



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 | | |
| Any TEAE 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 antiarrhythmic 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: