Clinical trial results:
An Adaptive Phase 2/3, Randomised, Open-Label Study Assessing Efficacy and Safety of Hydroxychloroquine for Hospitalised Patients with Moderate to Severe COVID-19

Summary

EudraCT number	2020-001270-29
Trial protocol	DK CZ DE GB FR
Global end of trial date	25 June 2020

Results information

Result version number	v1 (current)
This version publication date	24 October 2020
First version publication date	24 October 2020

Trial information

Trial identification

Sponsor protocol code	EFC16858

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1249-6096

Notes:

Sponsors

Sponsor organisation name	Sanofi-aventis Recherche & Développement
Sponsor organisation address	1, Avenue Pierre Brossolette, Chilly Mazarin, France, 91385
Public contact	Trial Transparency Team, Sanofi-aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi-aventis recherche & développement, Contact-US@sanofi.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	09 July 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 June 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of hydroxychloroquine (HCQ) in addition to standard of care as compared to standard of care only on oxygen saturation/fraction of inspired oxygen (SpO2/FiO2) ratio in adult subjects hospitalised with moderate to severe coronavirus disease 2019 (COVID-19).

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject was participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 April 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	United Kingdom: 1
Country: Number of subjects enrolled	Czech Republic: 7
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	France: 3
Worldwide total number of subjects	14
EEA total number of subjects	14

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)	9
From 65 to 84 years	4
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 20 study centers in 5 countries between 15 April 2020 and 25 June 2020.

Pre-assignment

Screening details:

A total of 14 subjects were randomised and treated in 4 countries.

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	Hydroxychloroquine + Standard of care

Arm description:

Subjects received a loading dose of HCQ orally on Day 1 followed by a maintenance dose for 9 days (Days 2 to 10) plus standard of care.

Arm type	Experimental
Investigational medicinal product name	Hydroxychloroquine
Investigational medicinal product code	SAR321068
Other name	Plaquenil®, Quensyl®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received loading dose of HCQ (i.e., 800 milligram (mg) on Day 1, then 400 mg 6 hours later) orally on Day 1 along with meals, followed by maintenance doses of 200 mg three times daily (TID) orally for 9 days (Days 2 to 10).

Arm title	Standard of care

Arm description:

Subjects received standard of care only i.e., the usual care provided to COVID-19 subjects in the country/investigational site.

Arm type	Standard of care

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Hydroxychloroquine + Standard of care	Standard of care
Started	8	6
Completed	7	4
Not completed	1	2
Consent withdrawn by subject	-	1
Adverse Event (AE)	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Hydroxychloroquine + Standard of care
Reporting group description:	
Subjects received a loading dose of HCQ orally on Day 1 followed by a maintenance dose for 9 days (Days 2 to 10) plus standard of care.	
Reporting group title	Standard of care
Reporting group description:	
Subjects received standard of care only i.e., the usual care provided to COVID-19 subjects in the country/investigational site.	

Reporting group values	Hydroxychloroquine + Standard of care	Standard of care	Total
Number of subjects	8	6	14
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	57.4	57.5	
standard deviation	± 19.4	± 24.4	-
Gender categorical Units: Subjects			
Female	7	5	12
Male	1	1	2
Body Mass Index (BMI) group Units: Subjects			
Less than (<) 30	3	2	5
Greater than or equal to (>=) 30	3	2	5
Not reported	2	2	4
Age group (per Interactive Response Technology [IRT]) Units: Subjects			
< 55 years old	3	3	6
>= 55 years old	5	3	8
Severity of Illness (per IRT) Units: Subjects			
Moderate	6	4	10
Severe	2	2	4
BMI			
The BMI was reported for a total of 10 subjects i.e., HCQ + Standard of care: 6 subjects and Standard of care: 4 subjects only.			
Units: kilogram per square meter (kg/m^2)			
arithmetic mean	29.443	29.876	
standard deviation	± 4.114	± 6.406	-
Number of days since symptoms start			
Data was reported for a total of 13 subjects i.e., HCQ + Standard of care: 7 subjects and Standard of care: 6 subjects only.			
Units: days			

arithmetic mean	6.7	4.8	
standard deviation	± 4.8	± 3.3	-
Oxygen Saturation/Fraction of Inspired Oxygen (SpO2/FiO2) Ratio			
Units: ratio			
median	4.52	3.32	
full range (min-max)	2.3 to 4.6	2.9 to 4.5	-

End points

End points reporting groups

Reporting group title	Hydroxychloroquine + Standard of care
Reporting group description:	
Subjects received a loading dose of HCQ orally on Day 1 followed by a maintenance dose for 9 days (Days 2 to 10) plus standard of care.	
Reporting group title	Standard of care
Reporting group description:	
Subjects received standard of care only i.e., the usual care provided to COVID-19 subjects in the country/investigational site.	

Primary: Change From Baseline in Oxygen Saturation/Fraction of Inspired Oxygen Ratio at Day 15

End point title	Change From Baseline in Oxygen Saturation/Fraction of Inspired Oxygen Ratio at Day 15[1]
End point description:	
SpO2/FiO2 ratio determined oxygenation status of the subjects. The higher the SpO2/FiO2 ratio is, the better it is for the subject. Intent-to-treat (ITT) population included all randomised subjects. Here, 'number of subjects analysed' = subjects with available data at Day 15 for this endpoint.	
End point type	Primary
End point timeframe:	
Baseline, Day 15	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to limited data available following study termination, no statistical analysis was performed. Only descriptive summary.

End point values	Hydroxychloroquine + Standard of care	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	0[2]		
Units: ratio				
median (full range (min-max))	0.93 (0.0 to 1.3)	(to)		

Notes:

[2] - No data available at specified time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Oxygen Saturation/Fraction of Inspired Oxygen Ratio at Day 30

End point title	Change From Baseline in Oxygen Saturation/Fraction of Inspired Oxygen Ratio at Day 30
End point description:	
SpO2/FiO2 ratio determined oxygenation status of the subjects. The higher the SpO2/FiO2 ratio is, the better it is for the subject. ITT population included all randomised subjects. Here, 'number of subjects analysed' = subjects with available data at Day 30 for this endpoint.	

End point type	Secondary

End point timeframe:

Baseline, Day 30

End point values	Hydroxychloroquine + Standard of care	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	0[3]		
Units: ratio				
median (full range (min-max))	0.44 (0.0 to 1.5)	(to)		

Notes:

[3] - No data available at specified time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Mean Body Temperature at Day 15

End point title	Change From Baseline in Mean Body Temperature at Day 15

End point description:

Baseline body temperature was defined as the highest temperature recorded prior to the 1st HCQ dosing for HCQ + Standard of care group and recorded on randomisation date for Standard of care only group. ITT population included all randomised subjects. Here, 'number analysed' = subjects with available data at Day 15 for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Day 15

End point values	Hydroxychloroquine + Standard of care	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	2		
Units: degree Celsius				
arithmetic mean (standard deviation)	-0.66 (± 0.72)	-0.25 (± 0.92)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Each Severity Rating on the 7-Point Ordinal Scale

End point title	Number of Subjects Reporting Each Severity Rating on the 7-Point Ordinal Scale

End point description:

Clinical status of the subjects as per 7-point ordinal scale was described as: Category 1. Death; Category 2. Hospitalised, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); Category 3. Hospitalised, on non-invasive ventilation or high flow oxygen devices; Category 4. Hospitalised, requiring supplemental oxygen; Category 5. Hospitalised, not requiring supplemental oxygen-requiring ongoing medical care (COVID-19 related or otherwise); Category 6. Hospitalised, not requiring supplemental oxygen-no longer requires ongoing medical care and Category 7. Not hospitalised; where higher score indicates better outcomes. Only those scale categories in which at least 1 subject had data were reported. ITT population included all randomised subjects. Here, "n" = subjects with 7-point ordinal scale data available at the specified timepoint.

End point type	Secondary

End point timeframe:

Baseline, Day 15

End point values	Hydroxychloroquine + Standard of care	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	6		
Units: subjects				
number (not applicable)				
Baseline: Category 4 (n=8,4)	2	3		
Baseline: Category 5 (n=8,4)	5	0		
Baseline: Category 6 (n=8,4)	1	1		
Day 15: Category 2 (n=6,3)	1	0		
Day 15: Category 6 (n=6,3)	1	0		
Day 15: Category 7 (n=6,3)	4	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Quantitative Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Virus Load in the Nasopharyngeal (NP) Sample at Days 1, 2, 5, 10 and 15

End point title	Number of Subjects Reporting Quantitative Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Virus Load in the Nasopharyngeal (NP) Sample at Days 1, 2, 5, 10 and 15

End point description:

Quantitative SARS-CoV-2 virus in NP samples were evaluated by reverse transcription polymerase chain reaction (RT-PCR). The results were categorized as positive, negative or missing data. A positive result means SARS-COV2 detected; where as a negative result means SARS-COV2 not detected, with virus load highly probable less than 509 copies per milliliter. ITT population included all randomised subjects. Here, "n"= subjects with SARS-Cov-2 data available at the specified timepoint.

End point type	Secondary

End point timeframe:

Days 1, 2, 5, 10 and 15

End point values	Hydroxychloroquine + Standard of care	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	6		
Units: subjects				
number (not applicable)				
Day 1: Positive (n=6,5)	6	4		
Day 1: Negative (n=6,5)	0	1		
Day 1: Missing Data (n=6,5)	0	0		
Day 2: Positive (n=6,5)	4	4		
Day 2: Negative (n=6,5)	1	1		
Day 2: Missing Data (n=6,5)	1	0		
Day 5: Positive (n=5,3)	3	2		
Day 5: Negative (n=5,3)	2	1		
Day 5: Missing Data (n=5,3)	0	0		
Day 10: Positive (n=5,1)	4	1		
Day 10: Negative (n=5,1)	1	0		
Day 10: Missing Data (n=5,1)	0	0		
Day 15: Positive (n=3,0)	1	0		
Day 15: Negative (n=3,0)	2	0		
Day 15: Missing Data (n=3,0)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Severe Adverse Events and Adverse Events Leading to Treatment or Study Discontinuation

End point title	Number of Subjects With Severe Adverse Events and Adverse Events Leading to Treatment or Study Discontinuation

End point description:

An AEs was any untoward medical occurrence in a patient or clinical study subject, temporally associated with the use of study intervention, whether or not considered related to the study intervention. Severe AEs were defined as an event that prevents normal everyday activities. TEAEs were defined as AEs that developed, worsened or became serious during the treatment-emergent period (defined as the day from randomisation to the end of study i.e., Day 30). Safety population included all subjects who were randomized to standard of care alone group, and all subjects who were randomized to HCQ + standard of care group with at least one dose of HCQ use. Analysed by treatment as actually received.

End point type	Secondary

End point timeframe:

From Baseline to Day 30

End point values	Hydroxychloroquine + Standard of care	Standard of care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	6		
Units: subjects				
number (not applicable)				
Any severe TEAE	1	1		
AnyTEAE led to permanent treatment discontinuation	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected from time of first dose of study drug up to end of study (Day 30) regardless of seriousness or relationship to investigational product. SAEs, severe AEs and AEs leading to treatment or study discontinuation were collected as AE data.

Adverse event reporting additional description:

Reported AEs and deaths are TEAEs that developed/worsened during 'treatment period' (defined as the day from randomisation to the end of study i.e., Day 30). Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Hydroxychloroquine + Standard of care

Reporting group description:

Subjects received a loading dose of HCQ orally on Day 1 followed by a maintenance dose for 9 days (Days 2 to 10) plus standard of care.

Reporting group title	Standard of Care

Reporting group description:

Subjects received standard of care only i.e., the usual care provided to COVID-19 subjects in the country/investigational site.

Serious adverse events	Hydroxychloroquine + Standard of care	Standard of Care	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 8 (12.50%)	2 / 6 (33.33%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic Carcinoma			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Hypertensive Crisis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Covid-19			

subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Hydroxychloroquine + Standard of care	Standard of Care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 8 (37.50%)	0 / 6 (0.00%)	
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Urinary Tract Infection Fungal			
subjects affected / exposed	1 / 8 (12.50%)	0 / 6 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 April 2020	Following main changes were made: Electrocardiogram (ECG) assessments were added; following exclusion criteria were added: use of antiarythmic medications, subjects with the following ECG findings at screening: QTcF >470 milliseconds (msec) for women or >450 msec for men or heart rate <50 beats/minute, subjects with known G6PD deficiency; pregnant or breastfeeding women. Requirement for contraceptive methods in women of childbearing potential and contraceptive guidance was added in inclusion criteria; clarifications on standard of care, discharge from hospital, schedule of activities SAE reporting. Details of nasopharyngeal swab analysis were added.
16 April 2020	Following main changes were made: update on inclusion criteria: onset of symptoms was changed from within <= 5 days to within two weeks of randomisation. List of contraindicated medications and medications with precautions for use was updated. Clarification on discharge and schedule of activities.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
25 May 2020	The study was prematurely discontinued by the Sponsor due to enrollment and feasibility challenges that made study completion infeasible and as data from other studies did not suggest a benefit of HCQ for both COVID-19 treatment and prevention.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to premature discontinuation, only descriptive analysis were performed.

Notes: