (2.10%) 3 | |
| General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) | 6 / 281 (2.14%) 6 10 / 281 (3.56%) 10 6 / 281 (2.14%) 6 | 0 / 143 (0.00%) 0 2 / 143 (1.40%) 4 2 / 143 (1.40%) 2 | |
| Gastrointestinal disorders Abdominal pain | | | |

| | | | |
|--|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 4 / 281 (1.42%) 4 | 4 / 143 (2.80%) 5 | |
| Constipation subjects affected / exposed occurrences (all) | 9 / 281 (3.20%) 9 | 7 / 143 (4.90%) 7 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 21 / 281 (7.47%) 21 | 12 / 143 (8.39%) 14 | |
| Nausea subjects affected / exposed occurrences (all) | 6 / 281 (2.14%) 6 | 11 / 143 (7.69%) 11 | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 12 / 281 (4.27%) 12 | 3 / 143 (2.10%) 4 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 3 / 281 (1.07%) 3 | 3 / 143 (2.10%) 3 | |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 6 / 281 (2.14%) 6 | 1 / 143 (0.70%) 1 | |
| Insomnia subjects affected / exposed occurrences (all) | 3 / 281 (1.07%) 3 | 4 / 143 (2.80%) 4 | |
| Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all) | 3 / 281 (1.07%) 3 | 4 / 143 (2.80%) 4 | |
| Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all) | 4 / 281 (1.42%) 4 | 5 / 143 (3.50%) 5 | |
| Hyperkalaemia subjects affected / exposed occurrences (all) | 6 / 281 (2.14%) 7 | 6 / 143 (4.20%) 6 | |

| | | | |
|-----------------------------|-----------------|-----------------|--|
| Hypokalaemia | | | |
| subjects affected / exposed | 8 / 281 (2.85%) | 7 / 143 (4.90%) | |
| occurrences (all) | 9 | 8 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 281 (0.36%) | 3 / 143 (2.10%) | |
| occurrences (all) | 1 | 4 | |
| Hypoproteinaemia | | | |
| subjects affected / exposed | 4 / 281 (1.42%) | 3 / 143 (2.10%) | |
| occurrences (all) | 4 | 4 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------|---|
| 20 May 2020 | The main change of this amendment was the update of inclusion and exclusion criteria based on the evolving understanding of COVID-19 disease. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported