



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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.1
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Reporting groups

Reporting group title	Ruxolitinib 5 mg
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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
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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