Clinical trial results:
Proactive Prophylaxis with Azithromycin and Hydroxychloroquine Patients Hospitalized with COVID

Summary

EudraCT number	2020-001198-55
Trial protocol	DK
Global end of trial date	02 February 2021

Results information

Result version number	v1 (current)
This version publication date	04 July 2021
First version publication date	04 July 2021

Trial information

Trial identification

Sponsor protocol code	KronLungesyg_COVID_19_protokol_2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04322396
WHO universal trial number (UTN)	-
Other trial identifiers	Videnskabsetisk Komite: H-20023010

Notes:

Sponsors

Sponsor organisation name	Gentofte Hospital
Sponsor organisation address	Gentofte Hospitalsvej 1D, Hellerup, Denmark, 2900
Public contact	www.coptrin.dk, COP:TRIN, 45 28938168, jens.ulrik.jensen@regionh.dk
Scientific contact	www.coptrin.dk, COP:TRIN, 45 28938168, jens.ulrik.jensen@regionh.dk

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	15 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 February 2021
Global end of trial reached?	Yes
Global end of trial date	02 February 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

In patients who are admitted urgently to hospital with coronavirus infection (COVID-19) and symptoms, treatment with virus-modifying agent Hydroxyhloroquine as well as virus-immunomodulatory and antibacterial drug Azithromycin can lead to a shorter hospitalization.

Protection of trial subjects:

Subjects were systematically monitored, and medication, including study medication, regulated when clinically indicated. The safety of the study subjects was ensured by following Good Clinical Practice

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 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: 117
Worldwide total number of subjects	117
EEA total number of subjects	117

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)	59
From 65 to 84 years	46
85 years and over	12

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

At each trial centre, screening of patients admitted with a positive SARS-CoV-2 test is performed. Patients are assessed against the inclusion and exclusion criteria of the attending physician who receives the patient's consent to contact the investigator. The Investigator then contacts the patient for recruitment to the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Control

Arm description:

This arm will receive standard care and placebo in 15 days.
Placebo oral tablet: Placebo Azithromycin
Placebo oral tablet: Placebo Hydroxychloroquine

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

Dosage and administration details:

500 mg azithromycin once daily plus 200 mg hydroxychloroquine twice daily on days 1–3 and then 250 mg azithromycin once daily plus 200 mg hydroxychloroquine twice daily on days 4–15

Investigational medicinal product name	Hydroxychloroquine PLACEBO
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

500 mg azithromycin once daily plus 200 mg hydroxychloroquine twice daily on days 1–3 and then 250 mg azithromycin once daily plus 200 mg hydroxychloroquine twice daily on days 4–15

Arm title	Intervention

Arm description:

This arm will receive standard care and azithromycin and hydroxychloroquine in 15 days.
Azithromycin: Azithromycin
Hydroxychloroquine: Hydroxychloroquine

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

Dosage and administration details:	
500 mg azithromycin once daily plus 200 mg hydroxychloroquine twice daily on days 1–3 and then 250 mg azithromycin once daily plus 200 mg hydroxychloroquine twice daily on days 4–15	
Investigational medicinal product name	Hydroxychloroquine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use
Dosage and administration details:	
500 mg azithromycin once daily plus 200 mg hydroxychloroquine twice daily on days 1–3 and then 250 mg azithromycin once daily plus 200 mg hydroxychloroquine twice daily on days 4–15	

Number of subjects in period 1	Control	Intervention
Started	56	61
Completed	56	61

Period 2	
Period 2 title	Overall trial
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor
Arms	
Are arms mutually exclusive?	Yes
Arm title	Control
Arm description:	
This arm will receive standard care and placebo in 15 days. Placebo oral tablet: Placebo Azithromycin Placebo oral tablet: Placebo Hydroxychloroquine	
Arm type	Placebo
Investigational medicinal product name	Azithromycin PLACEBO
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
500 mg azithromycin once daily plus 200 mg hydroxychloroquine twice daily on days 1–3 and then 250 mg azithromycin once daily plus 200 mg hydroxychloroquine twice daily on days 4–15	
Investigational medicinal product name	Hydroxychloroquine PLACEBO
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

500 mg azithromycin once daily plus 200 mg hydroxychloroquine twice daily on days 1–3 and then 250 mg azithromycin once daily plus 200 mg hydroxychloroquine twice daily on days 4–15

Arm title	Intervention

Arm description:

This arm will receive standard care and azithromycin and hydroxychloroquine in 15 days.
Azithromycin: Azithromycin
Hydroxychloroquine: Hydroxychloroquine

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

Dosage and administration details:

500 mg azithromycin once daily plus 200 mg hydroxychloroquine twice daily on days 1–3 and then 250 mg azithromycin once daily plus 200 mg hydroxychloroquine twice daily on days 4–15

Investigational medicinal product name	Hydroxychloroquine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

500 mg azithromycin once daily plus 200 mg hydroxychloroquine twice daily on days 1–3 and then 250 mg azithromycin once daily plus 200 mg hydroxychloroquine twice daily on days 4–15

Number of subjects in period 2	Control	Intervention
Started	56	61
Completed	56	61

Baseline characteristics

Reporting groups	
Reporting group title	Control
Reporting group description:	
This arm will receive standard care and placebo in 15 days. Placebo oral tablet: Placebo Azithromycin Placebo oral tablet: Placebo Hydroxychloroquine	
Reporting group title	Intervention
Reporting group description:	
This arm will receive standard care and azithromycin and hydroxychloroquine in 15 days. Azithromycin: Azithromycin Hydroxychloroquine: Hydroxychloroquine	

Reporting group values	Control	Intervention	Total
Number of subjects	56	61	117
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	63	68	
inter-quartile range (Q1-Q3)	52 to 74	52 to 80	-
Gender categorical Units: Subjects			
Female	27	25	52
Male	29	36	65
Race/ethnicity Units: Subjects			
Caucasian	45	53	98
African	1	0	1
Asian	6	6	12
Unknown/other	4	2	6

End points

End points reporting groups

Reporting group title	Control
Reporting group description:	
This arm will receive standard care and placebo in 15 days. Placebo oral tablet: Placebo Azithromycin Placebo oral tablet: Placebo Hydroxychloroquine	
Reporting group title	Intervention
Reporting group description:	
This arm will receive standard care and azithromycin and hydroxychloroquine in 15 days. Azithromycin: Azithromycin Hydroxychloroquine: Hydroxychloroquine	
Reporting group title	Control
Reporting group description:	
This arm will receive standard care and placebo in 15 days. Placebo oral tablet: Placebo Azithromycin Placebo oral tablet: Placebo Hydroxychloroquine	
Reporting group title	Intervention
Reporting group description:	
This arm will receive standard care and azithromycin and hydroxychloroquine in 15 days. Azithromycin: Azithromycin Hydroxychloroquine: Hydroxychloroquine	

Primary: Number of Days Alive and Discharged From Hospital Within 14 Days

End point title	Number of Days Alive and Discharged From Hospital Within 14 Days[1]
End point description:	
End point type	Primary
End point timeframe:	
14 days	

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: Statistical analysis was not found to improve understanding of this outcome.

End point values	Control	Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	61		
Units: days				
median (inter-quartile range (Q1-Q3))	9 (7 to 10)	9 (3 to 11)		

Statistical analyses

No statistical analyses for this end point

Secondary: Categorization of Hospitalization Status

End point title	Categorization of Hospitalization Status

End point description:

The patient will becategorized into one of the following 8 categories depending on status of their hospitalization:

(1) Dead (yes/no)
(2) Hospitalized and receiving mechanical ventilation or ExtraCorporalMembraneOxygenation (ECMO) (yes/no)
(3) Hospitalized and receiving Non-invasive ventilation or "high-flow oxygen device" (yes/no)
(4) Hospitalized and given oxygen supplements different from (2) and (3) (yes/no)
(5) Hospitalized and without oxygen treatment, but receiving other treatment (both related to COVID-19 or other) (yes/no)
(6) Hospitalized for observation (yes/no)
(7) Discharged from hospital with restriction of activity level (yes/no)
(8) Discharged from hospital without any restrictions of activity level (yes/no)

Only one category can be "yes".

End point type	Secondary

End point timeframe:

14

End point values	Control	Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	61		
Units: participants				
(1)	2	1		
(2)	2	1		
(3)	0	1		
(4)	2	2		
(5)	2	1		
(6)	0	1		
(7)	27	26		
(8)	22	26		

Statistical analyses

No statistical analyses for this end point

Secondary: Admitted to Intensive Care Unit, if Admitted to ICU Then Length of Stay

End point title	Admitted to Intensive Care Unit, if Admitted to ICU Then Length of Stay

End point description:

End point type	Secondary

End point timeframe:

14 days

End point values	Control	Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	61		
Units: days				
median (inter-quartile range (Q1-Q3))	11 (4 to 14)	14 (9.5 to 14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Have Used Non-invasive Ventilation (NIV) During Hospitalization

End point title	Have Used Non-invasive Ventilation (NIV) During Hospitalization

End point description:

End point type	Secondary

End point timeframe:

14 days

End point values	Control	Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	61		
Units: participants	1	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Mortality

End point title	Mortality

End point description:

End point type	Secondary

End point timeframe:

30 days

End point values	Control	Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	61		
Units: participants	2	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Length of Hospitalization

End point title	Length of Hospitalization

End point description:

End point type	Secondary

End point timeframe:

14 days

End point values	Control	Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	61		
Units: days				
median (inter-quartile range (Q1-Q3))	4 (3 to 6)	4 (2 to 8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Days Alive and Discharged From Hospital

End point title	Days Alive and Discharged From Hospital

End point description:

End point type	Secondary

End point timeframe:

30 days

End point values	Control	Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	61		
Units: days				
median (inter-quartile range (Q1-Q3))	26 (23 to 27)	26 (21 to 28)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Readmissions (All Causes)

End point title	Number of Readmissions (All Causes)

End point description:

End point type	Secondary

End point timeframe:

30 days

End point values	Control	Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	61		
Units: participants	6	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Days Using Non-invasive Ventilation (NIV)

End point title	Number of Days Using Non-invasive Ventilation (NIV)

End point description:

End point type	Secondary

End point timeframe:

14 days

End point values	Control	Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	61		
Units: days				
arithmetic mean (confidence interval 95%)	9 (9 to 9)	6.7 (-9.1 to 22.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Patient's Oxygen Partial Pressure

End point title	Change in Patient's Oxygen Partial Pressure
End point description:	
Delta PaO2 measured in arterial puncture	
End point type	Secondary
End point timeframe:	
4 days	

End point values	Control	Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	61		
Units: mmHg				
arithmetic mean (confidence interval 95%)	-0.2 (-8.3 to 7.8)	-3.0 (-9.8 to 3.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Patient's Carbondioxid Partial Pressure

End point title	Change in Patient's Carbondioxid Partial Pressure
End point description:	
Delta PaCO2 measured in arterial puncture	
End point type	Secondary
End point timeframe:	
4 days	

End point values	Control	Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	61		
Units: mmHg				
arithmetic mean (confidence interval 95%)	1.4 (-0.4 to 3.3)	-3.0 (-9.8 to 3.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change of pH in Blood

End point title	Change of pH in Blood
End point description:	
Change in pH measured in arterial puncture	
End point type	Secondary
End point timeframe:	
4 days	

End point values	Control	Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	61		
Units: pH				
arithmetic mean (confidence interval 95%)	0.0 (-0.02 to 0.01)	0.0 (-0.03 to 0.01)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time for no Oxygen Supplement (or Regular Oxygen Supplement "LTOT")

End point title	Time for no Oxygen Supplement (or Regular Oxygen Supplement "LTOT")
End point description:	
Unadjusted HR	
End point type	Secondary
End point timeframe:	
14 days	

End point values	Control	Intervention		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56[2]	61		
Units: HR				
number (confidence interval 95%)	1 (1 to 1)	0.8 (0.5 to 1.5)		

Notes:

[2] - Reference

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded during the period beginning when the patient received their first dose of trial medication up to and including day 15.

Adverse event reporting additional description:

A serious adverse event (SAE) was defined as an event or adverse event that, regardless of dose, was life-threatening, resulted in significant or persistent disability or incapacity, or led to a congenital anomaly or malformation. Because comorbidities and mortality are common in this patient group, prolonged admission, re-admission, non-invasive

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	Control

Reporting group description:

This arm will receive standard care and placebo in 15 days.
Placebo oral tablet: Placebo Azithromycin
Placebo oral tablet: Placebo Hydroxychloroquine

Reporting group title	Intervention

Reporting group description:

This arm will receive standard care and azithromycin and hydroxychloroquine in 15 days.
Azithromycin: Azithromycin
Hydroxychloroquine: Hydroxychloroquine

Serious adverse events	Control	Intervention	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 25 (8.00%)	0 / 31 (0.00%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events		0	
Cardiac disorders			
Ventricular arrhythmia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 31 (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			
Hearing loss			
subjects affected / exposed	1 / 25 (4.00%)	0 / 31 (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: 0 %

Non-serious adverse events	Control	Intervention	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 25 (100.00%)	31 / 31 (100.00%)	
Vascular disorders			
Bleeding			
subjects affected / exposed	0 / 25 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Cardiac disorders			
Chest pain			
subjects affected / exposed	4 / 25 (16.00%)	3 / 31 (9.68%)	
occurrences (all)	4	3	
Prolonged QTc			
subjects affected / exposed	7 / 25 (28.00%)	4 / 31 (12.90%)	
occurrences (all)	7	4	
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 25 (12.00%)	10 / 31 (32.26%)	
occurrences (all)	3	10	
Headache			
subjects affected / exposed	5 / 25 (20.00%)	3 / 31 (9.68%)	
occurrences (all)	5	3	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 25 (28.00%)	7 / 31 (22.58%)	
occurrences (all)	7	7	
Diarrhoea			
subjects affected / exposed	3 / 25 (12.00%)	12 / 31 (38.71%)	
occurrences (all)	3	12	
Nausea			
subjects affected / exposed	6 / 25 (24.00%)	11 / 31 (35.48%)	
occurrences (all)	6	11	
Vomiting			
subjects affected / exposed	2 / 25 (8.00%)	2 / 31 (6.45%)	
occurrences (all)	2	2	
Respiratory, thoracic and mediastinal			

disorders Bronchospasm subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2	3 / 31 (9.68%) 3	
Skin and subcutaneous tissue disorders Itching/Rash subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0	3 / 31 (9.68%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Early termination based on recommendations from the DSMB leading to small numbers of subjects analyzed.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34083403