Clinical trial results:
Efficacy and safety of novel treatment options for adults with COVID-19 pneumonia. A double-blinded, randomized, multi-stage, 6-armed placebo-controlled trial in the framework of an adaptive trial platform

Summary

EudraCT number	2020-001367-88
Trial protocol	DK
Global end of trial date	17 June 2020

Results information

Result version number	v1 (current)
This version publication date	27 September 2020
First version publication date	27 September 2020

Trial information

Trial identification

Sponsor protocol code	25032020

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04345289
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Thomas Benfield
Sponsor organisation address	Kettegaard Alle 30, Hvidovre, Denmark, 2650
Public contact	Charlotte Kastberg Levin, Department of infectious diseases, +45 38622941, charlotte.kastberg.levin.01@regionh.dk
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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	11 August 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 June 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The aim of this study is to evaluate the efficacy and safety of convalescent anti-SARS-CoV-2 plasma, hydroxychloroquine, sarilumab and baricitinib compared with placebo in combination with standard of care (SOC) for the treatment of moderate-to-severe COVID-19 pneumonia on the basis of the composite endpoint: All-cause mortality or need of invasive mechanical ventilation up to 28 days.

Protection of trial subjects:

The adaptive study design allowed each treatment group to be evaluated separately. If necessary, each treatment group could be discontinued due to futility, effect, safety or new knowledge on specific treatment of COVID-19.
This was the case for hydroxychloroqunie which was withdrawn from the study 2020-06-09 due to new research results (from other studies) indicating severe adverse events, when giving to COVID-19 patients.
Due to the introduction of dexamethason (and Remdesevir) as first line treatment, we considered it unnecessary to continue baricitinib and sarilumab as the effect immuno-suppressive.
The trial will continue as a non-drug trial with convalescence SARS-CoV-2 plasma.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 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	Denmark: 6
Worldwide total number of subjects	6
EEA total number of subjects	6

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

Subject disposition

Recruitment

Recruitment details:

Recruiment period went from 01-05-2020 to 11-06-2020.
Only one sites was initiated, and all 6 patients were recruited from and hospitalized at Hvidovre Hospital, Denmark.
All patients with SARS-Covid-19 positive swap or traceal sputum hospitalized patiens during the period were screened for participation by treating physicians.

Pre-assignment

Screening details:

60 patients in total went through screening.

Period 1

Period 1 title	Inclusion (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Eligible patients who signed informed content, were enrolled. Randomization was performed in RedCap by unblinded personel. Patients were randomized to one of the six study arms. Study treatment were prepared and administrated by unblinded personel. All six patients were randomized to oral treatment. All oral treatment were capsulated in identical opaque capsules to maintain blinding for all other personel than the unblinded personel.

Arms

Are arms mutually exclusive?	Yes
Arm title	Hydroxychloroquin

Arm description:

Hydroxychloroquine (Plaquenil) (capsulated), administred600 mg once daily for 7 days

Arm type	Experimental
Investigational medicinal product name	Plaquenil
Investigational medicinal product code	P01BA02
Other name	Hydroxychloroquine
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

tablets contains 200 mg
Patients received 600 mg daily

Arm title	Baricitinib

Arm description:

Baricitinib (Olumiant) (capsulated), administred 4 mg daily for 7 days

Arm type	Experimental
Investigational medicinal product name	Olumiant
Investigational medicinal product code	L04AA37
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablets of 2 mg
2 tablets (4 mg) daily for 7 days

Arm title	Placebo

Arm description:

Placebo tablet containing glucosemonohydrat (capsulated) administred once daily for 7 days

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:

3 capsulated placebo tablets once daily for 7 days

Number of subjects in period 1	Hydroxychloroquin	Baricitinib	Placebo
Started	1	4	1
Completed	0	4	1
Not completed	1	0	0
Adverse event, non-fatal	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Inclusion

Reporting group description: -

Reporting group values	Inclusion	Total	
Number of subjects	6	6	
Age categorical			
Participant age			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	3	3	
From 65-84 years	2	2	
85 years and over	1	1	
Gender categorical			
3/6 (50%) participants were female and 3/6 (50%) were male.			
Units: Subjects			
Female	3	3	
Male	3	3	
Comorbidity			
Number of comorbidities at the time of inclusion			
Units: Subjects			
Cardiac disease	0	0	
Cerebral disease	0	0	
Peripheral vascular disease	0	0	
Nephrological disease	0	0	
Chronical Obstructive Lung Disease (COLD)	0	0	
Asthma	0	0	
Diabetes	1	1	
Cancer	0	0	
Connective tissue disease	0	0	
Ulcus	0	0	
Liver disease	0	0	
Other	0	0	
None	5	5	
Etnicity			
Etnicity			
Units: Subjects			
Caucasian	3	3	
Middle East	3	3	
Asian	0	0	

Latin American	0	0	
Smoking			
Smoking at baseline			
Units: Subjects			
Yes	0	0	
No	4	4	
Previous	2	2	
Close contact to COVID-19 case			
Close contact to COVID-19 case prior to admission			
Units: Subjects			
Yes	4	4	
No	2	2	
Location of transmission			
Suspected location of transmission			
Units: Subjects			
Home	2	2	
Travel	0	0	
Workplace	1	1	
Unknown	3	3	
Other	0	0	
Nursing home resident			
Units: Subjects			
Yes	0	0	
No	6	6	
Functional level			
Functional level prior to admission			
Units: Subjects			
Self-reliant	6	6	
Home Help	0	0	
Need of home nursing support	0	0	
Dyspnenia			
Dyspnenia as debut COVID-19 symptom			
Units: Subjects			
Yes	4	4	
No	2	2	
Dry Coughing			
Dry Coughing as debut COVID-19 symptom			
Units: Subjects			
Yes	4	4	
No	2	2	
Coughing with sputum			
Coughing with sputumas debut COVID-19 symptom?			
Units: Subjects			
Yes	3	3	
No	3	3	
Chest tightness			
Chest tightness as debut COVID-19 symptom?			
Units: Subjects			
Yes	0	0	
No	6	6	
Fever			

Fever as debut COVID-19 symptom?			
Units: Subjects			
Yes	6	6	
No	0	0	
Sore throught			
Sore throught as debut COVID-19 symptom?			
Units: Subjects			
Yes	1	1	
No	5	5	
Muscle and/or joint pain			
Muscle and/or joint pain as debut COVID-19 symptom?			
Units: Subjects			
Yes	2	2	
No	4	4	
Headache			
Headache as debut COVID-19 symptom?			
Units: Subjects			
Yes	2	2	
No	4	4	
Changes in smell and/or taste			
Changes in smell and/or taste as debut COVID-19 symptom?			
Units: Subjects			
Yes	1	1	
No	5	5	
Nausea/vomit			
Nausea as debut COVID-19 symptom?			
Units: Subjects			
Yes	2	2	
No	4	4	
Diarrhea			
Diarrhea as debut COVID-19 symptom?			
Units: Subjects			
Yes	2	2	
No	4	4	
Erythema			
Erythema as debut COVID-19 symptom?			
Units: Subjects			
Yes	0	0	
No	6	6	
Other debut symptoms			
Other debut COVID-19 symptom?			
Units: Subjects			
Yes	1	1	
No	5	5	
Weight			
Weight at baseline			
Units: kg			
arithmetic mean	86		
full range (min-max)	66 to 157	-	
Height			
Height at baseline			

Units: cm			
arithmetic mean	172		
full range (min-max)	157 to 183	-	
Symptom debut			
Days with symptoms prior to admission			
Units: days			
arithmetic mean	7		
full range (min-max)	3 to 11	-	

End points

End points reporting groups

Reporting group title	Hydroxychloroquin
Reporting group description:	
Hydroxychloroquine (Plaquenil) (capsulated), administred600 mg once daily for 7 days	
Reporting group title	Baricitinib
Reporting group description:	
Baricitinib (Olumiant) (capsulated), administred 4 mg daily for 7 days	
Reporting group title	Placebo
Reporting group description:	
Placebo tablet containing glucosemonohydrat (capsulated) administred once daily for 7 days	

Primary: All-cause mortality or need of invasive mechanical ventilation up to 28 days

End point title	All-cause mortality or need of invasive mechanical ventilation up to 28 days
End point description:	
End point type	Primary
End point timeframe:	
28 days	

End point values	Hydroxychloroquin	Baricitinib	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	4	1	
Units: Subjects	0	0	1	

Statistical analyses

Statistical analysis title	Placebo
Comparison groups	Hydroxychloroquin v Baricitinib v Placebo
Number of subjects included in analysis	6
Analysis specification	Post-hoc
Analysis type	other[1]
P-value	= 0
Method	None
Parameter estimate	none

Notes:

[1] - One patient died during the study. No causality between IMP and mortality was suspected. The patient who died received placebo.

Secondary: Frequency of adverse events

End point title	Frequency of adverse events

End point description:

End point type	Secondary

End point timeframe:

90 days

End point values	Hydroxychloroquin	Baricitinib	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	4	1	
Units: number of AE	4	10	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of severe adverse events

End point title	Frequency of severe adverse events

End point description:

End point type	Secondary

End point timeframe:

90 days

End point values	Hydroxychloroquin	Baricitinib	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	4	1	
Units: number of SAE	1	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Ventilator-free days to day 28

End point title	Ventilator-free days to day 28

End point description:

End point type	Secondary

End point timeframe:
28 days

End point values	Hydroxychloroquin	Baricitinib	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	4	1	
Units: days	1	4	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Organ failure-free days to day 28

End point title	Organ failure-free days to day 28

End point description:

End point type	Secondary

End point timeframe:
28 days

End point values	Hydroxychloroquin	Baricitinib	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	4	1	
Units: days	1	4	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of ICU stay

End point title	Duration of ICU stay

End point description:

End point type	Secondary

End point timeframe:
90 days

End point values	Hydroxychloroquin	Baricitinib	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	4	1	
Units: days	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Mortality rate

End point title	Mortality rate

End point description:

End point type	Secondary

End point timeframe:

90 days

End point values	Hydroxychloroquin	Baricitinib	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	4	1	
Units: subjects	0	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Length of hospital stay

End point title	Length of hospital stay

End point description:

End point type	Secondary

End point timeframe:

90 days

End point values	Hydroxychloroquin	Baricitinib	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	4	1	
Units: days	6	10	7	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of supplemental oxygen

End point title	Duration of supplemental oxygen

End point description:

End point type	Secondary

End point timeframe:

90 days

End point values	Hydroxychloroquin	Baricitinib	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1	4	1	
Units: days	5	6	7	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
90 days	
Adverse event reporting additional description:	
Adverse events were collected by reviewing medical records during hospitalizations and by telephone follow-up at day 7, 14, 28 and 90.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups	
Reporting group title	Hydroxychloroquin
Reporting group description:	
Hydroxychloroquine (Plaquenil) (capsulated), administred600 mg once daily for 7 days	
Reporting group title	Baricitinib
Reporting group description:	
Baricitinib (Olumiant) (capsulated), administred 4 mg daily for 7 days	
Reporting group title	Placebo
Reporting group description:	
Placebo tablet containing glucosemonohydrat (capsulated) administred once daily for 7 days	

Serious adverse events	Hydroxychloroquin	Baricitinib	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	0 / 4 (0.00%)	1 / 1 (100.00%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
QTc-prolongation			
subjects affected / exposed	1 / 1 (100.00%)	0 / 4 (0.00%)	0 / 1 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory, thoracic and mediastinal disorders			
Death			
subjects affected / exposed	0 / 1 (0.00%)	0 / 4 (0.00%)	1 / 1 (100.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

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

Non-serious adverse events	Hydroxychloroquin	Baricitinib	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	3 / 4 (75.00%)	1 / 1 (100.00%)
Cardiac disorders			
EKG changes			
subjects affected / exposed	1 / 1 (100.00%)	0 / 4 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 4 (25.00%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 4 (25.00%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 4 (0.00%)	1 / 1 (100.00%)
occurrences (all)	0	0	1
Thrombocytosis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 4 (25.00%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Headache			
subjects affected / exposed	0 / 1 (0.00%)	1 / 4 (25.00%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Hyperamylasaemia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 4 (25.00%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Incread transaminases			
subjects affected / exposed	0 / 1 (0.00%)	1 / 4 (25.00%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
pulmonary edema	Additional description: High pressure pulmonary edema		

subjects affected / exposed	0 / 1 (0.00%)	0 / 4 (0.00%)	1 / 1 (100.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Skin rash			
subjects affected / exposed	1 / 1 (100.00%)	0 / 4 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Hair loss			
subjects affected / exposed	1 / 1 (100.00%)	0 / 4 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Memory impairment			
subjects affected / exposed	1 / 1 (100.00%)	1 / 4 (25.00%)	0 / 1 (0.00%)
occurrences (all)	1	1	0
Renal and urinary disorders			
hematuria			
subjects affected / exposed	0 / 1 (0.00%)	1 / 4 (25.00%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Nephropathy	Additional description: Worsening of chronic nephropathy		
subjects affected / exposed	0 / 1 (0.00%)	1 / 4 (25.00%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Fever			
subjects affected / exposed	0 / 1 (0.00%)	1 / 4 (25.00%)	0 / 1 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 June 2020	The hydroxychloroquine arm closed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
17 June 2020	Pre-mature termination of the study. The trial continues as a non-drug trial with convalescense plasma.	-

Notes:

Limitations and caveats

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

The trial is terminated pre-maturely. Only 6 patients were included (1500 predicted) therefore results are not analysed.

Notes: