



Clinical trial results:

Mestinon and Salbutamol Tolerability and Efficacy as therapy for Post-COVID-19 Myopathy - A randomized, placebo-controlled, rater and subject-blinded, 2x2 crossover study.

Summary

EudraCT number	2021-002610-14
Trial protocol	DK
Global end of trial date	30 April 2024

Results information

Result version number	v1 (current)
This version publication date	02 January 2026
First version publication date	02 January 2026

Trial information

Trial identification

Sponsor protocol code	79835
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Aarhus University Hospital
Sponsor organisation address	Palle Juul-Jensens Boulevard 99, Aarhus N, Denmark, 8200
Public contact	Research assistant Atle Vigild Lomstein, Aarhus University Hospital, Department of Neurology, 45 28, atllom@rm.dk
Scientific contact	Sponsor Professor Henning Andersen, Aarhus University Hospital, Department of Neurology, 45 7845 4250, hennande@rm.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	11 September 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 April 2024
Global end of trial reached?	Yes
Global end of trial date	30 April 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determining tolerability and efficacy of Salbutamol as treatment for Post-COVID-19 myopathy without neuromuscular transmission defect.

Determining tolerability and efficacy of Salbutamol and Mestinon as treatments for Post-COVID-19 myopathy with neuromuscular transmission defect.

Protection of trial subjects:

The study is conducted in compliance with ICH GCP E6 (R2). The project was monitored according to guidelines of Good Clinical practice by GCP-coordinator, GCP-unit Aalborg and Aarhus University Hospitals. Study data and information will be stored and handled in accordance to local/national laws and regulations. The study apply to the specifications of GDPR.

Written and oral information concerning the present trial was provided. Adequate time to consideration was provided (up to 30 days). Prior to any study related procedures, a signed informed consent form was obtained.

History of heart disease, diabetes or any other illness putting a participant at risk when treated with study drugs were exclusion criteria. Moderate or severe hypertension, ecg-abnormalities, thyroid disease or diabetes discovered at screening led to exclusion.

Any adverse reaction deemed too distressful or potentially harmful let to termination of participation by sponsor and investigator. Participants were screened with ecg and blood pressure measurement at every visit and screened for adverse events.

The doses of the study drugs were within a normally well tolerated level and the study drugs are thoroughly tested and, in general, well tolerated.

Background therapy:

None

Evidence for comparator:

The β_2 -adrenergic agonist Salbutamol registered for treatment of asthma is also known to increase muscle strength and endurance in healthy individuals. It's use as a doping agent in professional cycling is well known and the effects of the drug has been demonstrated in multiple clinical studies.

Physiologically, Salbutamol is thought to increase T3-levels and post-exercise Growth Hormone (GH) levels after few weeks of treatment and induce muscular growth and increased contractility after longer treatment regimens. Salbutamol is well tolerated and increasingly used as an established treatment in neuromuscular disorders like congenital myasthenic syndrome as well as we have had promising experiences for its use in autoimmune myasthenia gravis in a currently running trial (NCT number: NCT03914638) and for off label use in our Neurology Clinic at AUH.

Pyridostigmine (Mestinon) is the preferred first-line symptomatic treatment for myasthenia gravis. Mestinon increases the availability of acetylcholine outside the nervous system. The reduced amount of accessible nicotinic acetylcholine-receptors in the neuromuscular junction is counteracted by increased availability of the ligand, reducing symptoms of muscle weakness and fatigability. The mechanisms behind long-term fatigue, muscle weakness, and exercise intolerance in post COVID-19 patients are unknown, but our experiences indicate that myopathy and neuromuscular transmission dysfunction is prominent. Salbutamol and Mestinon is known to improve disability in disorders with similar symptoms.

Actual start date of recruitment	01 October 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: 45
Worldwide total number of subjects	45
EEA total number of subjects	45

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)	45
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Long COVID-19 patients from Northern Region, Central Region and Southern Region in Denmark. Possible candidates were examined at the Department of Neurology and referred to EMG. A pre-screening was conducted and patients eligible for inclusion were invited to screening. Screening was initiated nov. 11th 2021 and last screening was dec 19th 2023

Pre-assignment

Screening details:

Adults age 18-65 with fatigue after COVID-19 infection for at least 3 months with either abnormal EMG-findings or proximal weakness. 147 evaluated for screening and 45 invited and passes screening. 2 weeks of run-in before initiation of study drug.

Period 1

Period 1 title	Treatment period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

Both study drug and Placebo tablets was encapsulated in gelatin-capsules and looked identical. Neither investigator, rater nor subject knew whether contents are active or placebo. Subjects were randomized through computer-based randomization software at Hospitalsapoteket. Randomization envelopes were supplied by Hospitalsapoteket and sealed until end of trial was confirmed and approved by GCP-monitor.

Arms

Are arms mutually exclusive?	No
Arm title	Active treatment Arm A

Arm description:

Participants with abnormal jitter on EMG suggesting neuromuscular transmission defect. Active treatment period.

Arm type	Experimental
Investigational medicinal product name	Pyridostigmine
Investigational medicinal product code	N07AA02
Other name	Mestinon
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

60 mg, 3 times daily, oral ingestion

Investigational medicinal product name	Salbutamol
Investigational medicinal product code	R03CC02
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

4 mg, 3 times daily, ingested orally

Arm title	Active treatment Arm B
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Arm description:

Subjects included did not have abnormal jitter in single fiber EMG. Instead, participants included had either myopathic changes in the EMG or proximal weakness upon physical neurological examination. Active treatment period.

Arm type	Experimental
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Investigational medicinal product name	Salbutamol
Investigational medicinal product code	R03CC02
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 4 mg, 3 times daily, ingested orally	
Arm title	Placebo Arm A

Arm description:

Participants with abnormal jitter on EMG suggesting neuromuscular transmission defect. Placebo period. Placebo resembles mestinon and salbutamol treatment in active treatment period.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: Place capsules resembling active treatment.	
Arm title	Placebo Arm B

Arm description:

Subjects included did not have abnormal jitter in single fiber EMG. Instead, participants included had either myopathic changes in the EMG or proximal weakness upon physical neurological examination. Placebo period. Placebo resembles salbutmol from active treatment period.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: Placebo capsule	

Number of subjects in period 1	Active treatment Arm A	Active treatment Arm B	Placebo Arm A
Started	24	21	24
Wash-out after week 6	23	20	24
Completed	23	20	24
Not completed	1	1	0
Physician decision	1	-	-
Consent withdrawn by subject	-	1	-

Number of subjects in period 1	Placebo Arm B
Started	21
Wash-out after week 6	21
Completed	21
Not completed	0

Physician decision	-
Consent withdrawn by subject	-

Period 2

Period 2 title	Run-in screening period
Is this the baseline period?	Yes ^[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Both study drug and Placebo tablets was encapsulated in gelatin-capsules and looked identical. Neither investigator, rater nor subject knew whether contents are active or placebo. Subjects were randomized through computer-based randomization software at Hospitalsapoteket. Randomization envelopes were supplied by Hospitalsapoteket and sealed until end of trial was confirmed and approved by GCP-monitor.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Participants with abnormal jitter on EMG suggesting neuromuscular transmission defect.

Arm type	Experimental
Investigational medicinal product name	Pyridostigmine
Investigational medicinal product code	N07AA02
Other name	Mestinon
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

60 mg, 3 times daily, oral ingestion

Investigational medicinal product name	Salbutamol
Investigational medicinal product code	R03CC02
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

4 mg, 3 times daily, ingested orally

Arm title	Arm B
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Arm description:

Subjects included did not have abnormal jitter in single fiber EMG. Instead, participants included had either myopathic changes in the EMG or proximal weakness upon physical neurological examination.

Arm type	Experimental
Investigational medicinal product name	Salbutamol
Investigational medicinal product code	R03CC02
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
4 mg, 3 times daily, ingested orally

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: It is in accordance with the protocol

Number of subjects in period 2	Arm A	Arm B
Started	24	21
Completed	24	21

Baseline characteristics

Reporting groups

Reporting group title	Arm A
Reporting group description: Participants with abnormal jitter on EMG suggesting neuromuscular transmission defect.	
Reporting group title	Arm B
Reporting group description: Subjects included did not have abnormal jitter in single fiber EMG. Instead, participants included had either myopathic changes in the EMG or proximal weakness upon physical neurological examination.	

Reporting group values	Arm A	Arm B	Total
Number of subjects	24	21	45
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	24	21	45
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Group A, age at inclusion			
Units: years			
arithmetic mean	52.6	45.2	
standard deviation	± 9.65	± 9.23	-
Gender categorical			
Units: Subjects			
Female	16	16	32
Male	8	5	13

Subject analysis sets

Subject analysis set title	Per protocol analysis
Subject analysis set type	Per protocol
Subject analysis set description: All subjects adhering to protocol and treatment periods.	

Reporting group values	Per protocol analysis		
Number of subjects	45		
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)	45		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Group A, age at inclusion			
Units: years			
arithmetic mean	49.1		
standard deviation	± 10.1		
Gender categorical			
Units: Subjects			
Female	32		
Male	13		

End points

End points reporting groups

Reporting group title	Active treatment Arm A
Reporting group description: Participants with abnormal jitter on EMG suggesting neuromuscular transmission defect. Active treatment period.	
Reporting group title	Active treatment Arm B
Reporting group description: Subjects included did not have abnormal jitter in single fiber EMG. Instead, participants included had either myopathic changes in the EMG or proximal weakness upon physical neurological examination. Active treatment period.	
Reporting group title	Placebo Arm A
Reporting group description: Participants with abnormal jitter on EMG suggesting neuromuscular transmission defect. Placebo period. Placebo resembles mestinon and salbutamol treatment in active treatment period.	
Reporting group title	Placebo Arm B
Reporting group description: Subjects included did not have abnormal jitter in single fiber EMG. Instead, participants included had either myopathic changes in the EMG or proximal weakness upon physical neurological examination. Placebo period. Placebo resembles salbutmol from active treatment period.	
Reporting group title	Arm A
Reporting group description: Participants with abnormal jitter on EMG suggesting neuromuscular transmission defect.	
Reporting group title	Arm B
Reporting group description: Subjects included did not have abnormal jitter in single fiber EMG. Instead, participants included had either myopathic changes in the EMG or proximal weakness upon physical neurological examination.	
Subject analysis set title	Per protocol analysis
Subject analysis set type	Per protocol
Subject analysis set description: All subjects adhering to protocol and treatment periods.	

Primary: Neuro QoL Fatigue

End point title	Neuro QoL Fatigue
End point description: Primary efficacy parameter is improvement of fatigue as assessed by patient reported outcome (PRO). The Neuro QOL fatigue scale is a patient reported outcome used to rate fatigue and impact on quality of life. Investigations in neuromuscular disease show that Neuro-QOL correlate with disease severity and quality of life, and can improve after treatment. Neuro-QOL fatigue scale consists of 19 items rated on a scale from 1-5. From the total score, a T-score is calculated from 0-100. A T-score of 50 represents the mean score found in validation studies among a healthy population of American subjects. A T-score increase of 10 represents an increase of one standard deviation (translating to more fatigue) and a decrease of 10 represents a decrease of one standard deviation (translating to less fatigue).	
End point type	Primary
End point timeframe: Before and after each of the treatment periods. Expressed as a mean difference in change in fatigue score before and after treatment with placebo compared to treatment with study drug.	

End point values	Active treatment Arm A	Active treatment Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	19		
Units: Index				
median (standard deviation)	-1.87 (± 7.32)	-3.11 (± 8.93)		

Statistical analyses

Statistical analysis title

Results NeuroQOL

Statistical analysis description:

If patients had missing data at visit 2, data from visit 1 (screening) was used if available. Change in endpoint during active and placebo periods were calculated as absolute difference (start-of-period-visit subtracted from end-of-period-visit). Difference in change during periods (effect of treatment) were assessed as absolute differences by paired t-test. Assumptions hereof were checked by visual inspection of Bland-Altman plot and Q-Q plot of the difference.

Comparison groups	Active treatment Arm A v Active treatment Arm B
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-1.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.92
upper limit	2.19

Notes:

[1] - Comparison of reporting group 1 (Active treatment group A) and reporting group 3 (placebo group A)

Statistical analysis title

Results NeuroQOL

Statistical analysis description:

If patients had missing data at visit 2, data from visit 1 (screening) was used if available. Change in endpoint during active and placebo periods were calculated as absolute difference (start-of-period-visit subtracted from end-of-period-visit). Difference in change during periods (effect of treatment) were assessed as absolute differences by paired t-test. Assumptions hereof were checked by visual inspection of Bland-Altman plot and Q-Q plot of the difference.

Comparison groups	Active treatment Arm B v Active treatment Arm A
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-3.11

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.41
upper limit	1.2

Notes:

[2] - Comparison of reporting group 2 (active treatment group B) and reporting group 4 (placebo group B)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs/ARs that occur during the trial were recorded

Assessment type	Systematic
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Dictionary used

Dictionary name	unknown
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Dictionary version	0
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Reporting groups

Reporting group title	Group A
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Reporting group description: -

Reporting group title	Group B
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Reporting group description: -

Serious adverse events	Group A	Group B	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)	0 / 21 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Group A	Group B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 24 (100.00%)	21 / 21 (100.00%)	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	14 / 24 (58.33%)	11 / 21 (52.38%)	
occurrences (all)	14	11	
Tremor			
subjects affected / exposed	16 / 24 (66.67%)	15 / 21 (71.43%)	
occurrences (all)	16	15	
Dizziness			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			

Headache			
subjects affected / exposed	5 / 24 (20.83%)	6 / 21 (28.57%)	
occurrences (all)	5	6	
Mucosal dryness			
subjects affected / exposed	2 / 24 (8.33%)	1 / 21 (4.76%)	
occurrences (all)	2	1	
Toothache			
subjects affected / exposed	0 / 24 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 24 (8.33%)	1 / 21 (4.76%)	
occurrences (all)	2	1	
Nausea			
subjects affected / exposed	1 / 24 (4.17%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Diarrhoea			
subjects affected / exposed	5 / 24 (20.83%)	1 / 21 (4.76%)	
occurrences (all)	5	1	
Heartburn			
subjects affected / exposed	1 / 24 (4.17%)	2 / 21 (9.52%)	
occurrences (all)	1	2	
Dyspepsia			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Burning sensation			
subjects affected / exposed	1 / 24 (4.17%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Sweating			
subjects affected / exposed	4 / 24 (16.67%)	3 / 21 (14.29%)	
occurrences (all)	4	3	
Edema			
subjects affected / exposed	0 / 24 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Hematoma			

subjects affected / exposed occurrences (all)	0 / 24 (0.00%) 0	1 / 21 (4.76%) 1	
Renal and urinary disorders Urge incontinence subjects affected / exposed occurrences (all)	2 / 24 (8.33%) 2	1 / 21 (4.76%) 1	
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all)	13 / 24 (54.17%) 13	7 / 21 (33.33%) 7	
Infections and infestations cold subjects affected / exposed occurrences (all) Herpes genitalis subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1 0 / 24 (0.00%) 0	0 / 21 (0.00%) 0 1 / 21 (4.76%) 1	
Metabolism and nutrition disorders Weight loss poor subjects affected / exposed occurrences (all)	1 / 24 (4.17%) 1	0 / 21 (0.00%) 0	

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

None reported