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Clinical Trial Results Website

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Generic Drug Name

Ruxolitinib

Trial Indication(s)

COVID-19 disease

Protocol Number

CINC424J12301

Protocol Title

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)

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase 4

Study Start/End Dates

Study Start Date: May 2020 (Actual)
Primary Completion Date: October 2020 (Actual)
Study Completion Date: October 2020 (Actual)

Study Design/Methodology

This was a Phase III, multicenter, double-blind, randomized, placebo-controlled study to assess the efficacy and safety of ruxolitinib in patients aged ≥12 years with COVID-19 disease. The study enrolled patients to ruxolitinib or placebo, in addition to standard-of-care (SoC) per local practice. Patients who meet the inclusion/exclusion criteria were randomized in a 2:1 ratio to either oral ruxolitinib 5 mg twice daily + SoC or oral matching-image placebo + SoC for a total of 14 days. An additional 14 days of study drug could be given if in the opinion of the investigator the patient's clinical signs and symptoms did not improve, or worsen, and the potential benefit outweighed the potential risk. The study included:

- Screening period of 0-2 days.
- Study period of 29 days (treatment of 14 days with possible extension of treatment to 28 days).

Centers

61 centers in 12 countries: United Kingdom(5), United States(11), Spain(5), Germany(3), Russia(9), Brazil(6), Argentina(3), Colombia(3), Peru(4), Mexico(3), France(5), Turkey(4)

Objectives:

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 intensive care unit care) of ruxolitinib + standard-of-care (SoC) therapy compared with placebo + SoC therapy, for the treatment of COVID-19 by Day 29.

The secondary objectives were:

- To evaluate the efficacy of ruxolitinib + SoC therapy compared with placebo + SoC therapy in patients with COVID-19 in terms of:
  - Clinical status assessed using a 9-point ordinal scale at Day 15 and Day 29
  - Percentage of patients with at least two-point improvement in clinical status at Day 15 and at Day 29
  - Percentage of patients with at least one-point improvement in clinical status at Day 15 and at Day 29
  - Percentage of patients with at least one-point deterioration in clinical status at Day 15 and at Day 29

  - Time to improvement from baseline category to one less severe category of the ordinal scale of clinical status
  - Mean change in the 9-point ordinal scale of clinical status from baseline to Days 15 and 29
  - Mortality rate at Day 15 and at Day 29
  - Proportion of patients requiring mechanical ventilation by Day 29
  - Duration of hospitalization
  - Time to hospital discharge or to a National Early Warning Score 2 (NEWS2) of ≤ 2
  - Change from baseline to Days 3, 5, 8, 11, 15, and 29 in NEWS2 score
  - Change from baseline to Days 15 and 29 in peripheral oxygen saturation / fraction of inspired oxygen ratio (SpO2/FiO2 ratio)
  - Proportion of patients with no oxygen therapy at Days 15 and 29
- To evaluate the safety of ruxolitinib + SoC therapy, compared with placebo + SoC therapy, in the treatment of patients with COVID-19.

Test Product (s), Dose(s), and Mode(s) of Administration

Ruxolitinib 5 mg tablets or matching placebo were administered orally twice per day approximately 12 hours apart (morning and night). The planned duration of treatment was 14 days with possible extension of treatment to 28 days. The actual median duration of exposure to ruxolitinib 5 mg and placebo was 14.0 and 15.0 days, respectively.

Statistical Methods

The statistical hypothesis tested for the primary endpoint was that there was no difference in the proportion of patients meeting the composite primary endpoint by Day 29 with ruxolitinib + SoC versus placebo + SoC therapy.

Let p_i denote the proportion of patients meeting the primary endpoint for treatment groups j, j = 0, 1 where, 0 corresponds to placebo + SoC and 1 corresponds to ruxolitinib + SoC. The following statistical hypothesis was tested to address the primary objective: H_0: $p_0 = p_1$, H_1: $p_0 \neq p_1$.

The odds of meeting the primary endpoint was analyzed by a logistic regression model with treatment group, region, baseline clinical status based on the 9-point ordinal scale (≤ 3, ≥ 4), age, and gender as covariates. The estimated odds ratio, p-values, and 95% CIs were presented. The study would be considered positive if ruxolitinib demonstrated a statistically significant greater reduction in the proportion of patients who die, develop respiratory failure (require mechanical ventilation), or ICU care by Day 29. This implies observing an odds ratio of < 1.

For the secondary efficacy analyses no multiplicity adjustments were done.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
Patient or guardian/health proxy must provide informed consent (and assent if applicable) before any study assessment is performed.
Male and female patients aged ≥ 12 years (or ≥ the lower age limit allowed by Health Authority and/or Ethics Committee/Institutional Review Board approvals).
Patients with coronavirus (SARS-CoV-2) infection confirmed by polymerase chain reaction (PCR) test or another rapid test from the respiratory tract prior to randomization.
Patients currently hospitalized or will be hospitalized prior to randomization.
Patients, who meet at least one of the below criteria:
- Pulmonary infiltrates (chest X ray or chest CT scan);
- Respiratory frequency ≥ 30/min;
- Requiring supplemental oxygen;
- Oxygen saturation ≤ 94% on room air;
- Arterial oxygen partial pressure (PaO2)/ fraction of inspired oxygen (FiO2) < 300mmHg (1mmHg=0.133kPa) (corrective formulation should be used for higher altitude regions (over 1000m).

Exclusion Criteria:
History of hypersensitivity to any drugs or metabolites of similar chemical classes as ruxolitinib.
Presence of severely impaired renal function defined by serum creatinine > 2 mg/dL (>176.8 µmol/L), or have estimated creatinine

clearance < 30 ml/min measured or calculated by Cockroft Gault equation or calculated by the updated bedside Schwartz equation.
Suspected uncontrolled bacterial, fungal, viral, or other infection (besides COVID-19).
Currently intubated or intubated between screening and randomization.
In intensive care unit (ICU) at time of randomization.
Intubated or in ICU for COVID-19 disease prior to screening.
Patients who are on anti-rejection, immunosuppressant or immunomodulatory drugs (i.e. tocilizumab, ruxolitinib, canakinumab, sarilumab, anakinra).
Unable to ingest tablets at randomization.
Pregnant or nursing (lactating) women

Participant Flow Table

Overall Study

	Ruxolitinib 5 mg	Placebo	Total
Arm/Group Description	Ruxolitinib 5 mg tablets twice daily (b.i.d.) for 14 days with possible extension of treatment to 28 days	Matching-image placebo for 14 days with possible extension of treatment to 28 days	
Started	287	145	432
Safety Set	281	143	424
Completed	269	139	408
Not Completed	18	6	24
Death	9	3	12
Patient decision	6	3	9
Adverse Event	1	0	1
Lost to Follow-up	1	0	1
Protocol deviation	1	0	1

Baseline Characteristics

	Ruxolitinib 5 mg	Placebo	Total
Arm/Group Description	Ruxolitinib 5 mg tablets twice daily (b.i.d.) for 14 days with possible extension of treatment to 28 days	Matching-image placebo for 14 days with possible extension of treatment to 28 days	
Number of Participants [units: participants]	287	145	432
Age Continuous (units: years) Mean ± Standard Deviation			
	56.4±13.7	56.9±12.5	56.5±13.3
Sex: Female, Male (units: participants) Count of Participants (Not Applicable)			
Female	125	72	197
Male	162	73	235
Race/Ethnicity, Customized (units: participants) Count of Participants (Not Applicable)			
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

Primary Outcome Result(s)

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

(Time Frame: Day 1 - Day 29)

	Ruxolitinib 5 mg	Placebo
Arm/Group Description	Ruxolitinib 5 mg tablets twice daily (b.i.d.) for 14 days with possible extension of treatment to 28 days	Matching-image placebo for 14 days with possible extension of treatment to 28 days
Number of Participants Analyzed [units: participants]	284	144
Proportion of patients who die, develop respiratory failure [require mechanical ventilation] or require intensive care unit (ICU) care (units: participants) Count of Participants (Not Applicable)		
	34 (11.97%)	17 (11.81%)

Statistical Analysis

Groups	Ruxolitinib 5 mg, Placebo	
P Value	0.769	
Method	Regression, Logistic	
Odds Ratio (OR)	0.91	Comparison is ruxolitinib 5 mg/placebo. An odds ratio < 1 favors the ruxolitinib 5 mg arm
95 % Confidence Interval 2-Sided	0.48 to 1.73	

Secondary Outcome Result(s)

Clinical status

(Time Frame: Baseline, Day 15, Day 29)

	Ruxolitinib 5 mg	Placebo
Arm/Group Description	Ruxolitinib 5 mg tablets twice daily (b.i.d.) for 14 days with possible extension of treatment to 28 days	Matching-image placebo for 14 days with possible extension of treatment to 28 days
Number of Participants Analyzed [units: participants]	287	145
Clinical status (units: score on scale) Mean ± Standard Deviation		
Baseline (n=286, 145)	3.7 ± 0.56	3.7 ± 0.53
Day 15 (n=280, 142)	1.8 ± 1.54	1.8 ± 1.41
Day 29 (n=278, 142)	1.1 ± 1.61	1.0 ± 1.41

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

(Time Frame: Baseline, Day 15, Day 29)

	Ruxolitinib 5 mg	Placebo
Arm/Group Description	Ruxolitinib 5 mg tablets twice daily (b.i.d.) for 14 days with possible extension of treatment to 28 days	Matching-image placebo for 14 days with possible extension of treatment to 28 days
Number of Participants Analyzed [units: participants]	286	145

Percentage of patients with at least two-point improvement from baseline in clinical status (units: participants) Count of Participants (Not Applicable)		
Day 15 (n=286, 145)	206 (72.03%)	108 (74.48%)
Day 29 (n=286, 145)	252 (88.11%)	129 (88.97%)

Statistical Analysis

Groups	Ruxolitinib 5 mg, Placebo	Day 15
P Value	0.647	
Method	Regression, Logistic	
Odds Ratio (OR)	0.89	Comparison is ruxolitinib 5 mg/placebo. An odds ratio > 1 favors the ruxolitinib 5 mg arm
95 % Confidence Interval 2-Sided	0.55 to 1.46	

Statistical Analysis

Groups	Ruxolitinib 5 mg, Placebo	Day 29
P Value	0.997	
Method	Regression, Logistic	
Odds Ratio (OR)	1.00	Comparison is ruxolitinib 5 mg/placebo. An odds ratio > 1 favors the ruxolitinib 5 mg arm

95 % Confidence Interval 2-Sided	0.52 to 1.92

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

(Time Frame: Baseline, Day 15, Day 29)

	Ruxolitinib 5 mg	Placebo
Arm/Group Description	Ruxolitinib 5 mg tablets twice daily (b.i.d.) for 14 days with possible extension of treatment to 28 days	Matching-image placebo for 14 days with possible extension of treatment to 28 days
Number of Participants Analyzed [units: participants]	286	145
Percentage of patients with at least one-point improvement from baseline in clinical status (units: participants) Count of Participants (Not Applicable)		
Day 15 (n=286, 145)	250 (87.41%)	128 (88.28%)
Day 29 (n=286, 145)	261 (91.26%)	136 (93.79%)

Statistical Analysis

Groups	Ruxolitinib 5 mg, Placebo	Day 15
P Value	0.946	
Method	Regression, Logistic	
Odds Ratio (OR)	0.98	Comparison is ruxolitinib 5 mg/placebo. An odds ratio > 1 favors the ruxolitinib 5 mg arm

95 % Confidence Interval 2-Sided	0.51 to 1.87

Statistical Analysis

Groups	Ruxolitinib 5 mg, Placebo	Day 29
P Value	0.573	
Method	Regression, Logistic	
Odds Ratio (OR)	0.79	Comparison is ruxolitinib 5 mg/placebo. An odds ratio > 1 favors the ruxolitinib 5 mg arm
95 % Confidence Interval 2-Sided	0.35 to 1.79	

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

(Time Frame: Baseline, Day 15, Day 29)

	Ruxolitinib 5 mg	**Placebo**
Arm/Group Description	Ruxolitinib 5 mg tablets twice daily (b.i.d.) for 14 days with possible extension of treatment to 28 days	Matching-image placebo for 14 days with possible extension of treatment to 28 days
Number of Participants Analyzed [units: participants]	286	145
Percentage of patients with at least one-point deterioration from baseline in clinical status (units: participants) Count of Participants (Not Applicable)		
Day 15 (n=286, 145)	16 (5.59%)	9 (6.21%)
Day 29 (n=286, 145)	14 (4.9%)	5 (3.45%)

Statistical Analysis

Groups	Ruxolitinib 5 mg, Placebo	Day 15
P Value	0.532	
Method	Regression, Logistic	
Odds Ratio (OR)	0.75	Comparison is ruxolitinib 5 mg/placebo. An odds ratio < 1 favors the ruxolitinib 5 mg arm
95 % Confidence Interval 2-Sided	0.31 to 1.83	

Statistical Analysis

Groups	Ruxolitinib 5 mg, Placebo	Day 29
P Value	0.764	
Method	Regression, Logistic	
Odds Ratio (OR)	1.18	Comparison is ruxolitinib 5 mg/placebo. An odds ratio < 1 favors the ruxolitinib 5 mg arm
95 % Confidence Interval 2-Sided	0.40 to 3.49	

Time to improvement in clinical status

(Time Frame: 29 days)

	Ruxolitinib 5 mg	Placebo
Arm/Group Description	Ruxolitinib 5 mg tablets twice daily (b.i.d.) for 14 days with possible extension of treatment to 28 days	Matching-image placebo for 14 days with possible extension of treatment to 28 days
Number of Participants Analyzed [units: participants]	286	145
Time to improvement in clinical status (units: days) Median (95% Confidence Interval)		
	9.0 (8.0 to 10.0)	9.0 (8.0 to 12.0)

Statistical Analysis

Groups	Ruxolitinib 5 mg, Placebo	
P Value	0.330	
Method	Other Proportional hazards model	
Hazard Ratio (HR)	1.11	Between group comparison using competing risk framework. A hazard ratio > 1 favors the ruxolitinib 5 mg arm
95 % Confidence Interval 2-Sided	0.90 to 1.37	

Mean change from baseline in the clinical status

(Time Frame: Baseline, Day 15, Day 29)

	Ruxolitinib 5 mg	Placebo
Arm/Group Description	Ruxolitinib 5 mg tablets twice daily (b.i.d.) for 14 days with possible extension of treatment to 28 days	Matching-image placebo for 14 days with possible extension of treatment to 28 days
Number of Participants Analyzed [units: participants]	287	145
Mean change from baseline in the clinical status (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 Analysis

Groups	Ruxolitinib 5 mg, Placebo	Day 15
P Value	0.831	
Method	ANCOVA	
Other Least squares (LS) mean	-0.03	
Standard Error of the mean	0.144	
95 % Confidence Interval 2-Sided	-0.31 to 0.25	

Statistical Analysis

Groups	Ruxolitinib 5 mg, Placebo	Day 29
P Value	0.624	
Method	ANCOVA	
Other LS Mean	0.08	
Standard Error of the mean	0.155	
95 % Confidence Interval 2-Sided	-0.23 to 0.38	

Mortality rate

(Time Frame: Day 15, Day 29)

	Ruxolitinib 5 mg	Placebo
Arm/Group Description	Ruxolitinib 5 mg tablets twice daily (b.i.d.) for 14 days with possible extension of treatment to 28 days	Matching-image placebo for 14 days with possible extension of treatment to 28 days
Number of Participants Analyzed [units: participants]	286	145
Mortality rate (units: participants) Count of Participants (Not Applicable)		
Day 15 (n=286, 145)	6 (2.1%)	2 (1.38%)
Day 29 (n=286, 145)	9 (3.15%)	3 (2.07%)

Statistical Analysis

Groups	Ruxolitinib 5 mg, Placebo	Day 15
P Value	0.944	
Method	Regression, Logistic	
Odds Ratio (OR)	0.94	Comparison is ruxolitinib 5 mg/placebo. An odds ratio < 1 favors the ruxolitinib 5 mg arm
95 % Confidence Interval 2-Sided	0.20 to 5.57	

Statistical Analysis

Groups	Ruxolitinib 5 mg, Placebo	Day 29
P Value	0.775	
Method	Regression, Logistic	
Odds Ratio (OR)	1.21	Comparison is ruxolitinib 5 mg/placebo. An odds ratio < 1 favors the ruxolitinib 5 mg arm
95 % Confidence Interval 2-Sided	0.35 to 5.11	

Proportion of patients requiring mechanical ventilation

(Time Frame: Day 1 - Day 29)

	Ruxolitinib 5 mg	Placebo
Arm/Group Description	Ruxolitinib 5 mg tablets twice daily (b.i.d.) for 14 days with possible extension of treatment to 28 days	Matching-image placebo for 14 days with possible extension of treatment to 28 days
Number of Participants Analyzed [units: participants]	286	145
Proportion of patients requiring mechanical ventilation (units: participants) Count of Participants (Not Applicable)		
	22 (7.69%)	10 (6.9%)

Statistical Analysis

Groups	Ruxolitinib 5 mg, Placebo	
P Value	0.987	
Method	Regression, Logistic	
Odds Ratio (OR)	0.99	Comparison is ruxolitinib 5 mg/placebo. An odds ratio < 1 favors the ruxolitinib 5 mg arm
95 % Confidence Interval 2-Sided	0.45 to 2.21	

Duration of hospitalization

(Time Frame: 29 days)

	Ruxolitinib 5 mg	Placebo
Arm/Group Description	Ruxolitinib 5 mg tablets twice daily (b.i.d.) for 14 days with possible extension of treatment to 28 days	Matching-image placebo for 14 days with possible extension of treatment to 28 days
Number of Participants Analyzed [units: participants]	286	145
Duration of hospitalization (units: days) Median (95% Confidence Interval)		
	9.0 (8.0 to 10.0)	9.0 (8.0 to 12.0)

Statistical Analysis

Groups	Ruxolitinib 5 mg, Placebo	
P Value	0.738	
Method	Other Proportional hazards model	
Hazard Ratio (HR)	1.04	Between group comparison using competing risk framework. A hazard ratio > 1 favors the ruxolitinib 5 mg arm
95 % Confidence Interval 2-Sided	0.84 to 1.28	

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

(Time Frame: 29 days)

	Ruxolitinib 5 mg	Placebo
Arm/Group Description	Ruxolitinib 5 mg tablets twice daily (b.i.d.) for 14 days with possible extension of treatment to 28 days	Matching-image placebo for 14 days with possible extension of treatment to 28 days
Number of Participants Analyzed [units: participants]	286	145
Time to hospital discharge or to a NEWS2 score of ≤2 (units: days) Median (95% Confidence Interval)		
	4.0 (3.0 to 4.0)	4.0 (3.0 to 5.0)

Statistical Analysis

Groups	Ruxolitinib 5 mg, Placebo	
P Value	0.869	
Method	Other Proportional hazards model	
Hazard Ratio (HR)	1.02	Between group comparison using competing risk framework. A hazard ratio > 1 favors the ruxolitinib 5 mg arm
95 % Confidence Interval 2-Sided	0.84 to 1.23	

Change from baseline in NEWS2 score

(Time Frame: Baseline, Days 3, 5, 8, 11, 15, and 29)

	Ruxolitinib 5 mg	Placebo
Arm/Group Description	Ruxolitinib 5 mg tablets twice daily (b.i.d.) for 14 days with possible extension of treatment to 28 days	Matching-image placebo for 14 days with possible extension of treatment to 28 days
Number of Participants Analyzed [units: participants]	287	145
Change from baseline in NEWS2 score (units: score on scale) 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

Change from baseline in SpO2/FiO2 ratio

(Time Frame: Baseline, Day 15, Day 29)

	Ruxolitinib 5 mg	Placebo
Arm/Group Description	Ruxolitinib 5 mg tablets twice daily (b.i.d.) for 14 days with possible extension of treatment to 28 days	Matching-image placebo for 14 days with possible extension of treatment to 28 days
Number of Participants Analyzed [units: participants]	287	145

Change from baseline in SpO2/FiO2 ratio (units: no units) 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

Proportion of patients with no oxygen therapy

(Time Frame: Day 15, Day 29)

	Ruxolitinib 5 mg	**Placebo**
Arm/Group Description	Ruxolitinib 5 mg tablets twice daily (b.i.d.) for 14 days with possible extension of treatment to 28 days	Matching-image placebo for 14 days with possible extension of treatment to 28 days
Number of Participants Analyzed [units: participants]	287	145
Proportion of patients with no oxygen therapy (units: participants) Count of Participants (Not Applicable)		
Day 15 (n= 274, 140)	255 (93.07%)	133 (95%)
Day 29 (n= 269, 139)	262 (97.4%)	136 (97.84%)

Statistical Analysis

Groups	Ruxolitinib 5 mg, Placebo	Day 15
P Value	0.325	
Method	Regression, Logistic	

Odds Ratio (OR)	0.61	Comparison is ruxolitinib 5 mg/placebo. An odds ratio > 1 favors the ruxolitinib 5 mg arm
95 % Confidence Interval 2-Sided	0.23 to 1.63	

Statistical Analysis

Groups	Ruxolitinib 5 mg, Placebo	Day 29
P Value		P-value was not estimable because >97% patients fall into one category (responders) in both groups, and very few patients fall into the other one (non-responders), which made the logistic regression model fail to converge even with Firth's correction
Method	Regression, Logistic	
Odds Ratio (OR)	1.22	Comparison is ruxolitinib 5 mg/placebo. An odds ratio > 1 favors the ruxolitinib 5 mg arm
95 % Confidence Interval 2-Sided	0.25 to 5.40	

Post Hoc Result(s)

All Collected Deaths

(Time Frame: 29 days)

	Ruxolitinib 5 mg	Placebo
Arm/Group Description	Ruxolitinib 5 mg tablets twice daily (b.i.d.) for 14 days with possible extension of treatment to 28 days	Matching-image placebo for 14 days with possible extension of treatment to 28 days
Number of Participants Analyzed [units: participants]	287	145
All Collected Deaths (units: participants)		
Deaths in the safety population (n=281, 143)	9	3
Total deaths (n=287, 145)	9	3

Safety Results

All-Cause Mortality

	Ruxolitinib 5 mg N = 281	Placebo N = 143
Arm/Group Description	Ruxolitinib 5 mg tablets twice daily (b.i.d.) for 14 days with possible extension of treatment to 28 days	Matching-image placebo for 14 days with possible extension of treatment to 28 days
Total participants affected	9 (3.20%)	3 (2.10%)

Serious Adverse Events by System Organ Class

Time Frame	From first dose of double-blind treatment and up to the last study visit (Day 29).
Additional Description	Adverse events are considered as treatment-emergent if the event started after the first dose of double-blind treatment or the event was present prior to start of double-blind treatment but increased in severity based on preferred term and up to the last study visit (Day 29). Adverse events and all-cause mortality are evaluated in the Safety Set that includes all participants who received at least one dose of double-blind treatment.
Source Vocabulary for Table Default	MedDRA (23.1)
Assessment Type for Table Default	Systematic Assessment

	Ruxolitinib 5 mg N = 281	Placebo N = 143
Arm/Group Description	Ruxolitinib 5 mg tablets twice daily (b.i.d.) for 14 days with possible extension of treatment to 28 days	Matching-image placebo for 14 days with possible extension of treatment to 28 days
Total participants affected	31 (11.03%)	15 (10.49%)

Blood and lymphatic system disorders		
Disseminated intravascular coagulation	1 (0.36%)	0 (0.00%)
Cardiac disorders		
Adams-Stokes syndrome	1 (0.36%)	0 (0.00%)
Atrial fibrillation	1 (0.36%)	0 (0.00%)
Cardiac arrest	1 (0.36%)	0 (0.00%)
Cardiopulmonary failure	0 (0.00%)	1 (0.70%)
Ear and labyrinth disorders		
Vertigo	0 (0.00%)	1 (0.70%)
Gastrointestinal disorders		
Pancreatitis	1 (0.36%)	0 (0.00%)
General disorders and administration site conditions		
Adverse event	1 (0.36%)	0 (0.00%)
General physical health deterioration	1 (0.36%)	0 (0.00%)
Multiple organ dysfunction syndrome	1 (0.36%)	1 (0.70%)
Performance status decreased	1 (0.36%)	0 (0.00%)
Infections and infestations		
Antibiotic associated colitis	1 (0.36%)	0 (0.00%)
Bacteraemia	1 (0.36%)	0 (0.00%)

COVID-19	8 (2.85%)	3 (2.10%)
COVID-19 pneumonia	1 (0.36%)	0 (0.00%)
Escherichia bacteraemia	0 (0.00%)	1 (0.70%)
Pneumonia	3 (1.07%)	0 (0.00%)
Pneumonia fungal	1 (0.36%)	0 (0.00%)
Urinary tract infection	0 (0.00%)	1 (0.70%)
Injury, poisoning and procedural complications		
Endotracheal intubation complication	1 (0.36%)	0 (0.00%)
Fall	0 (0.00%)	1 (0.70%)
Investigations		
Alanine aminotransferase increased	0 (0.00%)	1 (0.70%)
Transaminases increased	0 (0.00%)	1 (0.70%)
Nervous system disorders		
Cerebral infarction	1 (0.36%)	0 (0.00%)
Hypoglycaemic coma	1 (0.36%)	0 (0.00%)
Ischaemic stroke	1 (0.36%)	0 (0.00%)
Psychiatric disorders		
Mental status changes	1 (0.36%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders		
Acute respiratory distress syndrome	1 (0.36%)	1 (0.70%)
Acute respiratory failure	4 (1.42%)	1 (0.70%)

Dyspnoea	1 (0.36%)	0 (0.00%)
Hypoxia	4 (1.42%)	4 (2.80%)
Pneumothorax	1 (0.36%)	0 (0.00%)
Pulmonary fibrosis	1 (0.36%)	0 (0.00%)
Respiratory disorder	1 (0.36%)	0 (0.00%)
Respiratory distress	1 (0.36%)	0 (0.00%)
Respiratory failure	2 (0.71%)	2 (1.40%)
Vascular disorders		
Deep vein thrombosis	1 (0.36%)	0 (0.00%)
Shock	1 (0.36%)	0 (0.00%)

Other Adverse Events by System Organ Class

Time Frame	From first dose of double-blind treatment and up to the last study visit (Day 29).
Additional Description	Adverse events will be considered as treatment-emergent if the event starts after the first dose of double-blind treatment or the event is present prior to start of double-blind treatment but increased in severity based on preferred term and up to the last study visit (Day 29). Adverse events are evaluated in the Safety Set that includes all participants who received at least one dose of double-blind treatment.
Source Vocabulary for Table Default	MedDRA (23.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	2%

	Ruxolitinib 5 mg N = 281	**Placebo N = 143**
Arm/Group Description	Ruxolitinib 5 mg tablets twice daily (b.i.d.) for 14 days with	Matching-image placebo for 14 days with possible

	possible extension of treatment to 28 days	extension of treatment to 28 days
Total participants affected	113 (40.21%)	62 (43.36%)
Blood and lymphatic system disorders		
Leukocytosis	4 (1.42%)	4 (2.80%)
Neutropenia	6 (2.14%)	4 (2.80%)
Thrombocytosis	6 (2.14%)	3 (2.10%)
Gastrointestinal disorders		
Abdominal pain	4 (1.42%)	4 (2.80%)
Constipation	9 (3.20%)	7 (4.90%)
Diarrhoea	21 (7.47%)	12 (8.39%)
Nausea	6 (2.14%)	11 (7.69%)
General disorders and administration site conditions		
Asthenia	6 (2.14%)	0 (0.00%)
Fatigue	10 (3.56%)	2 (1.40%)
Pyrexia	6 (2.14%)	2 (1.40%)
Infections and infestations		
Urinary tract infection	3 (1.07%)	4 (2.80%)
Investigations		
Alanine aminotransferase increased	17 (6.05%)	6 (4.20%)
Aspartate aminotransferase increased	5 (1.78%)	3 (2.10%)

Transaminases increased	7 (2.49%)	2 (1.40%)
Metabolism and nutrition disorders		
Hyperglycaemia	4 (1.42%)	5 (3.50%)
Hyperkalaemia	6 (2.14%)	6 (4.20%)
Hypokalaemia	8 (2.85%)	7 (4.90%)
Hyponatraemia	1 (0.36%)	3 (2.10%)
Hypoproteinaemia	4 (1.42%)	3 (2.10%)
Nervous system disorders		
Dizziness	2 (0.71%)	4 (2.80%)
Headache	23 (8.19%)	11 (7.69%)
Psychiatric disorders		
Anxiety	6 (2.14%)	1 (0.70%)
Insomnia	3 (1.07%)	4 (2.80%)
Respiratory, thoracic and mediastinal disorders		
Cough	12 (4.27%)	3 (2.10%)
Dyspnoea	3 (1.07%)	3 (2.10%)
Vascular disorders		
Hypertension	4 (1.42%)	3 (2.10%)

Conclusion:

The purpose of this study was to evaluate the activity of ruxolitinib in the treatment of patients with COVID-19 disease. The study was a randomized, double-blind, placebo-controlled, 29 day, multicenter clinical trial to assess the efficacy and safety of ruxolitinib + SoC therapy, compared with placebo + SoC therapy, in ≥ 12 years male and female COVID-19 patients with severe respiratory disease.

432 patients were randomized in the study, 287 in the ruxolitinib arm and 145 in the placebo arm. Most patients (> 93% in both treatment arms) completed the study as per protocol. Demographics, disease characteristics at baseline were as could be anticipated for the population under study and generally similar in the two treatment arms. No pediatric patients were randomized. Mean and median duration of exposure were similar in the two treatment arms (approximately 15 days for both ruxolitinib and placebo arms) and a majority of patients (78.3% in ruxolitinib arm and 86.7% in placebo arm) were exposed to study drug for 8 to 15 days.

The proportion of patients who died, developed respiratory failure (requiring mechanical ventilation), or required ICU care by Day 29 was 12.0% in the ruxolitinib arm and 11.8% in the placebo arm. The study failed to meet its primary objective with an odds ratio of 0.91 (p value=0.769, 95% CI: 0.48-1.73).

There was no notable difference between the two treatment arms in any of the secondary efficacy analyses, such as change in clinical status, hospital discharge, oxygen therapy.

The safety profile of ruxolitinib was consistent with previous observations and the treatment was generally well tolerated. The occurrence of adverse events, serious adverse events and adverse events of special interest (including cytopenias and infections), as well as changes in hematology, biochemistry, and vital signs was generally comparable between ruxolitinib and placebo arms. Overall, no new safety signal was observed.

The results in this controlled clinical trial setting do not demonstrate that ruxolitinib improves outcomes of COVID-19 patients with severe respiratory disease; no positive benefit-risk was established for ruxolitinib in COVID-19.

Date of Clinical Trial Report

05-Mar-2021