Clinical trial results:
Amantadine for COVID-19: A randomized, placebo controlled, double-blinded, clinical trial

Summary

EudraCT number	2021-001177-22
Trial protocol	DK
Global end of trial date	28 April 2022

Results information

Result version number	v1 (current)
This version publication date	25 April 2024
First version publication date	25 April 2024

Trial information

Trial identification

Sponsor protocol code	02032021

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Department of Biomedical Sciences, Lab. for Molecular Pharmacology University of Copenhagen
Sponsor organisation address	Blegdamsvej 3B, Copenhagen, Denmark, 2200
Public contact	Department of Infectious diseases, Copenhagen University Hospital, Hvidovre, +45 38623514, Nina.Weis@regionh.dk
Scientific contact	Department of Infectious diseases, Copenhagen University Hospital, Hvidovre, +45 38623514, Nina.Weis@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	01 February 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 April 2022
Global end of trial reached?	Yes
Global end of trial date	28 April 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of the study is to investigate if early preemptive therapy with amantadine in non-hospitalized high-risk individuals with symptomatic COVID-19 disease can prevent disease progression.

Protection of trial subjects:

Amantadine is an approved therapy with a well-defined risk profile and has been used in clinical praxis for years. In this trial, amantadine was given for a short period of time (5 days). Consequently, the treatment was considered safe.
Persons with a known increased risk of adverse reactions to the drug due to allergy, disease, or medications were excluded from the study. Unblinding could happen at any point if necessary, to ensure the health of the study participant.

An interim analysis was performed to ensure a continuous evaluation of the outcome and safety of the study. This included identifying factors that could be considered harmful to the study participant and, as such, make the continuation of the study unethical.

The personal data was stored in a secure web application for managing online databases REDCap designed for non-commercial clinical research. Only personnel associated with the research project (sponsor, investigators, sub-investigators, and research personnel) had encoded access to the eCRFs via personal user ID and password.

Background therapy:

None

Evidence for comparator: -

Actual start date of recruitment	09 June 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 242
Worldwide total number of subjects	242
EEA total number of subjects	242

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)	215
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Information on potential study participants with a positive SARS-CoV-2 test was disclosed by the medical doctors at the Departments of Microbiology in the Capital Region and Region Zealand and Statens Serum Institut to the study investigators for the purpose of recruitment. Potential study participants received an invitation letter.

Pre-assignment

Screening details:

Basic screening was performed by a phone interview. Potential participants were asked about pregnancy, medication, comorbidity and if relevant body weight.

Period 1

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

Blinding implementation details:

Unblinded personnel at the regional pharmacy used Sealed Envelope for patient randomization into one of two arms (ratio 1:1). The randomization list was be generated centrally in random blocks. Blinded personnel did not have access to the randomization key. Pharmacy staff delivered sealed envelopes containing treatment allocation to blinded study personnel to use for emergency unblinding.
All investigators, outcome assessors, and study participants were blinded to the treatment allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Lactose monohydrate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Enteral use

Dosage and administration details:

1 capsule twice daily for 5 days

Arm title	Amantadine

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Amantadine
Investigational medicinal product code	N04BB
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Enteral use

Dosage and administration details:

100mg twice daily for five days

Number of subjects in period 1	Placebo	Amantadine
Started	121	121
Completed	121	121

Baseline characteristics

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

Reporting group values	Placebo	Amantadine	Total
Number of subjects	121	121	242
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	50.5	50.9	
inter-quartile range (Q1-Q3)	43.5 to 56.9	45.1 to 58.3	-
Gender categorical Units: Subjects			
Female	57	53	110
Male	62	63	125
Missing	2	5	7

Subject analysis sets	
Subject analysis set title	Final analysis
Subject analysis set type	Intention-to-treat
Subject analysis set description: Final analysis	

Reporting group values	Final analysis		
Number of subjects	242		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months)			

Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years median inter-quartile range (Q1-Q3)	 51 45 to 58		
Gender categorical Units: Subjects			
Female Male Missing	110 125 7		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Amantadine
Reporting group description: -	
Subject analysis set title	Final analysis
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Final analysis	

Primary: Clinical status day 14

End point title	Clinical status day 14
End point description:	
The primary outcome was 14th-day symptom status severity. The primary endpoint was assessed on an ordinal scale (levels I-VIII) with a proportional odds model.	
End point type	Primary
End point timeframe:	
14 days	

End point values	Placebo	Amantadine	Final analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	121	121	242	
Units: 242				
No limitations to activities	94	82	176	
Limitations to activities	25	37	62	
Hospitalized no oxygen therapy	0	0	0	
Oxygen by mask or nasal prongs	0	0	0	
Non-invasive ventilation or high flow oxygen	0	0	0	
Intubation and mechanical ventilation	0	0	0	
Ventilation + additional organ support - pressors,	0	0	0	
Death	0	0	0	

Statistical analyses

Statistical analysis title	proportional odds model
Statistical analysis description:	
proportional odds model adjusting for age, sex, CCI and vaccination.	
Comparison groups	Placebo v Amantadine

Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.051
Method	proportional odds model
Parameter estimate	Odds ratio (OR)
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	3.3

Secondary: Searous adverse Events

End point title	Searous adverse Events
End point description:	
Median number of serous adverse events within 90 days of randomization.	
End point type	Secondary
End point timeframe:	
90 days	

End point values	Placebo	Amantadine	Final analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	121	121	121	
Units: 1000				
median (inter-quartile range (Q1-Q3))	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Hospitalization

End point title	Hospitalization
End point description:	
Number of hospitalizations within 90 days.	
End point type	Secondary
End point timeframe:	
90 days	

End point values	Placebo	Amantadine	Final analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	121	121	242	
Units: Events	3	5	8	

Statistical analyses

No statistical analyses for this end point

Secondary: Mortality

End point title	Mortality

End point description:

Number of deaths within 90 days of randomization.

End point type	Secondary

End point timeframe:

90 days

End point values	Placebo	Amantadine	Final analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	121	121	242	
Units: Events	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Within 90 days of randomization.	
Assessment type	Systematic

Dictionary used	
Dictionary name	No dictionary used
Dictionary version	1

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

Serious adverse events	Placebo	Amantadine	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 121 (2.48%)	5 / 121 (4.13%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Headache			
subjects affected / exposed	0 / 121 (0.00%)	1 / 121 (0.83%)	
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			
Respiratory distress			
subjects affected / exposed	1 / 121 (0.83%)	0 / 121 (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 / 121 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			

subjects affected / exposed	1 / 121 (0.83%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
kidney stone			
subjects affected / exposed	1 / 121 (0.83%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Adjustment disorder with anxiety			
subjects affected / exposed	0 / 121 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 121 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Hip arthroplasty	Additional description: Planned		
subjects affected / exposed	1 / 121 (0.83%)	0 / 121 (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	Placebo	Amantadine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	115 / 121 (95.04%)	120 / 121 (99.17%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign tumor			
subjects affected / exposed	0 / 121 (0.00%)	1 / 121 (0.83%)	
occurrences (all)	0	1	
Cardiac disorders			
Chest pain			

subjects affected / exposed	3 / 121 (2.48%)	4 / 121 (3.31%)	
occurrences (all)	3	6	
Palpitations			
subjects affected / exposed	1 / 121 (0.83%)	2 / 121 (1.65%)	
occurrences (all)	1	3	
Nervous system disorders			
loss of sense of smell			
subjects affected / exposed	67 / 121 (55.37%)	72 / 121 (59.50%)	
occurrences (all)	72	75	
No sense of taste			
subjects affected / exposed	62 / 121 (51.24%)	68 / 121 (56.20%)	
occurrences (all)	63	70	
General disorders and administration site conditions			
general discomfort			
subjects affected / exposed	40 / 121 (33.06%)	54 / 121 (44.63%)	
occurrences (all)	46	63	
Fever			
subjects affected / exposed	34 / 121 (28.10%)	34 / 121 (28.10%)	
occurrences (all)	37	37	
Sore throat			
subjects affected / exposed	58 / 121 (47.93%)	60 / 121 (49.59%)	
occurrences (all)	63	70	
Headache			
subjects affected / exposed	86 / 121 (71.07%)	93 / 121 (76.86%)	
occurrences (all)	90	99	
Runny nose			
subjects affected / exposed	16 / 121 (13.22%)	19 / 121 (15.70%)	
occurrences (all)	16	19	
Sleeplessness			
subjects affected / exposed	2 / 121 (1.65%)	3 / 121 (2.48%)	
occurrences (all)	2	3	
Fatigue			
subjects affected / exposed	95 / 121 (78.51%)	107 / 121 (88.43%)	
occurrences (all)	107	125	
Ear and labyrinth disorders			

Ear pain			
subjects affected / exposed	5 / 121 (4.13%)	9 / 121 (7.44%)	
occurrences (all)	6	10	
Eye disorders			
Blurred vision			
subjects affected / exposed	8 / 121 (6.61%)	15 / 121 (12.40%)	
occurrences (all)	8	17	
Red eyes			
subjects affected / exposed	4 / 121 (3.31%)	6 / 121 (4.96%)	
occurrences (all)	4	6	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	40 / 121 (33.06%)	29 / 121 (23.97%)	
occurrences (all)	44	33	
Nausea			
subjects affected / exposed	57 / 121 (47.11%)	68 / 121 (56.20%)	
occurrences (all)	86	94	
Stomach pain			
subjects affected / exposed	25 / 121 (20.66%)	27 / 121 (22.31%)	
occurrences (all)	27	29	
Dry mouth			
subjects affected / exposed	4 / 121 (3.31%)	4 / 121 (3.31%)	
occurrences (all)	4	4	
Reproductive system and breast disorders			
vaginal bleeding			
subjects affected / exposed	1 / 121 (0.83%)	0 / 121 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	100 / 121 (82.64%)	101 / 121 (83.47%)	
occurrences (all)	107	101	
Laboured breathing			
subjects affected / exposed	45 / 121 (37.19%)	43 / 121 (35.54%)	
occurrences (all)	47	46	
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	11 / 121 (9.09%)	16 / 121 (13.22%)	
occurrences (all)	11	18	
Itch			
subjects affected / exposed	22 / 121 (18.18%)	16 / 121 (13.22%)	
occurrences (all)	23	17	
Edema			
subjects affected / exposed	8 / 121 (6.61%)	8 / 121 (6.61%)	
occurrences (all)	10	9	
Psychiatric disorders			
Mental disorder	Additional description: Nervousness, anxiety, lack of concentration		
subjects affected / exposed	39 / 121 (32.23%)	46 / 121 (38.02%)	
occurrences (all)	66	81	
Musculoskeletal and connective tissue disorders			
Muscle pain			
subjects affected / exposed	53 / 121 (43.80%)	60 / 121 (49.59%)	
occurrences (all)	63	69	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 July 2021	Inclusion criteria changed from Population at risk of developing severe COVID-19, defined as either: Age ≥ 50 years Age ≥ 18 years and at least one of the following comorbidities: Chronic heart disease without heart failure or proarrhythmic conditions or ventricular arrythmias, diabetes, chronic lung disease, hypertension, chronic kidney disease GFR<60 ml/minute, BMI ≥30 kg/m2. To Population at risk of developing severe COVID-19, defined as either: Age ≥ 40 years Age ≥ 18 years and at least one of the following comorbidities: Chronic heart disease without heart failure or proarrhythmic conditions or ventricular arrythmias, diabetes, chronic lung disease, hypertension, chronic kidney disease GFR<60 ml/minute, BMI ≥30 kg/m2.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported