Clinical trial results:
The effects of opioid receptor antagonism on acute pancreatitis: An investigator initiated, randomized, placebo-controlled, double-blind clinical trial

Summary

EudraCT number	2020-002313-18
Trial protocol	DK
Global end of trial date	20 April 2023

Results information

Result version number	v1 (current)
This version publication date	15 November 2024
First version publication date	15 November 2024
Summary attachment (see zip file)	primary results publication (no_effect_of_methylnaltrexone_on_acute.1208.pdf)

Trial information

Trial identification

Sponsor protocol code	PAMORA-AP_2020

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04743570
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aalborg University Hospital
Sponsor organisation address	Mølleparkvej 10, Aalborg, Denmark, 9000
Public contact	Asbjørn Mohr Drewes, Mech-Sense, Aalborg University Hospital, +45 97663520, amd@rn.dk
Scientific contact	Asbjørn Mohr Drewes, Mech-Sense, Aalborg University Hospital, +45 97663520, amd@rn.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	28 February 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 April 2023
Global end of trial reached?	Yes
Global end of trial date	20 April 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

In patients admitted with acute pancreatitis, 5 days treatment with intravenous methylnaltrexone will significantly reduce the disease severity compared to placebo.

Protection of trial subjects:

Most examinations (CT, blood samples, calculation of PASS-score) were adjusted to the standard of care so that subjects did not have to undergo additional examinations during acute illness. Furthermore, the study medication was administered continuously instead of as a bolus, to minimize side effects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 May 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: 105
Worldwide total number of subjects	105
EEA total number of subjects	105

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)	71
From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients admitted with AP were identified and contacted in the emergency department by study personnel upon or during admission. Information regarding current and previous medical conditions were passed on by the treatment-responsible physician from medical records to study personnel in order to identify eligible patients.

Pre-assignment

Screening details:

We screened 748 patients and included 105 patients. The most common reason for screening failure was not meeting inclusion criteria (n = 584), most of these were due to less than 2 SIRS criteria (n = 414). Other reason for exclusion were: declining to participate (n = 25) or other reasons (e.g. early discharge or transfer to other hospital, n= 34)

Period 1

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

Blinding implementation details:

Study medication was packaged and labeled into vials with methylnaltrexone and placebo having a similar appearance. Participants, study personnel, and treatment-responsible medical personnel were blinded to the allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Methylnaltrexone

Arm description: -

Arm type	Experimental
Investigational medicinal product name	methylnaltrexone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Participants were randomized (1:1) to receive a daily amount of either 0.15 mg/kg methylnaltrexone or a corresponding volume of placebo (lactated Ringer). This dosage aligned with the approved subcutaneous use of methylnaltrexone for opioid-induced constipation14 and previous intravenous use for research purposes.18 The daily dose of methylnaltrexone or placebo was mixed in 1000 ml of lactated Ringer and delivered by continuous intravenous infusion over 24 hours, which was repeated daily for a maximum of five days. Daily doses were reduced by 50% for severe renal impairment (estimated glomerular filtration rate < 30 mL/min) during study participation, but otherwise, the daily doses were fixed based on admission weight.

Arm title	Lactated Ringer

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Lactated Ringer
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Participants were randomized (1:1) to receive a daily amount of either 0.15 mg/kg methylnaltrexone or

a corresponding volume of placebo (lactated Ringer). This dosage aligned with the approved subcutaneous use of methylnaltrexone for opioid-induced constipation14 and previous intravenous use for research purposes.18 The daily dose of methylnaltrexone or placebo was mixed in 1000 ml of lactated Ringer and delivered by continuous intravenous infusion over 24 hours, which was repeated daily for a maximum of five days. Daily doses were reduced by 50% for severe renal impairment (estimated glomerular filtration rate < 30 mL/min) during study participation, but otherwise, the daily doses were fixed based on admission weight.

Number of subjects in period 1	Methylnaltrexone	Lactated Ringer
Started	51	54
Completed	45	46
Not completed	6	8
Consent withdrawn by subject	2	4
Physician decision	1	2
Protocol deviation	3	2

Baseline characteristics

End points

End points reporting groups	
Reporting group title	Methylnaltrexone
Reporting group description: -	
Reporting group title	Lactated Ringer
Reporting group description: -	

Primary: PASS-score	
End point title	PASS-score
End point description:	
End point type	Primary
End point timeframe: after 48 hours of treatment	

End point values	Methylnaltrexone	Lactated Ringer		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	46		
Units: points	45	46		

Statistical analyses

Statistical analysis title	Mixed Model of Random Effects

Statistical analysis description:

For the primary outcome, differences between treatment groups were tested using a robust linear mixed model of repeated measures. We included terms for the assessment timepoint, treatment group, and interaction between the assessment timepoints and treatment group. From this model, we extracted point estimates for the mean PASS score, standard error of the mean (SEM), and the mean difference with a 95% confidence interval (CI) after 48 hours (primary endpoint).

Comparison groups	Methylnaltrexone v Lactated Ringer
Number of subjects included in analysis	91
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.87
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	3.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.1
upper limit	47.6

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From time of screening until 45 hours after last administration of study treatment

Assessment type	Non-systematic

Dictionary used

Dictionary name	SNOMED CT
Dictionary version	1

Reporting groups

Reporting group title	MethylnaltrexoneReporting group description: -
Reporting group title	PlaceboReporting group description: -

Serious adverse events	Methylnaltrexone	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 51 (5.88%)	5 / 54 (9.26%)	
number of deaths (all causes)	3	1	
number of deaths resulting from adverse events	0	0	
Blood and lymphatic system disorders			
International normalised ratio abnormal			
subjects affected / exposed	0 / 51 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Sepsis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystectomy			
subjects affected / exposed	1 / 51 (1.96%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder rupture			

subjects affected / exposed	0 / 51 (0.00%)	1 / 54 (1.85%)	
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			
Pneumonia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	1 / 51 (1.96%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Allergy to chemicals	Additional description: suspected allergic reaction to medication (not study drug) which led to hospitalization		
subjects affected / exposed	1 / 51 (1.96%)	0 / 54 (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: 1 %

Non-serious adverse events	Methylnaltrexone	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 51 (49.02%)	21 / 54 (38.89%)	
Nervous system disorders			
Confusional state			
subjects affected / exposed	0 / 51 (0.00%)	3 / 54 (5.56%)	
occurrences (all)	0	3	
Headache			
subjects affected / exposed	2 / 51 (3.92%)	0 / 54 (0.00%)	
occurrences (all)	2	0	
Paraesthesia			
subjects affected / exposed	2 / 51 (3.92%)	0 / 54 (0.00%)	
occurrences (all)	2	0	
Somnolence			

subjects affected / exposed	0 / 51 (0.00%)	2 / 54 (3.70%)	
occurrences (all)	0	2	
Dizziness			
subjects affected / exposed	0 / 51 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 51 (19.61%)	9 / 54 (16.67%)	
occurrences (all)	10	9	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 51 (0.00%)	5 / 54 (9.26%)	
occurrences (all)	0	5	
International normalised ratio abnormal			
subjects affected / exposed	2 / 51 (3.92%)	1 / 54 (1.85%)	
occurrences (all)	2	1	
Vomiting			
subjects affected / exposed	1 / 51 (1.96%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 51 (1.96%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	2 / 51 (3.92%)	1 / 54 (1.85%)	
occurrences (all)	2	1	
Angioedema			
subjects affected / exposed	1 / 51 (1.96%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Flushing			
subjects affected / exposed	1 / 51 (1.96%)	0 / 54 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Hypokalaemia			

subjects affected / exposed	11 / 51 (21.57%)	8 / 54 (14.81%)	
occurrences (all)	11	8	
Hypophosphataemia			
subjects affected / exposed	1 / 51 (1.96%)	3 / 54 (5.56%)	
occurrences (all)	1	3	
Hyponatraemia			
subjects affected / exposed	1 / 51 (1.96%)	1 / 54 (1.85%)	
occurrences (all)	1	1	
Hypocalcaemia			
subjects affected / exposed	1 / 51 (1.96%)	1 / 54 (1.85%)	
occurrences (all)	1	1	
Hyperkalaemia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Hypomagnesaemia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 54 (1.85%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 54 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 November 2021	Until December 2021, we excluded patients with symptoms for more than 48 hours, but this criterion was omitted due to the lack of scientific rationale for 48 hours cut-off and stagnant enrollment

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported