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<td>Manuscript ID:</td>
<td>bmjopen-2014-007087</td>
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<td>Date Submitted by the Author:</td>
<td>02-Nov-2014</td>
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| Primary Subject Heading: | Gastroenterology and hepatology |
| Secondary Subject Heading: | Pharmacology and therapeutics, Radiology and imaging |
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Study protocol for a randomised, double-blinded, placebo-controlled, clinical trial of S-ketamine for pain treatment in patients with chronic pancreatitis (RESET trial)

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Running title:
RESET Trial

Potential competing interests:
None declared

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ABSTRACT

Introduction: Chronic pancreatitis (CP) is an inflammatory disease that causes irreversible damage to the pancreatic tissue. Pain is the most prominent symptom in. In the absence of pathology suitable for endoscopic or surgical interventions, pain treatment usually includes opioids. However, opioids often show limited effectiveness and side-effects are common. Hence, new treatments to control pain associated with CP are highly desirable. Sensitization of the central nervous system is reported to play a key role in pain generation and chronification. Fundamental to the process of central sensitization is abnormal activation of the N-methyl-D-aspartate receptor, which can be antagonized by S-ketamine. The RESET trial is investigating the analgesic and anti-hyperalgesic effect of S-ketamine in patients with CP.

Methods and analysis: Forty CP patients will be enrolled. Patients are randomized to receive 8 hours of intravenous S-ketamine followed by oral S-ketamine for 4 weeks or matching placebo. To improve blinding 1 mg of midazolam will be added to both active and placebo treatment. The primary endpoint is clinical pain relief documented by a daily pain diary based on a visual analogue scale. Secondary endpoints include changes in different questionnaires, opioid consumption, and documentation of side-effects. The endpoints are registered through the 4-week medication period and for an additional follow-up period of 8 weeks to investigate long-term effects. In addition, experimental pain measures also serves as secondary end-points, and
neurophysiological imaging parameters are collected. Furthermore, experimental baseline recordings are compared to recordings from a group of healthy controls to evaluate general aspects of pain processing in CP.

Ethics and dissemination: The protocol is approved by the North Denmark Region Committee on Health Research Ethics (N-20130040) and the Danish Health and Medicines Authorities (EudraCT-number: 2013-003357-17). The results will be disseminated in peer-reviewed journals and at scientific conferences.

Trial registration: The study is registered at www.clinicaltrialsregister.eu
• Chronic abdominal pain is the most severe and debilitating symptom in patients with chronic pancreatitis and is associated with reduced quality of life.

• Recent research have provided a better understanding of the mechanisms underlying pain in chronic pancreatitis and sensitization of the central nervous system is reported to play a key role in pain generation and pain chronification.

• Fundamental to the process of central sensitization is abnormal activation of the N-methyl-D-aspartate (NMDA) receptor, which can be antagonized by S-ketamine treatment.

• This article describes the study protocol for a randomized, double-blind, placebo-controlled trial assessing the efficacy and safety of S-ketamine for pain treatment in patients with chronic pancreatitis.

**Key messages**

• The treatment evaluated in this trial may provide long-term pain relief to patients with painful chronic pancreatitis.

**Strengths and limitations of the study**

• Both the clinical efficacy and the experimental investigation of the underlying mechanisms of the anti-hyperalgesic and analgesic properties of S-ketamine are addressed in this trial.
This is a single-centre trial, which may compromise the external validity of the findings. However, single-centre trials also have several advantages. They are often logistically easier, data collection is simpler and typically deal with a less heterogeneous population, thereby diminishing confounding.
Introduction

Chronic pancreatitis (CP) remains a major source of morbidity in Northern Europe with an annual incidence of approximately 10 per 100,000 inhabitants. A typical cause is long-term excessive use of alcohol, although genetic, environmental and autoimmune factors have also been associated with CP. It is a disease characterized by progressive destruction of the pancreatic gland and as it evolves, significant impairment of exocrine as well as endocrine functions. Pain, however, is the most common symptom in CP and up to 90% of patients have chronic abdominal pain, often worsened by acute pain exacerbations typically requiring hospitalisation. Hence, pain is a major burden for most CP patients and it has been associated with impaired psychosocial functioning, physical disability and decreased life quality. Analgesic medication is part of the initial pain treatment and often includes opioids in the absence of pathology suitable for endoscopic or surgical interventions. However, opioid-based analgesia often only shows limited effectiveness in these patients and it is frequently accompanied by undesirable side-effects. Hence, new treatments to control the pain associated with CP are highly desirable.

Pain mechanisms in chronic pancreatitis

The pathophysiology of pain in CP has yet to be fully elucidated and it is probably of multifactorial origin. Historically pain treatment has focused on the pancreatic gland assuming pain to be generated by ongoing pancreatic inflammation, parenchymal hypertension and ductal obstruction. Consequently, treatment was focused on pathology in or closely related to the pancreatic gland. However, there is not a direct relationship between abdominal pain and pancreatic morphology, and the experimental evidence supporting this is conflicting. The most recent explanation model of pain pathogenesis in CP is that recurrent inflammation beyond a certain threshold causes irreversible injury to the pancreatic tissue. This process of repeated inflammation is linked to
continuous damage of the pancreatic nerves along with peripheral and central sensitisation of the pain system. Key to the process of central sensitization is aberrant activation of the N-methyl-D-aspartate (NMDA) receptor as described below. An important outcome of central sensitization is that once the disease has advanced and the neural pathophysiological processes are firmly established, the generation of pain becomes self-perpetuating and independent of the initial nociceptive drive. Consequently, the management of pain becomes difficult and conventional treatment much less effective. This novel and improved understanding of the pain aetiology advocates a paradigm shift in pain management of CP.6,9

S-ketamine and central sensitization

Developed in 1960s as an anaesthetic drug, S-ketamine is currently used not only as a safe anaesthetic drug, but also as an analgesic drug in acute and per-operative pain as well as an antihyperalgesic drug in various chronic pain conditions.10 The different effects are dose-dependent. It is classified as a non-competitive NMDA receptor antagonist, but acts on multiple receptors including opioid-receptors.11 Ketamine exists in two distinct stereoisomeric forms the S- and the R-form. Both a racemic equimolar mixture and a pure S-enantiomer are available. The S-isomeric form has a four times higher affinity for the NMDA receptor compared to the R-isomeric form and will be used in the present study.11 In anaesthesia S-ketamine provides a dissociative anaesthetic state, by blocking the connections between the limbic system and thalamus, while it provides an analgesic and antihyperalgesic effect when used in sub-anaesthetic doses. The latter is mainly attributed to antagonism of the NMDA receptor, an excitatory inotropic glutamate receptor located in the central as well as the peripheral nervous system. At resting membrane potentials, the NMDA receptor ion channel is physically blocked by a magnesium ion so that no current flows if glutamate binds to it. Hence, activation of the NMDA receptor by glutamate produces excitation only when
this magnesium block is relieved by depolarization. Prolonged NMDA receptor activation results in removal of the magnesium ion blockade and a progressive increase in neuronal output. With ongoing activity, such activity dependent sensitization of central pain pathways ultimately becomes independent of the peripheral nociceptive drive and self-perpetuating. The mechanisms underlying this activity independent sensitization involves phosphorylation of different second messenger systems along with alterations in gene transcription. The resulting chronification of pain typically manifests as hyperalgesia and alldynia, which are the clinical hallmark of central sensitization although not specific for this entity. Central sensitization of the pain system is well documented in CP and it is increasingly accepted to play a prominent role in its pain pathogenesis.\textsuperscript{12-14}

S-ketamine exerts its anti-hyperalgesic effect by restoring the NMDA-receptor to its resting state condition through non-competitive antagonism. Thereby the “gain” of the pain system is restored to normal physiological status. Multiple studies have consistently produced positive results regarding the use of S-ketamine in patients with chronic pain. Thus it comprises an interesting remedy to depress central sensitisation and its associated hyperalgesia in painful CP. This was supported by a recent Dutch double-blinded crossover trial designed to evaluate the effect of S-ketamine infusion on hyperalgesia associated with CP. Infusion of S-ketamine temporarily reversed pressure pain hyperalgesia and the underlying sensitized state of the pain system. This study was, however, not powered or designed for clinical endpoints.\textsuperscript{15}

Experimental testing

The experimental testing of the study is based on quantitative sensory testing (QST) and provides information of the pain on both central and peripheral levels of the nervous system using controlled external pain stimuli. This evaluation of the sequential activation of the pain systems at different levels provides valuable information regarding the neuroplasticity in a sensitised nervous system.
Assessment of experimental pain measures will be employed at baseline, during S-ketamine infusion, after 4 weeks of treatment with oral S-ketamine and at follow-up 8 weeks after treatment to unravel the mechanisms of the underlying anti-hyperalgesic and analgesic effects of S-ketamine. Furthermore, experimental baseline assessments will be compared to assessments from a group of healthy controls to evaluate general aspects of pain processing in CP. The entities are summarized in Box 1.

**Hypothesis**

We hypothesise that a one-day infusion of S-ketamine followed by oral S-ketamine for four weeks decreases central sensitisation associated with CP and thereby induces clinical pain relief, which is also reflected in secondary endpoints and sensory testing as summarised in Box 1.

*****Box 1 near here*****

**Methods and analysis**

**Concomitant medication**

Patients will be instructed not to change their regular pain treatment during the trial period. Rescue pain medication, taken on an “as needed basis,” is allowed throughout the trial period and its use will be documented in the daily pain diary.

**Recruitment**

All eligible patients with CP from our outpatient clinic who agree to participate in the study and fill in an informed consent will be invited to participate in the study. Patients will be recruited via
personal correspondence and during sessions in the outpatients department, thus the initial contact will be in these settings.

**Randomisation**

Subjects will be randomised to the study providing they fulfil the entry criteria at screening (see Box 2 and 3). A computer-generated pseudo-random code will be used to assign subjects to treatment arms. A block randomization will be used, allowing 8 subjects at the time to be randomized in equal proportions for S-ketamine or matching placebo.

*****Box 2 near here*****

*****Box 3 near here*****

**Study overview**

Participation in the study will involve four clinical visits as shown in figure 1. The baseline visit, one week prior to the first administration of study medication, includes written informed consent, a physical examination and experimental pain testing. Furthermore patients will be instructed in the use of a pain diary to record pain intensity on daily basis. These assessments will commence 7 days prior to medicine administration. Average and maximum daily pain intensities are assessed using the pain diary. This is based on a visual analogue scale (VAS) where 0 equals no pain and 10 equals the worst pain imaginable.

*****Figure 1 near here*****
Infusion of S-ketamine

Duration and dosage of S-ketamine treatment were chosen based on a review of the literature and expert opinions as well as feasibility considerations. At the second visit the patients will receive intravenous S-ketamine (0.1 mg · kg\(^{-1}\) · h\(^{-1}\)) for 8 hours or matching placebo (i.e. isotonic saline). In addition, 1 mg of midazolam is administered together with ketamine/placebo to mask the patients’ awareness of central effects of ketamine and to ensure sufficient blinding.

Preparation and administration of oral S-ketamine and placebo

Both S-ketamine and placebo oral solutions will be prepared and provided by Skanderborg Apotek, Denmark. The placebo solution is similar to the vehicle used for ketamine solution. Thus, flavour and colour will match the characteristics of S-ketamine solution. During the second week of the study, patients will receive an increasing dose of oral S-ketamine or matching placebo starting on the day after S-ketamine infusion. The initial dose is 0.25 mg · kg\(^{-1}\) S-ketamine three times daily (TID). After 3 days, this is increased to 0.50 mg · kg\(^{-1}\) S-ketamine TID, with a further increase to 0.75 mg · kg\(^{-1}\) S-ketamine TID after 6 days and for the following 3 weeks. An equivalent dose-escalating regime is followed in the placebo arm. All patients follow the same oral dosing schedule, with administration of study medication at 08:00, 14:00 and 20:00 ± 1 hour. If the patients experience unacceptable side effects, a single downward dose titration is allowed, with the patient staying on that final dosage for the remaining study period.

Study procedures

Visit 1 (baseline)

At the baseline visit informed consent is obtained for further progress in the study. After this is secured, physical examination is conducted, blood samples drawn for biochemical screening, and
patients’ medical history recorded. Moreover, a secretin enhanced magnetic resonance
cholangiopancreatography (MRCP) is performed to ensure that patients do not have any pathology
suitable for endoscopic or surgical therapy. Next, instruction to all questionnaires will be given and
reporting of daily pain intensity in the pain diary will begin. Quality of life will be registered using
the European Organization for Research and Treatment of Cancer Quality of Life questionnaire
EORTC-QLQ-C30\textsuperscript{16} while pain and physical functioning will be registered using the modified brief
pain inventory-short form (mBPI-sf),\textsuperscript{17} Izbicki pain score.\textsuperscript{18} Patient Global Impression of Change
(PGIC) is introduced for later use.\textsuperscript{19} Lastly Beck’s Depression Inventory (BDI) are used to assess
depressive symptoms\textsuperscript{20} and Edmonton Symptom Assessment System (ESAS) are used for
monitoring side-effects and tolerability.\textsuperscript{21} Daily, patients will report pain levels. Average and
maximal pain will be assessed for a period of 24 hours prior to recording. The use of rescue pain
medication will also be reported in the diary. Furthermore, patient will have a thorough
experimental pain examination at this visit (Box 1). Finally, a magnetic resonance imaging (MR-I)
scan of the brain will be carried out in relation to this visit to assess both functionally and
morphologically entities.

Visit 2

At the second visit, the biochemical screening from visit 1 is checked and questionnaires will be
reviewed to secure compliance. Resting state electroencephalography, contact heat evoked
potentials (CHEPS) on the pancreatic viscerotome (Th10) and a control area (Th4), and conditioned
pain modulation (CPM) are performed before, during and after the infusion of S-ketamine or
placebo. Fourteen blood samples will be drawn during the infusion in order investigate the
pharmacokinetics of S-ketamine and its metabolites.
Monitoring between visit 2 and 3

Patients are monitored closely during the entire study with frequent telephone interviews. Initially when medication is titrated participant have 2-3 telephone interviews per week to monitor potential side-effects and safety and to ensure compliance. During follow-up patients have at least one telephone interview allocated per week.

Visit 3

At the third visit, the experimental tests described for the first visit will be repeated. Pain diary and questionnaires will be collected. Blood for clinical chemistry will be drawn. Brain MR-I of the cerebrum will be carried out as described for visit 1. There are no further experimental medical interventions after this visit.

Follow-up between visit 3 and 4

During follow-up the patients are continually filling in their pain diary and questionnaires. The follow-up is employed to monitor the long-term effect of the study medication after the discontinuation of study medication.

Visit 4 (End of study)

The last visit takes place approximately 13 weeks after baseline. This visit is similar to the first and the third visit. All questionnaires will be filled in and collected. The experimental tests described for these visits will be repeated as well as brain MR-I. After this visit patients are monitored as usual through our out-patients clinic.
Dissemination

Positive as well as negative and inconclusive results of the study will be reported in international peer-reviewed journals in the field of gastroenterology, pain or neurophysiology and presented at conferences. Authorship will be ascribed in accordance with the Vancouver system. After the conclusion a report will be submitted to the Danish Health and Medicines Authority and the North Denmark Region Committee on Health Research Ethics as requested by law.

Safety considerations

Some patients may experience nausea and dizziness for a brief period after administration. Moreover, adverse effects like vivid dreams, nightmares and hallucinations have been described after anaesthesia and analgesia with S-ketamine. Adverse effects are directly related to the dose used. In the present study the doses are low and sub-anaesthetic, and severe adverse effects are unlikely to be seen. Adverse effects are self-assessed using a 5-point Likert Scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe/unbearable) and the ESAS questionnaire. In regard to potential abuse of S-ketamine, we find the potential benefits in the treatment of chronic pain to outweigh the risk of recreational use of the drug. Virtually all of the patients eligible for this study are using opioids, a group of drugs that has a potential for abuse of its own, this without any reports of opioid abuse. The abuse potential of S-ketamine is related to parenteral use and this part of the study will be conducted at the hospital under strict control. Furthermore, a well-known or suspected substance abuse potential such as excess alcohol consumption will lead to exclusion from the trial. Patients will continue on their usual analgesic medication when the trial ends. This also applies for dropouts.
Sample size

The study is powered to detect a minimal difference between the groups of 30% on the average pain diary score during four weeks of study treatment (primary endpoint). On the basis of a standard deviation of 25% of the mean we determined that a study with 15 patients per group is needed to provide a power of 90%, with the use of a two-sided significance level of 0.05. Hence, the sample size is set at 20 patients per group to allow for possible dropouts.

Data analysis

The principal analysis of endpoints will be by intention-to-treat, meaning that all randomised patients are included in their initially assigned study arm, regardless of adherence to study protocol. Experimental endpoints will be by per-protocol, meaning that only patients completing the experimental setup are included. The primary endpoint will be compared between the treatment groups by mixed models and subsequent analyses directed at the secondary, experimental, and safety endpoints are analysed using appropriate statistics.

Contributors

JJ, SSO, AEO, AD, OWS, JLP, AM, JFB and AMD have conceived and designed the study and participated in logistical planning of the study. JJ drafted the initial version of the manuscript and made the initial data acquisition. AOE is continuing the acquisition of data. SSO provided the statistical support for the sample size estimates and the design of the statistical analysis. All authors made significant contributions to the development and conceptualisation of the protocol. All authors reviewed the draft versions of this paper and have read and approved the final manuscript.
Funding

The study is conducted as an investigator initiated study with financial support the Danish Council for Strategic Research.

Competing interests

None declared.

Trial status

Recruitment of healthy volunteers for the control group began on 20 February 2014. The trial is ongoing.
References


Box 1

Primary endpoints

- The primary efficacy parameter is pain relief. This efficacy is assessed as changes in the daily experience of pain, which will be measured using a patient pain diary based on a visual analog scale (VAS). Maximum pain intensity and average daily pain will be recorded every day during the study.

Secondary endpoints

Clinical outcomes:
- The ratio of responders versus non-responders defined by decrease in VAS > 30% after four weeks compared to baseline.
- Change in opioid consumption.
- Change in quality of life using the European Organization for Research and Treatment of Cancer Quality of Life questionnaire EORTC-C30.
- Changes in pain and physical functioning composite scores of the modified brief pain inventory-short form (mBPI-sf).
- Change in Izbicki pain score.
- Patient Global Impression of Change (PGIC).
- Change in Beck’s Depression Inventory (BDI).
- Change in Edmonton Symptom Assessment System (ESAS) for monitoring side-effects and tolerability.

Experimental outcomes:

- Change in tolerance to pressure stimulation of the pancreatic viscerotome, control areas, and the quadriceps.
- Change in tolerance to tetanic electric stimulation of the pancreatic viscerotome and control area.
- Temporal summation to repetitive electric stimulations on the pancreatic viscerotome and a control area.
- Change in conditioned pain modulation (CPM).
- Change in resting state electroencephalography (EEG).
- Change in contact heat evoked potentials (CHEPS) evoked by stimulating the pancreatic viscerotome and a control area.
- Change in somatosensory evoked potentials (EPs) with recovery cycle estimation evoked by electrical stimulation of the median nerve.
- Change in nociceptive reflexes.
- Change in Offset-analgesia and according evoked potentials.
Box 2

Inclusion Criteria

- Patients from the ages of 18 years with a diagnosis of CP diagnosed using the Mayo Clinic diagnostic criteria. Both diabetic and non-diabetic patients will be allowed to enter the study.
- The participants must be able to read and understand Danish.
- The patients must suffer from chronic abdominal pain characteristic for CP, meet the criteria for chronic pain (pain ≥ 3 days per week in at least 3 months) and must consider their pain as insufficiently treated with their usual analgesic treatment.
- Personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the trial.
- Patients willing and able to comply with the scheduled visits, treatment plan, laboratory tests and other trial procedures.
Box 3
Exclusion Criteria

- Patients with any clinically significant laboratory abnormalities that in the opinion of the investigator may increase the risk associated with trial participation or may interfere with the interpretation of the trial results.
- Undiagnosed or untreated severe hypertension
- Unstable angina.
- Congestive heart failure.
- Any condition with elevated intracranial pressure.
- Untreated thyrotoxicosis.
- Alcohol dependence (alcohol use in accordance with the recommendations by the Danish Health and Medicines Authority are allowed).
- Illegal drug dependencies.
- Patients with evidence or history of medical or surgical disease of importance for this study as evaluated by the investigators.
- Patients treated with S-ketamine during the previous 4 months.
- Treatment with an investigational drug within 4 months preceding the first dose of study medication of importance for this study as judged by investigator.
- Female patients who are pregnant or lactating, or intend to become pregnant and male patients who intend to father a child during the course of the study. A pregnancy test will be conducted at baseline and after 4 weeks to ensure that female patients are not pregnant during the study medication period. The investigator will have to ensure that fertile female patients use a safe contraception method during the study and for at least 15 hours after termination of the study medication period. The following methods are considered as safe contraception methods:
  - Combined oral contraceptive pills
  - Intra-uterine device
  - Gestagen injection
  - Sub-dermal implantation
  - Hormone vaginal ring
  - Trans-dermal plaster
- Patients must not suffer from painful conditions other than CP that make them unable to distinguish the pain associated with CP from chronic pain of other origins.
- Patients with known hypersensitivity to S-ketamine or any of its components.
Figure 1
Legends

**Figure 1:** Visit 1 (Baseline): Experimental testing and MR-I

Visit 2: Infusion, experimental testing

Visit 3: Experimental testing, MR-I

Visit 4 (End of study): Experimental testing, MR-I

Week 1: No study medication

Week 2: Oral study medication. Ascending dosage of study medication.

Week 3-5: Fixed dosage of study medication

Week 6-13: Follow-up for eight weeks.
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Journal: BMJ Open

Manuscript ID: bmjopen-2014-007087.R1

Article Type: Protocol

Date Submitted by the Author: 09-Feb-2015

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Abstract

Introduction: Chronic pancreatitis (CP) is an inflammatory disease that causes irreversible damage to the pancreatic tissue. Pain is the most prominent symptom in. In the absence of pathology suitable for endoscopic or surgical interventions, pain treatment usually includes opioids. However, opioids often have limited efficacy. Moreover, side effects are common and bothersome. Hence, novel approaches to control pain associated with CP are highly desirable. Sensitization of the central nervous system is reported to play a key role in pain generation and chronification. Fundamental to the process of central sensitization is abnormal activation of the N-methyl-D-aspartate receptor, which can be antagonized by S-ketamine. The RESET trial is investigating the analgesic and anti-hyperalgesic effect of S-ketamine in patients with CP.

Methods and analysis: Forty CP patients will be enrolled. Patients are randomized to receive 8 hours of intravenous S-ketamine followed by oral S-ketamine for 4 weeks or matching placebo. To improve blinding 1 mg of midazolam will be added to both active and placebo treatment. The primary endpoint is clinical pain relief as assessed by a daily pain diary. Secondary endpoints include changes in patient reported outcome measures, opioid consumption, and rates of side-effects. The endpoints are registered through the 4-week medication period and for an additional follow-up period of 8 weeks to investigate long-term effects. In addition, experimental pain measures also serves as secondary endpoints, and neurophysiological imaging parameters are collected. Furthermore, experimental baseline recordings are compared to recordings from a group of healthy controls to evaluate general aspects of pain processing in CP.

Ethics and dissemination: The protocol is approved by the North Denmark Region Committee on Health Research Ethics (N-20130040) and the Danish Health and Medicines Authorities (EudraCT number: 2013-003357-17). The results will be disseminated in peer-reviewed journals and at scientific conferences.
Trial registration: The study is registered at www.clinicaltrialsregister.eu.
Article summary

Strengths and limitations of the study

• Both the clinical efficacy and the experimental investigation of the underlying mechanisms of the anti-hyperalgesic and analgesic properties of S-ketamine are addressed in this trial.

• This is a single-centre trial, which may compromise the external validity of the findings. However, single-centre trials also have several advantages. They are often logistically easier, data collection is simpler and typically deal with a less heterogeneous population, thereby diminishing confounding.
Introduction

Chronic pancreatitis (CP) remains a major source of morbidity in Northern Europe with an annual incidence of approximately 10 per 100,000 inhabitants.¹ A typical cause is long-term excessive use of alcohol, although genetic, environmental and autoimmune factors have also been associated with CP. It is a disease characterized by progressive destruction of the pancreatic gland and as it evolves, significant impairment of exocrine as well as endocrine functions. Within 5 years of diagnosis endocrine and exocrine insufficiencies develop in approximately 50 % and 80 % of patients with CP, respectively. These conditions are usually managed sufficiently with anti-diabetic treatment and pancreatic enzymes to optimize metabolic and nutritional status, whereas the treatment of pain in CP is more intricate. This progressive destruction also leads to pain, which is the most common symptom in CP, and up to 90 % of patients have chronic abdominal pain, often worsened by acute pain exacerbations typically requiring hospitalisation.² Hence, pain is a major burden for most CP patients and it has been associated with impaired psychosocial functioning, physical disability and decreased life quality.³ ⁴ It is recognized that chronic pain may alter central pain processing e.g. central sensitization, as the continuous damage of the pancreatic nerves may in time lead to central sensitisation of the pain system. The key component in this process is aberrant activation of the N-methyl-D-aspartate (NMDA) receptor. The initial analgesic medication in painful chronic pancreatitis will often involve opioids in the absence of pathology suitable for endoscopic or surgical interventions. However, opioid-based analgesia often only shows limited effectiveness in these patients and it is frequently accompanied by undesirable side-effects.⁵ However, a NMDA receptor antagonist, e.g. S-ketamine, could potentially be able to reverse this central sensitization by its action on the NMDA receptor. Thus providing long-term pain relief in sufferers of chronic pain.⁶
Pain mechanisms in chronic pancreatitis

The pathophysiology of pain in CP has yet to be fully elucidated and it is probably of multifactorial origin. Historically pain treatment has focused on the pancreatic gland assuming pain to be generated by on-going pancreatic inflammation, parenchymal hypertension and ductal obstruction. Consequently, treatment was focused on pathology in or closely related to the pancreatic gland. However, there is not a direct relationship between abdominal pain and pancreatic morphology, and the experimental evidence supporting this is conflicting. The most recent explanation model of pain pathogenesis in CP is that recurrent inflammation beyond a certain threshold causes irreversible injury to the pancreatic tissue. This process of repeated inflammation is linked to continuous damage of the pancreatic nerves along with peripheral and central sensitisation of the pain system. Key to the process of central sensitization is aberrant activation of the N-methyl-D-aspartate (NMDA) receptor as described below. An important outcome of central sensitization is that once the disease has advanced and the neural pathophysiological processes are firmly established, the generation of pain becomes self-perpetuating and independent of the initial nociceptive drive. Consequently, the management of pain becomes difficult and conventional treatment much less effective. This novel and improved understanding of the pain aetiology advocates a paradigm shift in pain management of CP.

S-ketamine and central sensitisation

Developed in 1960s as an anaesthetic drug, S-ketamine is currently used not only as a safe anaesthetic drug, but also as an analgesic drug in acute and per-operative pain as well as an antihyperalgesic drug in various chronic pain conditions. The different effects are dose-dependent. It is classified as a non-competitive NMDA receptor antagonist, but acts on multiple receptors including opioid-receptors. Hence, analgesia induced by S-ketamine may be partly mediated by...
actions on opioid receptors, however the main analgesia is induced by the NMDA receptor antagonism. Ketamine exists in two distinct stereoisomeric forms the S- and the R-form. Both a racemic equimolar mixture and a pure S-enantiomer are available. The S-isomeric form has a four times higher affinity for the NMDA receptor compared to the R-isomeric form and will be used in the present study. In anaesthesia S-ketamine provides a dissociative anaesthetic state, by blocking the connections between the limbic system and thalamus, while it provides an analgesic and antihyperalgesic effect when used in sub-anaesthetic doses. The latter is mainly attributed to antagonism of the NMDA receptor, an excitatory inotropic glutamate receptor located in the central as well as the peripheral nervous system. At resting membrane potentials, the NMDA receptor ion channel is physically blocked by a magnesium ion so that no current flows if glutamate binds to it. Hence, activation of the NMDA receptor by glutamate produces excitation only when this magnesium block is relieved by depolarization. Prolonged NMDA receptor activation results in removal of the magnesium ion blockade and a progressive increase in neuronal output. With ongoing activity, such activity dependent sensitization of central pain pathways ultimately becomes independent of the peripheral nociceptive drive and self-perpetuating. The mechanisms underlying this activity independent sensitization involves phosphorylation of different second messenger systems along with alterations in gene transcription. The resulting chronification of pain typically manifests as hyperalgesia and allodynia, which are the clinical hallmark of central sensitization although not specific for this entity. Central sensitization of the pain system is well documented in CP and it is increasingly accepted to play a prominent role in its pain pathogenesis.

S-ketamine exerts its anti-hyperalgesic effect by restoring the NMDA-receptor to its resting state condition through non-competitive antagonism. Thereby the “gain” of the pain system is restored to normal physiological status. Multiple studies have consistently produced positive results regarding the use of S-ketamine in patients with chronic pain. Thus it comprises an interesting
remedy to depress central sensitisation and its associated hyperalgesia in painful CP. This was supported by a recent Dutch double-blinded crossover trial designed to evaluate the effect of S-ketamine infusion on hyperalgesia associated with CP. Infusion of S-ketamine temporarily reversed pressure pain hyperalgesia and the underlying sensitized state of the pain system. This study was, however, not powered or designed for clinical endpoints.16

**Experimental testing**

The experimental testing of the study is based on quantitative sensory testing (QST) and provides information of the pain on both central and peripheral levels of the nervous system using controlled external pain stimuli. This evaluation of the sequential activation of the pain systems at different levels provides valuable information regarding the neuroplasticity in a sensitised nervous system. Assessment of experimental pain measures will be employed at baseline, during S-ketamine infusion, after 4 weeks of treatment with oral S-ketamine and at follow-up 8 weeks after treatment to unravel the mechanisms of the underlying anti-hyperalgesic and analgesic effects of S-ketamine. Furthermore, experimental baseline assessments will be compared to assessments from a group of healthy controls to evaluate general aspects of pain processing in CP. The entities are summarized in Box 1.

**Hypothesis**

We hypothesise that a one-day infusion of S-ketamine followed by oral S-ketamine for four weeks decreases central sensitisation associated with CP and thereby induces clinical pain relief, which is also reflected in secondary endpoints and sensory testing as summarised in Box 1.

**Box 1 near here**
Methods and analysis

Concomitant medication

Patients will be instructed not to change their regular pain treatment during the trial period. Rescue pain medication, taken on an “as needed basis,” is allowed throughout the trial period and its use will be documented in the daily pain diary.

Recruitment

All eligible patients with CP from our outpatient clinic who agree to participate in the study and fill in an informed consent will be invited to participate in the study. Patients will be recruited via personal correspondence and during sessions in the outpatients department, thus the initial contact will be in these settings.

Randomisation

Subjects will be randomised to the study providing they fulfil the entry criteria at screening (see Box 2 and 3). A computer-generated pseudo-random code will be used to assign subjects to treatment arms. A block randomization will be used, allowing 8 subjects at the time to be randomized in equal proportions for S-ketamine or matching placebo.

*****Box 2 near here*****

*****Box 3 near here*****
Study overview

Participation in the study will involve four clinical visits as shown in figure 1. The baseline visit, one week prior to the first administration of study medication, includes written informed consent, a physical examination and experimental pain testing. Furthermore patients will be instructed in the use of a pain diary to record pain intensity on daily basis. These assessments will commence 7 days prior to medicine administration. Average and maximum daily pain intensities are assessed using the pain diary. This is based on a visual analogue scale (VAS) where 0 equals no pain and 10 equals the worst pain imaginable.

****Figure 1 near here****

Infusion of S-ketamine

Duration and dosage of S-ketamine treatment were chosen based on a review of the literature and expert opinions as well as feasibility considerations. At the second visit the patients will receive intravenous S-ketamine (0.1 mg · kg\(^{-1}\) · h\(^{-1}\)) for 8 hours or matching placebo (i.e. isotonic saline). In addition, 1 mg of midazolam is administered together with ketamine/placebo to mask the patients’ awareness of central effects of ketamine and to ensure sufficient blinding.

Preparation and administration of oral S-ketamine and placebo

Both S-ketamine and placebo oral solutions will be prepared and provided by Skanderborg Apotek, Denmark. The placebo solution is similar to the vehicle used for ketamine solution. Thus, flavour and colour will match the characteristics of S-ketamine solution. During the second week of the study, patients will receive an increasing dose of oral S-ketamine or matching placebo starting on the day after S-ketamine infusion. The initial dose is 0.25 mg · kg\(^{-1}\) S-ketamine three times daily
(TID). After 3 days, this is increased to 0.50 mg · kg⁻¹ S-ketamine TID, with a further increase to 0.75 mg · kg⁻¹ S-ketamine TID after 6 days and for the following 3 weeks. An equivalent dose-escalating regime is followed in the placebo arm. All patients follow the same oral dosing schedule, with administration of study medication at 08:00, 14:00 and 20:00 ± 1 hour. If the patients experience unacceptable side effects, a single downward dose titration is allowed, with the patient staying on that final dosage for the remaining study period. If side effects are intolerable on the minimum dose during the oral phase, participants have the options to drop out of the study, an option always available to participant at any stage of the study.

Blood samples

The following biochemical parameters will monitored during the study:

- Alanine transaminase
- Aspartate transaminase
- Albumin
- Alkaline phosphatase
- Bilirubins
- Gamma glutamyl transpeptidase
- C-reactive protein
- Urea
- Creatinine
- Hemoglobin
- Potassium
- International normalisation ratio
- Lactate dehydrogenase
• Sodium
• White blood cell count
• Thrombocytes

Study procedures
Visit 1 (baseline)
At the baseline visit informed consent is obtained for further progress in the study. After this is secured, physical examination is conducted, blood samples drawn for biochemical screening, and patients’ medical history recorded. Moreover, a secretin enhanced magnetic resonance cholangiopancreatography (MRCP) is performed to ensure that patients do not have any pathology suitable for endoscopic or surgical therapy. Next, instruction to all questionnaires will be given and reporting of daily pain intensity in the pain diary will begin. Quality of life will be registered using the European Organization for Research and Treatment of Cancer Quality of Life questionnaire EORTC-QLQ-C30 while pain and physical functioning will be registered using the modified brief pain inventory-short form (mBPI-sf). Izbicki pain score. Patient Global Impression of Change (PGIC) is introduced for later use. Lastly Beck’s Depression Inventory (BDI) are used to assess depressive symptoms and Edmonton Symptom Assessment System (ESAS) are used for monitoring side-effects and tolerability. Daily, patients will report pain levels. Average and maximal pain will be assessed for a period of 24 hours prior to recording. The use of rescue pain medication will also be reported in the diary. Furthermore, patient will have a thorough experimental pain examination at this visit (Box 1). Finally, a magnetic resonance imaging (MR-I) scan of the brain will be carried out in relation to this visit to assess both functionally and morphologically entities.
Visit 2

At the second visit, the biochemical screening from visit 1 is checked and questionnaires will be reviewed to secure compliance. Resting state electroencephalography, contact heat evoked potentials (CHEPS) on the pancreatic viscerotome (Th10) and a control area (Th4), and conditioned pain modulation (CPM) are performed before, during and after the infusion of S-ketamine or placebo. Fourteen blood samples will be drawn during the infusion in order investigate the pharmacokinetics of S-ketamine and its metabolites.

Monitoring between visit 2 and 3

Patients are monitored closely during the entire study with frequent telephone interviews. Initially when medication is titrated participant have 2-3 telephone interviews per week to monitor potential side-effects and safety and to ensure compliance. During follow-up patients have at least one telephone interview allocated per week.

Visit 3

At the third visit, the experimental tests described for the first visit will be repeated. Pain diary and questionnaires will be collected. Blood for clinical chemistry will be drawn. Brain MR-I of the cerebrum will be carried out as described for visit 1. There are no further experimental medical interventions after this visit.

Follow-up between visit 3 and 4

During follow-up the patients are continually filling in their pain diary and questionnaires. The follow-up is employed to monitor the long-term effect of the study medication after the discontinuation of study medication.
Visit 4 (End of study)

The last visit takes place approximately 13 weeks after baseline. This visit is similar to the first and the third visit. All questionnaires will be filled in and collected. The experimental tests described for these visits will be repeated as well as brain MR-I. After this visit patients are monitored as usual through our outpatients clinic.

MRI studies

The MRI studies of the cerebrum have been included in the protocol, as an investigation at baseline, during ketamine or placebo treatment, and at the end of the study to assess any potential changes in the cerebrum.

Dissemination

Positive as well as negative and inconclusive results of the study will be reported in international peer-reviewed journals in the field of gastroenterology, pain or neurophysiology and presented at conferences. Authorship will be ascribed in accordance with the Vancouver system. After the conclusion a report will be submitted to the Danish Health and Medicines Authority and the North Denmark Region Committee on Health Research Ethics as requested by law.

Safety considerations

Some patients may experience nausea and dizziness for a brief period after administration. Moreover, adverse effects like vivid dreams, nightmares and hallucinations have been described after anaesthesia and analgesia with S-ketamine. Adverse effects are directly related to the dose used. In the present study the doses are low and sub-anaesthetic, and severe adverse effects are
unlikely to be seen. Adverse effects are self-assessed using a 5-point Likert Scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe/unbearable) and the ESAS questionnaire. In regard to potential abuse of S-ketamine, we find the potential benefits in the treatment of chronic pain to outweigh the risk of recreational use of the drug. Virtually all of the patients eligible for this study are using opioids, a group of drugs that has a potential for abuse of its own, this without any reports of opioid abuse. The abuse potential of S-ketamine is related to parenteral use and this part of the study will be conducted at the hospital under strict control. Furthermore, a well-known or suspected substance abuse potential such as excess alcohol consumption will lead to exclusion from the trial. Patients will continue on their usual analgesic medication when the trial ends. This also applies for dropouts.

**Sample size**

The study is powered to detect a minimal difference between the groups of 30% on the average pain diary score during four weeks of study treatment (primary endpoint). On the basis of a standard deviation of 25% of the mean we determined that a study with 15 patients per group is needed to provide a power of 90%, with the use of a two-sided significance level of 0.05. Hence, the sample size is set at 20 patients per group to allow for possible dropouts.

**Data analysis**

The principal analysis of endpoints will be by intention-to-treat, meaning that all randomised patients are included in their initially assigned study arm, regardless of adherence to study protocol. Experimental endpoints will be by per-protocol, meaning that only patients completing the experimental setup are included. The primary endpoint will be compared between the treatment groups by mixed models and subsequent analyses directed at the secondary, experimental, and
safety endpoints are analysed using appropriate statistics.

**Contributors**

JJ, SSO, AEO, AD, OWS, JLP, AM, JFB and AMD have conceived and designed the study and participated in logistical planning of the study. JJ drafted the initial version of the manuscript and made the initial data acquisition. AOE is continuing the acquisition of data. SSO provided the statistical support for the sample size estimates and the design of the statistical analysis. All authors made significant contributions to the development and conceptualisation of the protocol. All authors reviewed the draft versions of this paper and have read and approved the final manuscript.

**Funding**

The study is conducted as an investigator initiated study with financial support the Danish Council for Strategic Research.

**Registration**

The study is registered with [www.clinicaltrialsregister.eu](http://www.clinicaltrialsregister.eu) (EudraCT Number: 2013-003357-17).

Owing to an unknown mistake of the North Denmark Region Committee on Health Research Ethics, the approval was not forwarded automatically to the Danish Health and Medicines Authority, which are responsible for the registration at [www.clinicaltrialsregister.eu](http://www.clinicaltrialsregister.eu), hence the registration was delay and not online until November 2014 and not immediately after the approval of the former authorities as normal procedure.

**Competing interests**

None declared.
Trial status

Recruitment of healthy volunteers for the control group began on 20 February 2014. The trial is ongoing.
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Box 1

Primary clinical endpoints

- The primary efficacy parameter is pain relief. This efficacy is assessed as changes in the daily experience of pain, which will be measured using a patient pain diary based on the visual analog scale (VAS). Maximum pain intensity and average daily pain will be recorded at set times every day during the study.

Secondary clinical endpoints

- The ratio of responders versus non-responders defined by a decrease in VAS > 30% after four weeks compared to baseline.
- Change in opioid consumption.
- Change in quality of life using the European Organization for Research and Treatment of Cancer Quality of Life questionnaire EORTC-C30.
- Changes in pain and physical functioning composite scores of the modified brief pain inventory-short form (mBPI-sf).
- Change in Izbicki pain score.
- Patient Global Impression of Change (PGIC).
- Change in Beck’s Depression Inventory (BDI) to track changes in depressive symptoms.
- Change in Edmonton Symptom Assessment System (ESAS) for monitoring side-effects and tolerability.

Experimental pain testing

- Pressure stimulation of the pancreatic viscerotome, control areas, and the quadriceps.
- Tetanic electric stimulation of the pancreatic viscerotome and control area.
- Temporal summation to repetitive electric stimulations on the pancreatic and a control area.
- Conditioned pain modulation (CPM)
- Resting state electroencephalography (EEG).
- Contact heat evoked potentials (CHEPS) on the pancreatic viscerotome and a control area.
- Somatosensory EPs with recovery cycle estimation on the median nerve.
- Nociceptive reflexes.
- Offset-analgesia with recording of evoked potentials.
Box 2

Inclusion Criteria

- Patients from the ages of 18 with a diagnosis of CP diagnosed using the Mayo Clinic diagnostic criteria. Both diabetic and non-diabetic patients will be allowed to enter the study.
- The participants must be able to read and understand Danish.
- The patients must suffer from chronic abdominal pain characteristic for CP, meet the criteria for chronic pain (pain ≥ 3 days per week in at least 3 months) and must consider their pain as insufficiently treated with their usual analgesic treatment.
- Personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the trial.
- Patients willing and able to comply with the scheduled visits, treatment plan, laboratory tests and other trial procedures.
Box 3

Exclusion Criteria

- Patients with any clinically significant laboratory abnormalities that in the opinion of the investigator may increase the risk associated with trial participation or may interfere with the interpretation of the trial results.
- Undiagnosed or untreated severe hypertension
- Unstable angina.
- Congestive heart failure.
- Any condition with elevated intracranial pressure.
- Untreated thyrotoxicosis.
- Alcohol dependence (Alcohol use in accordance with the recommendations by the Danish Health and Medicines Authority are allowed).
- Illegal drug dependencies.
- Patients with evidence or history of medical or surgical disease of importance for this study as judged by investigator.
- Patients treated with S-ketamine during the previous 4 months.
- Treatment with an investigational drug within 4 months preceding the first dose of study medication of importance for this study as judged by investigator.
- Female patients who are pregnant or lactating, or intend to become pregnant and male patients who intend to father a child during the course of the study. A pregnancy test will be conducted at baseline and after 4 weeks to ensure that female patients are not pregnant during the study medication period. The investigator will have to ensure that fertile female patients use a safe contraception method during the study and for at least 15 hours after termination of the study medication period. The following methods are considered as safe contraception methods:
  - The combined oral contraceptive pill
  - Intra-uterine device
  - Gestagen injection
  - Sub-dermal implantation
  - Hormone vaginal ring
  - Trans-dermal plaster
- Patients must not suffer from painful conditions other than CP that make them unable to distinguish the pain associated with CP from chronic pain of other origin.
- Patients with known hypersensitivity to S-ketamine or any of its components.
Visit 1  Visit 2  Visit 3  Visit 4
Week 1  Week 2  Week 2 6  Week 6-12
Day -7  Day 1  Day 30  Day 90

Questionnaires throughout the entire study period

254x190mm (180 x 180 DPI)
Legends

**Figure 1:** Visit 1 (Baseline): Experimental testing and MR-I

Visit 2: Infusion, experimental testing

Visit 3: Experimental testing, MR-I

Visit 4 (End of study): Experimental testing, MR-I

Week 1: No study medication

Week 2: Oral study medication. Ascending dosage of study medication.

Week 3-5: Fixed dosage of study medication

Week 6-13: Follow-up for eight weeks.
SPIRIT Checklist

If any details are missing, it is because they are in the full and approved protocol the Danish Health and Medicines Authority and the North Denmark Region Committee on Health Research Ethics and not in the printed version at BMJ. A full protocol can be provided on request. Only formalities have been left out of this version in consideration of space.

Pages refers to page numbering in the manuscript file (Protocol_v2).

[1] Title: (Information can be found in the file Title).

Study protocol for a randomised, double-blinded, placebo-controlled, clinical trial of S-ketamine for pain treatment in patients with chronic pancreatitis (RESET trial).

[2] Trial registration: (Information can be found in the abstract and on page 13).

The study is registered at www.clinicaltrialsregister.eu (EudraCT-number: 2013-003357-17).


Version: 10
Issue Date: 4 Nov 2014

[4] Funding: (Page 13)

The study is conducted as an investigator initiated study with financial support the Danish Council for Strategic Research.

[5] Roles and responsibility

Contribution (In cover letter, Title, and page 13)

JJ, SSO, AEO, AD, OWS, JLP, AM, JFB and AMD have conceived and designed the study and participated in logistical planning of the study. JJ drafted the initial version of the manuscript and made the initial data acquisition. AOE is continuing the acquisition of data. SSO provided the statistical support for the sample size estimates and the design of the statistical analysis. All authors made significant contributions to the development and conceptualisation of the protocol. All authors reviewed the draft versions of this paper and have read and approved the final manuscript.

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[6] Background and rationale (Page 2-5)

[7] Objectives (Page 5 and Box 1)

[8] Trial design (Title page)

[9] Study setting (Title)
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[10] Eligibility criteria (BOX 2+3)


[12] Outcomes (Box 1).

[13] Participant timeline (Figure 1).


[16] Allocation (Page 5).

[18] Data collection methods (BOX 1)


[22] Harms, procedures in TMF in study lab.

[23] Auditing None planned. However audits may occur without notice.


[26] Consent (In full protocol and TMF. Approved doctors as recorded in the TMF will have charge to obtained informed consent).

[27] Confidentially

In full protocol and accordingly log in TMF. All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with limited access. All laboratory specimens, reports, data collection, process, and administrative forms will be identified by a coded ID [identification] number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.


[29] Access to data. All investigators will be given access to the cleaned data sets. In TMF and full protocol.

[30] Ancillary and post-trial care. None, all subjects are protected by the insurance of the hospital according to Danish legislation.

[31] Dissemination policy (Page 11)

[32] Informed consent. A model consent form provided by the Danish Health and Medicines Authority and the North Denmark Region Committee on Health Research Ethics. In TMF and case report forms.
[33] **Biological specimens.** Blood samples will collected according to the protocol on page 8-9. Further details in full protocol. All specimens will be handled according to Danish legislation.
# Study protocol for a randomised, double-blinded, placebo-controlled, clinical trial of S-ketamine for pain treatment in patients with chronic pancreatitis (RESET trial)

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| Primary Subject Heading: | Gastroenterology and hepatology |
| Secondary Subject Heading: | Pharmacology and therapeutics, Radiology and imaging |
| Keywords: | PAIN MANAGEMENT, Pancreatic disease < GASTROENTEROLOGY, Magnetic resonance imaging < RADIOLOGY & IMAGING |
Study protocol for a randomised, double-blinded, placebo-controlled, clinical trial of S-ketamine for pain treatment in patients with chronic pancreatitis (RESET trial)

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RESET Trial

Potential competing interests:

None declared

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Abstract

Introduction: Chronic pancreatitis (CP) is an inflammatory disease that causes irreversible damage to the pancreatic tissue. Pain is the most prominent symptom in. In the absence of pathology suitable for endoscopic or surgical interventions, pain treatment usually includes opioids. However, opioids often have limited efficacy. Moreover, side effects are common and bothersome. Hence, novel approaches to control pain associated with CP are highly desirable. Sensitization of the central nervous system is reported to play a key role in pain generation and chronification. Fundamental to the process of central sensitization is abnormal activation of the N-methyl-D-aspartate receptor, which can be antagonized by S-ketamine. The RESET trial is investigating the analgesic and anti-hyperalgesic effect of S-ketamine in patients with CP.

Methods and analysis: Forty CP patients will be enrolled. Patients are randomized to receive 8 hours of intravenous S-ketamine followed by oral S-ketamine for 4 weeks or matching placebo. To improve blinding 1 mg of midazolam will be added to both active and placebo treatment. The primary endpoint is clinical pain relief as assessed by a daily pain diary. Secondary endpoints include changes in patient reported outcome measures, opioid consumption, and rates of side-effects. The endpoints are registered through the 4-week medication period and for an additional follow-up period of 8 weeks to investigate long-term effects. In addition, experimental pain measures also serves as secondary endpoints, and neurophysiological imaging parameters are collected. Furthermore, experimental baseline recordings are compared to recordings from a group of healthy controls to evaluate general aspects of pain processing in CP.

Ethics and dissemination: The protocol is approved by the North Denmark Region Committee on Health Research Ethics (N-20130040) and the Danish Health and Medicines Authorities (EudraCT number: 2013-003357-17). The results will be disseminated in peer-reviewed journals and at scientific conferences.
**Trial registration:** The study is registered at www.clinicaltrialsregister.eu (EudraCT number 2013-003357-17).

**Article summary**

**Strengths and limitations of the study**

- Both the clinical efficacy and the experimental investigation of the underlying mechanisms of the anti-hyperalgesic and analgesic properties of S-ketamine are addressed in this trial.

- This is a single-centre trial, which may compromise the external validity of the findings. However, single-centre trials also have several advantages. They are often logistically easier, data collection is simpler and typically deal with a less heterogeneous population, thereby diminishing confounding.
Introduction

Chronic pancreatitis (CP) remains a major source of morbidity in Northern Europe with an annual incidence of approximately 10 per 100,000 inhabitants. A typical cause is long-term excessive use of alcohol, although genetic, environmental and autoimmune factors have also been associated with CP. It is a disease characterized by progressive destruction of the pancreatic gland and as it evolves, significant impairment of exocrine as well as endocrine functions. Within 5 years of diagnosis endocrine and exocrine insufficiencies develop in approximately 50% and 80% of patients with CP, respectively. These conditions are usually managed sufficiently with anti-diabetic treatment and pancreatic enzymes to optimize metabolic and nutritional status, whereas the treatment of pain in CP is more intricate. This progressive destruction also leads to pain, which is the most common symptom in CP, and up to 90% of patients have chronic abdominal pain, often worsened by acute pain exacerbations typically requiring hospitalisation. Hence, pain is a major burden for most CP patients and it has been associated with impaired psychosocial functioning, physical disability and decreased life quality. It is recognized that chronic pain may alter central pain processing e.g. central sensitization, as the continuous damage of the pancreatic nerves may in time lead to central sensitisation of the pain system. The key component in this process is aberrant activation of the N-methyl-D-aspartate (NMDA) receptor. The initial analgesic medication in painful chronic pancreatitis will often involve opioids in the absence of pathology suitable for endoscopic or surgical interventions. However, opioid-based analgesia often only shows limited effectiveness in these patients and it is frequently accompanied by undesirable side-effects. However, a NMDA receptor antagonist, e.g. S-ketamine, could potentially be able to reverse this central sensitization by its action on the NMDA receptor. Thus providing long-term pain relief in sufferers of chronic pain.
Pain mechanisms in chronic pancreatitis

The pathophysiology of pain in CP has yet to be fully elucidated and it is probably of multifactorial origin. Historically pain treatment has focused on the pancreatic gland assuming pain to be generated by on-going pancreatic inflammation, parenchymal hypertension and ductal obstruction. Consequently, treatment was focused on pathology in or closely related to the pancreatic gland.

However, there is not a direct relationship between abdominal pain and pancreatic morphology, and the experimental evidence supporting this is conflicting. The most recent explanation model of pain pathogenesis in CP is that recurrent inflammation beyond a certain threshold causes irreversible injury to the pancreatic tissue. This process of repeated inflammation is linked to continuous damage of the pancreatic nerves along with peripheral and central sensitisation of the pain system. Key to the process of central sensitization is aberrant activation of the N-methyl-D-aspartate (NMDA) receptor as described below. An important outcome of central sensitization is that once the disease has advanced and the neural pathophysiological processes are firmly established, the generation of pain becomes self-perpetuating and independent of the initial nociceptive drive. Consequently, the management of pain becomes difficult and conventional treatment much less effective. This novel and improved understanding of the pain aetiology advocates a paradigm shift in pain management of CP.

S-ketamine and central sensitisation

Developed in 1960s as an anaesthetic drug, S-ketamine is currently used not only as a safe anaesthetic drug, but also as an analgesic drug in acute and per-operative pain as well as an antihyperalgesic drug in various chronic pain conditions. The different effects are dose-dependent. It is classified as a non-competitive NMDA receptor antagonist, but acts on multiple receptors including opioid-receptors. Hence, analgesia induced by S-ketamine may be partly mediated by
actions on opioid receptors, however the main analgesia is induced by the NMDA receptor antagonism. Ketamine exists in two distinct stereoisomeric forms the S- and the R-form. Both a racemic equimolar mixture and a pure S-enantiomer are available. The S-isomeric form has a four times higher affinity for the NMDA receptor compared to the R-isomeric form and will be used in the present study. In anaesthesia S-ketamine provides a dissociative anaesthetic state, by blocking the connections between the limbic system and thalamus, while it provides an analgesic and antihyperalgesic effect when used in sub-anaesthetic doses. The latter is mainly attributed to antagonism of the NMDA receptor, an excitatory inotropic glutamate receptor located in the central as well as the peripheral nervous system. At resting membrane potentials, the NMDA receptor ion channel is physically blocked by a magnesium ion so that no current flows if glutamate binds to it. Hence, activation of the NMDA receptor by glutamate produces excitation only when this magnesium block is relieved by depolarization. Prolonged NMDA receptor activation results in removal of the magnesium ion blockade and a progressive increase in neuronal output. With on-going activity, such activity dependent sensitization of central pain pathways ultimately becomes independent of the peripheral nociceptive drive and self-perpetuating. The mechanisms underlying this activity independent sensitization involves phosphorylation of different second messenger systems along with alterations in gene transcription. The resulting chronification of pain typically manifests as hyperalgesia and allodynia, which are the clinical hallmark of central sensitization although not specific for this entity. Central sensitization of the pain system is well documented in CP and it is increasingly accepted to play a prominent role in its pain pathogenesis.  

S-ketamine exerts its anti-hyperalgesic effect by restoring the NMDA-receptor to its resting state condition through non-competitive antagonism. Thereby the “gain” of the pain system is restored to normal physiological status. Multiple studies have consistently produced positive results regarding the use of S-ketamine in patients with chronic pain. Thus it comprises an interesting
remedy to depress central sensitisation and its associated hyperalgesia in painful CP. This was supported by a recent Dutch double-blinded crossover trial designed to evaluate the effect of S-ketamine infusion on hyperalgesia associated with CP. Infusion of S-ketamine temporarily reversed pressure pain hyperalgesia and the underlying sensitized state of the pain system. This study was, however, not powered or designed for clinical endpoints.\textsuperscript{16}

**Experimental testing**

The experimental testing of the study is based on quantitative sensory testing (QST) and provides information of the pain on both central and peripheral levels of the nervous system using controlled external pain stimuli. This evaluation of the sequential activation of the pain systems at different levels provides valuable information regarding the neuroplasticity in a sensitised nervous system. Assessment of experimental pain measures will be employed at baseline, during S-ketamine infusion, after 4 weeks of treatment with oral S-ketamine and at follow-up 8 weeks after treatment to unravel the mechanisms of the underlying anti-hyperalgesic and analgesic effects of S-ketamine. Furthermore, experimental baseline assessments will be compared to assessments from a group of healthy controls to evaluate general aspects of pain processing in CP. The entities are summarized in Box 1.

**Hypothesis**

We hypothesise that a one-day infusion of S-ketamine followed by oral S-ketamine for four weeks decreases central sensitisation associated with CP and thereby induces clinical pain relief, which is also reflected in secondary endpoints and sensory testing as summarised in Box 1.

****Box 1 near here****
**Methods and analysis**

**Concomitant medication**

Patients will be instructed not to change their regular pain treatment during the trial period. Rescue pain medication, taken on an “as needed basis,” is allowed throughout the trial period and its use will be documented in the daily pain diary.

**Recruitment**

All eligible patients with CP from our outpatient clinic who agree to participate in the study and fill in an informed consent will be invited to participate in the study. Patients will be recruited via personal correspondence and during sessions in the outpatients department, thus the initial contact will be in these settings.

**Randomisation**

Subjects will be randomised to the study providing they fulfil the entry criteria at screening (see Box 2 and 3). A computer-generated pseudo-random code will be used to assign subjects to treatment arms. A block randomization will be used, allowing 8 subjects at the time to be randomized in equal proportions for S-ketamine or matching placebo.

*****Box 2 near here*****

*****Box 3 near here*****
Study overview

Participation in the study will involve four clinical visits as shown in figure 1. The baseline visit, one week prior to the first administration of study medication, includes written informed consent, a physical examination and experimental pain testing. Furthermore patients will be instructed in the use of a pain diary to record pain intensity on daily basis. These assessments will commence 7 days prior to medicine administration. Average and maximum daily pain intensities are assessed using the pain diary. This is based on a visual analogue scale (VAS) where 0 equals no pain and 10 equals the worst pain imaginable.

****Figure 1 near here****

Infusion of S-ketamine

Duration and dosage of S-ketamine treatment were chosen based on a review of the literature and expert opinions as well as feasibility considerations. At the second visit the patients will receive intravenous S-ketamine (0.1 mg · kg\(^{-1}\) · h\(^{-1}\)) for 8 hours or matching placebo (i.e. isotonic saline). In addition, 1 mg of midazolam is administered together with ketamine/placebo to mask the patients’ awareness of central effects of ketamine and to ensure sufficient blinding.

Preparation and administration of oral S-ketamine and placebo

Both S-ketamine and placebo oral solutions will be prepared and provided by Skanderborg Apotek, Denmark. The placebo solution is similar to the vehicle used for ketamine solution. Thus, flavour and colour will match the characteristics of S-ketamine solution. During the second week of the study, patients will receive an increasing dose of oral S-ketamine or matching placebo starting on the day after S-ketamine infusion. The initial dose is 0.25 mg · kg\(^{-1}\) S-ketamine three times daily
(TID). After 3 days, this is increased to 0.50 mg · kg$^{-1}$ S-ketamine TID, with a further increase to
0.75 mg · kg$^{-1}$ S-ketamine TID after 6 days and for the following 3 weeks. An equivalent dose-
escalating regime is followed in the placebo arm. All patients follow the same oral dosing schedule,
with administration of study medication at 08:00, 14:00 and 20:00 ± 1 hour. If the patients
experience unacceptable side effects, a single downward dose titration is allowed, with the patient
staying on that final dosage for the remaining study period. If side effects are intolerable on the
minimum dose during the oral phase, participants have the options to drop out of the study, an
option always available to participant at any stage of the study.

**Blood samples**

The following biochemical parameters will monitored during the study:

- Alanine transaminase
- Aspartate transaminase
- Albumin
- Alkaline phosphatase
- Bilirubins
- Gamma glutamyl transpeptidase
- C-reactive protein
- Urea
- Creatinine
- Hemoglobin
- Potassium
- International normalisation ratio
- Lactate dehydrogenase
• Sodium
• White blood cell count
• Thrombocytes

Study procedures

Visit 1 (baseline)

At the baseline visit informed consent is obtained for further progress in the study. After this is secured, physical examination is conducted, blood samples drawn for biochemical screening, and patients’ medical history recorded. Moreover, a secretin enhanced magnetic resonance cholangiopancreatography (MRCP) is performed to ensure that patients do not have any pathology suitable for endoscopic or surgical therapy. Next, instruction to all questionnaires will be given and reporting of daily pain intensity in the pain diary will begin. Quality of life will be registered using the European Organization for Research and Treatment of Cancer Quality of Life questionnaire EORTC-QLQ-C30\textsuperscript{17} while pain and physical functioning will be registered using the modified brief pain inventory-short form (mBPI-sf),\textsuperscript{18} Izbicki pain score,\textsuperscript{19} and Patient Global Impression of Change (PGIC) is introduced for later use.\textsuperscript{20} Lastly Beck’s Depression Inventory (BDI) are used to assess depressive symptoms\textsuperscript{21} and Edmonton Symptom Assessment System (ESAS) are used for monitoring side-effects and tolerability.\textsuperscript{22} Daily, patients will report pain levels. Average and maximal pain will be assessed for a period of 24 hours prior to recording. The use of rescue pain medication will also be reported in the diary. Furthermore, patient will have a thorough experimental pain examination at this visit (Box 1). Finally, a magnetic resonance imaging (MR-I) scan of the brain will be carried out in relation to this visit to assess both functionally and morphologically entities.
Visit 2

At the second visit, the biochemical screening from visit 1 is checked and questionnaires will be reviewed to secure compliance. Resting state electroencephalography, contact heat evoked potentials (CHEPS) on the pancreatic viscerotome (Th10) and a control area (Th4), and conditioned pain modulation (CPM) are performed before, during and after the infusion of S-ketamine or placebo. Fourteen blood samples will be drawn during the infusion in order investigate the pharmacokinetics of S-ketamine and its metabolites.

Monitoring between visit 2 and 3

Patients are monitored closely during the entire study with frequent telephone interviews. Initially when medication is titrated patient have 2-3 telephone interviews per week to monitor potential side-effects and safety and to ensure compliance. During follow-up patients have at least one telephone interview allocated per week.

Visit 3

At the third visit, the experimental tests described for the first visit will be repeated. Pain diary and questionnaires will be collected. Blood for clinical chemistry will be drawn. Brain MR-I of the cerebrum will be carried out as described for visit 1. There are no further experimental medical interventions after this visit.

Follow-up between visit 3 and 4
During follow-up the patients are continually filling in their pain diary and questionnaires. The follow-up is employed to monitor the long-term effect of the study medication after the discontinuation of study medication.

**Visit 4 (End of study)**

The last visit takes place approximately 13 weeks after baseline. This visit is similar to the first and the third visit. All questionnaires will be filled in and collected. The experimental tests described for these visits will be repeated as well as brain MR-I. After this visit patients are monitored as usual through our outpatients clinic.

**MRI studies**

The MRI studies of the cerebrum have been included in the protocol, as an investigation at baseline, during ketamine or placebo treatment, and at the end of the study to assess any potential changes in the cerebrum.

**Subject Withdrawal**

If the patient between the telephone calls experiences unacceptable adverse effects, the patient is asked to contact the investigator. Based on a medical judgment, the dose of study drug may be reduced and the treatment continued or the patient may be withdrawn from the study. Follow up consultations and eventually additional blood tests will be arranged as judged by the investigator.

**Discontinuation criteria**

If the participants are not able to tolerate the dose 0.25 mg/kg of S-ketamine TID during the oral phase of the study, they will be excluded. Otherwise discontinuation will rely on the discretion of each participant. A healthy volunteer that discontinues will always be asked about the reason(s) for
discontinuation and the presence of any adverse events. If needed, they will be seen and assessed by investigator. New subjects will be replace dropouts.

**Dissemination**

Positive as well as negative and inconclusive results of the study will be reported in international peer-reviewed journals in the field of gastroenterology, pain or neurophysiology and presented at conferences, hence dissemination to both researchers and clinicians. Participants will be informed of the results of the trial by investigators. Authorship will be ascribed in accordance with the Vancouver system. After the conclusion a report will be submitted to the Danish Health and Medicines Authority and the North Denmark Region Committee on Health Research Ethics as requested by law.

**Safety considerations**

Some patients may experience nausea and dizziness for a brief period after administration. Moreover, adverse effects like vivid dreams, nightmares, and hallucinations have been described after anaesthesia and analgesia with S-ketamine. Adverse effects are directly related to the dose used. In the present study the doses are low and sub-anaesthetic, and severe adverse effects are unlikely to be seen. Adverse effects are self-assessed using a 5-point Likert Scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe/unbearable) and the ESAS questionnaire. In regard to potential abuse of S-ketamine, we find the potential benefits in the treatment of chronic pain to outweigh the risk of recreational use of the drug. Virtually all of the patients eligible for this study are using opioids, a group of drugs that has a potential for abuse of its own, this without any reports of opioid abuse. The abuse potential of S-ketamine is related to parenteral use and this part of the study will be conducted at the hospital under strict control. Furthermore, a well-known or suspected
substance abuse potential such as excess alcohol consumption will lead to exclusion from the trial. Patients will continue on their usual analgesic medication when the trial ends. This also applies for dropouts.

**Sample size**

The study is powered to detect a minimal difference between the groups of 30% on the average pain diary score during four weeks of study treatment (primary endpoint). On the basis of a standard deviation of 25% of the mean we determined that a study with 15 patients per group is needed to provide a power of 90%, with the use of a two-sided significance level of 0.05. Hence, the sample size is set at 20 patients per group to allow for possible dropouts.

**Data analysis**

The principal analysis of endpoints will be by intention-to-treat, meaning that all randomised patients are included in their initially assigned study arm, regardless of adherence to study protocol. Experimental endpoints will be by per-protocol, meaning that only patients completing the experimental setup are included. The primary endpoint will be compared between the treatment groups by mixed models and subsequent analyses directed at the secondary, experimental, and safety endpoints are analysed using appropriate statistics.

**Data Handling and Record Keeping**

The study is approved by the Danish Data Protection Agency. For each subject a Case Report Form is kept in which data for the subject is entered. Data will be stored under lock at Aalborg University Hospital, Department of Gastroenterology and Hepatology, for 5 years under the responsibility of the principal investigator, Prof Asbjørn Mohr Drewes. All forms are filled out during (or
immediately after) the assessment of a subject and must be legible. Errors are crossed out, corrections are added and next to the changes date and initials are applied. A patient identification list containing patient number, full name, social security number, study medication and treatment codes for all persons included in the study is created. The list is populated and updated by a project nurse or other competent person and be stored at the same facilities. 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.

**Contributors**

JJ, SSO, AEO, AD, OWS, JLP, AM, JFB and AMD have conceived and designed the study and participated in logistical planning of the study. JJ drafted the initial version of the manuscript and made the initial data acquisition. AOE is continuing the acquisition of data. SSO provided the statistical support for the sample size estimates and the design of the statistical analysis. All authors made significant contributions to the development and conceptualisation of the protocol. All authors reviewed the draft versions of this paper and have read and approved the final manuscript.

**Funding**

The study is conducted as an investigator initiated study with financial support the Danish Council for Strategic Research.

**Registration**

The study is registered with hwww.clinicaltrialsregister.eu (EudraCT Number: 2013-003357-17).

Owing to an unknown mistake of the North Denmark Region Committee on Health Research Ethics, the approval was not forwarded automatically to the Danish Health and Medicines
Authority, which are responsible for the registration at www.clinicaltrialsregister.eu, hence the registration was delay and not online until November 2014 and not immediately after the approval of the former authorities as normal procedure.

Competing interests
None declared.

Trial status
Recruitment of healthy volunteers for the control group began on 20 February 2014. The trial is ongoing.
References


Box 1

Primary clinical endpoints

- The primary efficacy parameter is pain relief. This efficacy is assessed as changes in the daily experience of pain, which will be measured using a patient pain diary based on the visual analog scale (VAS). Maximum pain intensity and average daily pain will be recorded at set times every day during the study.

Secondary clinical endpoints

- The ratio of responders versus non-responders defined by a decrease in VAS > 30% after four weeks compared to baseline.
- Change in opioid consumption.
- Change in quality of life using the European Organization for Research and Treatment of Cancer Quality of Life questionnaire EORTC-C30.
- Changes in pain and physical functioning composite scores of the modified brief pain inventory-short form (mBPI-sf).
- Change in Izbicki pain score.
- Patient Global Impression of Change (PGIC).
- Change in Beck’s Depression Inventory (BDI) to track changes in depressive symptoms.
- Change in Edmonton Symptom Assessment System (ESAS) for monitoring side-effects and tolerability.

Experimental pain testing

- Pressure stimulation of the pancreatic viscerotome, control areas, and the quadriceps.
- Tetanic electric stimulation of the pancreatic viscerotome and control area.
- Temporal summation to repetitive electric stimulations on the pancreatic and a control area.
- Conditioned pain modulation (CPM)
- Resting state electroencephalography (EEG).
- Contact heat evoked potentials (CHEPS) on the pancreatic viscerotome and a control area.
- Somatosensory EPs with recovery cycle estimation on the median nerve.
- Nociceptive reflexes.
- Offset-analgesia with recording of evoked potentials
Box 2

Inclusion Criteria

- Patients from the ages of 18 with a diagnosis of CP diagnosed using the Mayo Clinic diagnostic criteria. Both diabetic and non-diabetic patients will be allowed to enter the study.
- The participants must be able to read and understand Danish.
- The patients must suffer from chronic abdominal pain characteristic for CP, meet the criteria for chronic pain (pain ≥ 3 days per week in at least 3 months) and must consider their pain as insufficiently treated with their usual analgesic treatment.
- Personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the trial.
- Patients willing and able to comply with the scheduled visits, treatment plan, laboratory tests and other trial procedures.
Box 3

Exclusion Criteria

- Patients with any clinically significant laboratory abnormalities that in the opinion of the investigator may increase the risk associated with trial participation or may interfere with the interpretation of the trial results.
- Undiagnosed or untreated severe hypertension
- Unstable angina.
- Congestive heart failure.
- Any condition with elevated intracranial pressure.
- Untreated thyrotoxicosis.
- Alcohol dependence (Alcohol use in accordance with the recommendations by the Danish Health and Medicines Authority are allowed).
- Illegal drug dependencies.
- Patients with evidence or history of medical or surgical disease of importance for this study as judged by investigator.
- Patients treated with S-ketamine during the previous 4 months.
- Treatment with an investigational drug within 4 months preceding the first dose of study medication of importance for this study as judged by investigator.
- Female patients who are pregnant or lactating, or intend to become pregnant and male patients who intend to father a child during the course of the study. A pregnancy test will be conducted at baseline and after 4 weeks to ensure that female patients are not pregnant during the study medication period. The investigator will have to ensure that fertile female patients use a safe contraception method during the study and for at least 15 hours after termination of the study medication period. The following methods are considered as safe contraception methods:
  - The combined oral contraceptive pill
  - Intra-uterine device
  - Gestagen injection
  - Sub-dermal implantation
  - Hormone vaginal ring
  - Trans-dermal plaster
- Patients must not suffer from painful conditions other than CP that make them unable to distinguish the pain associated with CP from chronic pain of other origin.
- Patients with known hypersensitivity to S-ketamine or any of its components.
Visit 1  Visit 2  Visit 3  Visit 4

Week 1  Week 2  Week 2-6  Week 6-12

Day -7  Day 1  Day 30  Day 90

Questionnaires throughout the entire study period

90x67mm (300 x 300 DPI)
SPIRIT Checklist

If any details are missing, it is because they are in the full and approved protocol the Danish Health and Medicines Authority and the North Denmark Region Committee on Health Research Ethics and not in the printed version at BMJ. A full protocol can be provided on request. Only formalities have been left out of this version in consideration of space.

Pages refers to page numbering in the manuscript file (Clean_copy_v2).

[1] Title: (Information can be found in the file Title).
Study protocol for a randomised, double-blinded, placebo-controlled, clinical trial of S-ketamine for pain treatment in patients with chronic pancreatitis (RESET trial).

[2] Trial registration: (Information can be found in the abstract and on page 13).
The study is registered at www.clinicaltrialsregister.eu (EudraCT-number: 2013-003357-17).

Version: 10
Issue Date: 4 Nov 2014

[4] Funding: (Page 13)
The study is conducted as an investigator initiated study with financial support the Danish Council for Strategic Research.

[5] Roles and responsibility
Contribution (In cover letter, Title, and page 13)
JJ, SSO, AEO, AD, OWS, JLP, AM, JFB and AMD have conceived and designed the study and participated in logistical planning of the study. JJ drafted the initial version of the manuscript and made the initial data acquisition. AOE is continuing the acquisition of data. SSO provided the statistical support for the sample size estimates and the design of the statistical analysis. All authors made significant contributions to the development and conceptualisation of the protocol. All authors reviewed the draft versions of this paper and have read and approved the final manuscript.

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Background and rationale (Page 2-5)

Objectives (Page 5 and Box 1)

Trial design (Title page)

Study setting (Title)
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Eligibility criteria (BOX 2+3)

Interventions (Page 5-11).

Outcomes (Box 1).

Participant timeline (Figure 1).

Sample size (Page 12).

Recruitment (Page 6).

Allocation (Page 5).
[17] **Blinding** (Page 7).

[18] **Data collection methods** (BOX 1)


[21] **Monitoring** GCP unit at Aarhus and Aalborg University Hospitals. As well as investigator based monitoring of side-effects etc. Se pages 10-16 including biochemical blood samples.

[22] **Harms**, procedures in TMF in study lab.

[23] **Auditing** None planned. However audits may occur without notice.


[26] **Consent** (In full protocol and TMF. Approved doctors as recorded in the TMF will have charge to obtained informed consent).

[27] **Confidentially**

In full protocol and accordingly log in TMF. All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with limited access. All laboratory specimens, reports, data collection, process, and administrative forms will be identified by a coded ID [identification] number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

[28] **Declaration of interest.** None. Declared on title page.

[29] **Access to data.** All investigators will be given access to the cleaned data sets. In TMF and full protocol. For data security se page 16-17.

[30] **Ancillary and post-trial care.** None, all subjects are protected by the insurance of the hospital according to Danish legislation.

[31] **Dissemination policy** (Page 15)
[32] **Informed consent.** A model consent form provided by the Danish Health and Medicines Authority and the North Denmark Region Committee on Health Research Ethics. In TMF and case report forms.

[33] **Biological specimens.** Blood samples will be collected according to the protocol on page 8-9. Further details in full protocol. All specimens will be handled according to Danish legislation.
Study protocol for a randomised, double-blinded, placebo-controlled, clinical trial of S-ketamine for pain treatment in patients with chronic pancreatitis (RESET trial)

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BMJ Open 2015 5:
doi: 10.1136/bmjopen-2014-007087

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