Clinical trial results:
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

Summary

EudraCT number	2020-001870-32
Trial protocol	DE HU DK NL ES
Global end of trial date	24 December 2020

Results information

Result version number	v2 (current)
This version publication date	13 July 2022
First version publication date	01 December 2021
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	CDFV890D12201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04382053
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, 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	24 December 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the effect of DFV890 in addition to SoC, compared with SoC alone, on the Acute Physiology and Chronic Health Evaluation II (APACHE II) score

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	27 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	Argentina: 3
Country: Number of subjects enrolled	Brazil: 13
Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Hungary: 15
Country: Number of subjects enrolled	India: 12
Country: Number of subjects enrolled	Mexico: 9
Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Peru: 6
Country: Number of subjects enrolled	Russian Federation: 54
Country: Number of subjects enrolled	South Africa: 4
Country: Number of subjects enrolled	Spain: 10
Worldwide total number of subjects	143
EEA total number of subjects	42

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)	89
From 65 to 84 years	54
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from 30 sites in 12 countries.

Pre-assignment

Screening details:

Participants underwent a Screening period of up to 24 hours comprised of a Screening and a Baseline assessment.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	DFV890 + SoC

Arm 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.

Arm type	Experimental
Investigational medicinal product name	DFV890
Investigational medicinal product code	DFV890
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

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.

Arm title	Standard of Care (SoC)

Arm description:

SoC was used as an active comparator arm.

Arm type	Active comparator
Investigational medicinal product name	Standard of Care
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Solution for infusion, Tablet
Routes of administration	Intravenous use, Oral use, Inhalation use

Dosage and administration details:

SoC was used as an active comparator arm. SoC included a variety of supportive therapies that ranged from the administration of supplementary oxygen to full intensive care support, alongside the use of antiviral treatment, convalescent plasma, corticosteroids, antibiotics or other agents

Number of subjects in period 1	DFV890 + SoC	Standard of Care (SoC)
Started	71	72
Safety analysis set	70	72
PD analysis set	62	68
Completed	62	59
Not completed	9	13
Adverse event, serious fatal	6	8
Consent withdrawn by subject	2	1
Protocol Deviation	1	2
Lost to follow-up	-	2

Baseline characteristics

Reporting groups	
Reporting group title	DFV890 + SoC
Reporting 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.	
Reporting group title	Standard of Care (SoC)
Reporting group description:	
SoC was used as an active comparator arm.	

Reporting group values	DFV890 + SoC	Standard of Care (SoC)	Total
Number of subjects	71	72	143
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)	43	46	89
From 65-84 years	28	26	54
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	60.0	61.5	
standard deviation	± 13.31	± 10.38	-
Sex: Female, Male Units: Participants			
Female	22	24	46
Male	49	48	97
Race (NIH/OMB) Units: Subjects			
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

End points

End points reporting groups

Reporting group title	DFV890 + SoC
Reporting 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.	
Reporting group title	Standard of Care (SoC)
Reporting group description:	
SoC was used as an active comparator arm.	

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

End point title	APACHE II severity of disease score on Day 15 or on the day of discharge (whichever is earlier)
End point description:	
The APACHE II ("Acute Physiology And Chronic Health Evaluation II") is a severity-of-disease classification system. An integer score from 0 to 71 is computed based on several measurements; higher scores correspond to more severe disease and a higher risk of death. In practice, it is rare for any participant to accumulate more than 55 points. APACHE II score was measured on Day 15 or on the day of discharge (whichever was earlier). Participants who died on Day 15 or earlier were assigned the highest observed APACHE II score of any of the participants at any time during the trial (worst case imputation for deaths). Missing data values of the parameters required for the derivation of the APACHE II score were replaced by the last available assessment.	
End point type	Primary
End point timeframe:	
up to Day 15	

End point values	DFV890 + SoC	Standard of Care (SoC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	72		
Units: Score on a scale				
least squares mean (standard error)	8.7 (± 1.06)	8.6 (± 1.05)		

Statistical analyses

Statistical analysis title	Superiority analysis
Comparison groups	DFV890 + SoC v Standard of Care (SoC)

Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.467
Method	ANCOVA
Parameter estimate	Least squares mean difference
Point estimate	0.11
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2
upper limit	2.3
Variability estimate	Standard error of the mean
Dispersion value	1.297

Secondary: Serum C-reactive protein (CRP) levels

End point title	Serum C-reactive protein (CRP) levels

End point description:

C-reactive protein (CRP) is a blood test marker for inflammation in the body. It was analyzed on a log-scale fitting a repeated measures mixed model including treatment group, study day, the three stratification factors and log transformed baseline CRP as a covariate.

End point type	Secondary

End point timeframe:

Days 2, 4, 6, 8, 10, 12, 14 and 15

End point values	DFV890 + SoC	Standard of Care (SoC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	68		
Units: Milligram / Liter				
geometric mean (standard error)				
Day 2 n= 60, 66	31.4 (± 1.14)	46.6 (± 1.13)		
Day 4 n= 57, 61	22.2 (± 1.19)	26.5 (± 1.18)		
Day 6 n= 52, 60	11.5 (± 1.2)	15.1 (± 1.19)		
Day 8 n= 50, 55	7.7 (± 1.25)	10.9 (± 1.24)		
Day 10 n= 41, 40	7.0 (± 1.27)	8.0 (± 1.27)		
Day 12 n= 38, 28	7.5 (± 1.30)	7.1 (± 1.31)		
Day 14 n= 34, 26	8.1 (± 1.31)	6.3 (± 1.31)		
Day 15 / end of study n= 49, 51	6.9 (± 1.27)	8.2 (± 1.26)		

Statistical analyses

Statistical analysis title	Superiority Analysis
Comparison groups	DFV890 + SoC v Standard of Care (SoC)

Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.237
Method	Mixed models analysis

Secondary: Clinical status over time

End point title	Clinical status over time

End point description:

Clinical status was measured with World Health Organization (WHO) 9-point ordinal scale.

The scoring is - Uninfected patients have a score 0. - Ambulatory patients 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) 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, renal replacement therapy, extracorporeal membrane oxygenation). - Patients who die have a score 8.

Missing data values were handled as follows: For participants who died prior to Day 29, the score for death was imputed for all following visits up to and including day 29. For all the other participants, last observation carried forward was applied up to and including Day 29.

End point type	Secondary

End point timeframe:

Baseline, days 2, 4, 6, 8, 10, 12, 14, 15, 17, 19, 21, 23, 25, 27 and 29

End point values	DFV890 + SoC	Standard of Care (SoC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	72		
Units: Score on a scale				
arithmetic 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)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Number of participants with at least one-point improvement from baseline in clinical status, which was measured with WHO 9-point ordinal scale.

The scoring is - Uninfected patients have a score 0. - Ambulatory patients 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) 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). - Patients who die have a score 8.

Missing data values were handled as follows: For participants who died prior to Day 29, the score for death was imputed for all following visits up to and including day 29. For all the other participants, last observation carried forward was applied up to and including Day 29.

End point type	Secondary

End point timeframe:

Baseline, Day 15 and Day 29

End point values	DFV890 + SoC	Standard of Care (SoC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	72		
Units: Participants				
Day 15	59	53		
Day 29	61	60		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants not requiring mechanical ventilation for survival

End point title	Number of participants not requiring mechanical ventilation for survival

End point description:

Number of participants not requiring mechanical ventilation for survival until Day 15 and Day 29: defined by WHO 9-point ordinal scale score of < 6 points at all time points assessments.

The scoring is - Uninfected patients have a score 0. - Ambulatory patients 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) 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). - Patients who die have a score 8.

Missing data values were handled as follows: For participants who died prior to Day 29, the score for death was imputed for all following visits up to and including day 29. For all the other participants, last observation carried forward was applied up to and including Day 29.

End point type	Secondary

End point timeframe:

Until Day 15 (Assessment 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)

End point values	DFV890 + SoC	Standard of Care (SoC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	72		
Units: Participants				
Until Day 15	60	59		
Until Day 29	60	58		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the start of treatment to 30 days after end of treatment, assessed up to maximum duration of 45 days.

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	23.0

Reporting groups

Reporting group title	DFV890 + SoC

Reporting group description:

DFV890 + SoC

Reporting group title	Total

Reporting group description:

Total

Reporting group title	Standard of Care

Reporting group description:

SoC

Serious adverse events	DFV890 + SoC	Total	Standard of Care
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 70 (22.86%)	27 / 142 (19.01%)	11 / 72 (15.28%)
number of deaths (all causes)	8	16	8
number of deaths resulting from adverse events	0	0	0
Investigations			
Amylase increased			
subjects affected / exposed	1 / 70 (1.43%)	1 / 142 (0.70%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Arterial haemorrhage			
subjects affected / exposed	0 / 70 (0.00%)	1 / 142 (0.70%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery thrombosis			

subjects affected / exposed	1 / 70 (1.43%)	1 / 142 (0.70%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemodynamic instability			
subjects affected / exposed	0 / 70 (0.00%)	2 / 142 (1.41%)	2 / 72 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed	1 / 70 (1.43%)	1 / 142 (0.70%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 70 (0.00%)	1 / 142 (0.70%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 70 (0.00%)	1 / 142 (0.70%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Myocardial infarction			
subjects affected / exposed	0 / 70 (0.00%)	1 / 142 (0.70%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 70 (0.00%)	1 / 142 (0.70%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Polyneuropathy			
subjects affected / exposed	1 / 70 (1.43%)	1 / 142 (0.70%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration			

site conditions			
Condition aggravated			
subjects affected / exposed	1 / 70 (1.43%)	1 / 142 (0.70%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 70 (1.43%)	1 / 142 (0.70%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 70 (0.00%)	2 / 142 (1.41%)	2 / 72 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Acute respiratory failure			
subjects affected / exposed	0 / 70 (0.00%)	1 / 142 (0.70%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 70 (1.43%)	2 / 142 (1.41%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	4 / 70 (5.71%)	8 / 142 (5.63%)	4 / 72 (5.56%)
occurrences causally related to treatment / all	0 / 4	0 / 8	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 4	0 / 3
Pulmonary embolism			
subjects affected / exposed	1 / 70 (1.43%)	1 / 142 (0.70%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	0 / 70 (0.00%)	1 / 142 (0.70%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 70 (1.43%)	1 / 142 (0.70%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 70 (0.00%)	1 / 142 (0.70%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
COVID-19 pneumonia			
subjects affected / exposed	2 / 70 (2.86%)	4 / 142 (2.82%)	2 / 72 (2.78%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 3	0 / 1
Pneumonia			
subjects affected / exposed	1 / 70 (1.43%)	1 / 142 (0.70%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Sepsis			
subjects affected / exposed	1 / 70 (1.43%)	3 / 142 (2.11%)	2 / 72 (2.78%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Septic shock			
subjects affected / exposed	1 / 70 (1.43%)	2 / 142 (1.41%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	DFV890 + SoC	Total	Standard of Care
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 70 (17.14%)	18 / 142 (12.68%)	6 / 72 (8.33%)
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 70 (7.14%)	10 / 142 (7.04%)	5 / 72 (6.94%)
occurrences (all)	5	10	5
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	4 / 70 (5.71%)	6 / 142 (4.23%)	2 / 72 (2.78%)
occurrences (all)	4	6	2
Diabetes mellitus			
subjects affected / exposed	4 / 70 (5.71%)	4 / 142 (2.82%)	0 / 72 (0.00%)
occurrences (all)	4	4	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 June 2020	The primary purpose of this protocol amendment was to address comments raised by the Health Authorities and Ethics Committees during their review of the original protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported