NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Not applicable

Trial Indication(s)

COVID-19 pneumonia, impaired respiratory function

Protocol Number

CDFV890D12201

Protocol Title

Phase 2, randomized, controlled, open label multi-center study to assess efficacy and safety of DFV890 for the treatment of SARS-CoV-2 infected patients with COVID-19 pneumonia and impaired respiratory function

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase 2

Study Start/End Dates

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

Reason for Termination

Not applicable

Study Design/Methodology

This was a randomized, controlled, open-label, multicenter study in hospitalized adult participants with COVID-19-associated pneumonia and impaired respiratory function. This design supported the assessment of preliminary efficacy, safety and tolerability of DFV890 in addition to standard of care (SoC) in this critically ill patient population. Participants assigned to the DFV890 arm received DFV890 in addition to SoC and participants assigned to the control arm received SoC alone.

Centers

30 centers in 12 countries: Denmark(2), Hungary(1), Germany(3), Netherlands(1), Spain(2), Russia(8), South Africa(1), India(4), Argentina(2), Brazil(2), Peru(2), Mexico(2)

Objectives:

Primary:

- APACHE II severity of disease score on Day 15 or on the day of discharge (whichever is earlier)

Secondary:

- Serum C-reactive protein (CRP) levels
- Clinical status over time
- Number of participants not requiring mechanical ventilation for survival
- Number of participants with at least one-point improvement from baseline in clinical status

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

DFV890 50 mg was administered orally or nasogastrically twice per day (b.i.d) approximately 12 hours apart (morning and evening) for 14 days in addition to SoC.

Statistical Methods

The primary endpoint was analyzed by an analysis of covariance model including treatment group and the three stratification factors as factors and baseline APACHE II score as a covariate. The analysis was performed on the safety analysis set. The mean differences of DFV890 in addition to SoC versus SoC alone were reported with 90% confidence intervals (CI). The 1-sided p-value for the overall treatment factor were reported. The primary objective was achieved if the null hypothesis that DFV890 in addition to SoC was not different to SoC alone was rejected using a one side alpha level of 10%.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

• Male and female patients aged 18-80 years inclusive at screening.
• Clinically diagnosed with the SARS-CoV-2 virus by polymerase chain reaction (PCR) or by other approved diagnostic methodology within 7 days prior to randomization.
• Hospitalized with COVID-19-induced pneumonia evidenced by chest X-ray, computed tomography scan (CT scan) or magnetic resonance scan (MR scan), taken within 5 days prior to randomization (within 24 hours in patients in the Netherlands).
• Impaired respiratory function, defined as peripheral oxygen saturation (SpO2) ≤93% on room air or partial pressure of oxygen (PaO2) / fraction of inspired oxygen (FiO2) <300 millimeter of mercury (mmHg) at screening. For cities located at altitudes greater than 2500 m above sea level, these will be substituted with SpO2 <90% and PaO2/FiO2 <250 mmHg.
• APACHE II score of ≥10 at screening.
• C-reactive protein (CRP) ≥20 mg/L and/or ferritin level ≥600 µg/L at screening.
• Body mass index of ≥18 to <40kg/m2 at screening.

Exclusion Criteria:

• Suspected active or chronic bacterial (including Mycobacterium tuberculosis), fungal, viral, or other infection (besides SARS-CoV-2).
• In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatment.
• Intubated prior to randomization.
• Previous treatment with anti-rejection and immunomodulatory drugs within the past 2 weeks, or within the past 30 days or 5 half-lives (whichever is the longer) for immunomodulatory therapeutic antibodies or prohibited drugs, with the exception of

hydroxychloroquine, chloroquine or corticosteroids:
For COVID-19 infection, ongoing corticosteroid treatment is permitted at doses as per local SoC.For non-COVID-19 disorders, ongoing corticosteroid treatment is permitted at doses up to and including prednisolone 10 mg daily or equivalent.
In patients in the Netherlands only, the use of hydroxychloroquine and/or chloroquine in the past 2 weeks are exclusionary.
• Serum alanine transaminase (ALT) or aspartate transaminase (AST) >5 times upper limit of normal detected within 24 hours at screening or at baseline (according to local laboratory reference ranges) or other evidence if severe hepatic impairment (Child-Pugh Class C).
• Absolute peripheral blood neutrophil count of ≤1000/mm3.
• Estimated GFR (eGFR) ≤30 mL/min/1.73m2 (based on CKD-EPI formula).
• Patients currently being treated with drugs known to be strong or moderate inducers of isoenzyme CYP2C9 and/or strong inhibitors of CYP2C9 and/or strong inducers of cytochrome P450, family 3, subfamily A (CYP3A) and the treatment cannot be discontinued or switched to a different medication prior to starting study treatment.
• Patients with innate or acquired immunodeficiencies.
• Patients who have undergone solid organ or stem cell transplantation.

Participant Flow Table

Overall Study

	DFV890 + SoC	Standard of Care (SoC)	Total
Arm/Group Description	DFV890 50 mg was administered orally or nasogastrically twice per day (b.i.d) approximately 12 hours apart (morning and evening) for 14 days in addition to SoC.	SoC was used as an active comparator arm.	
Started	71	72	143

Safety analysis set	70[1]	72	142
PD analysis set	62	68	130
Completed	62	59	121
Not Completed	9	13	22
Death	6	8	14
Lost to Follow-up	0	2	2
Protocol Deviation	1	2	3
Withdrawal by Subject	2	1	3

[1] One participant that was randomized to the DFV890 + SoC arm did not attend any post-baseline visit

Baseline Characteristics

	DFV890 + SoC	Standard of Care (SoC)	Total
Arm/Group Description	DFV890 50 mg was administered orally or nasogastrically twice per day (b.i.d) approximately 12 hours apart (morning and evening) for 14 days in	SoC was used as an active comparator arm.	

	addition to SoC.		
Number of Participants [units: participants]	71	72	143
Age Continuous (units: Years) Mean ± Standard Deviation			
	60.0±13.31	61.5±10.38	60.8±11.91
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)			
Female	22	24	46
Male	49	48	97
Race (NIH/OMB) (units:) Count of Participants (Not Applicable)			
American Indian or Alaska Native	6	5	11
Asian	7	7	14
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	3	6
White	55	57	112
More than one race	0	0	0
Unknown or Not Reported	0	0	0

Primary Outcome Result(s)

APACHE II severity of disease score on Day 15 or on the day of discharge (whichever is earlier)

(Time Frame: up to Day 15)

	DFV890 + SoC	Standard of Care (SoC)
Arm/Group Description	DFV890 50 mg was administered orally or nasogastrically twice per day (b.i.d) approximately 12 hours apart (morning and evening) for 14 days in addition to SoC.	SoC was used as an active comparator arm.
Number of Participants Analyzed [units: participants]	70	72
APACHE II severity of disease score on Day 15 or on the day of discharge (whichever is earlier) (units: Score on a scale) Least Squares Mean ± Standard Error		
	8.7 ± 1.06	8.6 ± 1.05

Statistical Analysis

Groups	DFV890 + SoC, Standard of Care (SoC)
P Value	0.467

Method	ANCOVA
Other Least squares mean difference	0.11
Standard Error of the mean	1.297
90 % Confidence Interval 2-Sided	-2.0 to 2.3

Secondary Outcome Result(s)

Serum C-reactive protein (CRP) levels

(Time Frame: Days 2, 4, 6, 8, 10, 12, 14 and 15)

	DFV890 + SoC	Standard of Care (SoC)
Arm/Group Description	DFV890 50 mg was administered orally or nasogastrically twice per day (b.i.d) approximately 12 hours apart (morning and evening) for 14 days in addition to SoC.	SoC was used as an active comparator arm.
Number of Participants Analyzed [units: participants]	62	68

Serum C-reactive protein (CRP) levels (units: Milligram / Liter) Geometric Mean ± Standard Error		
Day 2	31.4 ± 1.14	46.6 ± 1.13
Day 4	22.2 ± 1.19	26.5 ± 1.18
Day 6	11.5 ± 1.2	15.1 ± 1.19
Day 8	7.7 ± 1.25	10.9 ± 1.24
Day 10	7.0 ± 1.27	8.0 ± 1.27
Day 12	7.5 ± 1.30	7.1 ± 1.31
Day 14	8.1 ± 1.31	6.3 ± 1.31
Day 15 / end of study	6.9 ± 1.27	8.2 ± 1.26

Statistical Analysis

Groups	DFV890 + SoC, Standard of Care (SoC)	
P Value	0.237	One-sided
Method	Mixed Models Analysis	p-value reported is for the treatment factor across all time points

Clinical status over time

(Time Frame: Baseline, days 2, 4, 6, 8, 10, 12, 14, 15, 17, 19, 21, 23, 25, 27 and 29)

	DFV890 + SoC	**Standard of Care (SoC)**
Arm/Group Description	DFV890 50 mg was administered orally or nasogastrically twice per day (b.i.d) approximately	SoC was used as an active comparator arm.

	12 hours apart (morning and evening) for 14 days in addition to SoC.	
Number of Participants Analyzed [units: participants]	70	72
Clinical status over time (units: Score on a scale) Mean ± Standard Deviation		
Baseline	4.3 ± 0.49	4.3 ± 0.44
Day 2	4.3 ± 0.58	4.3 ± 0.80
Day 4	4.3 ± 0.83	4.3 ± 0.95
Day 6	3.9 ± 1.11	4.2 ± 1.13
Day 8	3.8 ± 1.31	3.8 ± 1.50
Day 10	3.6 ± 1.48	3.6 ± 1.88
Day 12	3.4 ± 1.66	3.3 ± 1.98
Day 14	3.3 ± 1.75	3.1 ± 2.03
Day 15	2.8 ± 2.02	2.6 ± 2.24
Day 17	2.7 ± 2.01	2.5 ± 2.22
Day 19	2.6 ± 2.01	2.5 ± 2.27
Day 21	2.6 ± 2.01	2.5 ± 2.33
Day 23	2.6 ± 2.03	2.4 ± 2.31
Day 25	2.6 ± 2.07	2.4 ± 2.31
Dy 27	2.6 ± 2.10	2.4 ± 2.31
Day 29	1.9 ± 2.34	1.9 ± 2.57

Number of participants not requiring mechanical ventilation for survival

(Time Frame: Until Day 15 (Assessments on Days 2, 4, 6, 8, 10, 12, 14 and 15) and until Day 29 (Assessments on Days 17, 19, 21, 23, 25, 27 and 29))

	DFV890 + SoC	Standard of Care (SoC)
Arm/Group Description	DFV890 50 mg was administered orally or nasogastrically twice per day (b.i.d) approximately 12 hours apart (morning and evening) for 14 days in addition to SoC.	SoC was used as an active comparator arm.
Number of Participants Analyzed [units: participants]	70	72
Number of participants not requiring mechanical ventilation for survival (units: Participants) Count of Participants (Not Applicable)		
Until Day 15	60 (85.71%)	59 (81.94%)
Until Day 29	60 (85.71%)	58 (80.56%)

Number of participants with at least one-point improvement from baseline in clinical status

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

	DFV890 + SoC	Standard of Care (SoC)

Arm/Group Description	DFV890 50 mg was administered orally or nasogastrically twice per day (b.i.d) approximately 12 hours apart (morning and evening) for 14 days in addition to SoC.	SoC was used as an active comparator arm.
Number of Participants Analyzed [units: participants]	70	72
Number of participants with at least one-point improvement from baseline in clinical status (units: Participants) Count of Participants (Not Applicable)		
Day 15	59 (84.29%)	53 (73.61%)
Day 29	61 (87.14%)	60 (83.33%)

Safety Results

All-Cause Mortality

	DFV890 + SoC N = 70	**Standard of Care (SoC) N = 72**	**Total N = 142**

Arm/Group Description	DFV890 50 mg was administered orally or nasogastrically twice per day (b.i.d) approximately 12 hours apart (morning and evening) for 14 days in addition to SoC.	SoC was used as an active comparator arm.	Total
Total participants affected	8 (11.43%)	8 (11.11%)	16 (11.27%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse events were reported from the start of treatment to 30 days after end of treatment, assessed up to maximum duration of 45 days.
Additional Description	Any sign or symptom that occurs during the study treatment plus the 30 days post treatment
Source Vocabulary for Table Default	MedDRA (23.0)
Assessment Type for Table Default	Systematic Assessment

	DFV890 + SoC N = 70	**Standard of Care (SoC) N = 72**	**Total N = 142**
Arm/Group Description	DFV890 50 mg was administered orally or	SoC was used as an active	Total

	nasogastrically twice per day (b.i.d) approximately 12 hours apart (morning and evening) for 14 days in addition to SoC.	comparator arm.	
Total participants affected	16 (22.86%)	11 (15.28%)	27 (19.01%)
Cardiac disorders			
Acute myocardial infarction	0 (0.00%)	1 (1.39%)	1 (0.70%)
Cardiac arrest	0 (0.00%)	1 (1.39%)	1 (0.70%)
Cardiogenic shock	0 (0.00%)	1 (1.39%)	1 (0.70%)
Myocardial infarction	0 (0.00%)	1 (1.39%)	1 (0.70%)
General disorders and administration site conditions			
Condition aggravated	1 (1.43%)	0 (0.00%)	1 (0.70%)
Multiple organ dysfunction syndrome	1 (1.43%)	0 (0.00%)	1 (0.70%)
Infections and infestations			
COVID-19	0 (0.00%)	1 (1.39%)	1 (0.70%)
COVID-19 pneumonia	2 (2.86%)	2 (2.78%)	4 (2.82%)
Pneumonia	1 (1.43%)	0 (0.00%)	1 (0.70%)
Sepsis	1 (1.43%)	2 (2.78%)	3 (2.11%)
Septic shock	1 (1.43%)	1 (1.39%)	2 (1.41%)

Investigations			
Amylase increased	1 (1.43%)	0 (0.00%)	1 (0.70%)
Nervous system disorders			
Polyneuropathy	1 (1.43%)	0 (0.00%)	1 (0.70%)
Renal and urinary disorders			
Acute kidney injury	0 (0.00%)	1 (1.39%)	1 (0.70%)
Renal failure	1 (1.43%)	0 (0.00%)	1 (0.70%)
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome	0 (0.00%)	2 (2.78%)	2 (1.41%)
Acute respiratory failure	0 (0.00%)	1 (1.39%)	1 (0.70%)
Dyspnoea	1 (1.43%)	1 (1.39%)	2 (1.41%)
Pulmonary embolism	1 (1.43%)	0 (0.00%)	1 (0.70%)
Respiratory failure	4 (5.71%)	4 (5.56%)	8 (5.63%)
Vascular disorders			
Arterial haemorrhage	0 (0.00%)	1 (1.39%)	1 (0.70%)
Haemodynamic instability	0 (0.00%)	2 (2.78%)	2 (1.41%)
Peripheral artery thrombosis	1 (1.43%)	0 (0.00%)	1 (0.70%)
Shock haemorrhagic	1 (1.43%)	0 (0.00%)	1 (0.70%)

Other Adverse Events by System Organ Class

Time Frame	Adverse events were reported from the start of treatment to 30 days after end of treatment, assessed up to maximum duration of 45 days.
Additional Description	Any sign or symptom that occurs during the study treatment plus the 30 days post treatment
Source Vocabulary for Table Default	MedDRA (23.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	DFV890 + SoC N = 70	**Standard of Care (SoC) N = 72**	**Total N = 142**
Arm/Group Description	DFV890 50 mg was administered orally or nasogastrically twice per day (b.i.d) approximately 12 hours apart (morning and evening) for 14 days in addition to SoC.	SoC was used as an active comparator arm.	Total
Total participants affected	12 (17.14%)	6 (8.33%)	18 (12.68%)
Blood and lymphatic system disorders			
Anaemia	5 (7.14%)	5 (6.94%)	10 (7.04%)
Metabolism and nutrition disorders			

Diabetes mellitus	4 (5.71%)	0 (0.00%)	4 (2.82%)
Hyperglycaemia	4 (5.71%)	2 (2.78%)	6 (4.23%)

Other Relevant Findings

Not applicable

Conclusion:

In summary, there were no unexpected events for this disease indication and for this participant population. The safety findings are consistent with the early clinical safety profile and in combination with the observed PD effects confirming clinically relevant reduction of NLRP3 related inflammatory markers, the further clinical development of DFV890 in indications where NLRP3 related inflammation represents the underlying disease condition is supported by the results of this trial.

Date of Clinical Trial Report

16-Sep-2021