Clinical trial results:
HYCOVID - Hydroxychloroquine versus placebo chez les patients ayant une infection COVID-19 à risque d'aggravation secondaire : étude prospective multicentrique randomisée en double aveugle

Summary

EudraCT number	2020-001271-33
Trial protocol	FR
Global end of trial date	18 June 2020

Results information

Result version number	v1 (current)
This version publication date	18 April 2022
First version publication date	18 April 2022

Trial information

Trial identification

Sponsor protocol code	49RC20_0071

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04325893
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CHU Angers
Sponsor organisation address	4 rue Larrey, Angers, France, 49933
Public contact	chef de projets, CHU Angers, +33 0241353637, DRCI-Promotion-Interne@chu-angers.fr
Scientific contact	chef de projets, CHU Angers, +33 0241353637, DRCI-Promotion-Interne@chu-angers.fr

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	14 July 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 June 2020
Global end of trial reached?	Yes
Global end of trial date	18 June 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

L’objectif principal est d’évaluer l’efficacité de l’hydroxychloroquine versus placebo sur le taux de décès ou de recours à une ventilation invasive chez les patients ayant une infection COVID-19 à haut risque d’aggravation.

Protection of trial subjects:

Réalisation systématique d’un ECG après la dose de charge, puis toutes les 48 à 72 heures en cas de prise concomitante de médicaments à risque.
Le rapport bénéfice/risque n'a pas été modifié au cours de l'étude. Le comité de surveillance indépendant n'a pas demandé de modifications.
Les inclusions ont été suspendues le 26/05/2020, suite à la parution de l'étude parue dans le Lancet qui a conduit le Comité Scientifique de Solidarity à réaliser une analyse intermédiaire.

3 informations de sécurité ont été transmises aux investigateurs (10/04/2020 suite aux retours des centres de pharmacovigilance sur le risque avéré de troubles du rythme ventriculaire graves, 24/04/2020 suite à une information de l'EMA, et 10/05/2020 suite à l'information par l'Agence Espagnol des Médicaments d'un signal de sécurité sur des troubles neuropsychiatriques).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 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	France: 257
Worldwide total number of subjects	257
EEA total number of subjects	257

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)	85
From 65 to 84 years	92
85 years and over	80

Subject disposition

Recruitment

Recruitment details:

Ouverture de 48 centres investigateurs sur l'ensemble du territoire national français.
257 patients ont été inclus dans 42 centres.

Pre-assignment

Screening details:

1822 patients ont été screenés.
1568 patients n'ont pas été inclus pour défaut de critères d'inclusion (1080) et/ou de non inclusion (681), 54 patients ont refusé de participer à l'étude

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Plaquenil et placebo

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo

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

Dosage and administration details:

dose cumulée 4 000 mg

Arm title	Hydroxychloroquine

Arm description:

bras expérimental

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

Dosage and administration details:

800mg à J1
400mg de J2 à J9

Number of subjects in period 1[1][2]	Placebo	Hydroxychloroquine
Started	124	125
Completed	122	126
Not completed	2	0
Protocol deviation	2	-
Joined	0	1
Transferred in from other group/arm	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: I confirm
2 patients "placebo" did not start the treatment, 1 of them begin hydroxychloroquine treatment
[2] - The number of subjects transferring in and out of the arms in the period are not the same. It is expected the net number of transfers in and out of the arms in a period, will be zero.
Justification: I confirm.
2 patients "placebo" did not start the treatment, 1 of them begin hydroxychloroquine treatment

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo	
Reporting group title	Hydroxychloroquine
Reporting group description:	
bras expérimental	

Reporting group values	Placebo	Hydroxychloroquine	Total
Number of subjects	124	126	250
Age categorical			
Units: Subjects			
Adults (18-64 years)	43	40	83
From 65-84 years	37	53	90
85 years and over	44	33	77
Age continuous			
Units: years			
median	78	76	
full range (min-max)	57 to 87	60 to 85	-
Gender categorical			
Units: Subjects			
Female	68	61	129
Male	56	65	121

Subject analysis sets	
Subject analysis set title	Modified intention to treat
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

There were no significant differences between the two groups in demographic characteristics at inclusion, time from first signs of infection to inclusion, distribution of risk factors for adverse outcomes, and treatments received at inclusion

Reporting group values	Modified intention to treat		
Number of subjects	250		
Age categorical			
Units: Subjects			
Adults (18-64 years)	82		
From 65-84 years	89		
85 years and over	77		
Age continuous			
Units: years			
median	77		
full range (min-max)	58 to 86		

Gender categorical Units: Subjects			
Female	129		
Male	121		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Placebo	
Reporting group title	Hydroxychloroquine
Reporting group description: bras expérimental	
Subject analysis set title	Modified intention to treat
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

There were no significant differences between the two groups in demographic characteristics at inclusion, time from first signs of infection to inclusion, distribution of risk factors for adverse outcomes, and treatments received at inclusion

Primary: Rate of mortality and use of invasive ventilation among among non-severe COVID-19 patients at a high risk of complicated course

End point title	Rate of mortality and use of invasive ventilation among among non-severe COVID-19 patients at a high risk of complicated course

End point description:

End point type	Primary

End point timeframe:

Day 14

End point values	Placebo	Hydroxychloroquine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	124		
Units: percentage				
number (not applicable)	123	124		

Statistical analyses

Statistical analysis title	Analyse statistique

Statistical analysis description:

Les variables quantitatives seront décrites en moyenne +/- écart-type ou médiane et intervalle interquartile pour les distributions non-normales. Les variables qualitatives seront décrites en effectif et pourcentage. Les comparaisons de moyennes seront réalisées avec le test t de Student (test de Mann-Whitney si nécessaire) et les comparaisons de pourcentages avec le test du Chi2 (test exact de Fisher si nécessaire). L'analyse du critère de jugement principal sera réalisée en ITT

Comparison groups	Placebo v Hydroxychloroquine

Number of subjects included in analysis	247
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.82
Method	Chi-squared

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Day 28	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups	
Reporting group title	Placebo
Reporting group description: Placebo	
Reporting group title	Hydroxychloroquine
Reporting group description: -	

Serious adverse events	Placebo	Hydroxychloroquine	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 122 (14.75%)	23 / 126 (18.25%)	
number of deaths (all causes)	6	4	
number of deaths resulting from adverse events	6	4	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Small intestine carcinoma			
subjects affected / exposed	1 / 122 (0.82%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Ischaemic stroke			
subjects affected / exposed	0 / 122 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Subdural haematoma			
subjects affected / exposed	1 / 122 (0.82%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	2 / 122 (1.64%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 122 (0.82%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malaise			
subjects affected / exposed	1 / 122 (0.82%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 122 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 122 (0.82%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	0 / 122 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 122 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 122 (0.82%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			

subjects affected / exposed	1 / 122 (0.82%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 122 (2.46%)	4 / 126 (3.17%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 122 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 122 (0.82%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	1 / 122 (0.82%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric decompensation			
subjects affected / exposed	0 / 122 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 122 (0.00%)	2 / 126 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 122 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Incorrect product administration duration			
subjects affected / exposed	0 / 122 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product administration error			
subjects affected / exposed	0 / 122 (0.00%)	3 / 126 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 122 (1.64%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 122 (0.82%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 122 (0.82%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 122 (0.82%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Conduction disorder			
subjects affected / exposed	1 / 122 (0.82%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	0 / 122 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Stress cardiomyopathy			
subjects affected / exposed	0 / 122 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	0 / 122 (0.00%)	2 / 126 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 122 (0.82%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	0 / 122 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	0 / 122 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 122 (0.00%)	2 / 126 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 122 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diverticulum intestinal			

subjects affected / exposed	1 / 122 (0.82%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal perforation			
subjects affected / exposed	1 / 122 (0.82%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	1 / 122 (0.82%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 122 (0.00%)	2 / 126 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 122 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 122 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 122 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	0 / 122 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metabolism and nutrition disorders			
Adult failure to thrive			
subjects affected / exposed	1 / 122 (0.82%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dehydration			
subjects affected / exposed	0 / 122 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypokalaemia			
subjects affected / exposed	0 / 122 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Placebo	Hydroxychloroquine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 122 (40.98%)	46 / 126 (36.51%)	
Cardiac disorders			
heart rythm			
subjects affected / exposed	50 / 122 (40.98%)	46 / 126 (36.51%)	
occurrences (all)	92	118	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 April 2020	Mise à jour des centres investigateurs
09 April 2020	Ajout de 10 centres et changement de l'Investigateur Principal du CHU de Rennes
21 April 2020	Précision sur les critères d'inclusions (ajout de délai « dans les dernières 24h ») Ajout paragraphe pour la CNIL : transmission des consentements par fax aux ARC pour s'assurer qu'il n'y ait pas de déviation critique
26 May 2020	Suspension des inclusions sur la base d'un projet de suspension des essais avec hydroxychloroquine par l'ANSM
08 June 2020	Modifications des lettres d'information suite à l'amendement 5, Modification du paragraphe statistique Ajout du lien pour le Thésaurus ANSM (traitement interagissant avec l'hydroxychloroquine)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
26 May 2020	Suspension des essais sur l'hydroxychloroquine par l'ANSM Fin de la vague Covid suite au confinement	-

Notes:

Limitations and caveats

None reported