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Sponsor: Sanofi	**Study Identifiers:** U1111-1249-6168, NCT04333654, 2020-001269-35
Drug substance(s): Hydroxychloroquine	**Study code:** EFC16855

Title of the study: A phase 1b, randomized, double-blinded, placebo-controlled study of hydroxychloroquine in outpatient adults with COVID-19 (EFC16855)

Study center(s): Multicenter. This study was conducted in 4 study centers in 4 countries (Belgium, France, Netherlands and the United States).

Study period:

Date first participant enrolled: 12/Apr/2020

Date last participant completed: 26/May/2020

Phase of development: Phase 1b

Objectives:

The primary objective of this study was to assess the effect of hydroxychloroquine versus placebo on nasopharyngeal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load in outpatient adults with COVID-19. The secondary objectives were to assess the effect of hydroxychloroquine versus placebo on clinical signs and symptoms and progression of disease in outpatient adults with COVID19, and the safety and tolerability of hydroxychloroquine in outpatient adults with COVID-19.

Methodology:

This was a 2:1 randomized, multicenter, parallel, double-blinded, placebo-controlled study of hydroxychloroquine in outpatient adults with COVID-19. Randomization was stratified by the site.

Number of participants:

Planned: 210

Screened: 9

Randomized and Treated: 8 (hydroxychloroquine: 5; placebo: 3)

Evaluated:

Efficacy: 8

Safety: 8

Diagnosis and criteria for inclusion:

Outpatient male and female adults aged ≥18 ≤ 80 years with COVID-19 (diagnosed via approved or authorized molecular test) with onset of first symptoms within 96 hours and no previous history of cardiac conditions (ie. arrythmia, cardiac disease, bradycardia, QTc interval > 450 ms for men or > 470 ms for women), glucose-6-phosphate dehydrogenase (G6PD) deficiency, severe skin reactions (ie. Stevens-Johnson Syndrome, toxic epidermal necrolysis), retinopathy, or severe renal disease.

Study treatments

Investigational medicinal products: Tested drug - hydroxychloroquine (Plaquenil®); control drug – placebo.

Formulation: Hydroxychloroquine/placebo was supplied as tablets or capsules containing 200 mg of the active ingredient.

Route(s) of administration: Orally, right after the end of a meal.

Dose regimen: A loading dose of 1200 mg on Day 1 (administration of 1 dose of 800 mg, followed 6-8 hours later by 1 dose of 400 mg), followed by maintenance doses of 200 mg 3 times daily (TID) for 9 days (total duration of treatment of 10 days).

Participants had the option, where available, to receive the IMP at home using a Direct-To-Patient (DTP) service provider.

Duration of treatment: The total study duration per participant was up to approximately 18 days.

Duration of observation: The study consisted of a 1-2 day screening period; a 10-day treatment period and an end-of-study (EOS) visit 4-6 days after the last IMP dosing (final home visit up to 6 days after the last IMP).

Criteria for evaluation:

Due to early termination of the study, the current report is a synopsis-style report, and as such, only the safety results are being presented in full. No conclusions on efficacy from the study are provided. The following safety and efficacy criteria were evaluated (except those marked with an asterisk [*]):

Efficacy variables:

Primary endpoint was change from baseline in nasopharyngeal SARS-CoV-2 viral load on Day 3.

Secondary endpoints were:

- Change from baseline in nasopharyngeal SARS-CoV-2 viral load on Day 5
- Response rate (negative/positive Polymerase Chain Reaction [PCR]) in nasopharyngeal SARS-CoV-2 viral load
- Severity of COVID-19 symptoms (feverishness, sore throat, cough, shortness of breath, myalgias [muscle aches], headache*, fatigue*, chills*, nausea*, vomiting*, runny nose* and diarrhea*) scored by the participant on a 4-point scale.
- Percentage of participants with definitive resolution of fever at each day (definitive resolution of fever is defined as the first day of 2 consecutive days [without missing data] of temperatures ≤ 37.2 °C [oral] or ≤36.6°C [axilla or temporal], or ≤37.8°C [rectal or tympanic]
- *Percentage of participants with definitive resolution of each symptom at each day (definitive resolution of a symptom is defined as the first day of 2 consecutive days [without missing data] when a symptom previously scored ≥ 1 on the symptom intensity scale is scored as 0)
- *Number of days with fever (ie. number of days where the daily temperature is >37.2°C [oral], or >36.6°C [axilla or temporal], or >37.8°C [rectal or tympanic]
- Number of days with each symptom, ie. number of days with the corresponding daily symptom scored ≥1 on the symptom intensity scale.
- Percentage of participants hospitalized at each day

Safety variables:

Safety evaluations were based on adverse events (AEs) including serious adverse events (SAEs), AEs of special interest (AESIs) (ie, pregnancy, symptomatic overdose with IMP), as well as cardiac parameters, body temperature, and severity of symptoms.

Statistical methods:

Efficacy

Due to early termination of the study, the number of participants randomized (8 participants, instead of the planned sample size of 210 participants) was not large enough to perform the planned primary and secondary efficacy analyses. Only descriptive statistics are provided.

The primary and secondary efficacy analyses performed were based on the intention-to-treat (ITT) population, which consisted of all randomized participants regardless of whether the study treatment was received.

Safety

Safety analyses were performed using the safety population (defined as all randomized participants exposed to IMP, regardless of the amount of treatment administered). The safety analysis focused on the treatment emergent adverse event (TEAE) period.

Treatment Emergent Adverse Events (TEAEs) were tabulated (frequency and percent) by primary system-organ class (SOC), preferred term (PT) and treatment group. Adverse events reported in the study were coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 23.0.

Summary:

Population characteristics:

A total of 8 participants were randomized 2:1 to hydroxychloroquine (5 participants) and placebo (3 participants). All participants completed the study period.

One participant in the placebo group permanently discontinued study treatment on Day 6 due to TEAEs of rash and pruritus. The participant continued with the EOS visit and completed the study period.

All randomized participants were included in the ITT population and the safety population.

The overall mean age (standard deviation [SD]); was 36.9 years (16.2); the majority of participants (6/8 participant) were <50 years of age. The mean (SD) nasopharyngeal SARS-CoV-2 viral load (log10 cp/mL) at baseline, with 2 participants per treatment group, was 7.82 (1.40) in the hydroxychloroquine group and 6.13 (0.33) in the placebo group.

Efficacy results:

The nasopharyngeal SARS-CoV-2 viral load by time of measurement (screening, Day 3, Day 5 and EOS) is shown in Table 1. The response rate (negative/positive PCR) in nasopharyngeal SARS-CoV-2 viral load by time of measurement is shown in Table 2. Qualitative efficacy data was not available for all participants at each timepoint; in the placebo group, one participant refused all nasopharyngeal swabs after baseline (therefore no data was reported for this participant at Day 3, Day 5 and EOS) and one participant did not complete the EOS visit. In the hydroxychloroquine group, no data was reported for one participant at Day 3. In both treatment groups, a positive PCR result was reported by all participants tested at each timepoint, except for one participant in the hydroxychloroquine group who tested negative at EOS (Table 2).

Most participants in both treatment groups reported either no symptoms or symptoms with a mild severity throughout the study. In the hydroxychloroquine group, 2 participants reported symptoms of moderate and severe intensity (1 participant reported cough of severe intensity at Day 3 and Day 5, moderate intensity at Day 10; 1 participant reported severe feverishness and moderate myalgia at Day 3). In the placebo group no symptoms of severe or moderate intensity were reported.

In the hydroxychloroquine group, the percentage of participants with definitive resolution of fever was 80% (4/5 participants) at Day 3 and Day 5, and 100% (5/5 participants) at Day 10. In the placebo group, 100% of participants had definitive resolution of fever at each timepoint. The body temperature reported throughout the study ranged between 35.1 - 38.9°C in the hydroxychloroquine group and 35.8 - 37.4°C in the placebo.

No participant in either treatment group required hospitalization.

Table 1 - Nasopharyngeal SARS-CoV-2 viral load (in log10 cp/mL) - Descriptive statistics of raw data and change from baseline by treatment group and time of measurement– ITT population

	Raw data							Change from baseline						
	N	Mean	SD	SEM	Median	Min	Max	N	Mean	SD	SEM	Median	Min	Max
Placebo														
Screening	2	6.13	0.33	0.232	6.13	5.9	6.4	2	0.00	0.00	0.000	0.00	0.0	0.0
Day 3	2	7.04	1.48	1.047	7.04	6.0	8.1	2	0.92	1.81	1.279	0.92	-0.4	2.2
Day 5	2	4.74	0.61	0.431	4.74	4.3	5.2	2	-1.39	0.28	0.199	-1.39	-1.6	-1.2
EOS	1	3.17	NC	NC	3.17	3.2	3.2	1	-3.19	NC	NC	-3.19	-3.2	-3.2
Hydroxychloroquine 200 mg														
Screening	2	7.82	1.40	0.992	7.82	6.8	8.8	2	0.00	0.00	0.000	0.00	0.0	0.0
Day 3	2	7.79	0.10	0.072	7.79	7.7	7.9	2	-0.03	1.30	0.920	-0.03	-1.0	0.9
Day 5	2	7.63	2.11	1.491	7.63	6.1	9.1	2	-0.19	0.71	0.499	-0.19	-0.7	0.3
EOS	2	3.62	0.87	0.613	3.62	3.0	4.2	2	-4.20	0.54	0.379	-4.20	-4.6	-3.8

NC=Not Calculated

Note: Baseline is defined as the Day-2 or Day-1 assessment value (Brigham hospital center) or D1 pre-dose assessment value for all the other centers

<LOQ values are replaced by LOQ, <LOD values are replaced by LOD, No SARS-CoV-2 detected values are replaced by LOD/2.

PGM=PRODOPS/SAR321068/EFC16855/CSR/REPORT/PGM/eff_pcr_desc_i_t.sas OUT=REPORT/OUTPUT/eff_pcr_desc_i_t_i.rtf (07AUG2020 14:39)

Table 2 - Nasopharyngeal SARS-CoV-2 viral load - Number and % of participants according to qualitative result status (negative/positive PCR) by treatment group and time of measurement – ITT population

n(%)	Placebo (N=3)	Hydroxychloroquine 200 mg (N=5)
Screening		
Positive	3 (100)	5 (100)
Negative	0	0
Day 3		
Positive	2 (66.7)	4 (80.0)
Negative	0	0
Day 5		
Positive	2 (66.7)	5 (100)
Negative	0	0
EOS		
Positive	1 (33.3)	4 (80.0)
Negative	0	1 (20.0)

Note: Baseline is defined as the Day-2 or Day-1 assessment value (Brigham hospital center) or D1 pre-dose assessment value for all the other centers
PGM=PRODOPS/SAR321068/EFC16855/CSR/REPORT/PGM/eff_pcr_overview_i_t.sas OUT=REPORT/OUTPUT/eff_pcr_overview_i_t_i.rtf (07AUG2020 14:40)

Safety results:

The overall incidence of treatment-emergent AEs (TEAEs) was 80.0% (4/5 participants) for hydroxychloroquine and 66.7% (2/3 participants) for the placebo. A total of 11 TEAEs were reported in the hydroxychloroquine group; none of which were considered as related to study treatment by the Investigator. All 3 TEAEs reported in the placebo were considered as related to study treatment by the Investigator. There were no serious or fatal TEAEs reported in either treatment group. One participant in the placebo group reported TEAEs (rash and pruritus) leading to permanent treatment discontinuation. No AESI were reported in either treatment group. One participant in the hydroxychloroquine group reported a cardiac arrhythmia-related TEAE (palpitations), 2 days after exposure to the study drug. This event, which resolved in one day, was considered by the Investigator as not related to IMP and the participant continued with study treatment.

One participant treated with hydroxychloroquine reported an ECG finding of PR prolongation post-dose on the first day of dosing.

Overall, the safety data did not reveal any specific safety concerns in outpatients diagnosed with COVID-19 who were treated with hydroxychloroquine and the results are consistent with the known safety profile of hydroxychloroquine.

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