Effects of peripherally acting μ-opioid receptor antagonists on acute pancreatitis

An investigator-initiated, randomized, placebo-controlled, double-blind clinical trial

Aalborg University Hospital, Odense University Hospital,

Hvidovre University Hospital, and Bispebjerg University Hospital

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Investigator's statement:

I have read and understand the foregoing protocol entitled "Effects of peripherally acting μ-opioid receptor antagonists on acute pancreatitis" protocol no. PAMORA_2020 and agree to conduct the study in compliance with Good Clinical Practice (CPMP/ICH/135/95), designated Standard Operating Procedures, the Danish Medicines Agency, the Research Ethics Committee in Denmark, and within the principles of the Declaration of Helsinki (amended by the 52nd General Assembly, Edinburgh, Scotland, October 2000, clarified by the General Assembly in Washington 2002, Tokyo 2004, Seoul 2008, and Fortaleza 2013 as outlined herein).

Asbjørn Mohr Drewes	Professor, Chief Consultant
Principal investigator and sponsor	Principal investigator/sponsor's title
05-08-2020	
Date	Principal investigator/sponsor's signature

1. Glossary

OPAC	Odense pancreas center
ICH	International conference on harmonization
AP	Acute pancreatitis
SIRS	Systemic inflammatory response syndrome
PAMORAs	Peripherally acting μ-opioid receptor antagonists
SIBO	Small intestinal bacterial overgrowth
eGFR	Estimated glomerular filtration rate
CRF	Case report form
PASS	Pancreatitis activity scoring system
HbA1c	HemoglobinA1c
CRP	C-reactive protein
IL	Interleukin
TNF-α	Tumor necrosis factor alpha
CD163	Cluster of differentiation 163
PaO_2	Partial pressure of oxygen in arterial blood
GSRS	Gastrointestinal symptom rating scale
SOP	Standard operating procedure
GCP	Good clinical practice
AE	Adverse event
AR	Adverse reaction
SAE	Serious adverse event
SAR	Serious adverse reaction
SUSAR	Suspected unexpected serious adverse reaction

mSV	Millisievert

2. Project participants and study centers

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3. Funding

The study was conceived and initiated by Professor Asbjørn Mohr Drewes, Department of Gastroenterology & Hepatology, Aalborg University Hospital. It is economically supported by a free grant of 7.3 MIO DKK by the Novo Nordisk Foundation. This grant will be used to cover expenses related to equipment, medication and salary for study personnel. The Novo Nordisk Foundation does not have any specific rights related to publication of the results, and positive as well as negative and/or inconclusive results will be published in scientific journals. All data will be publicly available to anybody incl. the Novo Nordisk Foundation after publication. Various funds will be applied for, to cover any additional financial expenses. Alternatively, Mech-Sense, Aalborg University Hospital will cover the remaining expenses. The grant from the Novo Nordisk Foundation as well as potential grants from other funds are deposited in a project account at the Hospital, which principal investigator Asbjørn Mohr Drewes is responsible for. Any excess amount will be refunded after the study has been concluded. The involved researchers conduct the trial of general scientific interest without personal financial gain and none of the researchers involved in this study have economical interest in the Novo Nordisk Foundation or other financial supporters of this study.

4. Roles and responsibilities

The present clinical study will be conducted in compliance with this protocol, the guidelines of the World Medical Association Declaration of Helsinki in its revised edition (Fortaleza, Brazil, October 2013), the guidelines of International Conference on Harmonization (ICH) GCP (CPMP/ICH/135/95), and designated Standard Operating Procedures.

The study will be conducted at four referral centers for pancreatitis in Denmark, located at Aalborg, Odense, Bispebjerg and Hvidovre University Hospitals. Aalborg University Hospital will take leadership as main sponsor for the clinical trial and has the overall responsibility for the quality of the study. Professor Asbjørn Mohr Drewes who is specialist in gastroenterology, will be principal investigator and overall study coordinator. He will lead the study together with Associate Professor Søren Schou Olesen and other researchers at Centre for Pancreatic Diseases and Mech-Sense at Aalborg University Hospital. These will assist in design, write the protocol, handle all procedures with the regulatory authorities and be responsible for data management, data analysis as well as publications. They have a long track record on research in clinical and experimental pain research, pancreatitis, opioids, opioid antagonists, and imaging as well as a large network and major experience with leadership of multicenter studies.

Professor Jens Brøndum Frøkjær at the Department of Radiology, Aalborg University Hospital, will supervise the analysis of all cross-sectional imaging studies together with senior researcher Donghua Liao. The imaging research group at Department of Radiology is an integrated part of Centre for Pancreatic Diseases and the interdisciplinary research group Mech-Sense.

Researchers at Hvidovre and Bispebjerg Hospitals will undertake the analysis of blood and urine samples. They have major experience in these analyses and have previously undertaken several studies in patients with acute pancreatitis (AP).

Cecilie Siggaard Knoph, PhD-student at Centre for Pancreatic Diseases, Aalborg University Hospital will be responsible for managing and overseeing the study. This will be supported by PhD-student Camilla Ann Fjelsted, Mech-Sense. A Ph.D. student at Department of Radiology, Aalborg University Hospital (not yet appointed) will manage the advanced imaging analysis.

5. Time schedule

The study is expected to be initiated (first subject included) in December 2020 and concluded (last subject, last visit) by December 2023. A detailed overview is given in the diagram below.

	2020	**2021-2022**	**2023**
Submitting protocol			
Conducting studies			
Data analysis			
Writing and submitting articles			

6. Introduction

6.1. Background and rationale

Acute pancreatitis (AP) has an annual incidence rate of approximately 35 pr. 100.000 person years in Denmark and has become one of the most frequent gastrointestinal discharge diagnoses (1). AP is associated with an overall complication rate of about 20%, and despite improved treatment the mortality is still near 3%. Unfortunately, no targeted pharmacologic treatment exists, to effectively alter the disease course, and the initial management of AP is currently based on supportive therapy with intravenous fluid resuscitation and analgesics. In the later stages, treatment is directed against complications such as mono- or multiorgan failure and infections, especially infected pancreatic necrosis (2).

The early phase of AP is characterised by a localized pancreatic inflammatory process, which can progress to a systemic inflammatory response syndrome (SIRS), which may be associated with multiorgan dysfunction - and failure (3). In turn, a compensatory anti-inflammatory response, whereby the inflammation becomes controlled, counterbalances the inflammatory process. However, in some cases an inadequate control of this counterbalance may lead to further organ dysfunction, immune paresis and late complications - in particular infections.

Pain is the cardinal symptom of AP and induces release of endogenous opioids, which is further potentiated by exogenous administered opioids used for pain management (4). The increased opioid exposure leads to a number of harmful effects on the gastrointestinal organs and the immune system (see figure 1). This may further promote the inflammatory response and worsen the course of the disease (5).

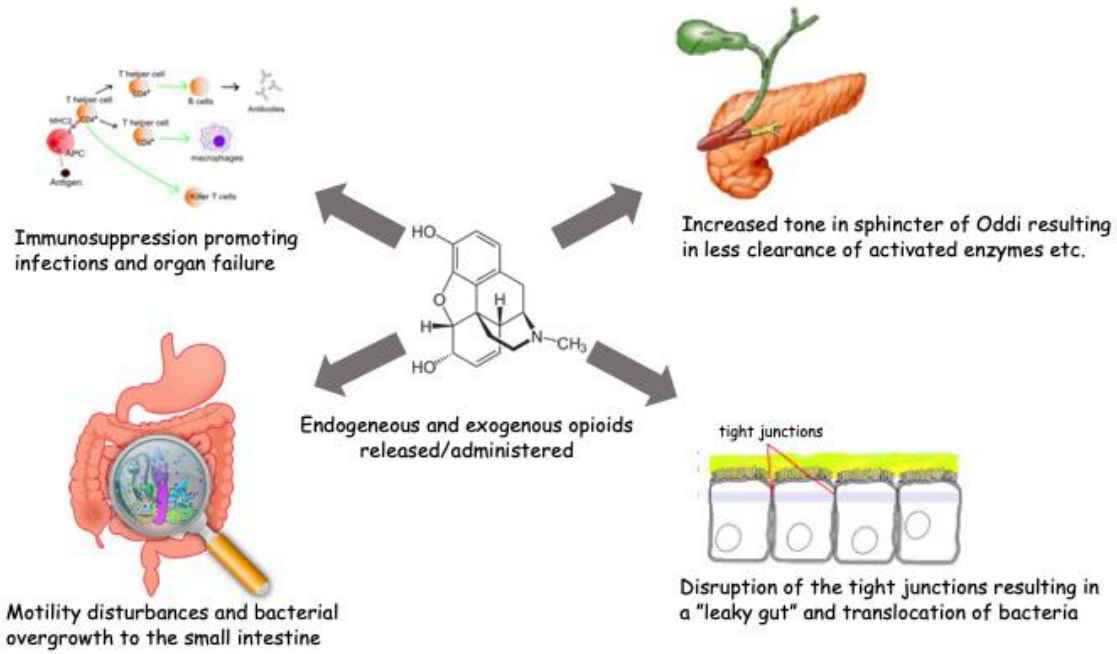

Figure 1: The effects of opioids on the gastrointestinal organs and the immune system

About 20% of patients with AP will develop recurrent acute pancreatitis (RAP). The etiology of this entity can in most cases be related to continuation of toxic exposure (e.g. alcohol and/or smoking) or occult biliary stones, that have been overlooked or inadequately treated during the index attack of AP. However, the etiology of approximately 10-30 % of RAP cases, remains unexplained despite a thorough diagnostic work up (6). Currently no treatment is available for these patients and many patients will continue to suffer from repeated attacks of pancreatitis. A large proportion will ultimately progress to chronic pancreatitis with loss of exocrine and endocrine pancreatic function, chronic abdominal pain, and an increased risk for developing pancreatic cancer (6) with great cost for both the individual patient and society.

Peripherally acting μ-opioid receptor antagonists (PAMORAs) have been developed for the treatment of opioid induced bowel dysfunction (7). This specific medication group may also have beneficial effects in patients with AP and RAP but has never been investigated for this indication. Hence, PAMORAs have been shown to potentiate immune responses (8) and increase survival in cancer patients partly due to counteracting the harmful effects of opioids on inflammation (9). Opioid administration induces paralysis of the small intestines by decreased and dyscoordination of gut motility, which may promote bacterial overgrowth (10). Opioids also seem to augment intestinal permeability due to damage of the tight junctions between mucosa cells (11). Together with small intestinal bacterial overgrowth (SIBO), translocation of

bacteria from the leaky gut to the peripancreatic tissues and the systemic circulation may be fatal in patients with AP. PAMORAs may ameliorate this by counteracting the above-mentioned effects of opioids on the intestines. As the medication also increases intestinal and pancreatic fluid production and has a relaxing effect on the sphincter of Oddi, the administration of PAMORAs are expected to enhance flow in the pancreatic duct system (10) resulting in increased washout of pathogenic substances during attacks of AP. Also, under normal circumstances, the tone in sphincter of Oddi and pancreatic secretion is partly controlled by endogenous opioids, and therefore prophylactic treatment with PAMORAs in patients with RAP may further support flow in the pancreatic duct system.

6.1.1. Study medication

In this study, the effects of PAMORA on disease development and progression in patients with AP will be investigated. Patients with AP will be administered Methylnaltrexone (Relistor®) intravenously. This medication is defined as the investigational product. Relistor® is approved and sold on the Danish marked for treatment of opioid-induced constipation. This PAMORA have not previously been investigated in patients with pancreatitis. The dose regimes for this study will be according to label. Please see the Summary of Product Characteristics for further details. For detailed description of possible side effects, see section 11.2. We have previously shown, in patients with opioid-induced obstipation and healthy subjects, that opioid antagonism incl. PAMORA treatment increases gut motility, relaxes gastrointestinal sphincters, increases the intestinal water content and improves the immune response, without affecting analgesia (10,12–15). The affinity of PAMORAs to the μ-opioid receptors is much stronger than opioid analgesics. Therefore, they as antagonists have the potential to counteract the harmful effects of opioids on the gut mucosa, bacterial translocation and inflammation despite the high levels of exogenous opioids present in patients with pancreatitis. PAMORAs do not cross the blood-brain barrier and consequently do not interfere with analgesia or other central effects of opioids (12).

We hypothesize that treatment with the PAMORA methylnaltrexone will antagonize the harmful effects of opioids without reducing analgesia in patients with AP and hence reduce disease severity and improve clinical outcomes. If successful, this sub-study will for the first time document the effects of a targeted pharmacotherapy in AP with the potential benefit of improved patient outcomes.

6.2. Hypothesis

In patients admitted with AP, 5 days treatment with intravenous methylnaltrexone will reduce the **disease severity** compared to placebo.

6.3. Trial design

This study is an investigator-initiated, double-blind, placebo-controlled, parallel-group of fixed methylnaltrexone dose conducted at four referral centers for pancreatitis in Denmark. A group of **90 patients with AP** will be prospectively included and randomized to receive intravenous methylnaltrexone or matching placebo in a 1:1 ratio. Patients will be treated for 5 days during hospital admission.

7. Methods: participants, interventions, and outcomes

7.1. Study setting

The study will be conducted at four referral centers for pancreatitis in Denmark, located at Aalborg, Odense, Bispebjerg, and Hvidovre University Hospitals. These centers have comprehensive experience in diagnosing, treating, and conducting research on patients with pancreatitis.

7.2. Eligibility criteria

7.2.1. Inclusion criteria

- Signed informed consent before any study specific procedures
- Able to read and understand Danish
- Male or female age between 18 and 85 years
- The researcher believes that the participant understands what the study entails, is capable of following instructions, can attend when needed, and is expected to complete the study
- The investigator will ensure that fertile female participants have a negative pregnancy test before treatment initiation and use contraception during the study period. The following methods of contraception, if properly used, are generally considered reliable: oral contraceptives, patch contraceptives, injection contraceptives, vaginal contraceptive ring, intrauterine device, surgical sterilization (bilateral tubal ligation), vasectomized partner, double barrier (condom and pessary), or sexual abstinence. Methods of contraception will be documented in the source documents
- Within the current hospital admission and prior to inclusion, the patient must fulfill at least two of the following criteria to establish a diagnosis of AP (according to the revised Atlanta criteria (20)): i) abdominal pain consistent with AP (acute onset of a persistent, severe, epigastric pain often radiating

to the back); ii) serum amylase activity at least three times greater than the upper limit of normal; and iii) characteristic findings of AP on diagnostic imaging

- Predicted moderate or severe AP based on the fulfillment of 2 or more SIRS criteria within the last 24 hours prior to inclusion (see figure 2)

7.2.2. Exclusion criteria

- Definitive chronic pancreatitis according to the M-ANNHEIM criteria (21) -
- Known allergy towards study medication
- Known or suspected major obstruction or perforation of the intestines
- Toxic megacolon
- Known or suspected abdominal cancer (incl. intestine, pancreas and the biliary tree)
- Pre-existing renal insufficiency (defined as habitual estimated glomerular filtration rate (eGFR) below 45 ml/min/1,73m^2)
- End-stage renal impairment requiring dialysis prior to inclusion
- Severe pre-existing comorbidities (assessed by investigator upon inclusion)
- Severe non-pancreaticobiliary infections or sepsis caused by non-pancreaticobiliary disease
- Child-Pugh class B or C liver cirrhosis
- Females that are currently lactating

7.3. Interventions

7.3.1. Methylnaltrexone dosage and treatment duration

To ensure standardization of the protocol, patients with AP will be treated with methylnaltrexone or placebo intravenously for the first 5 days of admission and assessments of endpoints will be done at fixed time points during this period. The dosage will be weight adjusted. Thus, 0.15 mg/kg methylnaltrexone or a corresponding volume of matching placebo (Ringer`s lactate) will be dissolved in 1000 mL Ringer`s lactate solution and given as a continues infusion over 24 hours using an infusion pump. In accordance with the summary of product characteristics for methylnaltrexone, a 50 % dose reduction will be made for patients with an eGFR below 30 ml/min/1,73m^2. the continuous infusion of study medication will be started no later than 24 hours after preparation. This will be ensured by keeping detailed record on the time of preparation

as well as time of infusion start. As methylnaltrexone is sensitive to light, the solution will be kept protected from light from the time of preparation until the time of infusion start. Two persons trained in the protocol and delegated to do so, will prepare the solution of study medication together. This will be done with one person assisting virtually in exceptional cases.

7.3.2. Discontinuation or withdrawal from the study

If the treatment-responsible doctor should at any point during the study asses that the patient suffers from end-stage renal impairment requiring dialysis, the treatment with methylnaltrexone will be discontinued.

Furthermore, a participant should be withdrawn from trial, if at any time:

- It is the wish of the participant for any reason
- The investigator judges it necessary due to medical reasons

If a participant is withdrawn from the trial, the investigator should always ensure that:

- Case report form (CRF) end of trial pages should be completed for withdrawn participants
- Any serious adverse events still ongoing after ended trial will be followed until the event has been resolved or the investigator assesses them as chronic or stable

7.3.3. Adherence

Patients with AP will be admitted during study participation. Thus, medication or placebo will be administered at fixed time points by medical professionals and subsequently registered within the patient's medical records as well as in the CRF.

7.3.4. Concomitant medication and care

Patients participating in the study will receive supportive treatment according to the IAP/APA evidence-based guidelines for the management of AP (2) as prescribed by the treatment-responsible physician. This includes supportive therapy with intravenous fluid therapy (Ringer´s lactate 5-10 ml/kg per hour), enteral feeding (elemental or polymeric enteral nutrition formulations via nasojejunal or nasogastric route, alternatively parenteral if nasojejunal tube feeding is not tolerated) and analgesics. As the patients will be admitted during participation in the study, all concomitant medication and care will be registered in the patient's medical files as with any other patient and subsequently transferred to the CRF. This specifically includes a detailed quantification of the need for analgesics (separated into opioids and non-opioids) as this is of great clinical significance.

7.4. Outcomes

7.4.1. Primary endpoint

Difference in Pancreatitis activity scoring system (PASS) score between the methylnaltrexone group and the placebo group 48 hours after randomization

7.4.2. Secondary endpoints

- Difference in daily **PASS scores** between subgroups
- Difference in daily assessments of circulating **pro- and anti-inflammatory markers** (including CRP, IL-6, IL-8, IL-18, TNF-α and CD163) as well as **intestinal barrier markers** between subgroups
- Difference in **intestinal permeability** between subgroups measured from 48 to 72 hours after randomization using the oral polyethylene glycol 400/4000 test
- Difference in **intestinal motility** assessed by means of gut/colon transit using a CT-based radiopaque marker method on day 5 (+/- 1 day) between subgroups
- Difference in **pancreatic complications** (e.g. edema, fluid collections and necrosis) assessed and quantified with contrast-enhanced CT on day 5 (+/- 1 day) after randomization (20)
- Difference between subgroups in the following **clinical outcome parameters**: pain intensity and gut function (assessed by questionnaires), quantification of analgesics (separated into opioids and non-opioids), need for nutritional support, disease severity, invasive treatments, intensive care and hospital stay, as well as mortality during total hospitalization
- Difference in **health resource utilization** during hospitalization between subgroups

7.5. Participant timeline

7.5.1. Study days

A detailed description of the study procedures is illustrated in Table 1. Patients will be evaluated daily during admission by medical personnel and treated in agreement with the IAP/APA evidence-based guidelines for the management of AP (2). As part of the study, they will receive daily infusions with methylnaltrexone or matching placebo, and have the following examinations performed: i) clinical outcome and patient symptoms will be evaluated by means of both well-validated questionnaires and information from the patient's medical records (see section 9.1.2.), ii) the PASS score will be obtained daily and used to document the primary endpoint 48 hours after randomization, iii) blood samples (including C-Reactive Protein (CRP), interleukin (IL)-6, IL-8, IL-18, tumor necrosis factor alpha (TNF-α) and cluster of differentiation 163 (CD163)) will be drawn

daily with the purpose of evaluating the systemic inflammatory response, and iv) an abdominal contrast-enhanced CT study will be performed at inclusion and after conclusion of treatment at day 5 (+/- 1 day) to document the presence and extent of pancreatic inflammation, fluid collections and necrosis according to the definitions given in the revised Atlanta criteria (20). As an integrated part of the CT exam at day 5 (+/- 1 day) patients will undergo assessment of the colon/gut transit time using radiopaque markers given orally in the morning on day 3 up to the planned CT exam. Finally, the intestinal permeability will be evaluated by a polyethylene glycol (PEG) 400/4000 test (see section 9.1.5.) 48 hours after randomization. At hospital discharge, patients are invited for a follow-up visit on day 14 (+/- 2 days) after randomization where the outcomes assessed during hospital admission (blood test and questionnaires including the PASS score) will be reassessed. Patients ready for discharge prior to completing five days treatment with methylnaltrexone will be handled according to the following:

- < 48 h of treatment: All data collection will be terminated upon discontinuation of the study medication and participant is regarded as dropout.
- ≥ 48 h of treatment, but discharge before day 5: Participant will be lost to follow-up on the following outcomes: daily PASS scores, blood samples, vital signs, quantification of need for analgesics, nutritional support, intravenous fluid resuscitation and antibiotics, and data will be analyzed using the Last-Observation-Carried-Forward method (see section 9.3.). The participant will be asked to complete questionnaires at home and they will be offered a follow-up CT scan in an outpatient setting on day 5 (+/− 1 day). Furthermore, they will be invited to participate in the 14-day follow-up and readmission rates as well as mortality will be registered retrospectively.

Randomization	**Methylnaltrexone or placebo (0.15 mg/kg/day)**				**End of study**	**Follow-up**
Baseline	*24±2 hours*	*48±2 hours*	*72±2 hours*	*96±2 hours*	*120±2 hours*	*14±2 days*
PASS Clinical outcome Blood samples	PASS Clinical outcome Blood samples	PASS Clinical outcome Blood samples Intestinal permeability	PASS Clinical outcome Blood samples Intestinal transit time	PASS Clinical outcome Blood samples	PASS Clinical outcome Blood samples	PASS Clinical outcome Blood samples

Computed tomography					Computed tomography	Health resource utilization

Table 1: Participant timeline. PASS; pancreatitis activity scoring system.

7.6. Sample size

We calculated that 41 patients per group will be needed to detect a difference in the PASS score of 25 points with a within-group standard deviation of 40 points (22), 80 % power and a 2-sided alfa level of 0.05. Hence, the sample size is set at 45 patients per group to allow for possible dropouts.

7.7. Recruitment

Patients admitted with AP will be identified and contacted by study personnel upon or during admission. Information regarding current and previous medical conditions will be passed on by the treatment-responsible physician from medical records to study personnel in order to identify eligible patients. This will be ensured by study personnel being in daily contact with the staff at the relevant departments at the respective inclusion sites with the purpose of monitoring the development of SIRS in patients with AP. This will be conducted in accordance to "Sundhedsloven § 46, stk. 1", under the responsibility of the primary investigator at the respective centers. AP is a relatively common disease and thus we expect approximately 10 patients to be admitted in total every week at our four inclusions sites. We expect at least half of these (i.e. 5) to be eligible for participation in the study.

7.8. Information about the study

All patients will be informed both oral and written before they decide whether they want to participate in the study. Furthermore, they will be informed that they can withdraw from the study at any given time without giving a reason. The participants are also allowed to have an assessor with them to the interview. Competent delegated personnel (medical doctors affiliated with the study or trained site staff with GCP-authorization as well as knowledge and experience with the disease involved and conduction of clinical randomized placebo-controlled studies) will give the oral information interview according to the Research Ethics Committee's guidelines. The interview will take place in quiet surroundings at one of our respective inclusion sites. During the interview, the participant will be informed thoroughly about the purpose of the study, the specific procedures the study entails, and potential benefits and risks. Any questions the participant have, will also be answered here.

The written information ("Deltagerinformation") is given to the participant upon contact. After the interview (see section 7.8.), where the participant has received information (oral and written), they are encouraged to consider whether they want to participate in the study or not before they sign the informed consent. As these patients are admitted with an acute condition the usual requirement of 24 hours for consideration before signing the informed consent is not deemed feasible. However, study personnel will ensure that patients will have sufficient time to consider participation before signing the informed consent. This includes adequate time to discuss with relativities in case the patient wishes to do so. In signing the informed consent, participants will be separately asked whether they want to contribute to the establishment of a biobank for both blood and urine samples. After the participant has signed the informed consent, they will be randomized to either active treatment (methylnaltrexone) or placebo (1:1) and receive an ID-number, which will be identical to the randomization-number. For more detailed information about informed consent and confidentiality see section 11.4.

8. Methods: Allocation of interventions

8.1. Allocation

Randomization will be conducted by the Hospital Pharmacy at Herlev Hospital in blocks of random size(block-randomization), using approved statistical software e.g. from the website www.randomization.com. A specific randomization will be assigned by the Hospital Pharmacy to the individual patient once study personnel have completed inclusion. This randomization number will be returned to study personnel, which alongside with participants will be blinded to the allocation. None of the collected data are expected to unblind the randomization. Methylnaltrexone and matching placebo will be ordered at and delivered by The Hospital Pharmacy to the respective investigational sites. All medication will be labeled with the randomization number corresponding the allocation as well as the information that it is intended for use in a clinical trial only. All sites will have trained personnel to carry out a documented acceptance testing to ensure the right delivery and to keep a strict study medication account.

8.2. Blinding

The study is double-blinded, and the blinding will be conducted by the Hospital Pharmacy at Herlev Hospital. This way of blinding will ensure that personnel involved in the project and participants included in the study are prevented from knowing information that might lead to bias of the results. All study medication will be labelled indicating "study medication", "id", "initials", "period", "daily dosing paradigm" and "contact information". Labelling will be performed by the Hospital Pharmacy at Herlev Hospital, according to Annex

13 of the Good Manufacturing Practice guidelines of the European Commission, ICH, GCP guidelines, and local law.

In case of an medical emergency (e.g. SUSAR, see section 10.2.3.) that necessitates knowledge of the treatment randomization, the individual treatment assignment for each subject will be available at each study center in sealed envelopes (provided by The Hospital Pharmacy) stored in a secure area accessible to study personnel allowed by the investigator to open the code for a single subject. The other study centers can always get in contact with the primary study center by a provided phone number in case of a situation where unblinding is necessary. This procedure allows unblinding of individual subjects, without revealing codes of the entire study. Thus, the study personnel will be able to determine which treatment a particular subject was given by opening the sealed envelope with the corresponding randomization number. The investigator must state the reason why the code was broken on the envelope, date and sign it.

A subject that discontinues will be asked about the reason(s) for discontinuation and the presence of any adverse events but are not obliged to provide this information. If needed, they will be seen and assessed by a medical doctor affiliated with the study. Dropouts will be replaced by new subjects and a mirror randomization will be performed i.e. they are part of the same randomization, but with a new number (e.g. 101 replaces 1 etc.).

Patients with AP will be admitted while participating in the study and hence have the study medication (Relistor® or matching placebo) administered to them by medical professionals. The medication and placebo will be delivered to the medical staff from the Hospital Pharmacy at Herlev Hospital in the form of fluid for infusion with similar appearance, so that the medical staff treating the patient will remain blinded.

9. Methods: Data collection, management, and analysis

9.1. Data collection methods

9.1.1. Pancreatitis Activity Scoring System

PASS is a validated assessment tool for AP based on five clinical parameters, which are weighed according to figure 2 (23). It quantitatively evaluates the course of AP and has proven useful for monitoring disease severity as well as predicting clinical outcome in patients admitted with AP (22). Organ failure (i.e. renal, respiratory and cardiovascular) will be assessed according to the Modified Marshall scoring system as defined in the Revised Atlanta criteria (20). Thus, organ failure of the cardiovascular and renal system, is assessed by

means of systolic blood pressure and serum creatinine respectively. The ratio between partial pressure of oxygen in arterial blood (PaO_2) and the fraction of inspired oxygen (FiO_2) is used to assess the respiratory system. Not all participants included into this study are expected to have PaO_2 values available. Thus, we will use the ratio between peripheral capillary oxygen saturation (SpO_2) and FiO_2 instead, as previous studies have shown that these two ratios correlate well (24,25).

Pancreatitis activity scoring system

Clinical feature	Weight
Organ failure	100 per system
Intolerance to solid diet	0/40 (N/Y)
Systemic inflammatory response syndrome (SIRS)	25 per criteria
Abdominal pain	(0-10) x 5
Intravenous morphine equivalent dose (mg)	(1/mg) x 5

EXAMPLE: Patient with acute pancreatitis
Kidney failure, tolerant to solid diet, fulfills 1 SIRS criteria,
scores abdominal pain 6, need of 20 mg intravenous morphine
*PASS = 100 + 0 + 25 +(6*5) + (20*5) = **255***

SIRS criteria

1. Body temperature > 38˚C or < 36˚C
2. Heart rate > 90/min
3. Respiration > 20/min or $PaCO_2$ < 32mmHg
4. White blood cell count > 12.0 x 10_9/L or <4.0 x 10_9/L

EXAMPLE: Patient with acute pancreatitis
Body temperature 37,8˚C, Heart rate 120, Respiration 19/min
White blood cell count 18.0 x 10 $_9$/L
*SIRS score = 0 + 1 + 0 + 1 = **2***

Figure 2: Pancreatitis Activity Scoring System (PASS)

9.1.2. Clinical outcome and health resource utilization

Clinical outcomes and health resource utilization are documented using preformed questionnaires and by means of the medical records. Thus, participants will be asked to fill out three questionnaires daily: i) The modified Brief Pain Inventory short form, ii) Bristol Stool Form Scale and iii) Gastrointestinal Symptom Rating Scale (GSRS). For a detailed description of these, see below. From the patients' medical records, the following will be registered: i) presence of local and systemic complications as well as organ failure (transient or persistent), used to classify the severity of AP according to the revised Atlanta criteria (20), ii) need for intensive care unit admission, iii) need for analgesics, iv) nutritional support, v) invasive treatment, vi) duration of hospitalization, and vii) mortality. Total duration of hospitalization, readmission rates and mortality will be determined retrospectively 30 and 90 days after admission using the patients' medical records.

9.1.3. Questionnaires

9.1.3.1. The modified Brief Pain Inventory short form

The modified Brief Pain Inventory short form is used to subjectively document patients' pain intensity at a visual analogue scale from 0-10 as well as relief from medication and impact on daily functions (interference score) (26).

9.1.3.2. Bristol Stool Form Scale

The Bristol Stool Form Scale is an objective assessment of parameters such as stool frequency as well as stool consistency and is used to assess intestinal function (27).

9.1.3.3. Gastrointestinal Symptom Rating Scale

The Gastrointestinal Symptom Rating Scale (GSRS) is a disease-specific instrument of 15 items combined into five symptom clusters depicting reflux, abdominal pain, indigestion, diarrhea and constipation. The GSRS has a seven-point graded Likert-type scale, where 1 represents absence of troublesome symptoms and 7 represents very troublesome symptoms. The reliability and validity of the GSRS are well-documented, and normal values for a general population are available (28).

9.1.4. Biochemistry

Patients with AP will have daily blood samples drawn with the purpose of measuring the systemic inflammatory response (including CRP, IL-6, IL-8, IL-18, TNF-α and CD163). Blood samples (31 ml blood per timepoint) will be drawn at baseline and daily at fixed time points for five consecutive days and two weeks after study termination. Blood samples will be separated by centrifugation and processed as plasma, serum, buffy coat and full blood and subsequently transferred in aliquots to vials labeled with the protocol number (PAMORA_2020), subject number, and date of sample collection. Samples will be frozen and stored at approximately -80°C or cooler in a freezer at the respective inclusion sites until analysis. The samples will be batch analyzed at a central laboratory to measure the analytes of interest. During the entire study period, a total of 186 ml of blood will be drawn from each AP participant.

After the analyses, all blood samples from both groups of patients will be kept in a biobank for future research purposes and destroyed at the latest 15 years after termination of the study. Ethics according to "databeskyttelsesforordningen" and "databeskyttelsesloven" will be ensured in this regard.

9.1.5. Imaging

Patients with AP will have an abdominal contrast enhanced CT scan performed at baseline and after 5 days (+/- 1 day) of treatment. Morphological changes related to AP will be evaluated and described according to the terminology and definitions of the revised Atlanta criteria and the modified CT severity index (20,29).

Furthermore, as an integrated part of the CT exam at day 5 (+/- 1 day) patients will undergo assessment of the intestinal transit time using radiopaque markers given orally on day 3 prior to the CT exam.

9.1.6. PEG 400/4000 test

Measurement of intestinal permeability and mucosal integrity in patients with AP, will be performed using the oral PEG 400/4000 test (30). In case of intestinal barrier function loss (a leaky gut), the large size molecules (PEG 4000) cross the intestinal barrier, appear into the circulation and becomes detectable in urine after renal excretion. The small size molecules (PEG 400) traverse the intestinal barrier freely, independent of barrier function loss, but is affected in the same way as the large molecules by the pre- and post-mucosal processes including gastric dilution, gastrointestinal motility, bacterial degradation, and renal function. Therefore, the ratio of the urinary concentration of both molecules (PEG 400/4000) more accurately reflect the intestinal permeability and integrity than isolated measurement of a single molecule (31). A PEG solution containing 5 g PEG 400 and 5 g PEG 4000 dissolved in 100 mL water, will be prepared. 48 hours after randomization, the PEG solution is enterally administered via oral intake or a feeding tube and followed by 24-hour urine output collection. Upon collection urine will be homogenized and centrifuged. The supernatant will be desalted by ion-exchange and transferred in aliquots to vials labeled with the protocol number (PAMORA_2020), subject number, and date of sample collection, which will subsequently be frozen and stored at approximately -80°C or cooler at the respective inclusion sites. Urine samples will be analyzed at a central laboratory to measure the analytes of interest. Excess urine samples will be kept frozen for future research purposes, thereby establishing a biobank. All samples will be destroyed at the latest 15 years after termination of the study. Ethics according to “databeskyttelsesforordningen” and ”databeskyttelsesloven” will be ensured in this regard.

9.2. Data management

The study will be submitted to the Northern Region of Denmark (“Forskningsanmeldelse Region Nordjylland – Registrering af forskningsprojekter”). Standard operating procedures (SOPs) for data handling and record keeping exists within the research center and these will be followed.

The principal investigator must maintain complete and accurate records to ensure that the execution of the study is fully documented, and the study data can be subsequently verified. These documents should be classified in 2 separate categories: i) researcher Trial Master File and ii) study/participant's clinical source documents (case report form).

Redcap, a secure browser-based software, will be used for filling in the eCRF form for each participant. RedCap meets all regulatory safety requirements and is approved for data collection by the North Danish

Region. Data recording will begin when a participant is included and will occur gradually to the end of the study trial. Any corrections will be made in such a way that information from the original version is still available. The changes endorsed by initials and date. All forms are filled out during (or immediately after) the assessment of a participant and must be legible.

Data will be stored at Aalborg University Hospital, Department of Medical Gastroenterology, for a minimum of 5 years after the study has ended. Relevant information from the participants' medical records will be given to the investigator if needed to assess the in- and exclusion criteria. After five years all data will be anonymized.

The trial master file must contain the protocol/amendments, correspondence with the Danish Health and Medicines Authority, The North Denmark Region Committee on Health Research Ethics and Danish Data Protection Agency, informed consent, staff curriculum vitae, forms, delegation-log, and other appropriate documents/correspondence etc.

The principal investigator at each study site, allows direct access to all source data and documents at monitoring, auditing, and inspection from the Danish Health and Medicines Authority or The Danish Data Protection Agency as well as the GCP-unit at Aalborg and Aarhus University Hospital.

A participant identification list is created for all persons included in the study. This list contains patient number, full name and civil registration number. The list is populated and updated by a study nurse or other competent person and is stored at Department of Gastroenterology, Aalborg University Hospital.

9.2.1. Case report forms

Data related to the primary outcomes (PASS score), clinical outcome and health resource utilization will be entered directly into electronic CRFs using REDCap, licensed by Aalborg University Hospital, and saved electronically. All forms are filled out during (or immediately after) the assessment of a subject and must be legible. Errors and corrections are logged as provided by the REDCap interface. It is possible to export validated data from REDCap to e.g. a statistical program (e.g. STATA) for further statistical analysis. When data have been entered, reviewed, and verified the data will be frozen to prevent editing. Digitalized data are backed up and stored on specific drives at each site under the responsibility of the principal investigators for a minimum of 5 years after the study has ended.

9.2.2. Source data identification and protection

A Patient Identification List containing patient number, full name, civil registration number for all participants included in the study is created, and ethics according to "databeskyttelsesforordningen" and "databeskyttelsesloven" is ensured. The list is populated and updated by a project nurse or other competent

person. A list of all source documents will be devised at the initiation of the study. All source documentation will be stored on a secure drive under the responsibility of the principal investigator.

9.3. Statistical methods

A repeated measures linear mixed effects model will be used for the primary analysis and will include terms for treatment group, assessment time point (day after randomization), and the interaction of treatment with assessment time point. Summary statistics and trend curves of PASS scores will be provided for the individual time points, and the difference in PASS scores between groups 48 hours after randomization is considered the primary efficacy parameter. Subgroup and covariate analyses will be performed if applicable and in case differences in patient subgroups deemed clinically relevant are evident. The primary analysis will be by intention to treat and in case of early hospital discharge or other reasons for missing values, the Last-Observation-Carried-Forward method will be employed. Trends in PASS and other secondary endpoints assessed consequently during the treatment period (biochemical tests and clinical outcome parameters) are analyzed using linear random-effects models and results presented as fitted trend curves. Outcomes assessed at single time points (baseline characteristics, CT features and gut permeability) are compared using Student´s t-test or non-parametric analysis for continues data as appropriate. Binary outcomes will be analyzed using Fisher's exact test. All secondary endpoints will be analyzed by per-protocol.

9.3.1. Criteria for the termination of the trial

The trial is terminated when full datasets for 90 patients with AP has been collected.

9.3.2. Missing data

Handling of missing data will be defined in the final statistical analysis plan and finalized before unblinding of data.

9.3.3. Deviations from the original statistical plan

It will be reported if any deviations from the original statistical plan occur.

10. Methods: monitoring

10.1. GCP monitor

A monitor will be allocated from the good clinical practice (GCP) unit at Aarhus and Aalborg University Hospitals, and an agreement between Aalborg University Hospital and the GCP unit will be signed. The responsible monitor will contact and visit the principal investigator on a regular basis. The monitor will be authorized to inspect the different study records (CRFs, source data/documents and other relevant data), provided that the subjects' information is kept confidential in accordance with the data protection agency

conditions. It will be the responsibility of the monitor to inspect CRFs regularly throughout the study to ensure compliance and completion of the protocol and that consistent and accurate data is entered in these. Monitor will check and verify that each subject has given written informed consent for direct access to study records as well as study procedures. Principal investigator (or his/her representative) agrees to cooperate with the monitor to ensure that all potential problems, discovered during the monitor's visit, will be solved. Investigator provides direct access to source data/documents (including medical records) during monitoring, auditing and/or inspection by the Danish Medicines Agency or The Danish Data Protection Agency.

10.2. Assessment of safety and harms

10.2.1. Adverse event and adverse reaction

An adverse event (AE) is according to the ICH-guideline defined as "any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment" and can be expected as well as unexpected. An adverse reaction (AR) concerns noxious and unintended responses to a medical product, meaning that a causal relationship between a medical product and an AE is at least a reasonable possibility. As these patients are acutely ill and admitted to hospital during participation in the study, they are expected to have certain symptoms and laboratory result deviations frequently associated with the disease. These are listed below:

Symptoms	**Laboratory result deviations**
abdominal pain	elevated plasma amylase or lipase
nausea	elevated plasma CRP
vomiting	elevated serum creatinine
	elevated serum liver enzymes and/or bile acids
	elevated blood sugar levels
	elevated white blood cell count

These will not be reported as AE's as well as AE's assessed clinically insignificant will not be reported. The evaluation hereof will fall upon study-affiliated doctors assessing the individual patient under the responsibility of the primary investigator. AE's and AR's will be registered for 45 hours after the study medication is discontinued. This corresponds five times the half-life of Methylnaltrexone (Relistor ®) which is 8-9 hours (32). Any AE or AR fulfilling the criteria for serious (SAE/SAR) will be reported according to the descriptions below. All expected and un-expected AEs and ARs to be reported, will be registered in the CRF and included in a final report which will be registered into EudraCT along with the results at the trial's termination. Information about AEs will be collected from the first administration of any investigational product until the end of the study.

10.2.2. Serious adverse event or serious adverse reaction

A serious adverse event (SAE) or a serious adverse reaction (SAR) is an AE or AR occurring during the study phase that fulfils one or more of the following criteria:

- Results in death
- Is life-threatening (NOTE: the term "life threatening" in the definition of serious refers to an event/reaction in which the subject is at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization (planned hospitalization is not to be reported as SAE or SAR)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect despite birth control during the study

All SAEs and SARs will be registered and reported to the sponsor by primary investigator as described below. A SAR is unexpected (i.e. suspected unexpected serious adverse reaction, SUSAR) if it is not consistent with the description in the medicinal product source document. The Research Ethics Committee and Danish Medicines Agency will annually be presented with a list of all SAR and SUSAR that have occurred during the trial as well as an evaluation of patient safety until the trial has concluded. All fatal or life threatening SUSARs are reported to the Danish Health and Medicines Authority and The Research Ethics Committee as soon as possible and no later than 7 days after the sponsor has been notified of SUSAR.

Investigator must report any SAE, SAR, or SUSAR to the sponsor immediately (within 24 hours) in order for sponsor to report to the Danish Healthy and Medicines Authority in time. As patients with AP often experience serious complications during admission as part of the disease, the list below entails SAEs that will not be reported to sponsor immediately (non-immediate reporting). These will instead be reported to sponsor within no more than 7 days:

- Sepsis or septic shock
- Kidney failure
- ARDS (acute respiratory distress syndrome)

Within 7 days after reporting of SUSAR, the sponsor must notify the Danish Health and Medicines Authority about all relevant information of the sponsor and investigator's follow-up on the SUSAR. All other SUSARs

should be reported to the Danish Health and Medicines Authority within 15 days after the sponsor has been notified of the SUSAR. SUSAR's will be unblinded prior to any report to authorities.

All SUSARs will be reported electronic to the Danish Health and Medicines Authority using the following e-form on their home page: "Reporting of suspected unexpected serious adverse reactions (SUSARs) seen in clinical trials". Additionally, all SUSARs must immediately be notified to The Research Ethics Committee. Any report must be accompanied with comments regarding possible consequences for the trial. The assessment of SUSAR will be made before unblinding.

10.2.3. Safety follow-up procedure

All SAE´s and related AE´s must be followed-up until the event has resolved or stabilized, or the relationship to study medication is clarified. All participants with unresolved events at the end of the study, except those who dropped out before randomization or starting active treatment, must be included in a safety follow-up visit in order to check response of events to de-challenge. The safety follow-up visit should take place one to two weeks after the Final Examination / Premature Termination. Events, which are not complete in this way by the end of the period of observation, must be followed-up on until this status has been achieved. Follow-up can be wavered in specific cases after consultation with sponsor. This permission must be documented per case and retained in the investigator site file and trial master file.

10.3. Quality control and quality assurance

Quality Control is defined as the operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the study related activities have been fulfilled. Quality Control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly, according to standard CGP-guidelines.

Quality Assurance is defined as the planned and systematic actions that are established to ensure that the study is performed, and the data are generated, documented (recorded), and reported in compliance with GCP and the applicable regulatory requirements. An independent audit at the study site may take place at any time during or after the study. The study will be monitored by an independent company/person not otherwise involved in the project. Furthermore, monitoring visits to the trial site will be made periodically during the trial to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of agreement with data on CRFs. The Investigator/institution guarantees direct access to source documents to appropriate regulatory agencies. The trial site may also be audited (quality assurance) or inspected by appropriate regulatory agencies. It is important that the investigator and their relevant

personnel are available during the monitoring visits and possible audits and that enough time is devoted to the process.

11. Ethics and dissemination

This clinical study will be conducted in compliance with Good Clinical Practice (CPMP/ICH/135/95), designated Standard Operating Procedures, the Danish Medicines Agency, the North Denmark Region Committee on Health Research Ethics, and within the principles of the Declaration of Helsinki (amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013). Additionally, this study will be undertaken in accordance with the Protocol and Good Clinical Practice on the conducting and monitoring of clinical studies. The trial will only be initiated once the approvals from the North Denmark Region Committee on Health Research Ethics and the Danish Medicines Agency are given. Any significant modifications to the protocol, will be submitted as protocol amendments and subsequently approved by the North Denmark Region Committee on Health Research Ethics and the Danish Medicines Agency before implementation.

11.1. Risks related to the experimental procedures

Biochemical tests including blood samples, PEG 400/4000 test, bear little risk for the patients and furthermore are all part of the standard evaluation of these diseases.

CT-scans involve radiation and careful consideration should always be applied when using this modality in clinical research. Patients admitted with AP will have CT-scans performed upon admission and at 5 day follow up (+/- 1 day). In Denmark, the estimated average radiation dose from one CT-scan of the abdomen is 11,9 millisievert (mSV) (33). Thus, the modality bears significant risk for individuals participating in the study. It is part of the standard diagnosis strategy to perform a CT-scan on patients admitted with symptoms of AP and many patients will have a follow up CT-scan prior to discharge to evaluate the presence of complications including pancreatic necrosis and fluid collections. The CT-scans will also be available for the attending physicians. Furthermore, we expect the utility of the data collected to potentially promote prevention and better treatment of AP, which is a severe medical condition. Hence, we find it ethically sound to perform the study as described.

11.2. Risks related to study medication

Treatment with PAMORA may be uncomfortable for patients as they may experience side effects like diarrhea or nausea. PAMORAs, especially methylnaltrexone, can worsen the clinical course of intestinal stenosis, because they increase motility and secretion in the intestine. At worst, this can cause perforation of the intestines which can be fatal. This has been accounted for in the exclusion criteria (see section 7.2.2.).

Participation in the study will be potentially beneficial for patients with AP receiving active medication and it is expected that this study will produce important knowledge on the treatment of AP for future patients. In

this regard, the use of placebo is crucial for evaluating the true effect of PAMORAs on the course of disease. Furthermore, all patients, regardless of whether they receive active treatment or placebo, may gain new insights and understanding into the pathophysiology of their disease and possible beneficial future treatment. The treatment of patients receiving placebo will not be affected by participation in the study as they still receive standard treatment.

In conclusion, the risk the participants are exposed to in this study is minimal compared to the beneficial information that will be gained from the study – both for the individual patient, but also for future treatment of patients with AP.

11.3. Patient insurance

Clinical responsibility befalls the University Hospitals involved in the study. All participants will be covered by the patient insurance of the respective site of trial conduction. Participation in a trial involving medical treatment may alter private insurance status, should the participant wish to travel during or right after study participation. Participants are advised to seek consultancy from their insurance agency if they plan to travel during or right after participation in the study.

11.4. Consent and confidentiality

The informed consent will be obtained following oral and written information has been given by competent delegated study personnel as previously described in section 7.8. Once informed consent is signed, this allows investigators; monitors from The Good Clinical Practice Unit at Aalborg and Aarhus University Hospitals; GCP inspection; and Danish Health as well as Medical Authority to assess patients' medical records with the purpose of retrieving information necessary for study conduction, monitoring and inspection. Detailed clinical characterization of the patient, complementary information in relation to the study will be made available from medical records so that sponsor and monitor can control the quality of the study regarding "informationsbekendtgørelsen". Information about participants is protected by "databeskyttelsesforordningen", "databeskyttelsesloven", and "sundhedsloven".

11.5. Declaration of interests

None.

11.6. Access to data

The trial will be registered at clinicaltrialregister.eu and EudraCT, and at the end of the study, the results will also be published at these websites. All results will be published as open access whenever possible using both

scientific and public media. When the clinical trial ends, the anonymized data will be made available to other researchers through relevant and actual public databases such as Zenodo.

11.7. Dissemination policy

Results, positive as well as negative and inconclusive, will be released to the public, and may be published in peer-reviewed scientific journals. Results may also be used in submission to regulatory authorities. The first author will be appointed according to the Vancouver system. The investigator will inform the Danish Medicines Agency and the Research Ethics Committee after the termination of the trial. No later than 90 days after trial termination, the "Declaration of the end of trial form" must be submitted to The Danish Medicines Agency, and as soon as possible or within 1 year the results will be registered with EudraCT. The Research Ethics Committee will be notified of results from this study. Published articles are sent to The Danish Medicines Agency and the Research Ethics Committee.

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