Radboudumc

Clinical Study Report

HEEL-2011-02

The analgesic efficacy of Δ9-THC (Namisol®) in chronic pancreatitis patients suffering from persistent abdominal pain

a randomized, double-blinded, placebo-controlled, parallel design

EudraCT 2012-000730-19
CME number 2012/092

PROTOCOL MANAGEMENT

Protocol ID	HEEL-2011-02
Short title	Δ9-THC (Namisol®) in chronic pancreatitis (Delta Pain II)
Name of test drug / investigational product:	Delta(9)-tetrahydrocannabinol
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Date	25Mar2016
Study Phase	II
Indication studied	Chronic pain

Investigator site

Responsible investigator	Prof. dr. H. van Goor
Coordinating investigator	M. de Vries, MSc
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Sponsor

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Study Dates	Delta Pain II
Start (first patient first visit)	15-OCT-2012
Completion clinical phase	17-DEC-2013
Completion external assays	03-SEP-2014

This study was performed in compliance with Good Clinical Practice (GCP), including the archiving of essential documents.

Confidentiality statement

The clinical trial described in this report is a part of the project 'Van zuivere THC naar Namisol®', with project number 2009-019329. The rules and responsibilities as laid down in the partnership agreement for this project will apply.

REPORT SIGNATURE SHEET

We, the undersigned, hereby declare that the work was performed according to the procedures herein described and that the report:

"The analgesic efficacy of Δ9-THC (Namisol®) in chronic pancreatitis patients suffering from persistent abdominal pain. A randomized, double-blinded, placebo-controlled, parallel design"

provides a correct and faithful record of the results obtained.

Name	Signature	Date
Prof. dr. H. van Goor Responsible Investigator		
Dr. O.H.G. Wilder -Smith Subinvestigator		
M. de Vries, MSc Coordinating Investigator		

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2. SYNOPSIS

Name of sponsor/company: Radboudumc	**Individual study table referring to part of the dossier** **Volume:** **Page:**	**(For National Authority use only)**
Name of finished product: Namisol		
Name of active ingredient: tetrahydrocannabinol		

TITLE

The analgesic efficacy of Δ9-THC (Namisol®) in chronic pancreatitis patients suffering from persistent abdominal pain: a randomized, double-blinded, placebo-controlled, parallel design

INVESTIGATORS Prof. dr. H. van Goor, dr. O.H.G. Wilder-Smith, M. de Vries, MSc

STUDY CENTER Department of Surgery, Radboud university medical center (Radboudumc), Nijmegen, the Netherlands

STUDY PERIOD Date of first patient first study day: 15 Oct 2012
Date of last patient completed study: 17 Dec 2013

PHASE II

RATIONALE

Pancreatic pain is described by most patients as severe dull epigastric pain, eventually radiating to the back. The pain is often recurrent, intense and long-lasting. The pathogenesis of pain in this disorder is poorly understood and its treatment has been largely empirical, often consisting of surgical or other invasive methods, with an outcome that is variable and frequently unsatisfactory. Ultimately, they are treated with increasing doses of opioid or undergone complex and expensive pain treatments, such as spinal cord stimulation. The adverse consequences of prolonged opioid use, including addiction, tolerance and opioid induced hyperalgesia, call for an alternative medical treatment. Cannabis has been used to treat pain for many centuries. Delta-9-tetrahydrocannabinol (Δ9-THC), the psychoactive substance of the cannabis plant, has been shown in previous studies to be a promising analgesic. The development of Namisol®, an oral tablet containing purified Δ9-THC showing an improved, reliable pharmacokinetic profile, provides the opportunity to test the analgesic potential of Δ9-THC.

OBJECTIVE

Primary objective:

- To investigate the analgesic efficacy, measured by a visual analogue scale (VAS) score, of a stable dose treatment Namisol® in CP patients suffering from chronic abdominal pain.

Secondary objectives:

- To investigate the efficacy of a stable dose treatment Namisol® on changes in pain experience (Izbicki), anxiety and depression (HADS), general health (SF-36), pain catastrophizing (PCS), global impression of change (PGIC), pain related anxiety (PASS) in CP patients suffering from chronic abdominal pain.
- To evaluate the safety and tolerability of a stable dose treatment Namisol® in CP patients suffering from chronic abdominal pain.
- To evaluate the pharmacokinetics (PK) of a stable dose treatment Namisol® in CP patients suffering from chronic abdominal pain.
- To evaluate (undesirable) pharmacodynamic (PD) effects of a stable dose treatment Namisol® of Δ9-THC in CP patients suffering from chronic abdominal pain.
- To investigate the effect of a stable dose treatment Namisol® on experimental pain mechanisms (measured by EEG, QST, and DNIC) in CP patients suffering from chronic abdominal pain.

STUDY DESIGN

A randomized, double-blind, placebo-controlled, parallel-group study design.

PLANNED SAMPLE

The planned study population consisted of 68 subjects with chronic abdominal pain resulting from chronic pancreatitis to assess the analgesic efficacy of Namisol® in patients suffering from chronic abdominal pain resulting from CP. The actual number of patients included in this trial is reported in the results section.

MAIN SELECTION CRITERIA

Selection criteria for CP patients

Key inclusion criteria:

- Chronic pancreatitis
- Chronic abdominal pain typical for pancreatitis, meet the criteria for chronic pain according ISAP (intermittent or persistent pain on a daily basis for at least 3 months), and pain is severe enough for medical treatment (average NRS ≥ 3)

Key exclusion criteria:

- Significant medical disorder or concomitant medication that may interfere with the study or may pose a risk for the patient
- Amitriptyline during the course of the study
- Positive urine drug screen for THC, cocaine, MDMA, or amphetamines
- Daily cannabis use in use in the past three years
- History of hypersensitivity to THC
- BMI above 33,0 kg/m^2
- Serious painful condition other than CP
- Major psychiatric illness in history
- Epileptic seizure in history

DRUGS AND DOSAGES

Namisol® with standardized Δ9-THC content or identical matching placebos was administered orally to evaluate the analgesic properties of Namisol® during a 52 days add-on treatment to other analgesics. The study consisted of two phases: a step-up phase (day 1-5: 3 mg TID; day 6-10: 5 mg TID), and a stable dose phase (day 11-52: 8 mg TID). The dosage was tapered to at least 5 mg TID, when 8 mg was not tolerated.

ENDPOINTS

Primary study parameter

- Delta VAS pain of the average pain score at day 50-52 minus baseline (mean day -5 to -1 pre-treatment)

Secondary study parameters

- Patient demographics and clinical characteristics
- Pain intensity (diary)
  - Minimal and maximal pain scores
- Concomitant pain medication
- Pharmacokinetics
  - C_{max}, AUC_{last}, $AUC\infty$, t_{max}, λ_z, and $t_{1/2term}$ for THC, 11-OH-THC and THC-COOH
- Pharmacogenetics
  - CYP2C9 and CYP2C19
- Pharmacodynamics
  - Questionnaires: VASBond and Lader, VASBowdle, PGIC, PCS, SF-36, HADS, PASS, Apple, TSQM, Izbicki
  - Body weight and supplementary feeding
  - Body Sway
- EEG
  - FFT spontaneous EEG (Resting state EEG)
  - Evoked EEG
    - ERPs to painful electrical stimuli
    - ERPs to auditory stimuli (oddball)
- QST
  - Pressure pain thresholds
  - Electric pain thresholds
  - Electric wind-up response
  - DNIC

Safety study parameters

- ECG, HF and BP
- Adverse events
- Laboratory

STATISTICAL METHODS

The primary outcome of this study was analgesic efficacy measured as difference in visual analogue scale (VAS) of the average pain score (VAS pain) at day 50-52 (last day of diary) minus baseline (mean day -5 to -1 pre-treatment) between placebo and Namisol®. The VAS pain was analyzed by an Analysis of Covariance (ANCOVA) that incorporates the baseline measurement score as covariate. All participants who received the study medication for at least 36 days were included in the efficacy analyses according to the intention to treat principle. Dropouts before day 36 were replaced and data of dropouts will be excluded from further analyses of the primary endpoint.

STUDY SCHEDULE

The timing of assessments is presented in flowchart A.

RESULTS

Twenty-nine (29) CP patients were randomized, from whom 12 patients in the Namisol® arm and 15 patients in the placebo arm were included in the safety analyses, whereas 8 patients in the Namisol® arm and 15 patients in the placebo arm were included in the efficacy analysis. Two patients had withdrawn consent before study treatment started and 4 patients dropped out within 36 days after the start of the trial.

Efficacy

Primary efficacy analysis of the average VAS pain at the end of the treatment period did not reveal any significant difference between Namisol® and placebo treatment in this small population. Delta VAS pain scores were similar with 1.7 points (50%) reduction for Namisol® compared to 2.1 points (43%) reduction for placebo. Similar results were observed for minimal and maximal reported VAS pain.

Pharmacokinetics

After a dose of 8 mg of Namisol®, THC was absorbed with a mean t_{max} of 1:63 hours(97.8 min) and mean C_{max} of 5,04 ng/mL, and eliminated with a mean $t_{1/2term}$ of 2,62H. Evaluation of the pharmacokinetics on an individual patient level revealed that some patients demonstrate a relatively late t_{max} accompanied with a relatively low C_{max}, which cannot be observed in the mean THC plasma concentration curves.

No differences were observed in THC plasma concentrations between extensive (normal), intermediate and ultra rapid metabolizers based on CYP2C9 and CYP2C19 polymorphism. However, it cannot be precluded that genetic polymorphisms may have contributed to the inter-individual variation in the pharmacokinetics of Namisol®.

Pharmacodynamics
No differences were observed in secondary pain questionnaires such as the pancreatitis-specific pain questionnaire, patient global impression of change, pain catastrophizing or pain related anxiety between the Namisol and placebo population. Measures of depression and generalized anxiety, quality of life, treatment satisfaction did not change after Namisol® treatment compared with placebo. Additionally, Namisol® did not affect psychedelic outcomes and subjective feelings corresponding to alertness, mood and calmness in CP patients.
Patients reported a significant improvement in appetite level compared to before the study period (p=.025). However, no statistically significant differences between Namisol® and placebo were observed for appetite level in the last week or body weight. Balance disturbances were shown in several individuals and did not increase during study treatment of both Namisol® and placebo.

Safety
Most frequently related or possibly related reported AEs after Namisol® treatment were: decreased appetite, dizziness, somnolence, dry mouth and hyperhidrosis. Increased appetite, somnolence, dizziness, confusional state and headache were most commonly related or possibly reported in the group receiving placebo treatment. All (potentially) related AEs were mild or moderate. Three SAEs occurred, which were considered not related to study treatment.

CONCLUSIONS
In this exploratory phase 2 study, Namisol® failed to demonstrate a significant reduction in pain scores after 50-52 days study treatment compared with placebo in CP patients with chronic abdominal pain as determined with VAS pain. The small study population, as well as a large placebo effect may have contributed to this lack of observed efficacy. Namisol® was well tolerated with potentially related AEs of only mild to moderate nature.

Flowchart A: measurement schedule

Protocol Activity	Screening	Study treatment									Follow-up
Day	**-35 to -7**	**-5**	**1**	**4-5**	**9-10**	**15**	**21-23**	**28-30**	**38-40**	**50-52**	**59-61**
Treatment			**start**	**I**	**II**	**III**				**stop**	
Visit outpatient clinic	X		X			X				X	
Telephone interview				X	X		X	X	X		X
Informed consent	X										
Patients characteristics											
Demo/ clinical data	X										
Medical history	X										
Physical examination	X										
Concomitant medication	X										
Laboratory											
Blood Hematology	X									X	
Blood Biochemistry	X									X	
Blood Serology (virology)	X										
Urinalysis	X										
Urine drug screening	X										
Urine pregnancy test	X										
Vital signs											
ECG	X									X	
BP / HF	X		X			X				X	
Randomization	X										
VAS pain diary [a]	X	- - - - - Daily - - - - -									
Concomitant medication [a]	X	- - - - - Daily - - - - -									X
Adverse events [a]	X	- - - - - Daily - - - - -									X
Suppl. feeding diary [a]	X	- - - - - Daily - - - - -									
Questionnaires											
PGIC						X				X	
PCS			X			X				X	
VAS Bond & Lader			X	X	X	X				X	
VAS Bowdle			X	X	X	X				X	
SF-36			X							X	
HADS			X							X	
PASS			X							X	
Apple										X	
TSQM										X	
Izbicki			X	X	X	X				X	
QST protocol			X			X				X	
EEG											
FFT in resting state			X							X	
ERPs to noxious stimuli			X							X	
Body sway			X			X				X	
Body weight	X		X			X				X	
Pharmacokinetics			X			X				X	

I Decision point day 5: continue 5mg TID or withdrawal. II Decision point day 10: continue 8mg TID or withdrawal (tapering to 5mg TID is permitted). III Decision point day 15: continue 8mg TID, taper to 5 mg TID or withdrawal.

[a] parameters will be recorded daily in a diary starting 5 days prior start of study treatment.

3. List Of Abbreviations And Definition Of Terms

ABL:	Analytisch Biochemisch Laboratorium
(e)CRF:	(electronic) Case Report Form
(S)AE:	(Serious) Adverse Event
ABR:	ABR form, General Assessment and Registration form (In Dutch, ABR = Algemene Beoordeling en Registratie)
AE:	Adverse Event
ANCOVA:	Analysis of covariance
AR:	Adverse Reaction
BMI:	Body Mass Index
BP:	Blood Pressure
BS:	Body Sway
CA:	Competent Authority
CB1/ 2:	Cannabinoid receptor type 1/ 2
CCMO:	Central Committee on Research Involving Human Patients; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CP:	Chronic Pancreatitis
CPT:	Cold Pressor Test
CRCN:	Clinical Research Centre Nijmegen
CBG:	College ter Beoordeling van Geneesmiddelen
DBP:	Diastolic blood pressure
DNIC:	Diffuse Noxious Inhibitory Control
DSMB:	Data Safety Monitoring Board
ECG:	Electrocardiogram
EEG:	Electroencephalogram
ERP:	Event Related Potential
EU:	European Union
EudraCT:	European drug regulatory affairs Clinical Trials
FFT:	Fast Fourier Transformation
GCP:	Good Clinical Practice
GLP:	Good Laboratory Practice
HF:	Heart Frequency
HRV:	Heart Rate Variability
IB:	Investigator's Brochure
IC(F):	Informed Consent (Form)
IMP:	Investigational Medicinal Product
IMPD:	Investigational Medicinal Product Dossier
ISAP:	International Association for the Study of Pain
METC:	Medical research ethics committee; in Dutch: medisch ethische toetsing commissie
NRS:	Numeric Rating scale
PAG:	Periaqueductal gray
PB:	Placebo
PD:	Pharmacodynamics

PK:	Pharmacokinetics
PPT:	Pressure Pain Threshold
QST:	Quantitative Sensory Testing
SBP:	Systolic blood pressure
SD:	Standard deviation
SEM:	Standard error of the mean
Sponsor:	The sponsor is the party that commissions the organisation or performance of the research. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SPSS:	Statistical Package for the Social Sciences
SUSAR:	Suspected Unexpected Serious Adverse Reaction
TMF:	Trial Master File
VAS:	Visual Analogue Scale
WBP:	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)
WMO:	Medical Research Involving Human Patients Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen
Δ9-THC:	Delta-9-tetrahydrocannabinol

4. ETHICS

4.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Before the start of the study, the protocol was submitted to the Medical Ethics Committee (METC) region Arnhem-Nijmegen and the Dutch competent authority (CCMO). On 23 August 2012, the METC approved the study protocol according protocol version 3.0 (ABR number NL39537.091.12). The CCMO gave a declaration of no objection on 12 March 2012 and the board of directors of the Radboud University Medical Centre Nijmegen gave approval on 23 August 2012.
The trial was registered and published on clinicaltrials.gov (NCT01551511) and the European Union drug regulating authorities Clinical Trials (EudraCT 2012-000730-19).

After initial approval, three study amendments have been submitted and approved:

1. The first study amendment (dated 26 September 2012) included two amendment research protocols. The first amendment protocol was titled: "*Signaling pathways of medicinal cannabis in peripheral blood*". The objective of this amendment was to explore the anti-inflammatory effect of cannabinoids by studying the effects of Namisol on the mTOR pathway. Furthermore, it was aimed to explore other signaling pathways of activation of cannabinoid receptors through kinome profiling.
The second amendment protocol was titled: "*The role of genetic CYP2C9 and CYP2C19 polymorphism on the pharmacokinetics, tolerability and efficacy of Δ9-THC (Namisol®)".* The aim of this amendment was to investigate the extent to which the variation in pharmacokinetics of Δ9-THC (Namisol®) could be explained by genetic polymorphisms in CYP2C9 and CYP2C19. A better understanding of the variation in pharmacokinetics of Δ9-THC (Namisol®) may help to improve the understanding of interindividual variation in clinical effects and adverse events.
The METC gave approval for both study amendments on 8 November 2012.

2. The second study amendment (dated 10 December 2012) resulted in a revised study protocol version 4.0. The METC gave approval on 3 January 2013. The amendment contained the following changes:

   - The treatment scheme was modified. The last dose (evening dose) on the last study day was eliminated from the treatment schedule.
   - Two extra questionnaires were added to the study protocol. The "Apple" is a self created questionnaire evaluating the effect of Namisol on the appetite of subjects, and the "TSQM v. II" is a questionnaire measuring the treatment satisfaction.
   - Two advertisement texts were written, an extended and a brief version, for the purpose of patient recruitment.

3. The third study amendment (dated 29 January 2014) resulted in a revised study protocol version 5.0. The METC gave approval on 16 June 2014. The amendment contained the following change:

- The primary outcome of this study in patients with chronic pancreatitis is integrated with another clinical study in patients with postsurgical pain that has an identical treatment scheme and exactly the same outcome parameters, titled: “The analgesic efficacy of Δ9-THC (Namisol®) in patients with persistent postsurgical abdominal pain: A randomized, double blinded, placebo-controlled, parallel design” (HEEL-2011-03; NL39962.091.12). Therefore, the analgesic efficacy of Namisol® will be evaluated in patients suffering from chronic abdominal pain resulting from two subpopulations: chronic pancreatitis or postsurgical pain.

4.2. Ethical Conduct of the Study

The study was conducted according to the principles of the Declaration of Helsinki (October 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and Good Clinical Practice (GCP) guidelines.

4.3. Patient Information and Consent

Subjects were given oral and written information about the study. After the patient gave written informed consent to participate in the study, a medical screening took place to assess eligibility. The subjects’ general practitioner was notified about study participation.

5. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Sponsor
Radboud university medical center, Nijmegen, the Netherlands.

Financial Support:
The researchers are supported by a grant of the European Union, the European Fund for Regional Development (EFRO, 'Here is an investment in your future'), and cooperate with Echo Pharmaceuticals in a consortium conducting several investigator-initiated phase 2 drug studies with Namisol. The researchers have not received any payments from Echo Pharmaceuticals.

Study sites and Investigators
The study was conducted at the department of surgery of the Radboudumc, Nijmegen, the Netherlands.

The principal investigator was prof. dr. H. van Goor and the coordinating investigator was M. de Vries (Radboudumc). A list of the investigators with their affiliations, their role in the study, and the qualifications (curriculum vitae) of prof. dr. H. van Goor are provided in Appendix A.

Monitoring
The study was monitored by qualified and trained staff from the Clinical Research Centre Nijmegen (CRCN) Radboudumc, Nijmegen, the Netherlands.

Data management and Statistics
Data management was performed at the Radboudumc, Nijmegen, the Netherlands under the responsibility of Clinical Research Centre Nijmegen (CRCN), Radboudumc, Nijmegen, the Netherlands.

Statistical data analysis was performed by the trial statistician dr. A.R.T. Donders, department of epidemiology, biostatistics and health technology assessment, Radboudumc, Nijmegen, the Netherlands.

Drug Safety Monitoring Committee (DSMC)
No DSMC was installed. The relatively small anticipated number of subjects would have provided insufficient data for a meaningful interim analysis halfway the study.

Clinical Study Report
The clinical study report was written by M. de Vries, Radboudumc, Nijmegen, The Netherlands. The responsible biostatistician was dr. A.R.T. Donders.

Clinical Trial Supplies
All clinical trial supplies and materials were managed by Radboudumc. Assignment to treatment groups was performed by the pharmacy of the Radboudumc using a randomization scheme prepared in MS Excel.

Drug supply

Namisol tablets, prepared under GMP, were provided by Echo Pharmaceuticals, Nijmegen, The Netherlands.

Clinical Laboratory Analyses

Clinical Chemistry of samples from Radboudumc was performed by the laboratory of the Radboudumc, Geert Grooteplein 10, 6525 GA, Nijmegen, The Netherlands.

Pharmacogenetic blood analyses were performed by the department of Human Genetics of the Radboudumc, Nijmegen, The Netherlands.

Pharmacokinetics blood analyses were performed by Analytical Biochemical Laboratory (ABL), Assen, the Netherlands.

6. INTRODUCTION AND RATIONALE

CP is an inflammatory disease of the pancreatic gland characterized by abdominal pain, repeated episodes of acute pancreatitis, and fibrotic destruction of the organ, resulting in irreversible morphologic changes that typically cause exocrine and endocrine insufficiency.(1-5) Studies from the United States and Northern European countries reported incidences of 4.1 - 8.6 CP patients per 100.000 inhabitants per year.(6-9) Hospital admissions peak in the 35–54 year aged group of CP patients.(6) Besides, a male predominance exists, with males about three to four times more likely to be affected by CP than females. Excessive alcohol consumption is reported to be the most frequent cause of CP in industrialized countries. It is estimated that in 60-70% of patients with CP alcohol use preceded onset of the disease.(10)

The most important symptom of CP is abdominal pain, that is present in 80-90% of patients along evaluation of the disease.(11) Pancreatic pain is described by most patients as severe dull epigastric pain, eventually radiating to the back. The pain is often recurrent, intense and long-lasting. The pathogenesis of pain in this disorder is poorly understood and its treatment has been largely empirical, often consisting of surgical or other invasive methods, with an outcome that is variable and frequently unsatisfactory.(12) Therefore, pancreatic pain frequently results in a poor quality of life, and may be associated with malnutrition, narcotic addiction and major socio-economical problems.(13) In addition, a recent study showed a decline in cognitive performance in chronic pancreatitis patients.(14)

Neuropathic pain mechanisms in CP

The pain mechanisms in CP are incompletely understood and multifactorial. So far, the following causes have been suggested: (1) increased intrapancreatic pressure within the pancreatic duct or parenchyma resulting in tissue ischemia; (2) inflammation in the pancreas; (3) extrapancreatic causes of pain such as bile duct and duodenal stenosis due to extensive pancreatic fibrosis and inflammation, and (4) alterations in pain processing, with peripheral causes including an increase in nerve fibers and neurogenic inflammation(15), and central causes including central sensitization and somatotopic reorganization.(16, 17) Because underlying pain mechanisms are poorly understood, treatment is often empirical and insufficient.

Peripheral mechanisms

Histological findings in the pancreas in patients with pain due to CP have revealed an increase in the number and diameter of pancreatic nerve fibers and in the amount of neurotransmitters. These findings are also seen after neuronal lesions in other tissues and have supported the theory that nerve damage plays a key role in the pain pathogenesis.(18) Support for a neuropathic component of the pain of chronic pancreatitis is also found in clinical observations, where the pain is typically described as largely constant background pain with shooting, burning and lancinating episodes that may mimic neuropathic pain.

Central mechanisms

Nerve damage is associated with characteristic changes in central pain processing, including supraspinal central sensitization, altered central somatotopy and pro-nociceptive pain modulation.(19, 20) Similar alterations to central pain processing are also seen in chronic pancreatitis patients. Thus patients with pain due to CP or PSP show spread of hyperalgesia (i.e. an increased pain sensitivity(21)) to non-damaged tissues, ultimately manifesting as generalized hyperalgesia as a sign of supraspinal (cortical) sensitization.(16) More direct evidence of central somatotopy has been provided by EEG studies in pancreatitis patients.(17) Furthermore, first evidence is now available demonstrating activation of descending inhibition in early CP patients, and loss of diffuse noxious inhibitory control (DNIC) in more advanced CP patients.(22) It should be noted in this context that when opioid treatment becomes less effective the more central sensitization an individual has.(23) Thus there is a clear need for alternatives (or adjuvants) to opioid treatment in patients with chronic abdominal pain.

Current pain management

Initial drug treatment of CP consists of low fat diet and non-narcotic analgesics, which can be supplemented by oral pancreatic enzymes and proton pump inhibitors. Currently, if an acceptable level of pain relief is not obtained with these drugs, opioids primarily remain for the management of pain. Opioids have a number of well-known adverse effects including elevation of smooth muscle tone (affecting gastrointestinal motility), toxicity in the central nervous system, induction of addiction, and opioid-induced hyperalgesia.(24, 25) Chronic administration of opioids, frequent in patients with CP, can result in decreased pain thresholds and produce opioid-induced hyperalgesia. Opioid-induced hyperalgesia is a paradoxical effect, in that opioid therapy enhances or exacerbates pre-existing pain, while it is originally prescribed as analgesic.(24, 25) This unintended and undesirable consequence of prolonged opioid exposure is likely the result of neural plasticity of the nervous system.(25) Furthermore, evidence for central neuroplastic findings and strong descending inhibition, which resembles the pain mechanisms in neuropathic pain have been found in recent studies.(26, 27) Finally, a negative association is found between the number of opioid users in a research population and the success rate of a subsequent surgical procedure.(28),(29) This suggests that the chance for successful surgical treatment is reduced once a patient takes opioids on a chronic basis. Therefore, it is desirable to avoid prolonged opioid prescription, and alternative analgesics in the treatment pain are highly desirable.

Alternatives to conservative medical treatment exist in the form of nerve blockade, lithotripsy and surgical treatment. However, results from studies of non-medical treatment modalities are equivocal and non-medical treatment is only applicable in a minority of patients. Therefore, medical analgesic therapy must still be considered as the first choice in the management of painful chronic pancreatitis.(30)

Analgesic efficacy of Δ9-THC

Delta-9-tetrahydrocannabinol (Δ9-THC) is the most abundant cannabinoid from the plant Cannabis sativa, and has been used to treat pain for many centuries. THC induces

pharmacological effects by binding non-selective to cannabinoid receptors. Two cannabinoid receptors have been identified, CB1 and CB2.(31, 32) CB1 receptors are localized to the central nervous system (CNS) and the periphery. CB1 receptors are densely found in brain areas associated with pain processing, including the periaqueductal gray (PAG), rostral ventromedial medulla (RVM), thalamus, amygdala, and cortex.(33) They are also concentrated in the superficial layers of the spinal dorsal horn, and found in the dorsal root ganglion (DRG), from which they are transported to both central and peripheral terminals of primary afferent neurons.(34-36) These areas provide peripheral, spinal, and supraspinal targets through which cannabinoids could modulate pain.
CB2 receptors are expressed in high quantities in human immune tissues and cells, e.g. in the spleen, tonsils and leucocytes. The CB2 receptor was originally believed to be restricted to the periphery, although they may be present neuronally in areas related to pain. CB2 receptor protein has been reported at low levels in the DRG, brainstem, thalamus, PAG, and cerebellum of naive rats.(37, 38)
While in animal studies, using either acute or chronic pain models, significant analgesic and antihyperalgesic effects could clearly be demonstrated, the role of cannabinoids in human is less obvious.(39) The (weak) analgesic effects in acute human pain models were accompanied by hyperalgesic effects, suggesting an cannabinoid induced sensitization.(40) In contrast, the analgesic effects of cannabinoids in chronic pain states seem to be more promising, given a significant pain reduction in the majority of these studies. Noyes et al. found progressive pain relief with increasing doses of THC, until 20 mg, in patients with chronic cancer pain.(41) In another study in patients with cancer pain, it was shown that the analgesic effect of doses of 10 and 20 mg THC is equivalent to doses of 60 and 120 mg codeine, respectively.(42) Despite these scientific indications, and a long history of medicinal cannabis use in the treatment of pain, the analgesic properties of Δ9-THC are indefinite and need to be investigated more extensively. Particularly the efficacy of Δ9-THC in the treatment of persistent abdominal pain need to be investigated, since this was not done before in this research population.

The efficacy of dronabinol (isomer of Δ9-THC) as an adjuvant treatment for chronic pain patients to opioid therapy was assessed by Narang et al.(43) Their results showed that patients who received dronabinol (10 mg or 20 mg) experienced decreased pain intensity and increased satisfaction compared with placebo. In an extended open-label titrated trial of dronabinol as add-on medication to patients on stable doses of opioids, titrated dronabinol contributed to significant relief of pain compared with baseline. Thus, the use of dronabinol was found to result in additional analgesia among patients taking opioids for chronic non-cancer pain. Interestingly, an animal study showed that a brainstem circuit that contributes to the pain suppressing effects of morphine is also required for the analgesic effects of cannabinoids.(44) Therefore, it was suggested that cannabis might be useful to treat pain if it has synergistic interactions with opioid analgesics or if its use improves the efficacy of pain treatment in patients with a tolerance to opioids.(43) As mentioned earlier, tolerance and adverse effects to opioids are major problems in especially CP patients. A synergistic interaction may reduce the opioid use in these patients and improve the efficacy of pain treatment. In addition, opioids and THC show

different side effect profiles, which make a combined medical treatment of both attractive.

Namisol®

Patients who take medicinal cannabis these days, usually take in THC by means of smoking cannabis. Smoking is known to produce a reliable pharmacokinetic profile, however it has some obvious disadvantages. First, smoking marihuana may be a boundary for patients who have never smoked before. Furthermore, cannabis contains a mixture of compounds, some of which are noxious and part of the active substances is lost by heat. To bypass such problems, methods have been developed to purify THC from cannabis. The present existing capsules or sprays containing THC, e.g. dronabinol or sativex, show a high variability in exposure to THC and its metabolites, resulting in considerably unreliable medicines. The development of Namisol®, a new potential analgesic, provides an oral alternative in the form of a tablet with less inter individual variability.

Namisol® is a tablet containing the psychoactive substance Δ9-THC. The metabolism of Δ9-THC mainly occurs in the liver by cytochrome P450 enzymes CYP2C9, CYP2C19 and CYP3A4. THC is rapidly converted to 11-hydroxy-delta 9 –THC (11-OH-THC). This metabolite is known to be at least equipotent to THC and therefore THC is not solely responsible for the pharmacodynamic response. 11-OH-THC is further metabolized into 11-Nor-9-carboxy-THC (THC-COOH) which is reported to have anti-inflammatory and analgesic properties. Only negligible amounts of THC are excreted as unchanged THC. Of the absorbed THC, most is excreted as metabolites in faeces (more than 55%) and in urine (approximately 30%). THC-COOH is mainly excreted in urine, and the major metabolite identified in faeces is 11-OH-THC. There is no indication of significant sex differences in Δ9-THC metabolism, disposition and kinetics.(45)
Although THC is well absorbed, oral bioavailability is low and variable, probably due to extensive first-pass metabolism. Namisol® is a tablet developed for decreasing the pharmacokinetic variability and improving patient convenience. A recent conducted phase I study in healthy volunteers with oral Namisol® (5 mg, 6.5 mg and 8 mg) showed a short time to reach maximal THC concentration (tmax= 39-56 min) and a short terminal half-life of Namisol® metabolites (t1/2term= 6-19 hours),(46, 47) compared to previous studies using oral THC (tmax= 60-168 min; t1/2term= 25-35 hours).(48) Therefore, Namisol® is expected to give quicker and easier to regulate effects compared to other current clinically used oral cannabinoids.

The adverse consequences of prolonged opioid use, including addiction, tolerance and opioid induced hyperalgesia, call for an alternative medical treatment, as mentioned earlier. THC has been shown in previous studies to be a promising analgesic.(49) The development of Namisol® provides the opportunity to test the analgesic potential of THC in a favourable administration route. In this study, we aimed to investigate the analgesic efficacy and safety of Namisol® of a 52 days step-up treatment period.

7. STUDY OBJECTIVES

7.1. Primary Objective

- To investigate the analgesic efficacy, measured by a visual analogue scale (VAS) score, of a stable dose treatment Namisol® in CP patients suffering from chronic abdominal pain.

7.2. Secondary Objective

- To investigate the efficacy of a stable dose treatment Namisol® on changes in pain experience (Izbicki), anxiety and depression (HADS), general health (SF-36), pain catastrophizing (PCS), global impression of change (PGIC), pain related anxiety (PASS), appetite level (Apple) and treatment satisfaction (TSQM v. II) in CP patients suffering from chronic abdominal pain.
- To evaluate the safety and tolerability of a stable dose treatment Namisol® in CP patients suffering from chronic abdominal pain.
- To evaluate the pharmacokinetics (PK) of a stable dose treatment Namisol® in CP patients suffering from chronic abdominal pain.
- To evaluate (undesirable) pharmacodynamic (PD) effects of a stable dose treatment Namisol® of Δ9-THC in CP patients suffering from chronic abdominal pain.
- To investigate the effect of a stable dose treatment Namisol® on experimental pain mechanisms (measured by EEG, QST, and DNIC) in CP patients suffering from chronic abdominal pain.

8. INVESTIGATIONAL PLAN

8.1. Overall Study Design and Plan - Description

Current study used a randomized, double-blind, placebo-controlled, parallel design. Namisol® with standardized THC content or identical matching placebos were administered orally to evaluate the analgesic properties of Namisol® during a 50-52 days add-on treatment. An overview of measurements and visits is shown in flowchart A.

First of all, potential participating patients were invited for a screening visit (visit 1). After informed consent was obtained, several screening tests were conducted according to the flowchart. Patients were included and randomized when they fulfilled the selection criteria. The treatment phase started 7-35 days after this screening visit.

After screening, the study consisted of two phases (figure 1):

Step-up phase:
In this phase, patients visited the outpatient clinic on two occasions. Baseline parameters were collected according to flowchart A on day 1 (visit 2). Thereafter, patients administered the first dose of study medication in the presence of the investigator, starting with 3 mg. Each patient was observed for at least 2 hours after the first intake, and received the study medication for the first 15 days.

On study day 4-5, patients were called in order to identify all symptoms and possibly related adverse events. The investigator evaluated the tolerability in consultation with the patient. The treatment was considered as tolerable, when both patient and investigator accepted the (severity of) adverse events. If tolerable, the dose was increased on day 6 to 5 mg TID, and if not, the patient was withdrawn.
The same procedure was conducted on day 9-10, when the tolerability of 5 mg TID was evaluated. When 5 mg TID dosage appeared to be tolerable for the patient, the dosage was further increased to 8 mg TID starting on day 11. The dosage could be tapered to 5 mg TID, when 8 mg appeared to induce unacceptable adverse events.

The patient visited the outpatient clinic on day 15 for several measurements according flowchart A (visit 3). Patient and investigator evaluated the tolerability of 8 mg TID, and decided whether to continue with 8 mg TID or, if necessary, taper to 5 mg TID. In case the patient did not tolerate 5 mg TID, the patient was withdrawn from the study and replaced.

Stable dose phase:
For a period of approximately 6 weeks (day 11-(50-52)) a stable dose of 8 mg TID was prescribed, unless the patient tolerated a maximum of 5 mg TID. This resulted in a maximum daily intake of 24 mg THC. At the end of this 6 week treatment, patients visited the outpatient clinic for post measurements at day 50-52 (visit 4). Patients were called on day 21-23, 28-30, 38-40 and 59-61 (follow-up) in order to evaluate any adverse events.

In the end, study participation resulted in 4 visits and at least 5 telephone interviews. All visits took place at the outpatient clinic of the Radboud University Medical Centre.

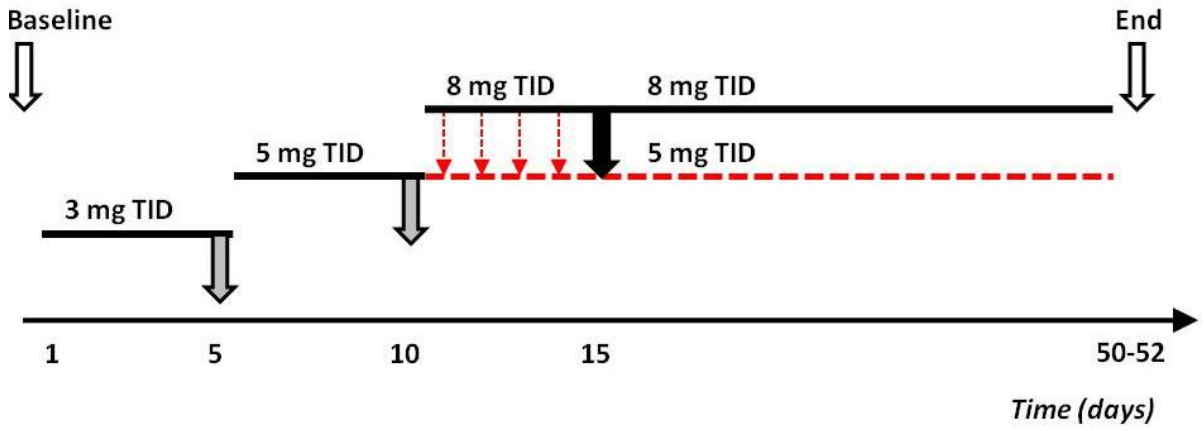

Figure 1: Study design. After a baseline measurement, patients administrated either Namisol® or placebo Namisol® of 3 mg TID from day 1 to 5. At day 5, tolerability was evaluated. The dosage of day 6 to 10 was increased to 5 mg TID or, when not tolerated, the patient was withdrawn. On day 10, the tolerability was evaluated again. From day 11 to 15, the dosage was further increased to 8 mg TID. This dosage could be tapered to 5 mg TID, when 8 mg appeared to induce unacceptable adverse events (red arrows). At day 15 the tolerability was evaluated again. If tolerable, patients proceeded with 8 mg TID till day 52, but if not, the dosage was reduced to 5 mg TID till day 52.
Grey filled arrows represent decision points I en II: increased dosage or withdrawal. Black filled arrow represents decision point III: continue 8 mg TID, taper to 5 mg TID, or withdrawal. Red dotted line represents the permitted dose adjustment of minimal 5 mg TID. Black lines represent the preferable dosage route.

8.2. Discussion of study design, including the choice of control groups

Patients with abdominal pain resulting from CP were recruited from the Radboud University Medical Centre. The pain was considered as severe enough for medical treatment, despite endoscopic, surgical or medical interventions so far. Namisol® or placebo Namisol® was administered as an add-on medication. Thus patients kept using their own (analgesic) medication, including opioids, during the entire study period.

Patients with exocrine and/ or endocrine failure due to CP were not excluded, despite the heterogeneous consequences for the research group. Opioid and non-opioid users were equally distributed in the Namisol® or placebo arm during the randomization procedure. Non-opioid users did not take opioids on a regular basis for the past 2 months on the day of screening. Furthermore, patients included may have received different treatments for the pain in the past, including surgery, and may had various severity, duration or causes of CP.

8.3. Selection of Study Population

8.3.1. Population Base

The planned study population consisted of 68 subjects with chronic abdominal pain resulting from chronic pancreatitis.

8.3.2. Inclusion Criteria

1. Patient has confirmed CP.
2. Patient suffers from chronic abdominal pain typical for pancreatitis, meet the criteria for chronic pain according ISAP (intermittent or persistent pain on a daily basis in at least 3 months)(50), and consider their pain as severe enough for medical treatment (average NRS ≥ 3).
3. Patient is 18 years or older on the day the informed consent form will be signed.
4. Patient takes stable doses of analgesics for the past 2 months. Stable dose intake is defined as a daily equivalent sum of analgesics according medical prescription within a small deviation range as judged by the investigator.
5. Patient is willing and able to comply with the scheduled visits, treatment plan, laboratory tests and other trial procedures.
6. Patient is able to speak, read and understand the local language of the investigational site, is familiar with the procedures of the study, and agrees to participate in the study program by giving oral and written informed consent prior to screening evaluations.

8.3.3. Exclusion Criteria

1. Patient used cannabinoids (by smoking cannabis or oral intake) on a daily basis in the past three years.
2. Patient has an indication for a pain treatment other then medication.
3. Patient does not feel a pinprick test in the lower extremities, due to affected sensory input (e.g. neuropathy as a result of diabetes mellitus).
4. CP patient has a body mass index (BMI) above 33,0 kg/m2.
5. Patient has (a history of) a significant medical disorder that, in the opinion of the investigator, may interfere with the study or may pose a risk for the patient.
6. Patient uses any kind of concomitant medication that, in the opinion of the investigator, may interfere with the study or may pose a risk for the patient (e.g. HIV antivirals).
7. Patient does not tolerate oral intake of medication or liquids, or is refrained from oral intake because of medical reasons.
8. Patient takes amitriptyline on a daily basis during the course of the study.
9. Patient demonstrates clinically relevant deviations in the electrocardiogram (ECG) at screening.
10. Patient has an actual moderate to severe renal impairment as judged by the investigator.
11. Patient has an actual moderate to severe hepatic impairment as judged by the investigator.

12. Patient has a presence or history of major psychiatric illness as judged by the investigator.
13. Patient has experienced an epileptic seizure in the past.
14. Patient demonstrates at screening 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.
15. Patient demonstrates a positive urine drug screen at screening visit for THC, cocaine, MDMA, and amphetamines.
16. Patient demonstrates an active hepatitis B, hepatitis C or HIV infection.
17. Patient has a history of sensitivity / idiosyncrasy to THC, compounds chemically related to these compounds, or to any other related drug used in the past.
18. Patient has a known or suspected lactose intolerance.
19. Female patient is pregnant (childbearing potential must have a negative pregnancy test prior to each study day) or breastfeeding during the course of the study.
20. Patient intends to conceive a child during the course of the study.
21. Patient participated in another investigational drug study within 90 days prior to the first dose or participated in more than 2 investigational drug studies in the last year (except previous Namisol® trial).
22. Patient has a clinical significant exacerbation in illness within two weeks before participating in this study.
23. Patient is unwilling or unable to comply with the lifestyle guidelines.

8.3.4. Prohibitions and restrictions

1. Patient is not allowed to use any cannabis from screening onwards until the last trial related activity/the end of the last treatment.
2. Patient has to take their regular medication, including painkillers, according prescription during the entire study period.
3. Patient may not consume products containing alcohol 24 hours before visit 2, visit 3 and visit 4.
4. Patients are not allowed to eat or drink caffeine containing products from 6 hours before visit 2, visit 3 and visit 4.
5. Patient should be spare with consuming beverages containing quinine (e.g., tonic water, bitter lemon, bitter alcoholic beverages containing quinine) during the entire study period (maximal one glass a day).
6. Patient should be spare with consuming grapefruit and grapefruit juice during the course of the study (maximal one glass or one piece a day).
7. Patient should be spare with consuming alcohol during the course of the study (maximal two standard glasses a day).
8. Childbearing potentials are required to use acceptable birth control measures including oral contraceptives, intrauterine devices or mechanical methods.
9. Patients are not allowed to drive during the step-up period (day 1 to 15). Thereafter, a medical doctor will assess if the patient is able to drive a car based on adverse events.

8.3.5. Removal of patients from therapy or assessment

Patients could leave the study at any time for any reason if they wish to do so without any consequences. The investigator could decide to withdraw a patient from the study for urgent medical reasons, e.g. after major exacerbation of pancreatitis, or if the patient does not comply with the lifestyle guidelines. Adverse events were followed until they had abated, or until a stable situation has been reached. Depending on the event, follow up may have required additional tests or medical procedures as indicated, and/or referral to a general physician or a medical specialist.

8.3.6. Allowed Use of Concomitant Medication

Preceding and during the entire study period, patients were asked to keep using their co-medication, including painkillers, according prescription. Thus, Namisol® was an add-on medication for patients suffering from pain despite the regular pain treatment.
Patients were asked to report additional pain medication (taken as needed) in their diary, which was subsequently recorded in the eCRF by the investigator.

8.4. Treatments

8.4.1. Treatments administered

Patients were randomly assigned to either a Namisol® or placebo treatment. Both groups (Namisol® and placebo Namisol®) followed the same dosage scheme. This means that patients in the placebo arm also received a step-up treatment and the dosage was adjusted if necessarily due to adverse events. The subject and investigator were both blinded regarding treatment.

Namisol® (3, 5 and 8 mg) were taken orally, three times daily (TID):

- 3 mg Namisol® (2 x 1.5 mg)
- 5 mg Namisol® (1 x 5 mg)
- 8 mg Namisol® (1 x 5 mg + 2 x 1.5 mg)

Placebo Namisol were taken orally, three times daily (TID)

- 3 mg placebo Namisol® (2 x 1.5 mg)
- 5 mg placebo Namisol® (1 x 5 mg)
- 8 mg placebo Namisol® (1 x 5 mg + 2 x 1.5 mg)

8.4.2. Active compound

Name :	Namisol®
Active ingredient :	Δ9-THC
Dosage form :	tablet
Strength :	1.5 mg (ECP002A/1.5; batch number 6002198/ 12P037)
	5 mg (ECP002A/5; batch number 6002197/ 12P038)
Manufacturer :	Echo Pharmaceuticals B.V.

8.4.3. Control product

Name :	Namisol® matching placebo tablets
Active ingredient :	none
Dosage form :	tablet
Strength :	1.5 mg (ECP002A/1.5P; batch number 6002199/ 12P034)
	5 mg (ECP002A/5P; batch number 6002196/ 12P035)
Manufacturer :	Echo Pharmaceuticals B.V.

8.4.4. Identity of Investigational Product(s)

The Investigational Medical Products (IMPs) Namisol® (Δ9-THC) and placebo tablets were manufactured and provided under the responsibility of Echo Pharmaceuticals. ECP002A (Δ9-THC) was available as 1.5 and 5 mg tablets (ECP002A/1.5 and ECP002A/5). IMP was produced and packed according to Good Manufacturing Practice (GMP).

The pharmacy of the UMC St Radboud prepared IMP patient kits and distributed it to guarantee blinding.

8.4.5. Method of assigning patients to treatment groups

The Radboud pharmacy determined the treatment condition by coding the study medication and placebo according to a computer-generated list of random numbers. After inclusion, each patient in the opioid subgroup received an identification number from 1 to 60, and each patient in the non-opioid subgroup from 61 to 99 in a consecutive order. Subsequently, patients were randomly assigned to either the active or placebo treatment condition using the randomization list composed of balanced blocks of 4 succeeding subjects.

8.4.6. Selection of Doses in the study

Pharmacokinetic characteristics for Namisol® were determined in the phase I study [16]: C_{max} increase was found to be dose-proportional. The average t_{max} that was found for a 5 mg was 56.0 min, for 6.5 mg 39.3 min and for 8 mg oral dosage of THC 43.6 min. In current study, 8 mg TID was administrated in order to achieve maximal effects.

8.4.7. Selection and timing of dose for each patient

The treatment scheme including dosages and timing of doses is provided in table 1. Patients were instructed to take all dosages spread over the day. Tablets were taken with at least 100 mL of water.

Table 1: Dosage scheme

	7:00H – 10:00H	**14:00H – 17:00H**	**21:00H – 24:00H**
Day 1	-	3 mg	3 mg
Day 2 - 5	3 mg	3 mg	3 mg
Day 6 - 10	5 mg	5 mg	5 mg
Day 11 - 15	8 mg*	8 mg*	8 mg*
Day 16 - (49-51)	8 mg*	8 mg*	8 mg*
Day 50-52	8 mg*	8 mg*	

* Tapering to 5 mg is allowed.

8.4.8. Blinding

The pharmacy of the Radboudumc determined the treatment order by coding the study medication and placebo according to a computer-generated list of random numbers. The study medication was labeled per patient and treatment. The randomization list for eventually unblinding in case of SUSAR reporting was kept at the hospital pharmacy, which was accessible 24 hours/day.

8.4.9. Prior and Concomitant Therapy

Patients were instructed to use their co-medication, including painkillers, according prescription. Co-medication, including dosage and time of intake were registered at screening and ongoing until the end of trial.

8.4.10. Treatment Compliance

The first IMP intake was done at the clinical site. Thereafter, patients received a batch of study medication to take home on day 1 for the period from day 1 until day 15. On day 15, the patient had to bring the remaining tablets of that period to the clinical site and received the medication for the period from day 16 till day 52. On the last study, patients returned all left over tablets. The amount of IMP that is dispensed and returned was counted twice and recorded in the patient specific drug accountability form by the staff authorized by the principal investigator or the study personnel dedicated to the study. All discrepancies between amounts of investigational products dispensed and returned were converted into missing dosages or extra administrated dosages per period.

8.5. Efficacy, Pharmacokinetics and Safety Variables

8.5.1. Efficacy and Safety Measurements Assessed and Flow Chart

The timing of assessments is shown in flowchart A.

8.5.2. Initial Subject Characteristics

Screening included demographics, medical history, concomitant medication, smoking habits, physical examination, 12-lead electrocardiogram (ECG), standard laboratory blood tests (hematology, biochemistry, virology), urine screening tests (urinalysis, drug screening and pregnancy test), and a pinprick test using a Semmes-Weinstein monofilament in order to assess the overall eligibility of the patient. Furthermore, all patients received a pain diary to fill in five days in a row, starting five days prior to the first study day.

8.5.3. Blood Sampling

Blood samples for hematology, biochemistry, and additional assessments and urine samples for urinalysis and drug screening were taken according to flowchart A.
The total volume of blood collected per patient for safety and PK samples will be approximately 155 mL (Table 2). Analyses of blood samples were conducted in a facility that operated in line with the principles of Good Laboratory Practice (GLP) and in accordance with Good Clinical Practice (GCP) guidelines. The laboratory reports were filed with the source documents. The lab report of the safety samples was interpreted, signed and dated by the investigator. Any clinically relevant abnormalities occurring during the trial, from time of first dosing onwards, was recorded in the AE section of the CRF.

Table 2: Total Blood volume collected over the entire study period

Assessment	**Number of samples**	**Amount blood/ sample (mL)**	**Total amount of blood (mL)**
THC + metabolites	10	10	100
Blood Biochemistry	2	8.5	17
Hematology	2	4	8
Serology	1	10	10
Genetics	2	10	20
		Total (mL)	**155**

8.5.4. Laboratory Tests

8.5.4.1. Pharmacokinetics of THC

Several plasma samples for pharmacokinetic (PK) analysis were taken (table 3). On day 1 and day 15, a predose sample was taken to confirm a baseline state, determine through levels and test the compliance. The PK sampling on day 50-52 was extended with 7 additional samples in order to evaluate the elimination of THC, 11-OH-THC, THC-COOH

after a long term treatment of Namisol® TID. The sampling on day 52 was performed time-locked after medication intake.

Table 3: Timing of PK samples

	Day 1	**Day 15**	**Day 50-52**
- 5 min			X
30 min			X
60 min			X
120 min			X
180 min			X
240 min			X
300 min			X
355 min (= -5 min)	X	X	X

Blood sampling for PK analysis was performed using a venflon (intravenous cannula). After each blood sample collection the cannula was flushed with approximately 5 ml of a 0.9% NaCl solution in order to maintain patency. Before each blood sample collection, approximately 4 ml of blood was discarded. After blood collection, the tubes were put immediately in ice water in aluminium foiled containers and were centrifuged within one hour for 10 minutes at 2000 G at 4 °C. The handling of THC samples was done with the lights dimmed. Thereafter, the plasma was removed and pipetted into two 1.5 mL cryotubes. The cryotubes were labeled and stored at a temperature of –80 °C until analysis. The samples were labelled with the following information: Trial number, sample number and sample day and time after dosing. During the trial, a total volume of approximately 100 ml of blood were sampled for THC, 11-OH-THC and THC-COOH.
The bioanalysis of the PK samples was performed by ABL BV, Assen, The Netherlands.

Based on the scheduled sampling times, the following PK-parameters for THC, 11-OH-THC, THC-COOH were calculated at the last study day: C_{max}, AUC_{last}, AUC_{inf}, t_{max}, λ_z, and $t_{1/2term}$.

For the PK parameters, definitions and methods of calculations are:

C_{max} Maximal plasma concentration.

AUC_{last} AUC from time of administration up to the last time point with a measurable concentration after dosing, calculated by linear trapezoidal summation.

AUC_{inf} AUC extrapolated to infinity, calculated as $AUC_{last} + C_{last}/ \lambda_z$, where C_{last} is the last measurable concentration

t_{max} Time to reach the maximal plasma concentration.

λ_z Elimination rate constant, determined by linear regression of the terminal points of the ln-linear plasma concentration-time curve.

$t_{1/2term}$ Terminal elimination half-life, defined as 0.693/ λ z.

Non-compartmental analysis to determine plasma PK parameters was performed using

the WinNonlin modeling and analysis software (version 2.1 a; Pharsight Inc., Apex, NC). The maximum plasma concentration (C_{max}), the time to reach C_{max} (T_{max}), and the AUC from 0 up to the last measurement (AUC_{0-6h}, using the linear log trapezoidal rule) were calculated from the individual plasma concentration-versus-time profiles. The terminal half-life ($t_{1/2}$) was calculated only if there were two or more points (excluding C_{max}) in the elimination phase of the plasma concentration–time curve with r^2>0.80. For that reason, several patients were excluded from this part of the analysis for THC, 11-OH-THC and THC-COOH. Subsequently, the areas under the plasma concentration curves extrapolated to infinity (AUC_{inf}) were calculated using the linear log trapezoidal rule and extrapolation to zero.

8.5.4.2. Pharmacogenetics

Genotyping of cytochrome P450 enzymes CYP2C9 and CYP2C19 was performed in order to investigate to which extent the variation in pharmacokinetics of Δ9-THC could be explained by genetic polymorphisms. Two variants in genetic CYP2C9 polymorphisms (CYP2C9*2 and CYP2C9*3) and three variants in genetic CYP2C19 polymorphisms (CYP2C19*2, CYP2C19*3 and CYP2C19*17) were genotyped.

8.5.4.3. Haematology

The following assessments were performed at screening and at the last study day: Hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular hemoglobin (MCH), hemoglobin distribution width (HDW), red cell count (RBC), red cell distribution width (RDW), total white cell count (WBC), leukocyte differential count and platelet count. No reference values exist for HDW and RDW.

8.5.4.4. Biochemistry

The following assessments were performed at screening and at the last study day: Sodium, potassium, calcium, inorganic phosphate, total protein, albumin, glucose, creatinine, uric acid, total bilirubin, conjugated bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GT), lactate dehydrogenase (LDH), and creatine phosphokinase (CPK).

8.5.4.5. Virology

At screening, serum HIV-1 and optional HIV-2 confirmation test was performed, Furthermore, blood tests were performed to test for hepatitis B infection (confirmed by hepatitis B surface antigen), and hepatitis C infection (confirmed by hepatitis C virus antibody) at trial screening.

8.5.4.6. Urinalysis

At screening and follow-up, urinalysis were performed by dipstick for leucocytes, blood, nitrite, protein, urobilinogen, bilirubin, pH, specific gravity, ketones, glucose. If abnormal, microscopic examination for WBC, RBC, and casts was considered.

8.5.4.7. Urine drug screening

At screening visit and at the beginning of each study day, an additional urine sample was provided for drug screening. Urine was tested for the current use of cocaine, amphetamine, methamphetamine, cannabis (THC), methadone, opiates, phencyclidine, barbiturate, benzodiazepine, and tricyclics.

8.5.4.8. Urine pregnancy test

At screening and on each study day, a pregnancy test was conducted in potential childbearing women by a HCG urine test.

8.5.5. Efficacy

8.5.5.1. VAS Pain

A visual analogue scale (VAS) was used in order to quantify the subjective pain intensity. Patients were asked to mark the average, minimal and maximal experienced pain in a diary. They were instructed to fill in this diary daily in the evening, starting five days before the first medication intake until the last study day as shown in flowchart A. The boundaries of these lines were "no pain" on the upper left site and "unbearable pain" on the upper right site. The score was determined as the distance from the left extreme to the patients' mark. Using a millimeter scale to measure the score provides 101 levels of pain intensity. Identical scales were used in all pain measurements.

8.5.6. Pharmacodynamics

8.5.6.1. Body sway

The body sway meter allows measurement of body movements in a two dimensional plane, providing a measure of postural stability. Left-right (roll) and anterior-posterior (pitch) postural oscillations were measured using a gyroscope-based measurement system (SwayStar™, Balance International Innovations GmbH, Switzerland), which was attached to the waist of the patient. Patients stood, without shoes, as motionless as possible in a standardized base of support with their arms hanging at both sides of their body. Body sway was measured according the flowchart for one minute with eyes open and one minute with eyes closed. During the task with eyes open patients were asked to fixate at one point. Subsequently, the patient will be asked to stand on one leg of his choice, in order to provoke balance difficulties. The patient has to stay in balance for 30 seconds.
The computerized measures used for analysis reflect the 90% range roll and pitch excursion in degrees from the centre of gravity.

8.5.6.2. Heart rate

Heart rate and blood pressure, measured in sitting position after at least 1 minute rest, was recorded as safety and pharmacodynamic parameter as indicated in the flowchart using an

automatic blood pressure device.

8.5.6.3. Questionnaires

The timing of questionnaires within the study period is shown in flowchart A.

8.5.6.3.1. Izbicki

The Izbicki is a pancreatitis-specific pain questionnaire, comprising a composed pain score of actual pain experience and use of analgesics.(51) This questionnaire was exclusively used in CP patients.

8.5.6.3.2. Patient Global Impression of Change (PGIC)

The Patient Global Impression of Change (PGIC) is a 7-point scale, from much improved to much worse, on which patients rate any change in their overall status they had experienced since beginning study medication.(52) The first question was: my pain status in last week is…". The second question was; "my pain status at this moment compared with before the start of study treatment is…".

8.5.6.3.3. Pain Catastrophizing Scale (PCS)

Pain catastrophizing affects how individuals experience pain. The PCS yields a three component solution comprising ruminating ("I can´t stop thinking about how much it hurts"), magnifying (e.g. "I´m afraid that something serious might happen"), and helplessness ("There is nothing I can do to reduce the intensity of my pain").(53, 54)

8.5.6.3.4. SF-36

The RAND SF-36 is a questionnaire that measures 8 health- related domains: Physical functioning, role-physical, bodily pain, role-emotional mental health, social functioning, vitality/fatigue and general health. Elevated scores on the RAND SF-36 represents a more favourable health status.(55)

8.5.6.3.5. HADS

The hospital anxiety and depression scale (HADS) is a 14 –item self report questionnaire constructed to measure comorbid depression and generalized anxiety. It was developed for use in patient populations with physical illnesses. Elevated scores have a high sensitivity and specificity for a DSM-IV major depression or generalized anxiety disorder.(56) Higher scores reflect greater anxiety or depression. Scores for each subscale (anxiety and depression) can range from 0–21 with normal = (0–7), mild = (8–10), moderate = (11–14), severe = (15–21).

8.5.6.3.6. PASS

The pain anxiety symptom scale measures four aspects of pain related anxiety: 1) fear for pain, 2) cognitive anxiety, 3) flight or avoidance behavior, 4) physiological symptoms of pain. Elevated scores on this 40-item questionnaire indicate a high level of pain-related anxiety.(57)

8.5.6.3.7. VAS Bond and Lader

For the measurement of feelings corresponding to alertness, mood and calmness, a set of 16 visual analogue scales (VAS) was used, as described by Norris(58, 59) and Bond and Lader.(60) At times specified in the flowchart, the patient indicated on sixteen horizontal visual analogue scales how he/she felt. Three main factors were calculated as described by Bond and Lader:(60) alertness (from nine scores), mood (from five scores), and calmness (from two scores).

In the Bond and Lader set of visual analogue scales, the 'directions' of different lines on a form are alternated, to avoid 'habitual scoring' by subjects. To reduce mistakes among the raters, all scores were measured in millimeters, from the beginning of the line on the left side to the point where the mark produced by the subject crosses the line. Scores that should be measured right sided were recalculated during the analysis.

The VAS as originally described by Norris have been used previously to quantify subjective effects of a variety of sedative agents.(59) The Dutch version is more often employed for a variety of sedative agents and circumstances.(61) The completion of all visual analogue lines usually takes about two minutes, but this period may increase when attention is reduced (*e.g.* by drug effects).

8.5.6.3.8. VAS Bowdle

Potential subjective psychotomimetic (psychedelic) effects of psychoactive agents can be evaluated using specific questionnaires.(62) Bowdle psychotomimetic effects scores have been used to quantify the psychotomimetic effects of ketamine.(63) No validated questionnaires were available for the Dutch language and population, but a translated version of the scales originally developed by Bowdle et al. has been used in the phase I study in healthy volunteers.(47) Bowdle psychotomimetic effects scores consist of thirteen 10 cm visual analogue lines ranging from 0 (‘not at all’) to 100 mm (‘extremely’), addressing various abnormal states of mind.(63)

8.5.6.3.9. Patient Appetite Level (AppLe)

The Patient Appetite Level (AppLe) is a 7-point scale, from much improved to much worse, on which patients rate any change in their appetite they have experienced since in the last week and compared to before the study period. The AppLe is a modification of the PGIC for the evaluation of this specific aspect and not validated for this use. It is filled out at the last study visit (day 50-52).

8.5.6.3.10. Treatment Satisfaction Questionnaire for Medication (TSQM) version II

The Treatment Satisfaction Questionnaire for Medication version II (TSQM v. II) is a validated list of eleven questions covering satisfaction with medication effectiveness, side effects, and convenience.(64) A Dutch translation of the original questionnaire is used in the current study. It is filled out at the last study visit (day 50-52).

8.5.7. Exploratory parameters

All explorative outcomes as described in this Section, will be reported in an addendum to

this CSR.

8.5.7.1. EEG

Two types of cortical activity were recorded in the electroencephalogram (EEG): Spontaneous brain activity in a resting state and event related potentials (ERPs) to noxious electrical stimuli. At baseline, the spontaneous EEG was recorded during both eyes open and eyes closed. After medication intake, the spontaneous EEG was measured only in the eyes closed condition. During the measurements, the patient was sitting in a comfortable chair and no further task was given.
ERPs were extracted from the EEG by averaging similar repetitive stimuli within a stimulus block. One surface electrode was attached to the non-dominant lower arm and connected to an electric stimulator. The individual pain threshold was determined by slowly ramping the current until the pain threshold was achieved. The strength of the stimuli was obtained as 150% of the individual pain threshold. In this experiment, patients received 20 painful electric doubled stimuli delivered with an inter-stimulus interval of 5 ms and a random inter-pair interval of 7-10 sec. The onset and offset of the stimulus are communicated from the Presentation software directly into the EEG-recording software. EEG was recorded with a multichannel Acti-cap (32-channels). To ensure an optimal signal-to-noise ratio, all electrode impedances were kept under 20 kΩ. EEG was recorded with a sampling rate of 2000 Hz.

8.5.7.2. QST

The presence of secondary hyperalgesia can be measured by determining thresholds in the segmental area of the affected pancreas. The thresholds obtained remote from the affected pancreas are an indication for the presence of a more generalized form of hyperalgesia. Quantitative Sensory Testing (QST) was performed using mechanical pressure and electrical stimulation.
The pressure pain threshold (PPT) was measured unilateral at the non-dominant side. The PPT was determined by pressing an electronic pressure algometer on a muscle group at three distinct sites. The referred or segmental pancreatic site was tested by pressing the algometer paravertebral at the dorsal side of T10 dermatome. The other two areas included the distal part of the clavicle within the C5 dermatome, and the proximal part of the quadriceps muscle within the L1 dermatome. The pressure was increased at a rate of approximately 50 kPa/sec until the PPT was reached. The patient was asked to say “stop” when the pressure felt unpleasant or just painful. The probe had a surface area of 1cm2. The average of 2 repetitive assessments were calculated.
Electrical QST was measured according the same screening protocol on two areas of the body, the m. rectus femoris and m. trapezius pars medialis. Electrical QST includes measurements of electric pain thresholds (EPT) and electric wind-up response (E-WUR). All QST measurements were performed at day 1 (baseline), day 15 and day 50-52.

8.5.7.3. DNIC

Diffuse noxious inhibitory control (DNIC) is part of a descending central pain modulatory system. This pain-inhibitory system was obtained by the difference in pain thresholds

before and after a cold pressor test (CPT).
Therefore, the DNIC measurement consisted of three parts:
- PPT determination on the dominant quadriceps muscle
- CPT on the non-dominant hand
- Repetition of the PPT determination on the dominant quadriceps muscle

CPT procedure: The non-dominant hand was immersed in ice-chilled water (1.0ºC ± 0.3ºC). After 2 minutes of immersion, or sooner if the pain was considered to be intolerable, the patient was asked to remove the hand from the water. Immediately after the CPT, the patient rated the amount of discomfort on a VAS.

8.5.8. Assessment of Safety

8.5.8.1. Vital signs

Systolic and diastolic blood pressure (SBP, DBP) and heart frequency (HF) were recorded at screening and on each study day. BP and HF were assessed with an automated device consisting of an inflatable cuff and an oscillatory detection system so that measurements are observer independent. Clinically relevant cardiovascular abnormalities occurring during the trial were recorded in the Adverse Event section of the CRF.
Twelve-lead ECGs were prepared supine and examined for abnormalities by a medical doctor, at screening and on the last study day. Clinically relevant cardiovascular abnormalities occurring during the trial were recorded in the Adverse Event section of the CRF.

8.5.8.2. Adverse Events

Adverse events are defined as any undesirable experience occurring to a patient during the study, whether or not considered related to Namisol®. All adverse events reported spontaneously by the patient or observed by the investigator or his staff were recorded on AE forms on an ongoing basis from time of inclusion, after informed consent, onwards until the last follow-up telephone call. AEs were reported in a daily diary, during telephone interviews and on visit days. The investigator collected all symptoms and recoded them in MedDRA preferred terms.
All adverse events were followed until they had abated, or until a stable situation had been reached. Depending on the event, follow up may have required additional tests or medical procedures as indicated, and/or referral to a general physician or a medical specialist.

8.5.8.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation (excluded pre-planned hospitalizations);
- results in persistent or significant disability or incapacity;

- is a congenital anomaly or birth defect;
- is a new event of the trial likely to affect the safety of the patients, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

8.5.9. Endpoints of the Study

8.5.9.1. Primary study parameter

- Average pain score (VASpain) at day 49-51 (last day of diary) minus baseline (mean day -5 to -1 pre-treatment)

8.5.9.2. Secondary study parameters

- Patients demographics and clinical characteristics
- Pain diary
  - Minimal and maximal pain scores
- Concomitant pain medication
- Pharmacogenetics
  - CYP2C9 and CYP2C19
- Pharmacokinetics
  - C_{max}, AUC_{last}, $AUC\infty$, t_{max}, λ_z, and $t_{1/2term}$ for THC, 11-OH-THC and THC-COOH
- Pharmacodynamics
  - Questionnaires: Izbicki, VASBond & Lader, VASBowdle, PGIC, PCS, SF-36, HADS, PASS, Apple, TSQM
  - Body weight and supplementary feeding
  - Body Sway
- EEG
  - ERPs to noxious electrical stimuli / auditory stimuli (odd ball)
  - FFT spontaneous EEG
- QST
  - Pressure pain thresholds
  - Electric pain thresholds
  - Electric wind-up response
  - DNIC

8.5.9.3. Safety study parameters

- ECG, HF and BP
- Adverse events
- Laboratory tests

8.5.10. Appropriateness of measurements

Pain is both a sensory and emotional experience, generally associated with tissue damage, or inflammation. Pain is ultimately a perception, and not an objective bodily state. In contrast, nociception does not describe psychological pain, but is the physiological sense for perception of physiological pain. The main goal of this trial is to study the effects of Namisol® in the treatment of chronic abdominal pain. Therefore, the VAS pain is a valid and reliable measure of chronic pain intensity, and widely used in diverse adult populations.(65)

However, when treating clinical pain analgesic effects are difficult to evaluate due to a number of confounding factors. These confounders may include variable baseline pain, complaints relating to psychological factors related to the illness, as well as systemic reactions such as fever and general malaise.(66) In assessing the efficacy of analgesics in clinical trials these confounders can bias the outcome. Experimental pain models, e.g. QST, EEG, and DNIC, are without many of the above confounders and therefore a valuable tool for characterizing analgesics.(67)

8.5.11. Quality Assurance

The study was conducted in compliance with the pertaining Standard Operating Procedures and Good Clinical Practice. All research staff was trained prior to trial conduction. An electronic database, MACRO (version 4.2.4, InferMed Limited), with audit trial was used for data entry. Source document review and verification was performed on a regular basis by Clinical Research Centre Nijmegen. No internal audits have been performed.

9. STATISTICAL METHODS AND SAMPLE SIZE

9.1. Analyses (GENERAL)

Analyses and statistics will be performed using Statistical Package for the Social Sciences (SPSS version 20, SPSS inc., Chicago, Illinois, USA). All statistical tests were performed two-tailed, and the chance for type one errors was set on 5%.

9.2. Primary Efficacy Analysis

The primary outcome of this study is analgesic efficacy measured as difference in visual analogue scale (VAS) of the average pain score (VAS pain) at day 49-51 (last day of diary) minus baseline (mean day -5 to -1 pre-treatment) between placebo and Namisol® in the patients with chronic abdominal pain including chronic pancreatitis and postsurgical pain. The VAS pain was analyzed by an Analysis of Covariance (ANCOVA) that incorporates the baseline measurement score as covariate.

All participants who have received the study medication for at least 36 days were included in the efficacy analyses according to the intention to treat principle. Dropouts before day 36 were replaced and data of dropouts were excluded from further analyses of the primary endpoint.

9.3. Secondary Analysis

Secondary study parameters include patient characteristics, general descriptives, concomitant medication, pharmacogenetics, pharmacokinetics, and pharmacodynamics including questionnaires and body sway.

All variables were listed by subject and data were summarised by treatment group. The distribution of variables was assessed qualitatively, i.e. histogram plot. Normally distributed continuous variables were described using mean and standard deviation (SD). Median and interquartile values were shown in case variables were not normally distributed. Qualitative or categorical variables were described using frequencies and percentages.

The efficacy outcomes of this study were analyzed by means of an Analysis of Covariance (ANCOVA) that incorporated the baseline measurement score as covariate. This analysis allows us also to include possible moderating variables such as substudy (pancreatitis/postsurgical) and opiate user (y/n), by observing the potential interaction between for example substudy and treatment.

Safety analyses will be performed on all randomized subjects who have been administered at least one dose of Namisol or placebo.

9.4. Sample size calculation

In the initial study protocol, a sample size calculation was performed based on a previous randomized, double-blinded, placebo-controlled study with another substance, pregabalin, but in a similar group of patients with chronic pancreatitis pain. The sample size calculation was based on the average pain intensity after Namisol® of at least 1.0 cm decrease in

VASpain compared with placebo (α = 0.05, one-sided, power =0.80) and resulted in a sample size of 68 subjects.

9.5. Changes in the conduct of the study or planned analyses

The study protocol was changed several times. An overview of protocol amendments is given in section 4.1.

10. STUDY PATIENTS

10.1. Disposition of Patients

Recruitment of subjects turned out to be extremely difficult. From a total of 243 CP patients, including CP patients treated within the Radboudumc, individual registrations of patients and clinicians from other medical centers, 80 patients were identified as potentially eligible and contacted by the investigator. Several patients did not suffer from (sufficient) pain (NRS< 3) and were not eligible for that reason. The main reasons for patients to decline from participation were: a ban to drive a car during the first two weeks of the treatment, the impossibility to use Namisol® after the study treatment has ended and the burden to participate appeared to be too big for these patients.

Thirty-one patients with CP visited the outpatient clinic for a screening. Two patients turned out to be not eligible; one patient had withdrawn consent and one patient did not meet the inclusion criteria. Twenty-nine CP patients were randomized according to the flowchart in figure 2. Thirteen patients were allocated to the Namisol® treatment arm and sixteen patients were allocated to the placebo arm. In the Namisol® arm, one patient had withdrawn consent before study treatment started and four patients discontinued study treatment. Two of them due to adverse events and two patients withdraw consent. In the placebo Namisol® arm, one patient had withdrawn consent before study treatment started and one patient discontinued study treatment due to an unrelated serious adverse event. Consequently, 12 patients in the Namisol® arm and 15 patients in the placebo arm were included in the safety analyses, whereas 8 patients in the Namisol® arm and 15 patients in the placebo arm were included in the efficacy analysis.

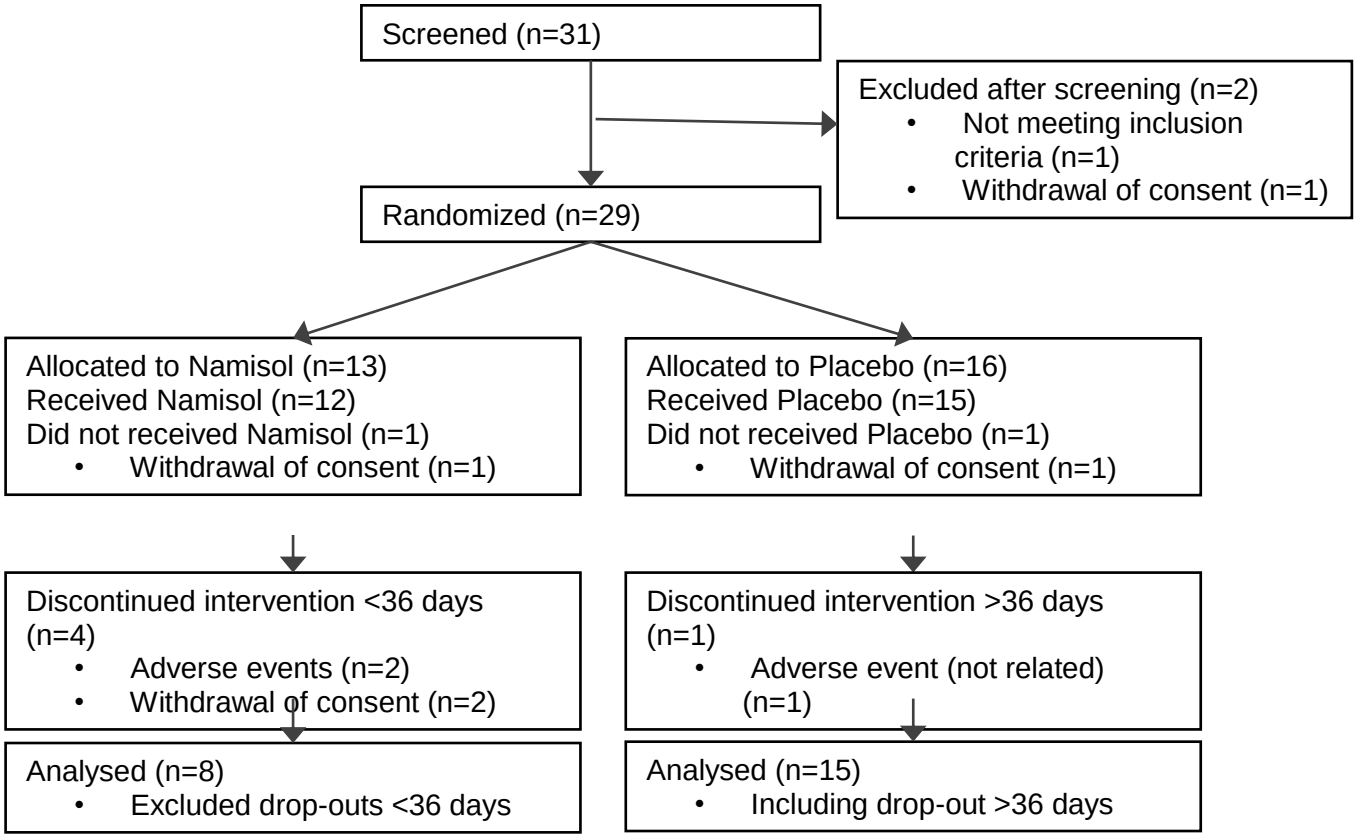

Figure 2: Participant flow chronic pancreatitis patients through the study

10.2. Protocol Deviations

All protocol deviations are reported and collected in the TMF.

Last day VASpain recoding diary

Patients were asked to mark the average, minimal and maximal experienced pain in a diary. According study protocol, the analyses of VASpain endpoints were performed until the last day of diary. However, patients were instructed to fill in this diary daily in the evening, which means that the last day of diary was 1 day prior the last study day. Therefore, all analyses of VASpain have been performed on study day 49-51 instead of day 50-52.

Rescreening of subject CP05

Subject CP05 was included after a screening visit on 12Oct12. However, the scheduled study days thereafter were cancelled due to private reasons. The subject wanted to start on a later moment. Therefore, the subject was screened for a second time on 2Aug13. The screening data collected on 12Oct12 were cancelled and the screening collected on 2Aug13 were considered as the valid data.

Label on study drug package

The packaging label of the study drug included a warning that the subject should not use any alcohol. This differs from the protocol and the patient information form where is stated that a maximum of two units alcohol per day is allowed. It was decided to inform each subject orally about this deviation.

Missing data drop-out CP12

Subject CP12 dropped-out due to an exacerbation of the CP and influenza like illness. The subject quit study treatment after day 36 and the last study day was cancelled due to continued illness. The questionnaires were sent by mail, filled in and returned. The subject returned the study medication and pain diary on a routine consultation with prof. van Goor at the outpatient clinic. Unfortunately, the study medication and as well as the pain diary were lost at the end of the same day. We did not manage to find it again.

Additional ECG subject CP14

The screening ECG of subject CP14 showed a deviating ECG. The PQ-time was prolonged, probably due to first-degree atrioventricular block. This is not clinically relevant without clinical symptoms, but for us a reason to repeat an ECG on day 15 for safety reasons. The ECG on day 15 was normal.

Screening CP09

Subject CP09 was originally screened for another study with Namisol (HEEL-2011-01), but excluded for this study. After that, the subject was informed about the current study and was willing to participate. The subject gave informed consent after 10 days and a screening was performed. However, the laboratory values from the previous screening

were still valid and thus used in order to decrease the burden of the patient.

Units QST algometer

The QST algometer was temporarily out of order and replaced by another device. In order to correct for the different settings all values measured with this device (CP25 day 15, CP62 day 15, CP26 day 1 and day 15) were divided by two.

Blood sampling for kinase

The kinase amendment was approved on 8Nov12. Subsequently, on 26Feb13 (CP12) we started with blood sampling for kinase analyses with four samples on day 50-52. That was extended with additional blood sampling on day 1 and day 15 from 10Jun13 till the end of the study.

Missing data

A few measurements could not be conducted through the occurrence of adverse events, difficulties in the execution or were accidently skipped. If a measurement was conducted or not is reported for each individual measurement and recorded in the eCRF.

Study medication of drop-outs

Drop-outs were asked to return it with their next routine appointment in the Radboudumc. or were allowed to return the residual study medication to their local pharmacy for destruction. The residual study medication of drop-outs was not counted any more.

11. STUDY RESULTS

11.1. Data Sets analyzed

For the safety analysis, 12 patients were included in the Namisol® arm and 15 patients in the placebo arm. A total of 4 patients dropped-out in the Namisol group within 36 days after the start of the trial, resulting in a total of 8 patients in the Namisol® arm. As 1 patient dropped out after 36 days after the start of the trial, all 15 patients in the placebo arm were included in the modified intention to treat efficacy analysis.

The integration of current study with a similar clinical study in patients with postsurgical pain (HEEL-2011-03) results in an evaluation in patients suffering from chronic abdominal pain resulting from two subpopulations: chronic pancreatitis or postsurgical pain. The results from this combined population are presented in appendix C.

11.2. Demographic and other Baseline Characteristics

A listing of subject demographics is shown in table 4. One subject in the placebo arm was of Asian origin. All other subjects were of Caucasian origin.
A listing of clinical characteristics is presented in table 5.

Table 4: Listing of subject demographics

		N	Mean	Median	SD	Min	Max
Chronic Pancreatitis (n=23)							
Namisol	Gender (male/female)	7/1					
	Age (years)		53,9	52,5	7,5	45,0	67,0
	BMI (kg/m2)		24,2	24,6	5,0	16,5	31,3
	Height (cm)		178,4	180,0	9,6	164,0	193,0
	Weight (kg)		76,9	76,8	17,5	49,2	101,3
Placebo	Gender (male/female)	11/4					
	Age (years)		53,9	52,0	10,3	39,0	76,0
	BMI (kg/m2)		24,3	24,9	3,8	18,0	31,9
	Height (cm)		173,3	174,0	9,9	157,0	189,0
	Weight (kg)		73,7	70,6	17,1	51,4	101,0

Table 5: Listing of subject clinical characteristics. Continuous data are expressed as mean ± SD and categorical data as numbers (n).

	Namisol	**Placebo**
Chronic Pancreatitis (n=23)		
Etiology CP		
Alcohol	6	3
Hereditary	0	1
Idiopathic	2	7
Neoplasm	0	2
Other	0	2
Smoking status		
Current smoker	6	6
Past smoker	1	6
No smoker	1	3
Concomitant medication		
Opioid user	7	12
Non-opioid user	1	3
NRS pain at screening	5.3 ± 1.7	5.9 ± 1.6

11.3. Concomitant medication

Twenty-three patients (100%) were taking analgesics for their CP, including paracetamol, NSAIDs, weak opioids such as codeine and tramadol, strong opioids such as oxycontin, fentanyl and morphine, and antiepileptics such as pregabalin. The number of patients taking one or more analgesics within each category is shown in table 6.

Patients kept their dosage constant throughout the study apart from predefined pain fluctuating medication. In line with the protocol, twenty patients used fluctuating dosages of analgesics within different categories. The total amount of fluctuating analgesics during 5 days at baseline was compared with the total amount during the last 5 days of study treatment. The number of patients who increased, reduced or kept the dosage of fluctuating analgesics equal is shown in table 7.

Table 6: Number of patients taking one or more analgesics within each category.

	Namisol	**Placebo**
Concomitant pain medication (n=23)		
None	0	0
PCM	3	12
NSAID	3	2
Weak opioids	3	6
Strong opioids	7	11
Antiepileptics	3	4

Weak opioids were defined as codeine and tramadol. Strong opioids were defined as opioid-based therapies such as oxycontin, fentanyl and morphine. Abbreviations: PCM=paracetamol, NSAID= non-steroidal anti-inflammatory drugs.

Table 7: Fluctuating analgesics during study treatment

	Namisol	**Placebo**
Fluctuating analgesics (n=20)		
Dosage increased	3	5
Dosage equal	1	2
Dosage reduced	4	3
Missing		2

11.4. Pharmacogenetics

Samples of 23 CP patients in the efficacy analysis were analyzed for genetic polymorphisms. These results are presented in table 8.
There were 14 normal and 9 intermediate metabolizers based on CYP2C9 polymorphism, and 13 normal, 7 intermediate and 3 ultra rapid metabolizers according to their CYP2C19 genotype (table 9).

Additionally, pharmacogenetic analysis was also performed in patients who dropped out when this sample was available. One sample from the two withdrawn patients due to possible related AEs was missing. The other patient (CP20) was wild type CYP2C9 being an extensive metabolizer based on CYP2C9 polymorphism, and heterozygote carrier of CYP2C19*2 and CYP2C19*17, resulting in an intermediate metabolizer based on CYP2C19 polymorphism.

Table 8: Genetic polymorphisms of CYP2C9 and CYP2C19. Data are expressed as number (n) of CP patients being wild type, heterozygous or homozygous carriers.

		Wild type (n)	Heterozygous (n)	Homozygous (n)
CYP2C9	*2 (C>T)	20	3	0
	*3 (A>C)	17	6	0
CYP2C19	*2 (G>A)	17	6	0
	*3 (G>A)	22	1	0
	*17 (C>T)	14	6	3

Table 9: Genetic polymorphisms of CYP2C9 and CYP2C19. Data are expressed as number (n) of CP patients being extensive, intermediate, poor or ultra rapid metabolizers.

	Polymorphisms	Metabolizer	N
CYP2C9	*1/*1	Extensive	14
	*1/*2, *1/*3	Intermediate	9
	*2/*2, *2/*3, *3/*3	Poor	0
CYP2C19	*1/*1, *1/*17	Extensive	13
	*1/*2, *1/*3, *2/*17, *3/*17	Intermediate	7
	*2/*2, *2/*3, *3/*3	Poor	0
	*17/*17	Ultra rapid	3

11.5. Measurements of Treatment Compliance

All patients, who dropped out due to adverse events, tapered the dosage to 5 mg TID before it was decided to quit study treatment. Thus patients who dropped out of the study did not tolerate a dosage of 5 mg TID Namisol® or matching placebo.

Actual treatment dosages of patients in the efficacy analysis are presented in table 10. One drop-out subject in the placebo arm did not taper the study medication before withdrawal. However, this subject decided to quit study treatment due to the occurrence of an unrelated serious adverse event.

Table 10: Treatment dosage schemes of patients in the intention to treat analysis

	Namisol	**Placebo**
Chronic Pancreatitis (n=23)		
Treatment according dosage scheme	8	12
Lowered to 5mg TID	0	2 (CP15, CP62)
Quit study treatment	0	1 (CP12)

A mean of 95% SD 7% of all placebo study medication was taken correctly compared with 98% SD 1% in the Namisol® treatment arm. There were no patients with a poor compliance (<75%), as measured by the amount of medication returned to the hospital after the treatment period.

11.6. Pharmacokinetic evaluation

PK samples on day 50-52 time-locked after medication intake were analysed for 8 CP patients. All subjects in the Namisol® treatment arm were using an 8 mg TID treatment regime.

The maximum plasma concentration (C_{max}), the time to reach C_{max} (t_{max}), and the AUC from 0 up to the last measurement ($AUC_{0\text{-}Last}$) using the linear log trapezoidal rule were calculated from the individual plasma concentration-versus-time profiles. The terminal half-life ($t_{1/2}$) was calculated only if there were two or more points (excluding C_{max}) in the elimination phase of the plasma concentration–time curve with r^2>0.80. One patient (CP07) was excluded from this part of the analysis for THC, two patients (CP07, CP09) for 11-OH-THC and five subjects (CP9, CP14, CP18, CP22, CP25) were excluded from this part of the analysis for THC-COOH. The areas under the plasma concentration curves extrapolated to infinity ($AUC_{0\text{-}inf}$) were calculated using the linear log trapezoidal rule and extrapolation to zero.
The exact timing of PK samples and individual PK curves for THC, 11-OH-THC and THC-COOH are presented in appendix D.

11.6.1. Trough levels

An additional trough level on day 15 was available for subject CP10 (drop-out). Trough levels on day 15 and day 50-52 are shown in table 11. Predose samples on day 1 were all below the lower limit of quantification.

Table 11: Trough levels for THC, 11-OH-THC and THC-COOH on day 15 and day 50-52

		N	Mean	Median	SD	Min	Max
Day 15	THC (ng/mL)	9	0,62	0,47	0,37	0,28	1,43
	11-OH-THC (ng/mL)	9	1,91	1,52	1,19	0,73	3,83
	THC-COOH (ng/mL)	9	94,82	90,60	29,51	49,80	134,00
Day 50-52	THC (ng/mL)	8	0,52	0,42	0,35	0,00	1,13
	11-OH-THC (ng/mL)	8	1,34	0,94	1,27	0,00	4,16
	THC-COOH (ng/mL)	8	70,59	65,25	45,71	0,00	147,00

11.6.2. Analysis of THC pharmacokinetics

Mean plasma concentration-versus-time curves of THC for 8 mg TID Namisol® as obtained on day 50-52 are shown in figure 3. Evaluation of the pharmacokinetics on an individual patient level revealed that some patients demonstrate a relatively late t_{max} accompanied with a relatively low C_{max} , which cannot be observed in the mean THC plasma concentration curves. Table 12 summarizes the calculated PK parameters of THC. A listing of individual pharmacokinetic parameters is provided in appendix D.

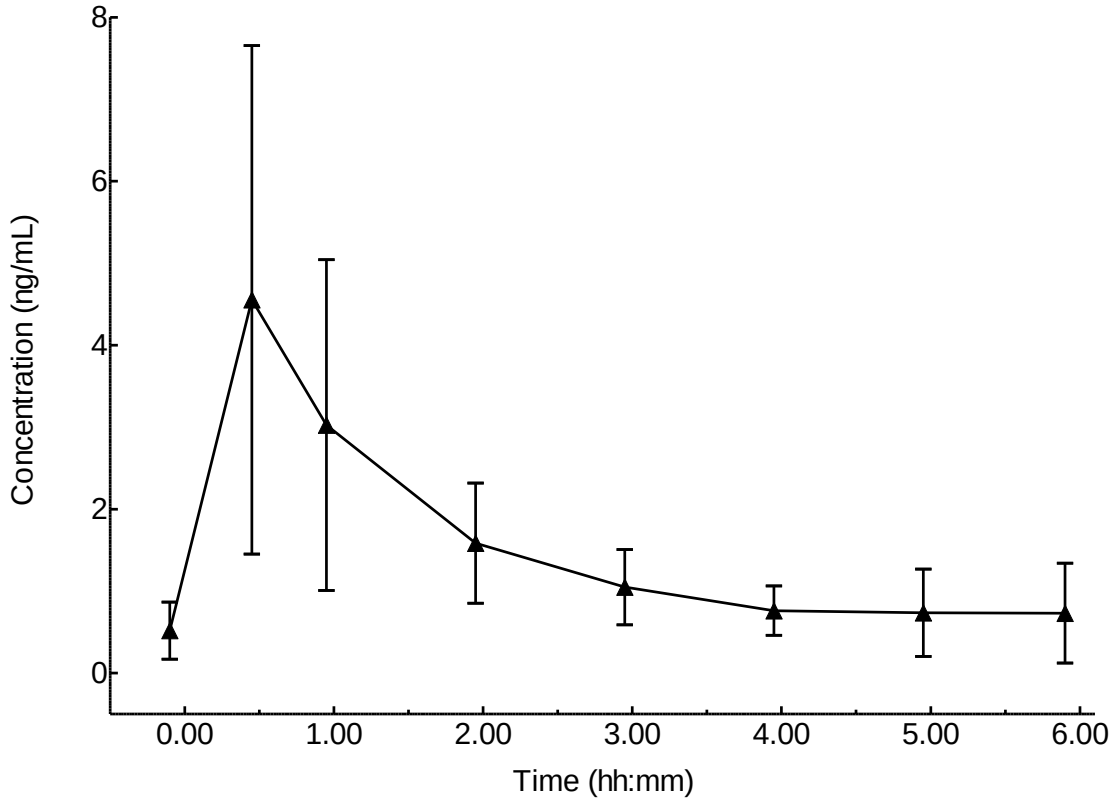

Figure 3: Mean plasma concentration curves with unilateral SD error bars of THC in chronic pancreatitis patients (n=8) taking 8 mg TID Namisol® on day 50-52

Table 12: Pharmacokinetics of THC in CP patients on day 50-52

	N	Mean	SD	Median	Minimum	Maximum
C_{max} (ng/mL)	8	5,04	2,74	5,20	1,11	9,16
t_{max} (h)	8	1,63	1,96	0,76	0,50	6,00
AUC $_{0\text{-Last}}$ (ng*h/mL)	8	8,90	2,56	9,17	4,81	12,07
AUC $_{0\text{-tau}}$ (ng*h/mL)	7	9,94	2,79	9,98	5,50	13,53
AUC $_{0\text{-inf}}$ (ng*h/mL)	7	11,12	3,02	10,76	6,21	15,60
$t_{1/2term}$ (h)	7	2,62	0,66	2,37	1,88	3,51
λ_z (L/h)	7	0,28	0,07	0,29	0,20	0,37

AUC $_{0\text{-inf}}$, AUC $_{0\text{-tau}}$, $t_{1/2term}$ and λ_z were calculated only if there were two or more points (excluding C_{max}) in the elimination phase of the plasma concentration–time curve with r^2>0.80.

Plasma concentration curves of THC are shown for extensive (normal), intermediate and ultra rapid metabolizers based on CYP2C9 and CYP2C19 polymorphism in patients taking 8 mg TID Namisol® (Figure 4 and 5). No differences were observed between metabolizer groups.

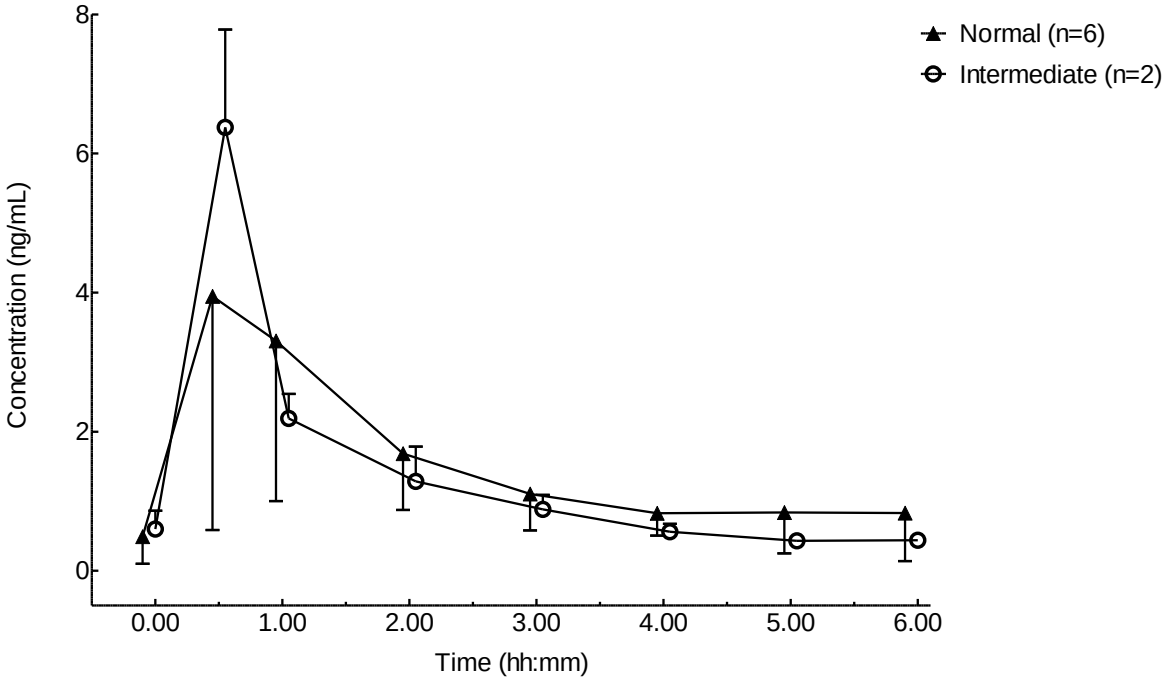

Figure 4: Mean plasma concentration curves with unilateral SD error bars of THC in chronic pancreatitis patients taking 8 mg TID Namisol® on day 50-52 subdivided in extensive (normal) (n=6) and intermediate (n=2) metabolizers based on CYP2C9 polymorphism

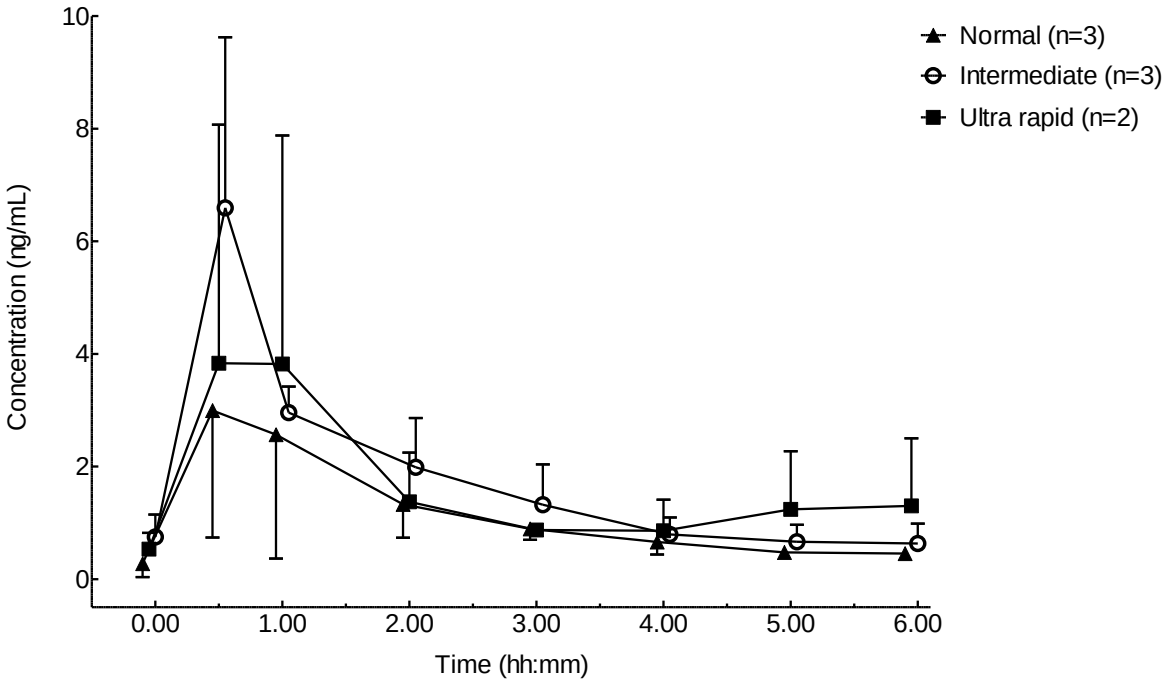

Figure 5: Mean plasma concentration curves with unilateral SD error bars of THC in chronic pancreatitis patients taking 8 mg TID Namisol® on day 50-52 subdivided in extensive (normal) (n=3), intermediate (n=3) and ultra rapid (n=2) metabolizers based on CYP2C19 polymorphism

11.6.3. Analysis of 11-OH-THC pharmacokinetics

Mean plasma concentration-versus-time curves of the active metabolite 11-OH-THC for 8 mg TID Namisol® as obtained on day 50-52 are shown in figure 6. Corresponding PK parameters of 11-OH-THC are listed in table 13.

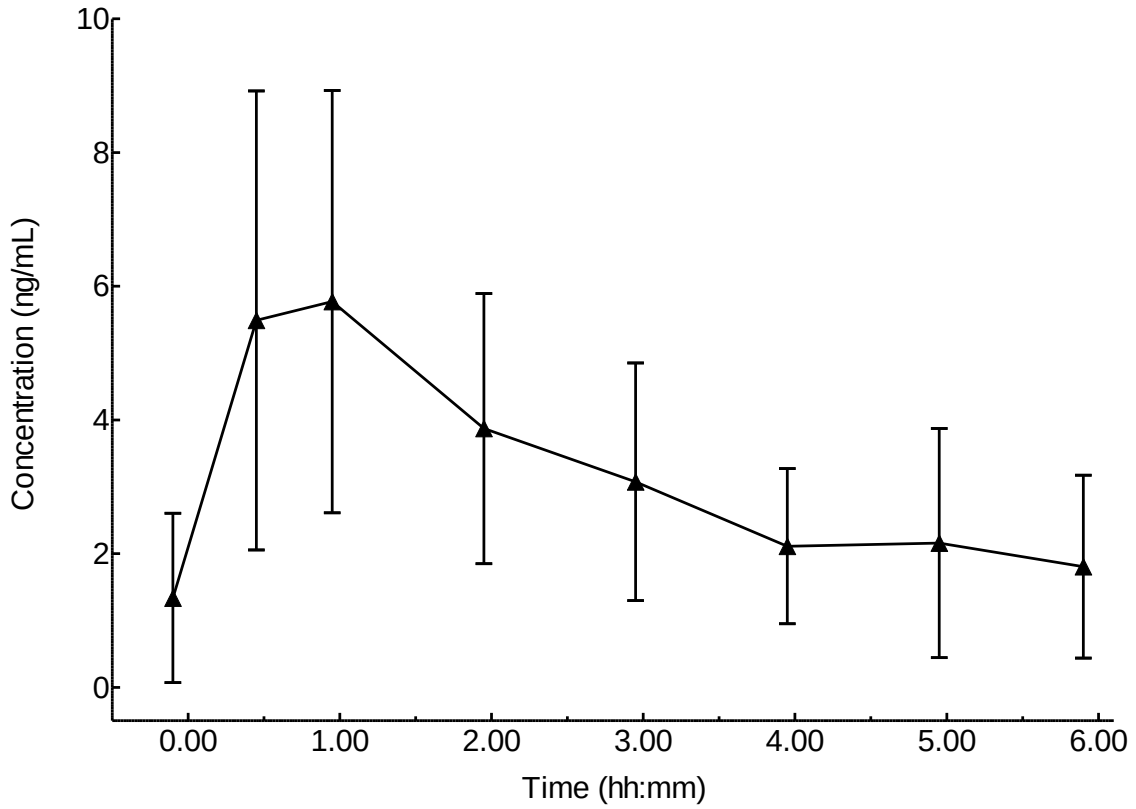

Figure 6: Mean plasma concentration curves with SD error bars of 11-OH-THC in chronic pancreatitis patients (n=8) taking 8 mg TID Namisol® on day 50-52

Table 13: Pharmacokinetics of 11-OH-THC in CP patients on day 50-52

	N	Mean	SD	Median	Minimum	Maximum
C_{max} (ng/mL)	8	6,83	3,29	7,29	2,82	11,30
t_{max} (h)	8	1,69	1,60	1,01	0,50	5,00
$AUC_{0\text{-}Last}$ (ng*h/mL)	8	19,19	8,62	18,41	9,15	35,39
$AUC_{0\text{-}tau}$ (ng*h/mL)	6	18,51	7,12	17,61	10,49	28,56
$AUC_{0\text{-}inf}$ (ng*h/mL)	6	21,04	7,94	19,83	13,30	33,22
$t_{1/2term}$ (h)	6	2,65	0,69	2,38	2,05	3,66
λ_z (L/h)	6	0,28	0,06	0,29	0,19	0,34

$AUC_{0\text{-}inf}$, $AUC_{0\text{-}tau}$, $t_{1/2term}$ and λ_z were calculated only if there were two or more points (excluding C_{max}) in the elimination phase of the plasma concentration–time curve with $r^2>0.80$.

11.6.4. Analysis of THC-COOH pharmacokinetics

Mean plasma concentration-versus-time curves of metabolite THC-COOH for 8 mg TID Namisol® as obtained on day 50-52 are shown in figure 7. Corresponding PK parameters of THC-COOH are listed in table 14.

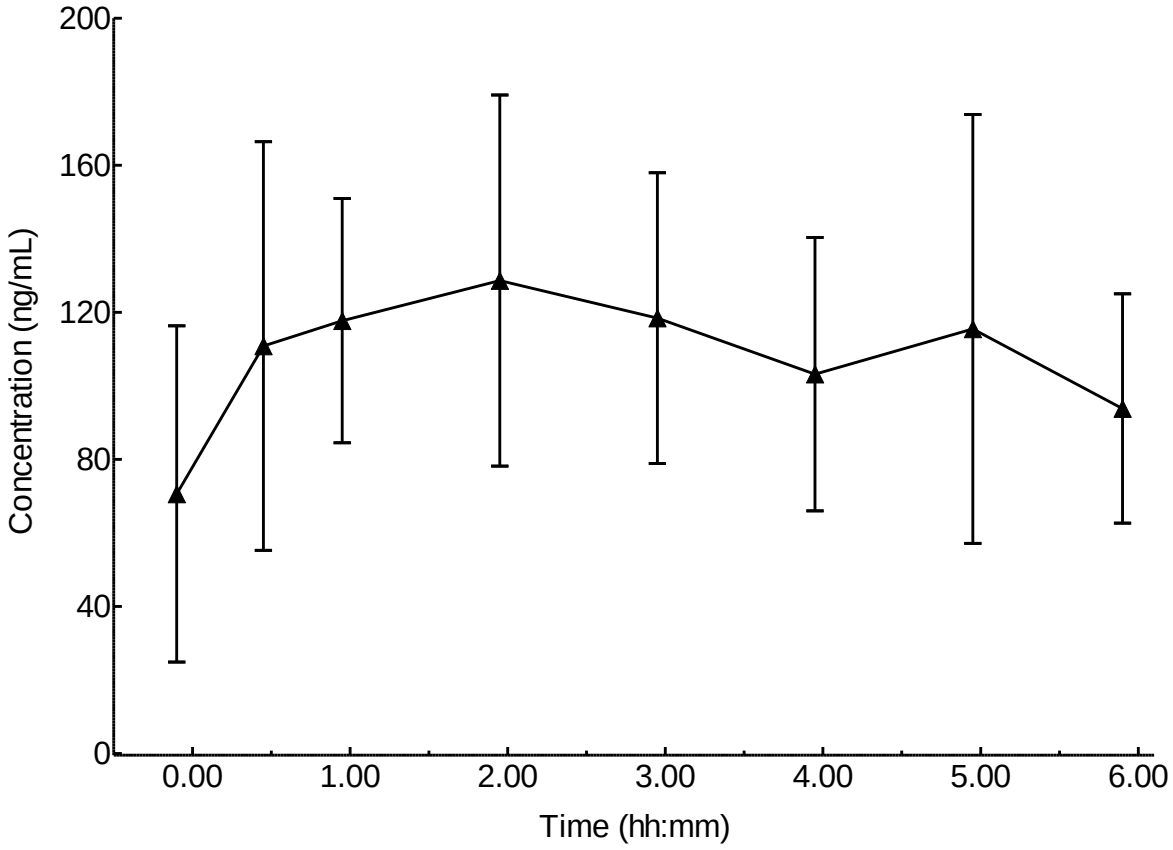

Figure 7: Mean plasma concentration curves with SD error bars of THC-COOH in chronic pancreatitis patients (n=8) taking 8 mg TID Namisol®

Table 14: Pharmacokinetics of THC-COOH in CP patients on day 50-52

	N	Mean	SD	Median	Minimum	Maximum
C_{max} (ng/mL)	8	147,48	59,23	142,50	77,20	236,00
t_{max} (h)	8	2,70	1,68	2,50	0,50	5,07
AUC $_{0\text{-Last}}$ (ng*h/mL)	8	664,05	230,03	650,18	352,17	1054,49
AUC $_{0\text{-tau}}$ (ng*h/mL)	3	948,79	135,28	1014,83	793,17	1038,35
AUC $_{0\text{-inf}}$ (ng*h/mL)	3	2093,39	960,40	1949,79	1212,88	3117,51
$t_{1/2term}$ (h)	3	8,17	4,50	6,95	4,41	13,16
λ_z (L/h)	3	0,10	0,05	0,10	0,05	0,16

AUC $_{0\text{-inf}}$, AUC $_{0\text{-tau}}$, $t_{1/2term}$ and λ_z were calculated only if there were two or more points (excluding C_{max}) in the elimination phase of the plasma concentration–time curve with r^2>0.80.

11.7. Primary efficacy analyses

11.7.1. VAS mean pain

Mean VAS pain scores during Namisol® and placebo treatment in CP patients are shown in figure 8. VASpain scores are shown until day 49, which is the last day of diary for most patients. A summary of mean VAS pain outcomes is presented in table 15.

The ANCOVA of the mean VAS pain score at the last day of diary showed no treatment effect of Namisol® compared with placebo in CP patients (F=.056; p=.816). The use of opioids as covariate did not affect these outcomes.

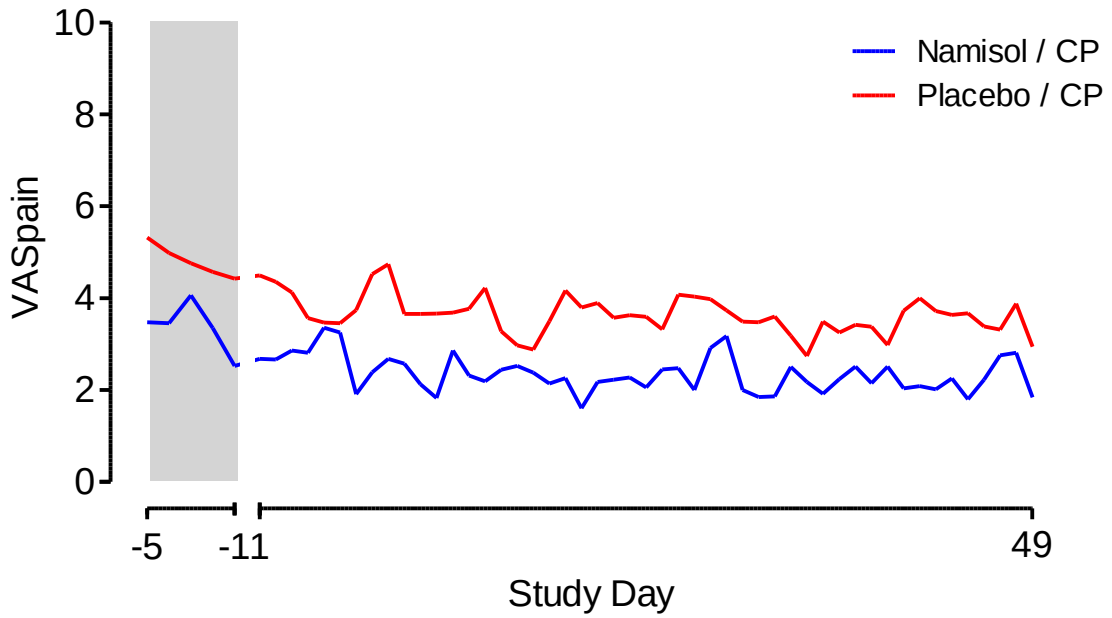

Figure 8: Mean VAS pain at baseline (day -5 to -1) and during study treatment (day 1 to 49) for Namisol and placebo in patients with chronic pancreatitis (n=23). The grey bar represents the baseline period. CP= chronic pancreatitis.

Table 15: Mean VAS pain scores

		N	Mean	SD	Min	Median	Max
Chronic Pancreatitis (n=23)							
Namisol	Baseline	8	3.4	2.32	0.2	2.3	7.8
	Last day	8	1.7	2.56	0.0	0.7	7.8
	Mean last 5 days	8	3.1	2.81	0.5	1.7	7.7
	Diff (last day minus baseline)	8	-1.7	1.61	-4.5	-1.4	0.0
Placebo	Baseline	15	4.9	1.94	1.9	5.0	8.6
	Last day	14	3.1	2.23	0.0	3.5	6.4
	Mean last 5 days	14	3.6	2.09	0.6	3.5	8.2
	Diff (last day minus baseline)	14	-2.1	2.28	-7.0	-1.8	1.3

11.7.2. VAS minimal pain

Minimal VASpain scores during Namisol® and placebo treatment in CP patients are shown in figure 9. VASpain scores are shown until day 49, which is the last day of diary for most patients. A summary of minimal VAS pain outcomes is presented in table 16.

The ANCOVA of the minimal VAS pain score at the last day of diary showed no treatment effect of Namisol® compared with placebo in CP patients (F=.158; p=.697).The use of opioids as covariate did not affect these outcomes.

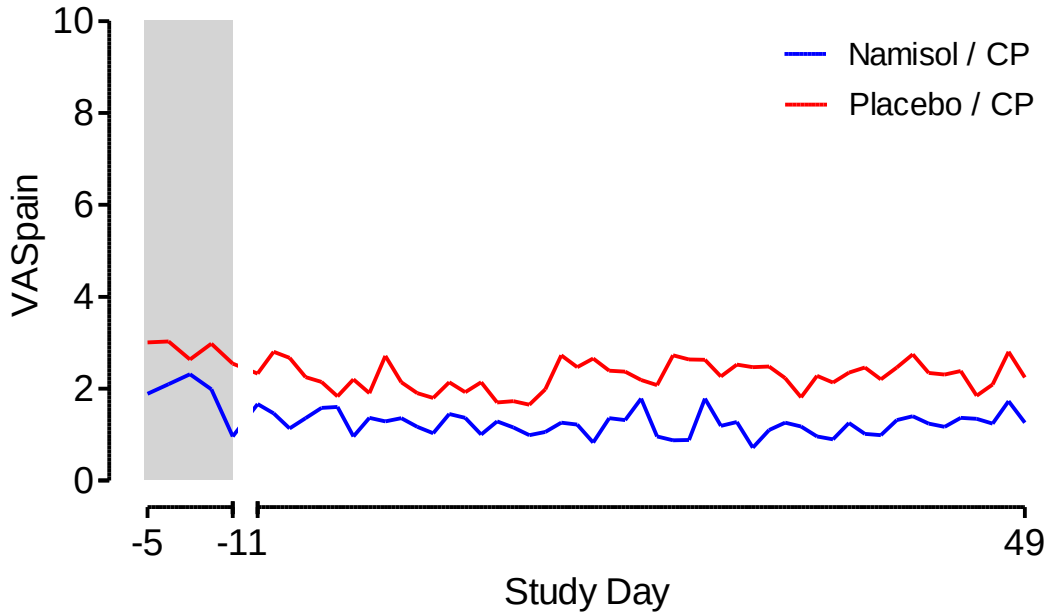

Figure 9: Mean of the VAS minimal pain at baseline (day -5 to -1) and during study treatment (day 1 to 49) for Namisol and placebo in patients with chronic pancreatitis (n=23). The grey bar represents the baseline period. CP= chronic pancreatitis.

Table 16: Minimal VAS pain scores

		N	Mean	SD	Min	Median	Max
Chronic Pancreatitis (n=23)							
Namisol	Baseline	6	1,84	1,41	0,52	1,49	4,46
	Last day	7	1,26	1,65	0,10	0,40	4,00
	Mean last 5 days	6	1,46	1,71	0,18	0,61	4,26
	Diff (last day minus baseline)	5	-0,70	0,77	-2,00	-0,34	-0,16
Placebo	Baseline	12	2,80	2,23	0,38	1,90	7,68
	Last day	13	2,25	1,95	0,00	1,80	6,70
	Mean last 5 days	13	2,31	1,75	0,30	1,94	6,58
	Diff (last day minus baseline)	11	-1,01	1,31	-3,30	-1,00	0,90

11.7.3. VAS maximal pain

Maximal VASpain scores during Namisol® and placebo treatment in CP patients are shown in figure 10. VASpain scores are shown until day 49, which is the last day of diary for most patients. A summary of maximal VAS pain outcomes is presented in table 17. The ANCOVA of the maximal VAS pain score at the last day of diary showed no treatment effect of Namisol® compared with placebo in CP patients (F=.011; p=.919). The use of opioids as covariate did not affect these outcomes.

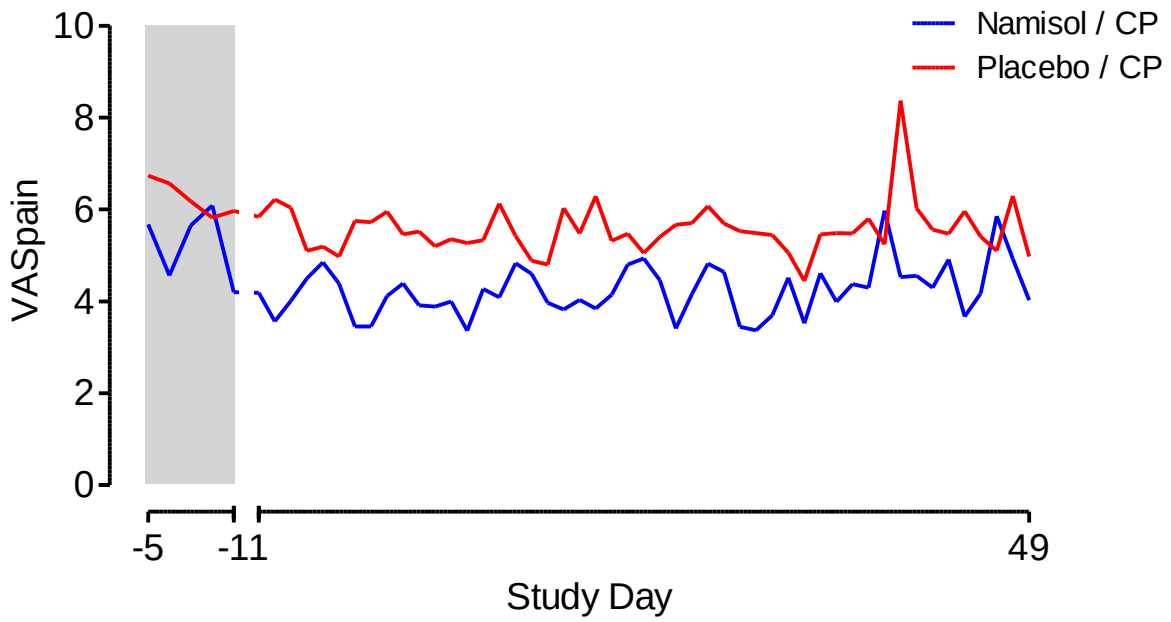

Figure 10: Mean of the VAS maximal pain at baseline (day -5 to -1) and during study treatment (day 1 to 49) for Namisol and placebo in patients with chronic pancreatitis (n=23). The grey bar represents the baseline period. CP= chronic pancreatitis.

Table 17: Maximal VAS pain scores

		N	Mean	SD	Min	Median	Max
Chronic Pancreatitis (n=23)							
Namisol	Baseline	8	4,64	2,64	1,08	4,77	7,90
	Last day	7	4,03	3,22	0,50	4,00	8,70
	Mean last 5 days	8	4,64	2,64	1,08	4,77	7,90
	Diff (last day minus baseline)	7	-0,57	0,94	-2,20	-0,54	0,80
Placebo	Baseline	14	5,58	2,23	2,02	5,09	8,44
	Last day	13	4,98	3,06	0,00	4,60	8,90
	Mean last 5 days	14	5,58	2,23	2,02	5,09	8,44
	Diff (last day minus baseline)	13	-0,40	1,76	-5,18	0,26	1,06

11.8. Secondary endpoints

11.8.1. Pharmacodynamics

11.8.1.1. VAS Bond & Lader questionnaire

The VAS Bond and Lader questionnaire was used for evaluation of alertness (figure 11), mood (figure 12) and calmness (figure 13). A smaller score (cm) reflects a higher degree of that specific factor. The RM ANCOVA showed no significant treatment effect between Namisol® and placebo for alertness (F=0.041, p=.842), mood (F=.210, p=.652) or calmness (F=1.265, p=.275) in CP patients.

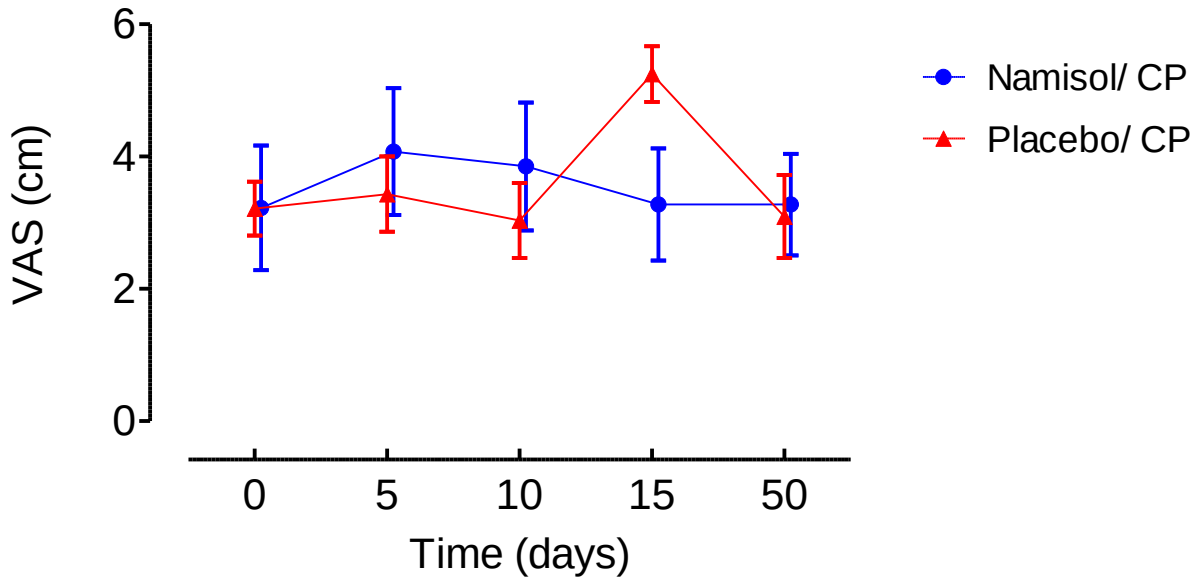

Figure 11: VAS Bond and Lader questionnaire. Mean (SEM) scores for alertness shown for Namisol and placebo treatment in chronic pancreatitis (CP) patients (n=23).

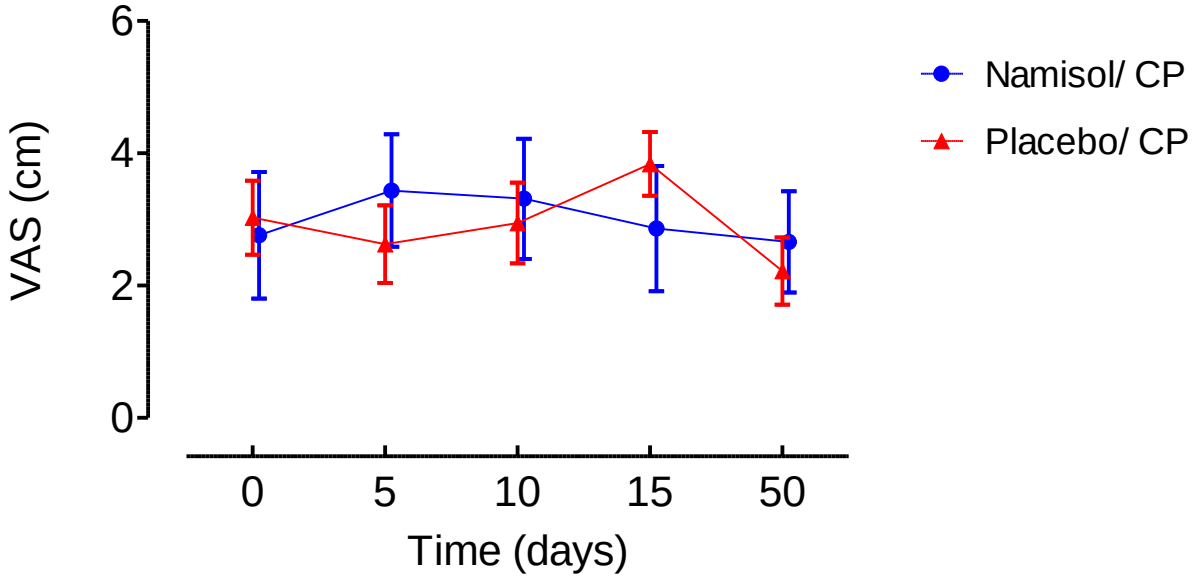

Figure 12: VAS Bond and Lader questionnaire. Mean (SEM) scores for mood shown for Namisol and placebo treatment in chronic pancreatitis (CP) patients (n=23).

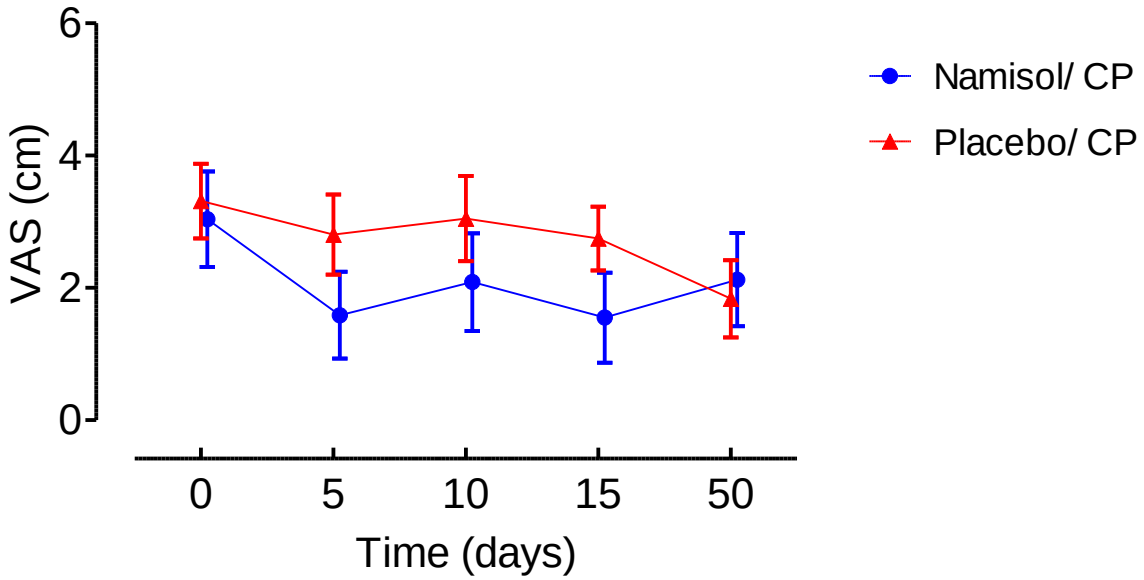

Figure 13: VAS Bond and Lader questionnaire. Mean (SEM) scores for calmness shown for Namisol and placebo treatment in chronic pancreatitis (CP) patients (n=23).

11.8.1.2. VAS Bowdle questionnaire

The VAS Bowdle questionnaire was used for the evaluation of psychedelic effects. Results for difficult to control thoughts (figure 14), feeling high (figure 15) and feeling drowsy (figure 16) are shown. A higher score (cm) reflects a higher degree of that specific factor. No significant differences were observed between Namisol® and placebo treatment patients for difficulties to control thoughts (F=.050; p=.903), feeling high (F=.688; p=.417) and feeling drowsy (F=.297; p=.592). Additionally, no differences were observed for other VAS Bowdle parameters between Namisol® and placebo and are not shown.

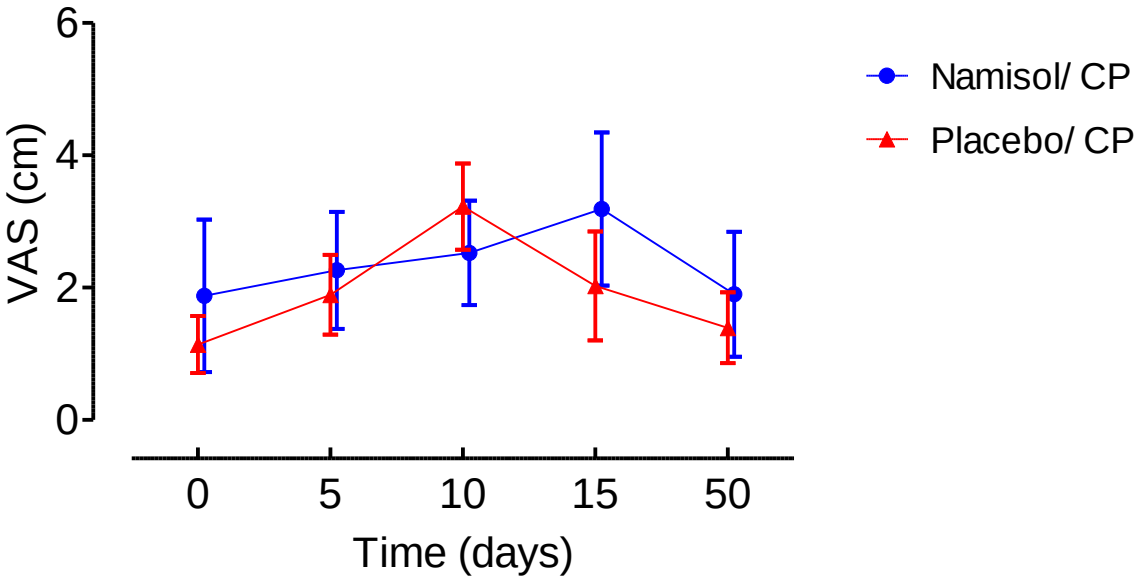

Figure 14: VAS Bowdle questionnaire. Mean (SEM) scores for difficult to control thoughts shown for Namisol® and placebo treatment in chronic pancreatitis (CP) patients (n=23).

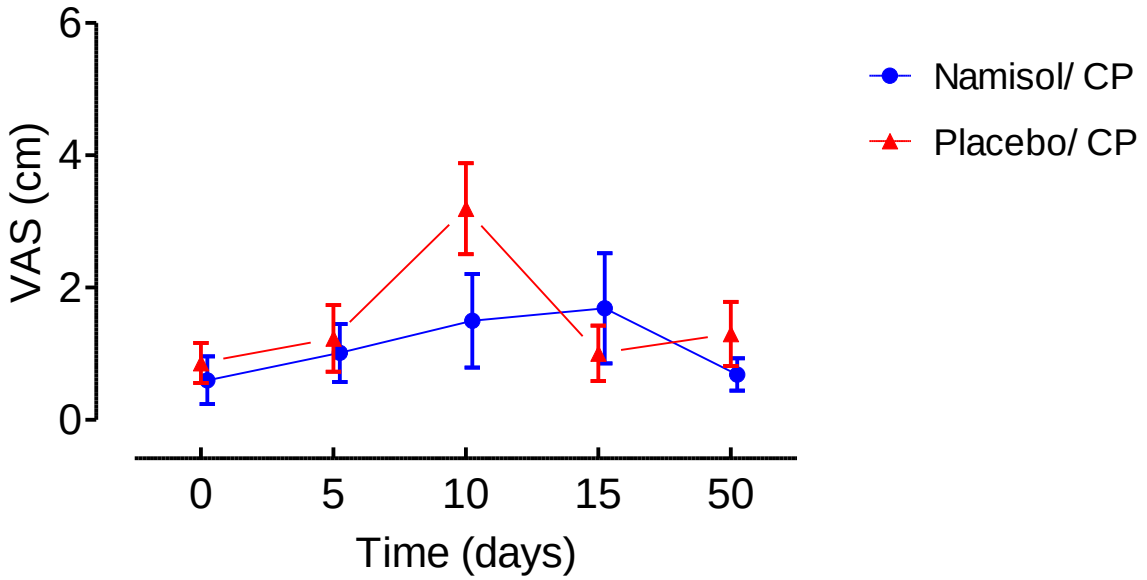

Figure 15: VAS Bowdle questionnaire. Mean (SEM) scores for feeling high shown for Namisol® and placebo treatment in chronic pancreatitis (CP) patients (n=23).

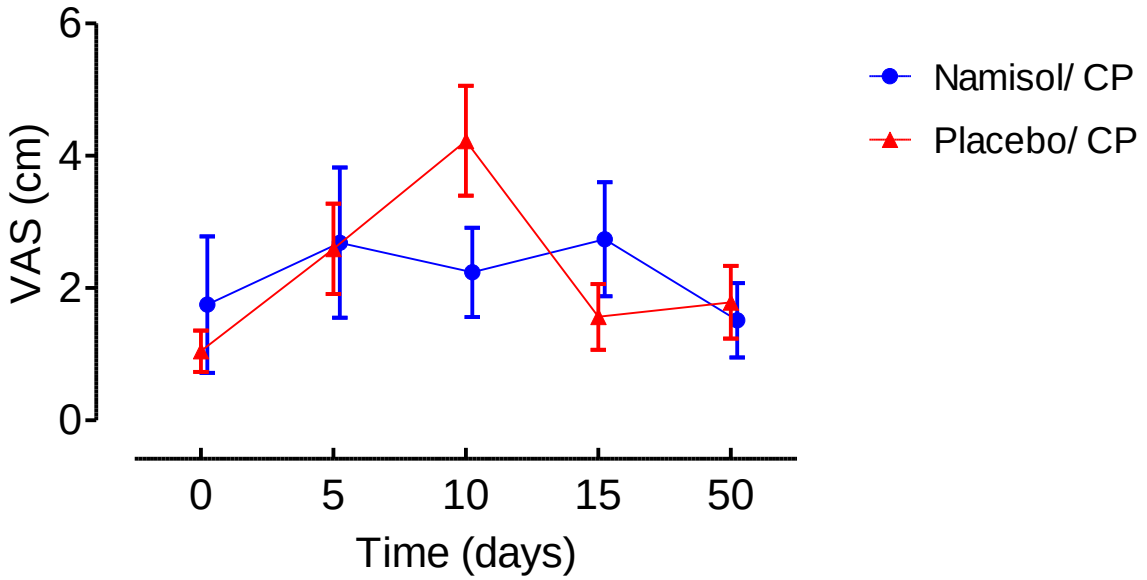

Figure 16: VAS Bowdle questionnaire. Mean (SEM) scores for feeling drowsy shown for Namisol® and placebo treatment in chronic pancreatitis (CP) patients (n=23).

11.8.1.3. HADS

The total HADS score, depression subscore and anxiety subscore are shown for Namisol® and placebo treatment in CP patients are shown in figure 17,18 and 19 respectively. Higher scores on the HADS indicate more symptoms of anxiety and/or depression. A summary of HADS outcomes is presented in table 18.
There were no statistically significant differences in depression (F=2.542; p=.127) or anxiety subscore (F=.787; p=.386) and total HADS score (F=2.929; p=.102) between the Namisol® and placebo treatment group in CP patients.

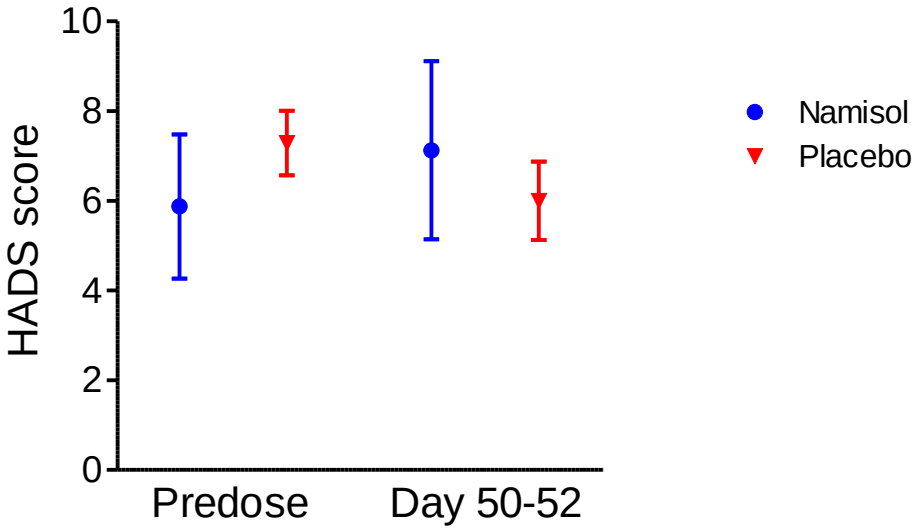

Figure 17: HADS questionnaire. Mean (SEM) scores for HADS total score shown for Namisol® and placebo treatment in chronic pancreatitis (CP) patients (n=23).

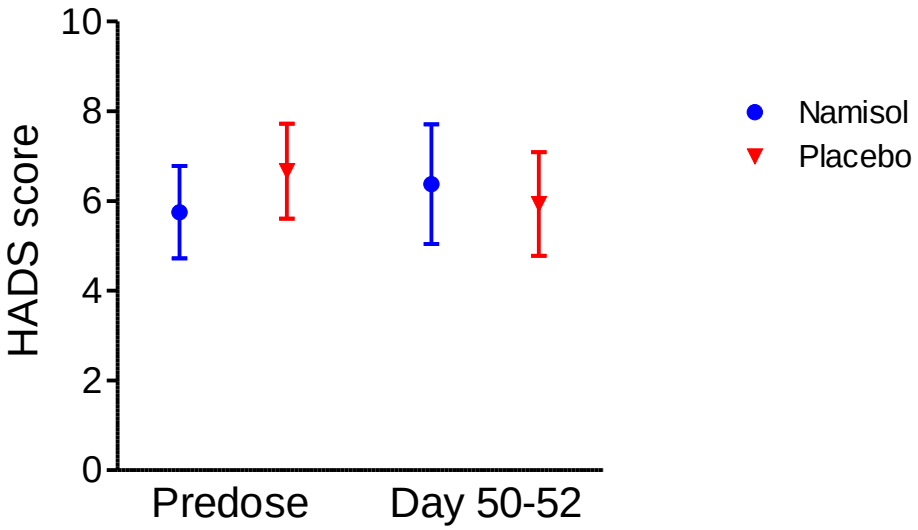

Figure 18: HADS questionnaire. Mean (SEM) scores for depression subscore shown for Namisol® and placebo treatment in chronic pancreatitis (CP) patients (n=23).

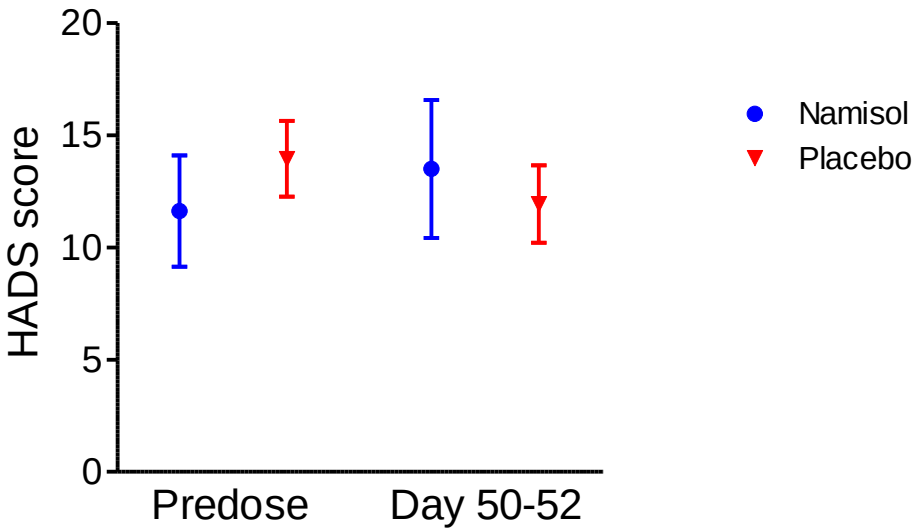

Figure 19: HADS questionnaire. Mean (SEM) scores for anxiety subscore shown for Namisol® and placebo treatment in chronic pancreatitis (CP) patients (n=23).

Table 18: HADS questionnaire scores

			N	Mean	Median	SD	Min	Max
Chronic Pancreatitis (n=23)								
Namisol	Baseline	Depresssion	8	5,9	7,0	4,5	0,0	13,0
		Anxiety	8	5,8	6,0	2,9	1,0	9,0
		Total	8	11,6	12,0	7,0	1,0	22,0
	Last day	Depression	8	7,1	7,0	5,6	1,0	15,0
		Anxiety	8	6,4	5,5	3,8	2,0	13,0
		Total	8	13,5	11,5	8,7	3,0	28,0
Placebo	Baseline	Depresssion	15	7,3	8,0	2,8	2,0	11,0
		Anxiety	15	6,7	7,0	4,1	1,0	15,0
		Total	15	14,0	14,0	6,5	3,0	25,0
	Last day	Depression	15	6,0	7,0	3,4	1,0	11,0
		Anxiety	15	5,9	5,0	4,5	0,0	16,0
		Total	15	11,9	13,0	6,7	1,0	23,0

11.8.1.4. SF-36

The outcomes of the RAND SF-36 questionnaire were presented per health-related domain: physical functioning (figure 20), role limitations due to physical health (figure 21), role limitations due to emotional problems (figure 22), energy/fatigue (figure 23), emotional well being (figure 24), social functioning (figure 25), pain (figure 26) and general health (figure 27). All questions were scored on a scale from 0 to 100, with 100 representing the highest level of functioning possible. There were no statistical differences observed in all these domains, including physical functioning (F=2.262; p=.148), role limitations due to physical health (F=.002; p=.963), role limitations due to emotional problems (F=.394; p=.537), energy/fatigue (F=2.922; p=.103), emotional well being (F=.150; p=.703), social functioning (F=.013; p=.912), pain (F=.314; p=.582) and general health (F=.098; p=.758). A summary of SF-36 outcomes is listed in table 19.

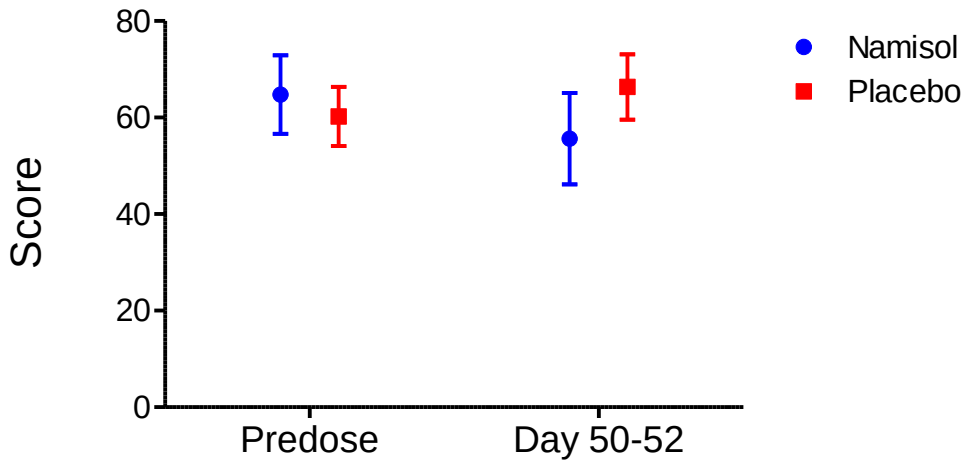

Figure 20: SF-36 questionnaire. Mean (SEM) scores for physical functioning shown for Namisol® and placebo treatment in chronic pancreatitis patients (n=23).

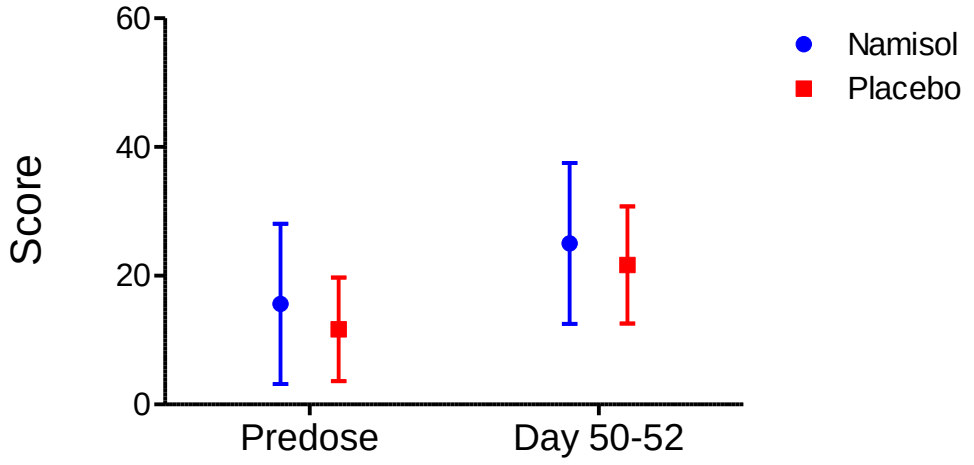

Figure 21: SF-36 questionnaire. Mean (SEM) scores for role limitations due to physical health shown for Namisol® and placebo treatment in chronic pancreatitis patients (n=23).

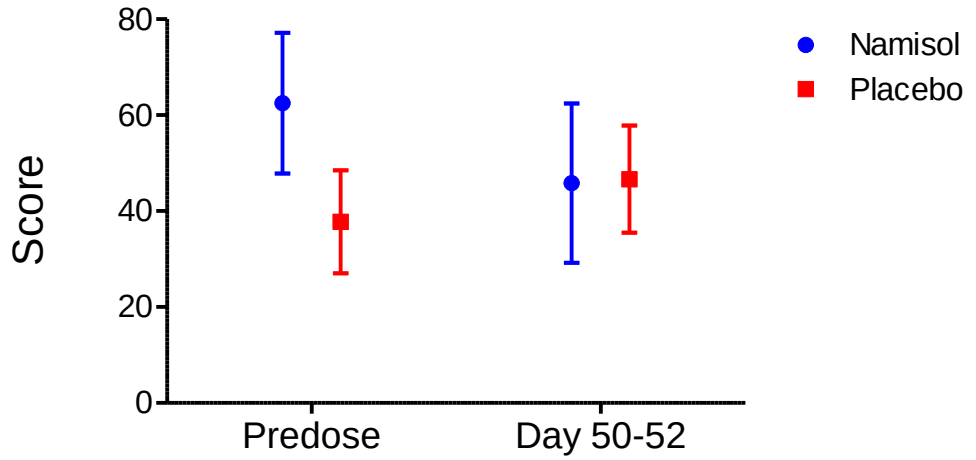

Figure 22: SF-36 questionnaire. Mean (SEM) scores for role limitations due to emotional problems shown for Namisol® and placebo treatment in chronic pancreatitis patients (n=23).

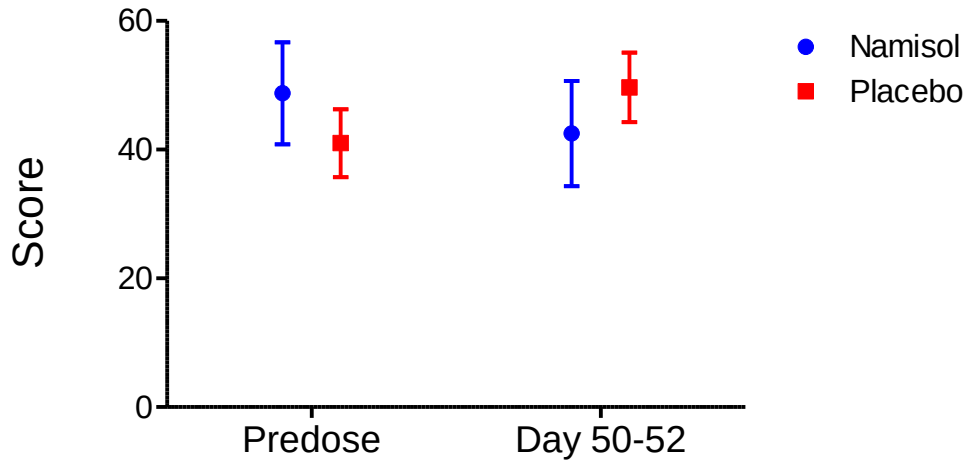

Figure 23: SF-36 questionnaire. Mean (SEM) scores for energy/ fatique shown for Namisol® and placebo treatment in chronic pancreatitis patients (n=23).

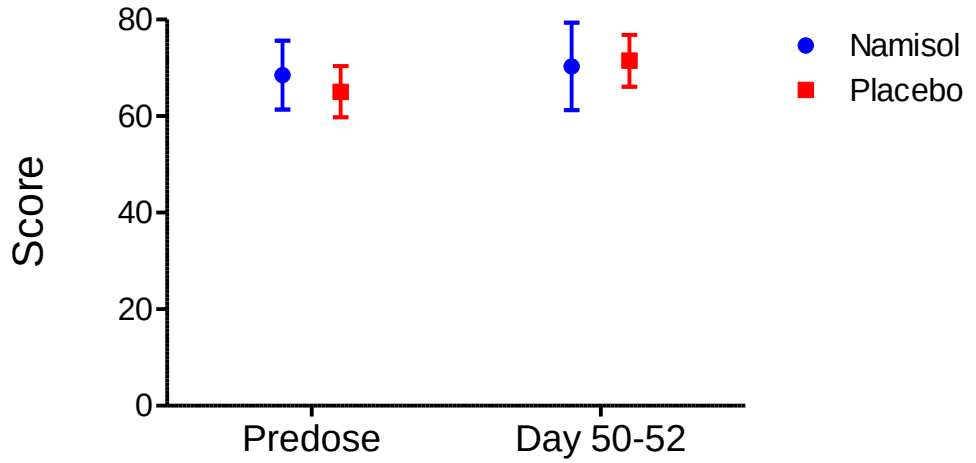

Figure 24: SF-36 questionnaire. Mean (SEM) scores for emotional well being shown for Namisol® and placebo treatment in chronic pancreatitis patients (n=23).

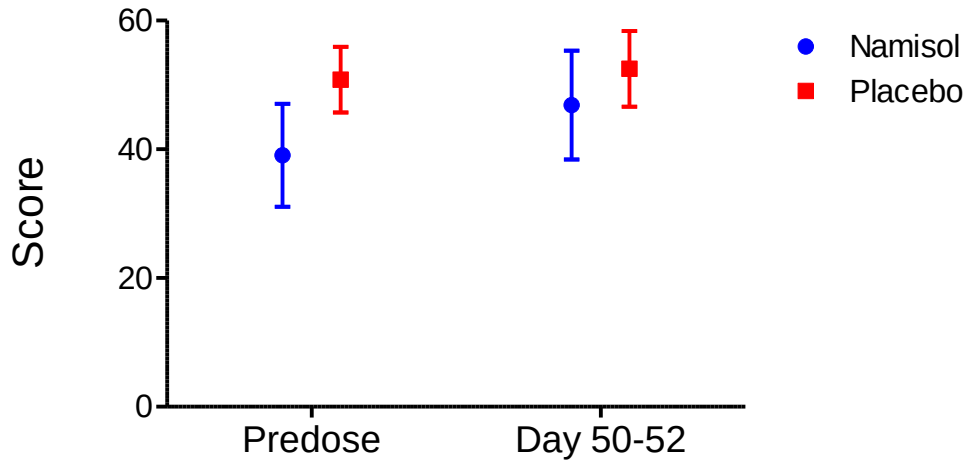

Figure 25: SF-36 questionnaire. Mean (SEM) scores for social functioning shown for Namisol® and placebo treatment in chronic pancreatitis patients (n=23).

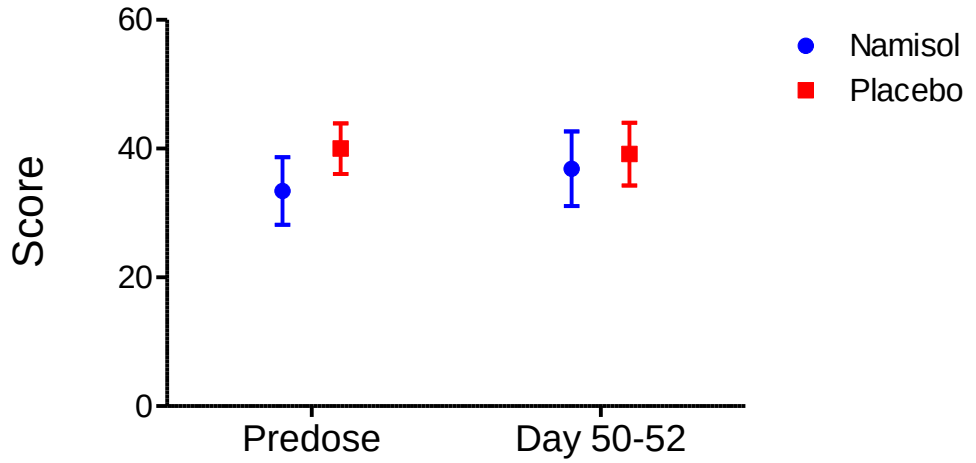

Figure 26: SF-36 questionnaire. Mean (SEM) scores for pain shown for Namisol® and placebo treatment in chronic pancreatitis patients (n=23).

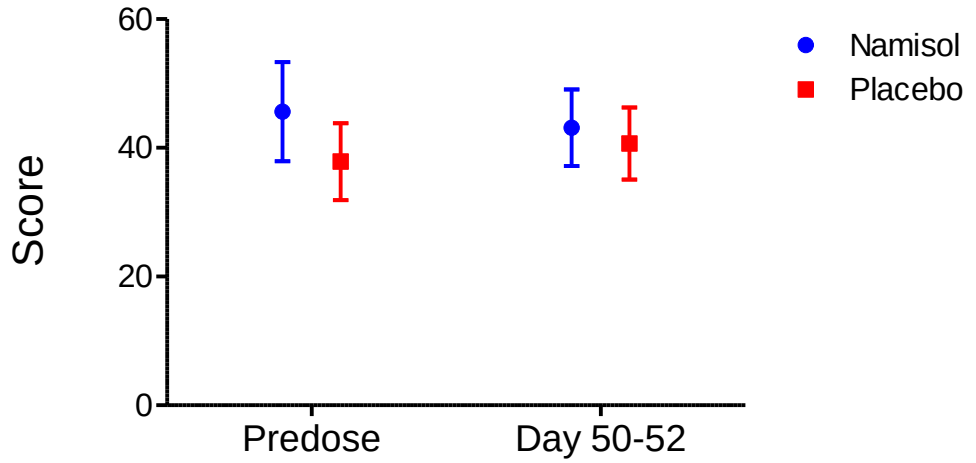

Figure 27: SF-36 questionnaire. Mean (SEM) scores for general health shown for Namisol® and placebo treatment in chronic pancreatitis patients (n=23).

Table 19: SF-36 questionnaire

		N	Mean	Median	SD	Min	Max
Namisol							
Physical functioning	Baseline	8	64,8	62,5	23,0	33,3	100,0
	Last day	8	55,6	47,5	26,8	25,0	100,0
Role - physical health	Baseline	8	15,6	0,0	35,2	0,0	100,0
	Last day	8	25,0	12,5	35,4	0,0	100,0
Role - emotional problems	Baseline	8	62,5	66,7	41,5	0,0	100,0
	Last day	8	45,8	33,3	46,9	0,0	100,0
Energy/ fatigue	Baseline	8	48,8	37,5	22,5	30,0	80,0
	Last day	8	42,5	40,0	23,1	10,0	75,0
Emotional well being	Baseline	8	68,5	72,0	20,1	28,0	96,0
	Last day	7	70,3	80,0	24,0	36,0	100,0
Social functioning	Baseline	8	39,1	37,5	22,6	12,5	75,0
	Last day	8	46,9	50,0	23,9	12,5	75,0
Pain	Baseline	8	33,4	35,0	14,8	0,0	45,0
	Last day	8	36,9	41,3	16,4	0,0	55,0
General health	Baseline	8	45,6	40,0	21,8	15,0	80,0
	Last day	8	43,1	40,0	16,9	25,0	80,0
Placebo							
Physical functioning	Baseline	15	60,3	65,0	23,8	18,8	85,0
	Last day	15	66,3	75,0	26,1	25,0	100,0
Role - physical health	Baseline	15	11,7	0,0	31,1	0,0	100,0
	Last day	15	21,7	0,0	35,2	0,0	100,0
Role - emotional problems	Baseline	15	37,8	33,3	41,5	0,0	100,0
	Last day	15	46,7	33,3	43,3	0,0	100,0
Energy/ fatigue	Baseline	15	41,0	40,0	20,4	20,0	90,0
	Last day	15	49,7	40,0	20,9	25,0	100,0
Emotional well being	Baseline	15	65,1	60,0	20,5	40,0	100,0
	Last day	15	71,5	64,0	20,9	40,0	100,0
Social functioning	Baseline	15	50,8	50,0	19,7	25,0	87,5
	Last day	15	52,5	50,0	22,8	0,0	100,0
Pain	Baseline	15	40,0	45,0	15,1	10,0	70,0
	Last day	15	39,2	45,0	18,9	0,0	80,0
General health	Baseline	14	37,9	30,0	22,3	15,0	100,0
	Last day	15	40,7	35,0	21,7	15,0	100,0

11.8.1.5. PGIC

Results of the two questions regarding pain status (last week status and actual status compared with before start study treatment) within the PGIC questionnaire are shown in figure 28 and table 20. A lower score represents a better outcome. There were no statistical differences observed for last week status (F=0.023; p=.881) and actual status compared with before start study treatment (F=.000; p=.984) between Namisol® and placebo treatment.

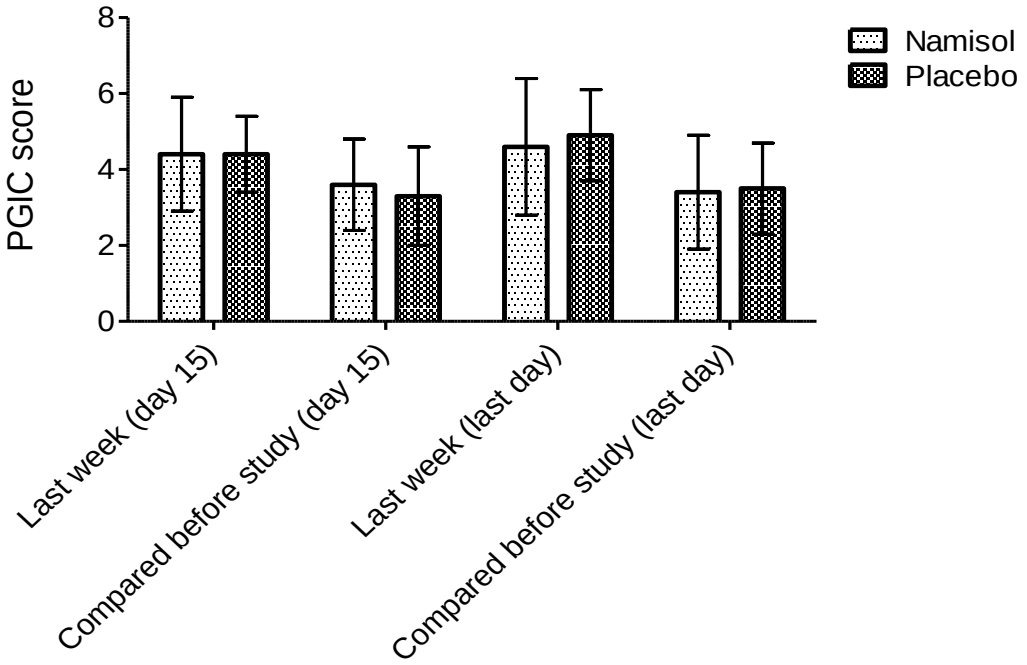

Figure 28: PGIC questionnaire. Mean (SD) scores of the patient global impression of change shown for Namisol and placebo in chronic pancreatitis patients (n=23).

Table 20: Patient global impression of change (PGIC) questionnaire

			N	Mean	Median	SD	Min	Max
Chronic Pancreatitis (n=23)								
Namisol	Day 15	Last week	8	4,4	5,0	1,5	2	6
		Compared before study	8	3,6	3,5	1,2	2	6
	Last day	Last week	8	4,6	5,0	1,8	2	7
		Compared before study	8	3,4	3,5	1,5	1	6
Placebo	Day 15	Last week	15	4,4	5,0	1,0	2	6
		Compared before study	15	3,3	3,0	1,3	1	6
	Last day	Last week	15	4,9	5,0	1,2	2	6
		Compared before study	15	3,5	4,0	1,2	1	6

11.8.1.6. TSQM

Results of satisfaction with medication effectiveness, side effects and convenience measured by the TSQM are shown in figure 29 and table 21. TSQM Scale scores range from 0 to 100, with a higher score indicating a higher level of satisfaction. There were no statistical differences in satisfaction with effectiveness (p=.862), side effects (p=.655), convenience (p=.483) and global satisfaction (p=.525) observed between Namisol® and placebo treatment.

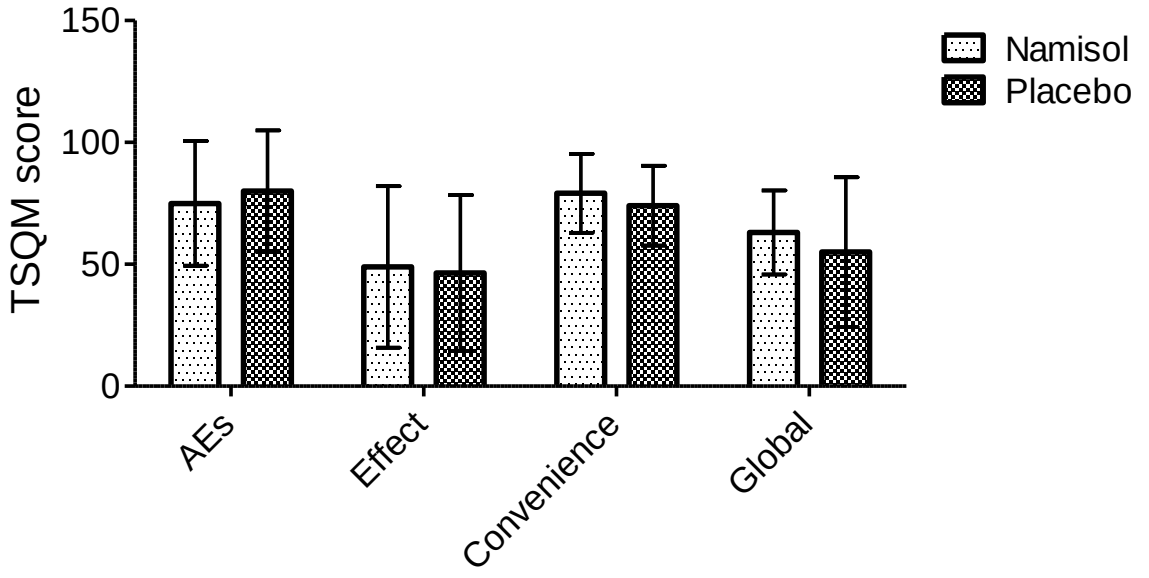

Figure 29: TSQM questionnaire. Mean (SD) scores to evaluate satisfaction shown for Namisol and placebo in chronic pancreatitis patients (n=23).

Table 21: TSQM questionnaire

		N	Mean	Median	SD	Min	Max
Chronic Pancreatitis (n=23)							
Namisol	AEs	8	75,0	79,2	25,6	33,3	100,0
	Effect	8	49,0	45,8	33,2	0,0	100,0
	Convenience	8	79,2	72,2	16,2	61,1	100,0
	Global	7	63,1	66,7	17,3	41,7	83,3
Placebo	AEs	15	80,0	91,7	25,0	25,0	100,0
	Effect	14	46,4	33,3	32,0	0,0	100,0
	Convenience	15	74,1	72,2	16,4	50,0	100,0
	Global	15	55,0	58,3	30,7	0,0	100,0

11.8.1.7. AppLe

Appetite level, evaluated by two questions within the AppLe questionnaire, is shown in table 22. The AppLe questionnaire was filed at the end of the study (day 50-52). A higher score on the “last week” question represents a better outcome, whereas a higher score on the “compared before study” question indicates a worse outcome. There was no difference observed between Namisol® and placebo treatment in how patients rated their appetite in the last week (p=.135). However, patients reported a significant improvement in appetite level compared to before the study period (p=.025).

Table 22: AppLe questionnaire

		N	Mean	Median	SD	Min	Max
Chronic Pancreatitis (n=23)							
Namisol	Last week	6	4,7	5,0	2,0	2	7
	Compared before study	6	3,2	4,0	1,3	1	4
Placebo	Last week	15	5,2	6,0	1,5	2	7
	Compared before study	15	4,6	4,0	1,2	2	7

11.8.1.8. PASS

Results of the total PASS score and PASS subscales cognitive anxiety symptoms (“I find it hard to concentrate when I hurt“), escape and avoidance responses (“I avoid important activities when I hurt“), fearful thoughts (“I think that if my pain gets too severe, it will never decrease“) and physiological symptoms of anxiety (“I become sweaty when in pain“) are shown in table 23. The total PASS score is also presented in figure 30. Higher scores represent a higher level of pain related anxiety. There were no significant differences observed for fear (F=.032; p=.859), avoidance (F=.024; p=.878) and other scales between Namisol® and placebo treatment.

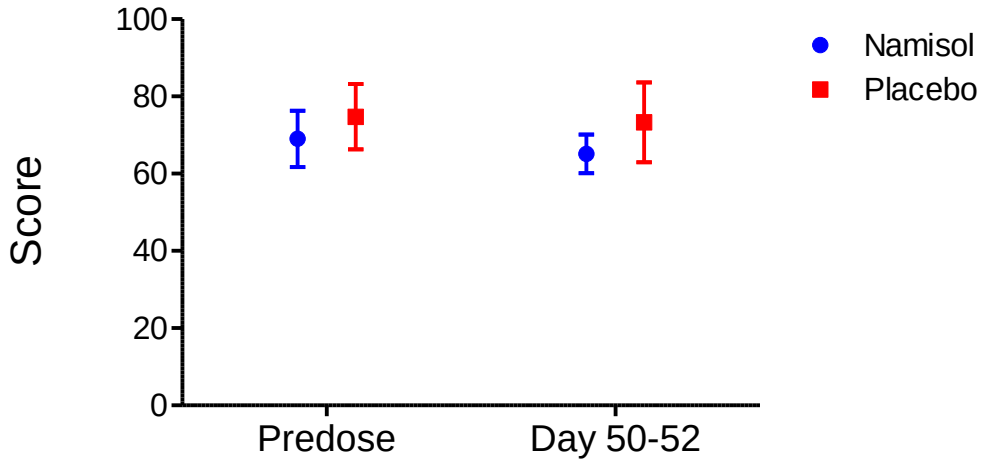

Figure 30: PASS questionnaire. Mean (SEM) scores to evaluate pain related anxiety shown for Namisol and placebo in chronic pancreatitis patients (n=23).

Table 23: PASS questionnaire

			N	Mean	Median	SD	Min	Max
Chronic pancreatitis (n=23)								
Namisol	Baseline	Fear	8	8,6	6,0	9,8	0,0	31,0
		Cognitive	8	22,8	25,5	8,2	6,0	33,0
		Avoidance	8	24,5	24,5	7,5	11,0	34,0
		Physiological	7	13,3	10,0	8,2	6,0	27,0
		Total	7	69,0	66,0	19,2	42,0	94,0
	Last day	Fear	8	10,9	10,0	5,1	4,0	20,0
		Cognitive	8	16,8	16,0	4,4	11,0	26,0
		Avoidance	8	24,4	23,5	4,9	19,0	31,0
		Physiological	8	13,1	14,5	7,3	2,0	21,0
		Total	8	65,1	63,5	14,1	50,0	95,0
Placebo	Baseline	Fear	15	11,5	11,0	8,3	0,0	26,0
		Cognitive	15	21,6	24,0	9,5	5,0	35,0
		Avoidance	15	24,6	26,0	11,1	9,0	45,0
		Physiological	15	17,0	20,0	11,8	0,0	37,0
		Total	15	74,7	88,0	32,8	21,0	118,0
	Last day	Fear	15	12,3	10,0	10,9	0,0	35,0
		Cognitive	15	21,5	18,0	11,0	6,0	42,0
		Avoidance	15	23,9	29,0	12,3	4,0	40,0
		Physiological	15	15,5	14,0	11,8	0,0	37,0
		Total	15	73,3	82,0	40,0	11,0	151,0

11.8.1.9. PCS

Pain catastrophizing, measured by the PCS, are shown in figure 31-34. Responses are summed to create a total score (max 52), with higher scores indicating greater pain catastrophizing levels. A score of more than 24 indicates a high level of catastrophizing. The items are divided into three subscales; namely rumination, helplessness and magnification. No significant differences were observed between Namisol® and placebo treatment for rumination (F=.259; p=.616), helplessness (F=1.610; p=.219), magnification (F=.050; p=.825) and total score (F=.957; p=.340).

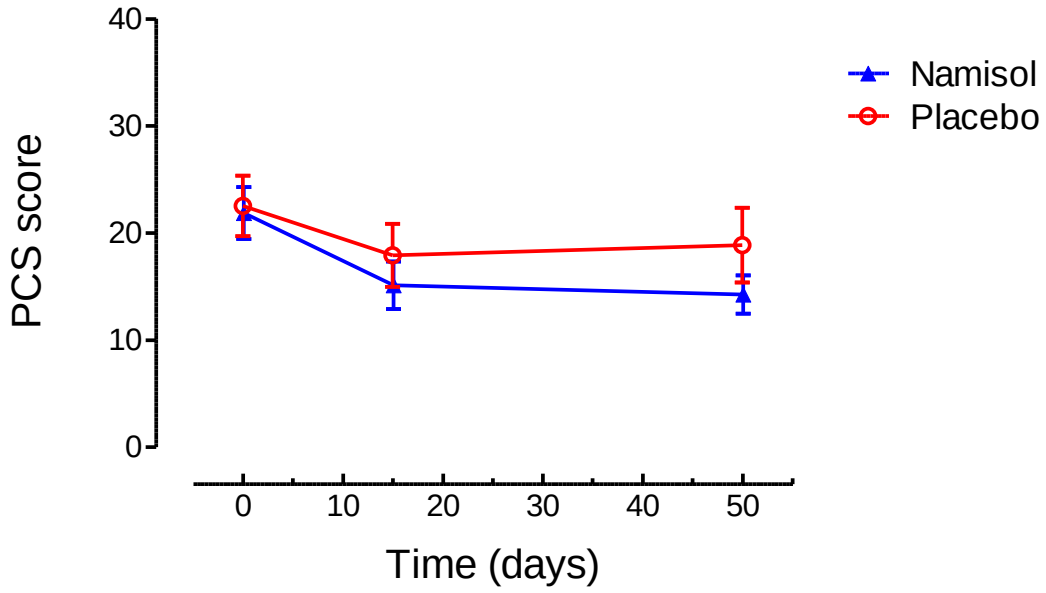

Figure 31: PCS questionnaire. Mean (SEM) scores for total level of catastrophizing shown for Namisol® and placebo treatment in chronic pancreatitis patients (n=23)

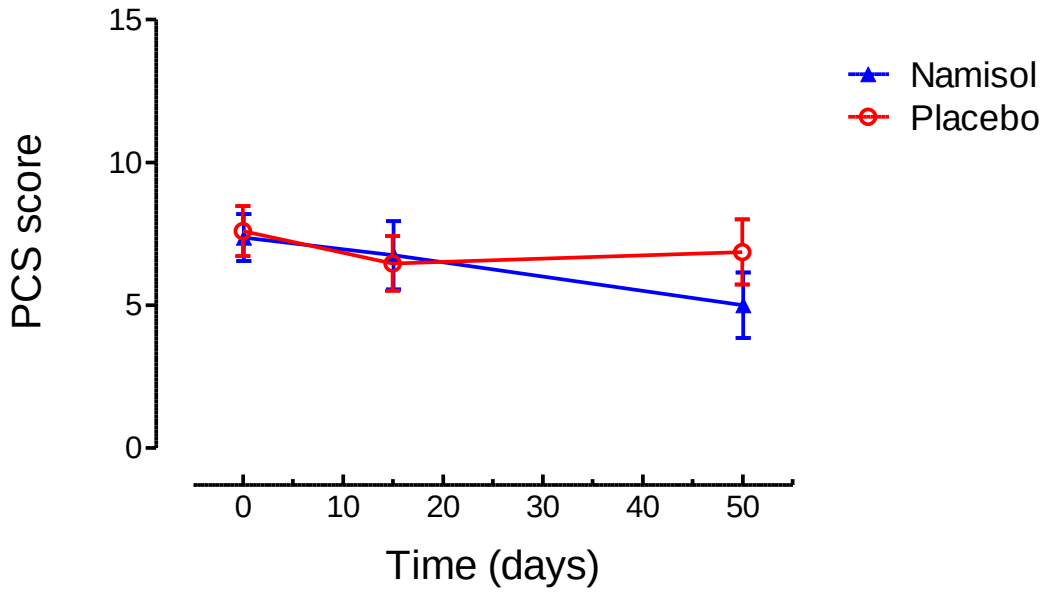

Figure 32: PCS questionnaire. Mean (SEM) scores for level of rumination shown for Namisol® and placebo treatment in chronic pancreatitis patients (n=23)

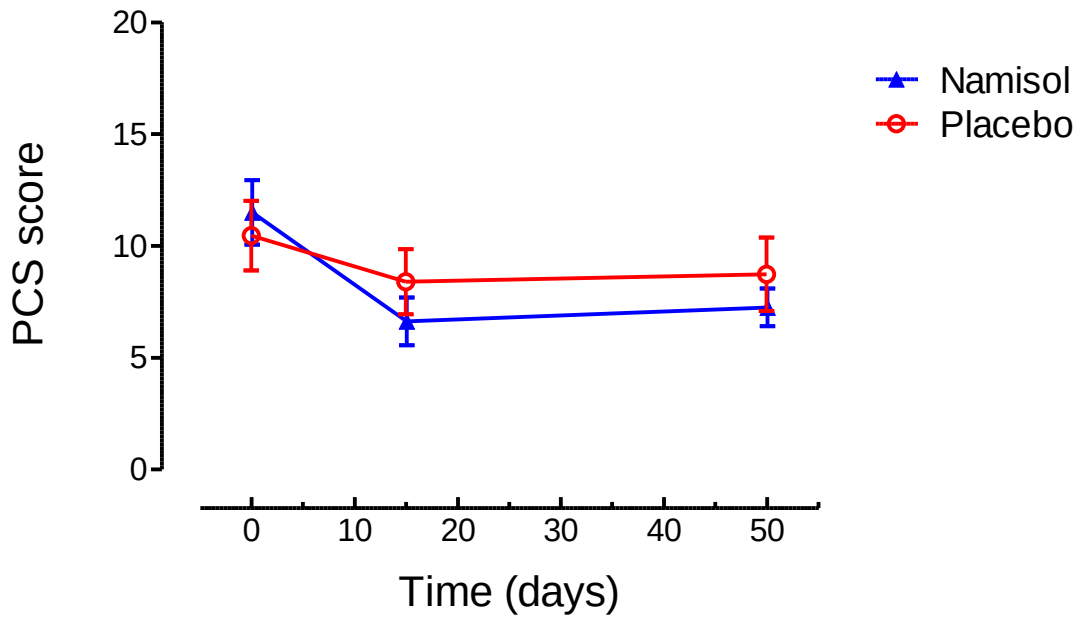

Figure 33: PCS questionnaire. Mean (SEM) scores for level of helplessness shown for Namisol® and placebo treatment in chronic pancreatitis patients (n=23)

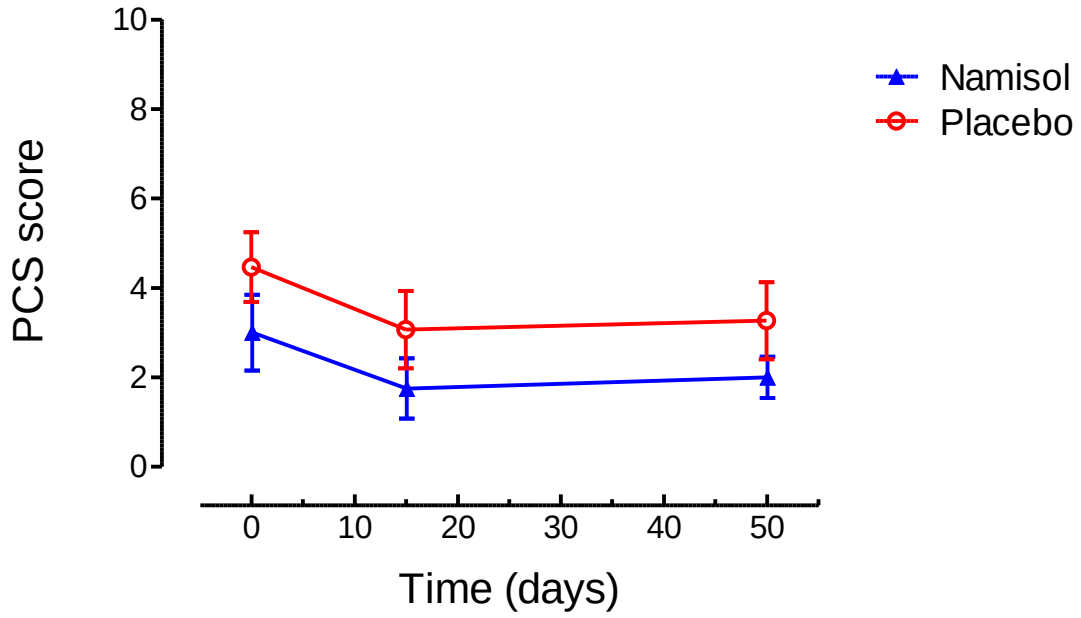

Figure 34: PCS questionnaire. Mean (SEM) scores for level of magnification shown for Namisol® and placebo treatment in chronic pancreatitis patients (n=23)

11.8.1.10. Izbicki

Results of the pancreatitis-specific pain questionnaire, comprising a composed pain score of actual pain experience and use of analgesics, are shown in figure 35. No significant differences were observed (F=.578; p=.461).

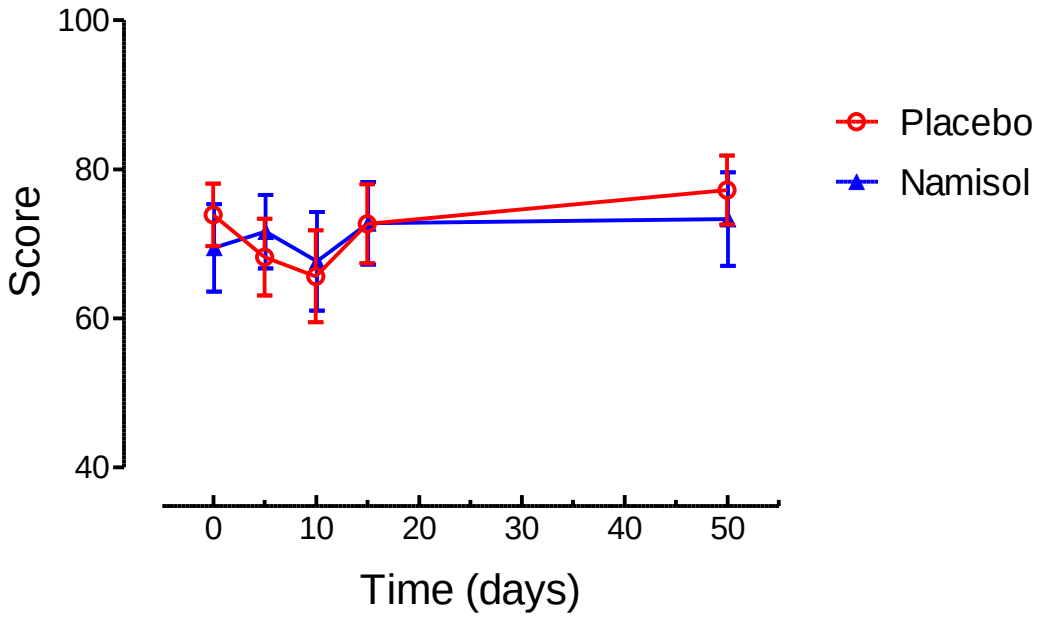

Figure 35: Izbicki questionnaire. Mean (SEM) scores for Izbicki scores for Namisol® and placebo treatment in chronic pancreatitis patients (n=23).

11.8.2. Body weight

Subjects in the Namisol® treatment group lost on average 0.1 kg and patients in the placebo group gained on average 0.9 kg in weight during study treatment (table 24). However, there was no statistical significant difference in body weight between Namisol® or placebo treatment (F=.203; p=.658).

Table 24: Body weight (kg)

		N	Mean	Median	SD	Min	Max
Chronic pancreatitis (n=23)							
Namisol	Day 1	8	76,5	77,0	17,6	48,5	102,5
	Day 15	8	76,9	77,0	16,4	50,0	99,0
	Last day	8	76,4	76,5	15,7	51,0	99,0
Placebo	Day 1	15	73,1	71,0	17,1	51,0	100,0
	Day 15	15	73,2	70,0	16,4	50,0	100,0
	Last day	14	74,0	73,5	17,2	50,0	100,0

Two patients (CP18 and CP25) used supplementary feeding on a stable bases during study treatment. So no further analyses was performed on supplementary feeding.

11.8.3. Body Sway

There were no group differences in balance outcomes in eyes open (F=2.379; p=.142), eyes closed (F=.954; p=.342) and in standing on one leg with eyes open condition (F=2.054; p=.177) between Namisol® and placebo (figure 36-38).
Four patients could not perform the standing on one leg with eyes closed condition task on day 1 and did not repeat the measurements on the following study days. In this condition, balance performance was considerably disturbed in a few individuals as shown in figure 39 and 40.

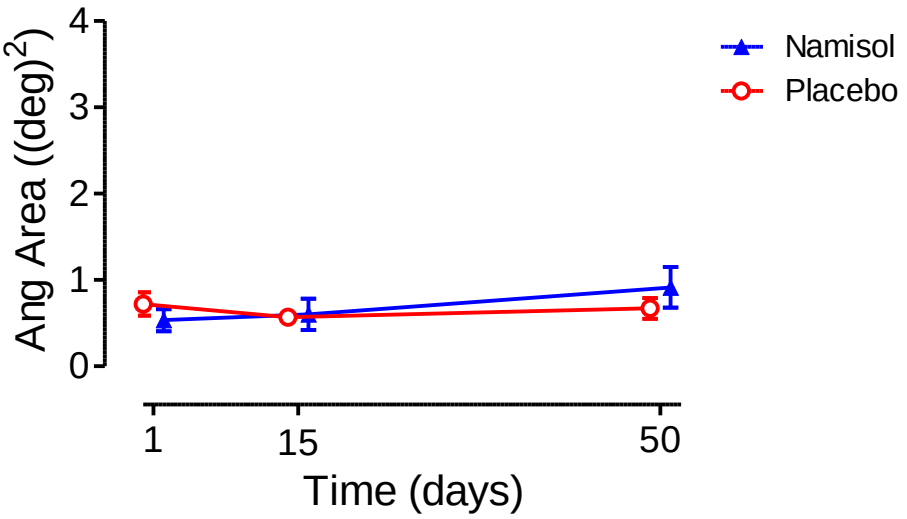

Figure 36: Body sway. Mean (SEM) of total angular area in eyes open condition shown for Namisol® and Placebo in chronic pancreatitis patients (n=23).

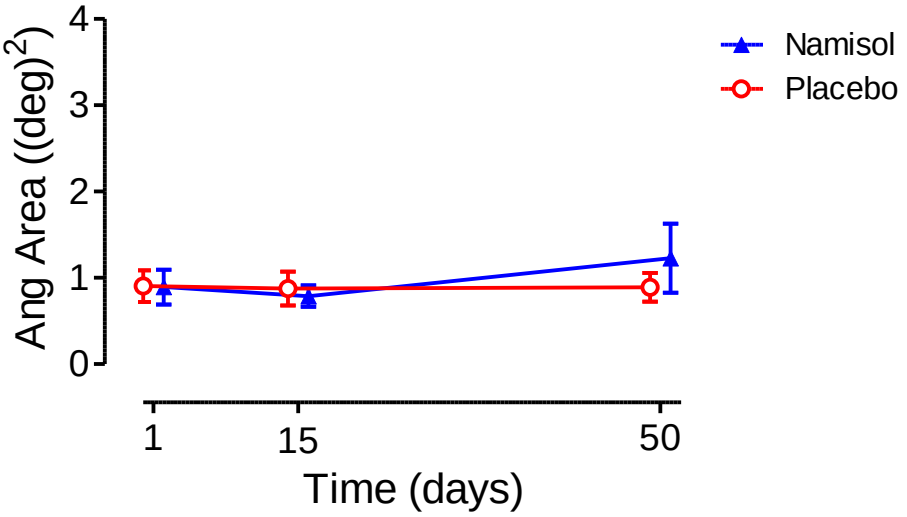

Figure 37: Body sway. Mean (SEM) of total angular area in eyes closed condition shown for Namisol® and Placebo in chronic pancreatitis patients (n=23).

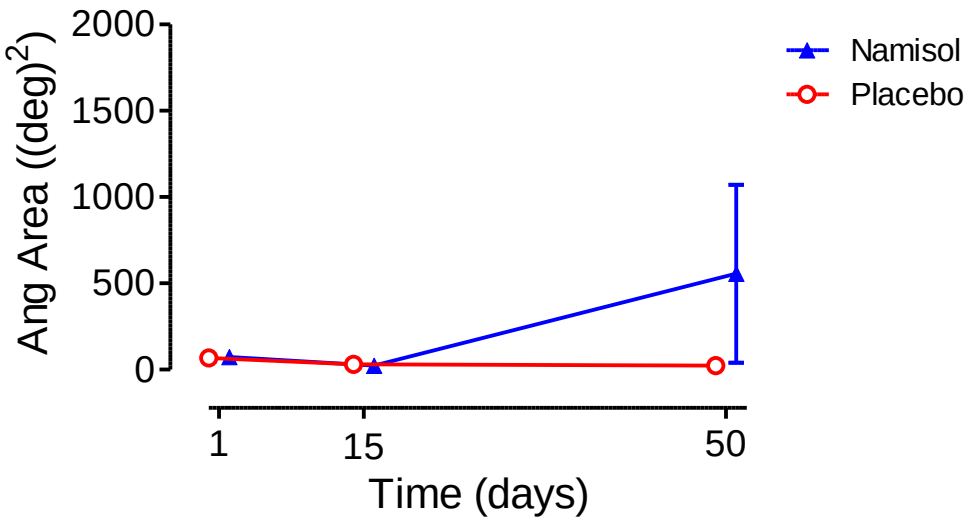

Figure 38: Body sway. Mean (SEM) of total angular area in standing on one leg in eyes open condition shown for Namisol® and placebo in chronic pancreatitis patients (n=19).

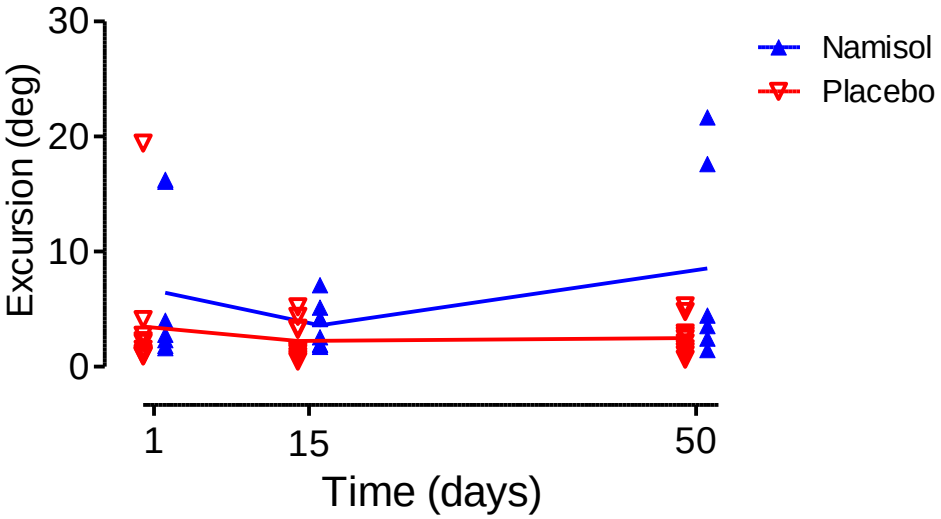

Figure 39: Body sway. Each replicate of 90% range roll excursion in standing on one leg in eyes open condition shown for Namisol® and placebo in chronic pancreatitis patients (n=19). Connecting lines represent mean.

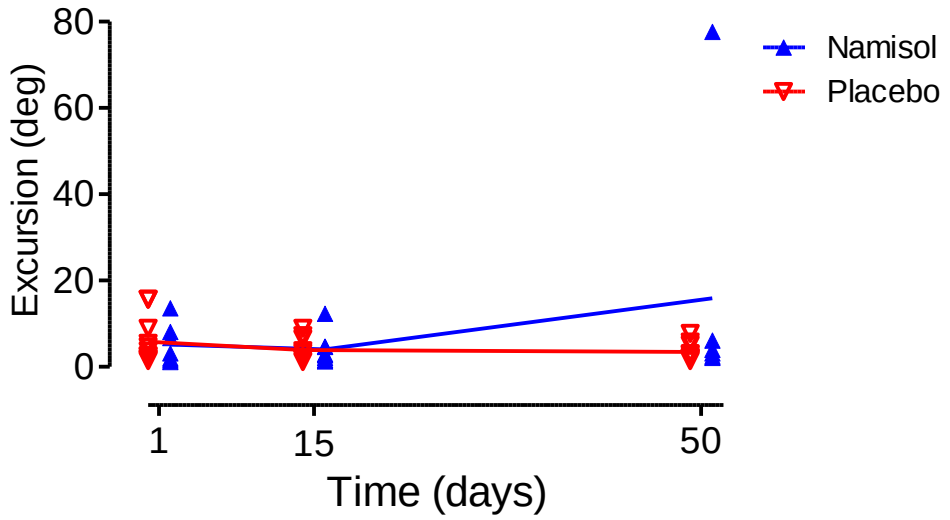

Figure 40: Body sway. Each replicate of 90% range pitch excursion in standing on one leg in eyes open condition shown for Namisol® and placebo in chronic pancreatitis patients (n=19). Connecting lines represent mean.

11.9. Statistical/Analytical Issues

IBM SPSS Statistics for Windows V20 was used for statistical analysis. All statistical tests were performed two-tailed, and the limit for statistical significance was set at $P<0.05$. All statistical procedures were described in a statistical analysis plan.(68)

11.9.1. Adjustment for Covariates

The efficacy outcomes of this study were analyzed by means of an (repeated measurement) ANCOVA that incorporates the baseline measurement score as covariate. Subgroup analyses between opioid and non-opioid users were performed. Opioid use was not integrated in the ANCOVA since an opioid effect was absent. No further adjustments for covariates were made.

11.9.2. Handling of Dropouts or Missing Data

Four patients withdrew from the study within 36 days after the start of the trial. Data from these subjects were used in examining safety data but not efficacy data. One patient withdrew from the study after 36 days after the start of the trial and was included in the modified intention to treat efficacy analysis.
A few measurements of some subjects were missing. Some of them were missing, because a question was accidentally skipped or could not be interpreted through incorrect filling in. Other measurements could not be conducted due to adverse events at that particular moment. However, this was only a marginal amount of measurements, which were randomly divided over all endpoints and subjects. Missing values are shown as empty spot in the listings.

11.9.3. Interim Analyses and Data Monitoring

No interim analysis was performed. Source data verification was conducted by an external monitor according to monitor plan.

11.9.4. Examination of subgroups

Post hoc subgroup analyses between opioid and non-opioid users were performed. No differences between subgroups were observed within the CP study population.
Regarding the combined population of CP and PSP subjects, post hoc analyses revealed similar variance comparing the treatments between these subgroups, as well as with adjustment for substudy or adjustment for opioid and non-opioid users.

11.9.5. Drug-Dose, Drug Concentration and Relationships to Response

All subjects in the active treatment arm administrated the same dosage regime of 8 mg TID Namisol®. Pharmacokinetic results are shown in section 10.5. Genetic polymorphism did not evidently affect the pharmacokinetics of Namisol®. The VASpain could not be associated with pharmacokinetic outcomes such as C_{max} and AUC_{last}.

11.9.6. Drug-Drug and Drug-Disease interactions

Drug-drug and drug-disease interactions were not observed in this small subject population.

11.9.7. Tabulation of individual response data

All individual results are listed in appendix D.

11.10. Efficacy Conclusions

This exploratory phase 2 study failed to demonstrate analgesic efficacy of Namisol® in PSP patients suffering from chronic abdominal pain. Primary efficacy analysis of the average VAS pain at the end of the 50-52 day treatment period did not reveal a significant difference between Namisol® and placebo treatment. The small patient population in combination with a large placebo effect might have contributed to this lack of observed efficacy. Secondary outcome parameters regarding pain, quality of life, treatment satisfaction or psychedelic outcomes did not differ after Namisol® compared with placebo treatment.

12. SAFETY EVALUATION

12.1. Extent of Exposure

The standard study treatment dosage scheme was:

Day 1-5	3 mg TID Namisol® or placebo
Day 6-10	5 mg TID Namisol® or placebo
Day 16-(50-52)	8 mg TID Namisol® or placebo

This results in a daily maximum dosage of 24 mg Namisol® for a maximum period of 52 days. The majority of subjects followed this dosage regime.
Actual treatment dosages of subjects who received at least one dosage study medication are presented in table 25. One drop-out subject in the placebo arm did not taper the study medication before withdrawal. However, this subject decided to quit study treatment due to the occurrence of an unrelated serious adverse event.

Table 25: Treatment dosage schemes

	Namisol	**Placebo**
Intention to treat group (n=23)		
Treatment according dosage scheme	8	12
Lowered to 5mg TID	0	2 (CP15, CP62)
Quit study treatment	0	1 (CP12)
Drop-outs <36 days (n=4)		
Quit study treatment (after lowering to 5mg TID)	4 (CP06, CP10, CP20, CP23)	0

12.2. Adverse Events (AEs)

12.2.1. Brief summary of Adverse Events

Most frequently related or possibly related reported AEs (≥20%) after Namisol® treatment were: decreased appetite, dizziness, somnolence, dry mouth and hyperhidrosis. Increased appetite, somnolence, dizziness, confusional state and headache were most commonly related or possibly related to placebo treatment.

12.2.2. Display of Adverse Events

All related, probably related and possibly related AEs are presented in table 26. All subjects fully recovered from AEs. All related, probably related and possibly AEs were mild or moderate. Serious adverse events are reported in Section **Fout! Verwijzingsbron niet gevonden.**.

Table 26: Display of adverse events

PT term MedDRA	Namisol CP (N=12)		Placebo CP (N=15)	
	N	%	N	%
General				
Decreased appetite	3	25%	1	7%
Fatigue			2	13%
Feeling of relaxation	1	8%	2	13%
Increased appetite	2	17%	4	27%
sleep disorder			1	7%
Weight increased	1	8%		
Nervous system disorders				
Amnesia			1	7%
Dizziness	7	58%	4	27%
Headache	2	17%	8	53%
Paraesthesia	1	8%	1	7%
Somnolence	5	42%	8	53%
Psychiatric disorders				
Abnormal dreams			1	7%
Confusional state	3	25%	3	20%
Decreased libido	1	8%		
Depressed mood			2	13%
Euphoric mood			2	13%
Irritability			2	13%
Tension	1	8%		
Gastro-intestinal system disorders				
Constipation			2	13%
Dry Mouth	4	33%	1	7%
Nausea	2	17%	2	13%
Throat irritation	1	8%		
Skin and subcutaneous tissue disorders				
Acne	1	8%		
Hair texture abnormal	1	8%		
Hyperhidrosis	3	25%	2	13%
Pruritus	1	8%		
Seborrhoea	1	8%		
Rash			2	13%

Musculoskeletal and connective tissue disorders				
Muscle spasms	1	8%		
Tremor			1	7%
Renal and urinary disorders				
Pollakiuria	1	8%		
Vision disorders				
Eye irritations	1	8%	1	7%
Visual impairment	1	8%	1	7%
Cardiac disorders				
Heart rate increased			1	7%
Sinus bradycardia			1	7%
Eye disorders				
Photophobia	1	8%		
TOTAAL	**46**		**56**	

12.2.3. Analysis of Adverse Events

Overall, AEs were experienced in equivalent frequency between conditions, with 46 AEs/ 12 patients in the Namisol® arm and 56 AEs/ 15 patients in the placebo arm. The number of related or possibly related AEs are listed in table 27.

Table 27: Number of AEs

	Namisol			Placebo		
	n	**AEs**	**AEs/n**	**n**	**AEs**	**AEs/n**
Chronic pancreatitis	12	46	3,8	15	56	3,7

12.2.4. Listing of Adverse Events by patient

All AEs listed per subject are presented in appendix D.

12.3. Deaths, other serious Adverse Events, and other significant Adverse Events

No deaths have been occurred during the clinical execution of this study. There were three SAEs (table 28). Subject CP12, CP15 and CP19 were admitted to the hospital due to an exacerbation (pain increase) in chronic pancreatitis. They received additional pain medication, continued study treatment and were recovered. The SAEs were considered not related.

Table 28: SAEs

Subject	Treatment	Diagnose	SAE type	SAE Start	SAE Stop
CP12	Placebo	Abdominal pain	Hospitalization	1-Feb-13	8-Feb-13
CP15	Placebo	Abdominal pain	Hospitalization	8-Apr-13	13-Apr-13
CP19	Placebo	Abdominal pain	Hospitalization	19-Mar-13	21-Mar-13

12.4. Clinical Laboratory Evaluation

No clinically significant abnormalities in laboratory parameters (haematology, biochemistry, and urinalysis) were observed during the study. A listing of all laboratory outcomes is included in appendix D.

12.5. Individual clinically significant abnormalities

12.5.1. Vital signs, physical findings and ECG observations

No clinically significant abnormalities of vital signs, physical findings, ECG results, or other observations related to safety were observed during the study. A listing of diastolic and systolic blood pressure, heart rate and ECG observations is included in the appendix.

12.5.2. Safety Conclusions

Namisol® was generally well tolerated resulting in only mild to moderate adverse events, which were very similar compared to previous studies in healthy volunteers (47) and CP patients (69). Three SAEs reported during this trial were not related to Namisol® administration.

13. DISCUSSION

Much of the literature on the efficacy of THC for pain treatment has been focused on central neuropathic pain syndromes such as multiple sclerosis (MS) and acute pain conditions such as early postoperative pain (70). Less is known about the efficacy of THC in chronic pain states including chronic abdominal pain due to CP. This study was designed to evaluate the efficacy, pharmacokinetics, pharmacodynamics, safety and tolerability of a stable dose Namisol® for a treatment period of 50 days compared with placebo in CP patients suffering from chronic abdominal pain. Results showed similar results between both treatment groups regarding the primary efficacy outcome as well as secondary outcomes.

Analgesic efficacy

Primary efficacy analysis of the average VAS pain at the end of the treatment period did not reveal any significant difference between Namisol® and placebo treatment in this patient population. As this clinical trial was powered to include 68 patients (34 on Namisol and 34 on placebo) and only 23 patients were included in the efficacy evaluation (8 patients on Namisol®, 15 patients on placebo) the lack of efficacy of Namisol® may be caused by this small population size. Delta VAS pain scores were similar with 1.7 points (50%) reduction in the Namisol® arm compared to 2.1 points (43%) reduction in the placebo arm. Clinically meaningful pain relief has been defined as an improvement of 2 points or a 30% reduction (71), which was observed in both treatment arms. Similar results were observed for minimal and maximal reported VAS pain, indicating that Namisol® does not affect the background pain or pain peaks.

It should be mentioned that, despite the randomisation procedure, patients in the Namisol® treatment group demonstrated pain of 1.5 points lower intensity at baseline than patients in the placebo group. A mean VAS pain score of 3.4 points in the Namisol® group is still substantial, but it is statistically more difficult to demonstrate an improvement when pain is low on entry.

Current study is the first randomized controlled trial (RCT) with THC in patients with chronic abdominal pain due to CP. A similar study in patients with chronic abdominal pain resulting from a surgical procedure was performed simultaneously. Several RCTs investigated the analgesic efficacy of different products containing THC in various pain states (49, 70, 72-74). In a majority of these studies, THC treatment resulted in pain reduction in chronic pain as discussed in De Vries and colleagues (2014). In these studies analgesic effects were generally weak compared to placebo and considerable placebo effects were observed in the comparative arm (70). A large number of analgesics have failed to prove superiority over placebo in randomized controlled trials (RCTs) on the primary endpoint. This may be related to insufficient analgesic potency of the investigational drug, but it could also be related to a high placebo response (75). The placebo analgesic response is the reduction in pain experienced by an individual after the administration of an inert treatment, in association with one or more events in the environment that induce the expectation that the pain will decrease (76). The study of placebo effects in visceral pain, that is primarily focused on patients with irritable bowel

syndrome, demonstrate large placebo responses. A meta-analysis of 73 eligible RCTs including 8.364 patients with irritable bowel syndrome allocated to placebo observed a pooled placebo response rate across all RCTs of 37.5% (77). Underlying mechanisms of the placebo effect can be derived from psychological and neurobiological viewpoints. Two well supported mechanisms from a psychological point of view are expectancy and conditioning (78). Factors that influence the magnitude of the placebo response in RCTs include type of active medication, randomization ratio, and the number of planned face-to-face visits, thereby supporting the expectancy hypothesis (75). Thus, high expectations toward treatment efficacy of Namisol® might have contributed to the substantial placebo response as observed in the present study.

The failure to proof efficacy can also be considered form a mechanistic point of view. Two major mechanisms are currently proposed to underlie chronic pain and its development: 1) sensitization of nociceptive pathways (central sensitization), and 2) alterations in central cognitive and autonomic processing (79, 80). Patients with persistent pain demonstrated increasing brain activity in areas considered to mediate emotion including the perigenual anterior cingulate cortex, the medial prefrontal cortex, and parts of the amygdala (79). Thus, the representation of pain in the brain shifts over time from the classical acute pain matrix to areas implicated in cognitive function, particularly emotion (70). The frontal-limbic distribution of cannabinoid receptors in the brain suggests that cannabis may preferentially target the affective qualities of pain. A study conducted by Lee et al. demonstrated that dronabinol reduced the reported unpleasantness, but not the intensity of ongoing pain and hyperalgesia. This suggests a shift in central nervous system function from nociceptive to cognitive, affective and autonomic sensitization in patients moving from acute to chronic pain (81). Therefore, an agent targeting particular brain areas related to the cognitive emotional feature of chronic pain, such as Namisol®, might be efficacious in our chronic pain population, but might be better measured using affective outcomes of pain.

Pharmacokinetics

The mean plasma concentration curves, as obtained after 50-52 days of 8 mg TID Namisol® treatment regimen, demonstrate that THC was generally well absorbed and further metabolized in 11-OH-THC, and THC-COOH in CP patients. THC was absorbed with a mean t_{max} of 1,63 hour (98 min) and mean C_{max} of 5,04 ng/mL, and eliminated with a mean $t_{1/2term}$ of 2,62 hour (157 min). Additionally, we observed that subjects with an early t_{max} demonstrate a relatively high C_{max} compared to those subjects with a late t_{max} showing a comparatively low C_{max}. This explains the discrepancy between the mean plasma concentration curves in figures and the computed statistics in tables.

Previous studies evaluating the pharmacokinetics of Namisol® were all accomplished after a single dose administration. Trough levels as obtained in current study on day 15 and day 50-52 demonstrate an altered predose baseline state. This makes postdose comparisons of the pharmacokinetics not possible. Additionally, CP is associated with malabsorption (82, 83), which potentially affects drug absorption and could explain the inter-individual PK variation in patients with CP and the higher than expected Tmax (84). Drug absorption in

CP patients might further be affected by alterations in gastrointestinal intraluminal pH, gastrointestinal motility, bacterial overgrowth and changed pancreatic gland secretion(84). In addition, bowel dysfunction is a common adverse effect of prolonged opioid use (85), which may affect the absorption of drugs as well. However, the pharmacokinetics of orally administrated THC showed reliable concentration-time curves as obtained after 50-52 days of 3 TID study treatment.

Pharmacogenetics

The effects of CYP2C9 and CYP2C19 polymorphisms on the pharmacokinetics of Namisol® were evaluated. Sachse-Seeboth et al. found that the homozygous CYP2C9*3 variant affected the pharmacokinetics of THC, resulting in a three folded area under the curve of THC, as well as a trend towards increased sedation after oral administration of THC (86). Alterations in pharmacokinetics might affect the efficacy and adverse effects. In current study, there were 9 intermediate metabolizers based on CYP2C9 polymorphism and 7 intermediate metabolizers based on CYP2C19 polymorphism. There were no slow metabolizers and 3 ultra rapid metabolizers according to their genotype. We did not observe clear differences in THC plasma concentrations between intermediate, extensive and ultra rapid metabolizers. This can be explained by the fact that there were no patients being homozygous carriers as well as by the small number of subjects with a genetic variant. However, it cannot be precluded that genetic polymorphisms might have contributed to the inter-individual variation in the pharmacokinetics of Namisol®.

Pharmacodynamics

Several questionnaires were used to evaluate a variety of potential effects during the 50-52 days treatment with Namisol®. No differences were observed in secondary pain questionnaires such as the pancreatitis-specific pain questionnaire (Izbicki), patient global impression of change, pain catastrophizing or pain related anxiety. Measures of depression and generalized anxiety, quality of life, treatment satisfaction did also not change after Namisol® treatment compared with placebo. Additionally, Namisol® did not affect psychedelic outcomes and subjective feelings corresponding to alertness, mood and calmness in CP patients.

Patients reported a significant improvement in appetite in comparison with their appetite level prior to start study treatment. However, no statistically significant differences between Namisol® and placebo were observed for appetite level in the last week or body weight. It should be mentioned that the AppLe is a modification of the PGIC for the evaluation of this specific aspect and not validated for this use.

Similar results were observed for the body sway measurements. Balance disturbances were shown in several individuals and did not increase during study treatment of both Namisol® and placebo. The absence of differences in most pharmacodynamic parameters can be explained by the nonappearance of these effects, but might also indicate a habituation effect in the step-up phase and following stable dose treatment phase.

Safety and tolerability

Two patients administrating Namisol® discontinued study treatment due to adverse events. These patients did not tolerate a dosage of 5 mg TID Namisol® and withdrew due to mild to moderate AEs. However, the majority of CP patients tolerated Namisol® at dosage regimens of 8 mg TID generally well. AEs were typical for THC, such as decreased appetite, dizziness, somnolence, dry mouth and hyperhidrosis. It should be mentioned that the majority of AEs reported by patients in clinical trials are often not caused by the study medication (87, 88). In current study, the considerable number of AEs reported in the placebo group as well as the withdrawal of patients because of AEs, although being in the placebo arm, indicate that AEs were partly determined by nonpharmacological effects (89). This so called nocebo effect induces negative effects due to negative expectations. Cannabis is a generally well known product, particularly as recreational drug to induce desired psychotropic effects such as euphoria, relaxation, and perceptual alterations. Therefore, it is plausible that patients in this study were influenced by these negative expectations, that might have influenced the occurrence of AEs.
In general, Namisol® was well tolerated resulting in only mild to moderate adverse events, Additionally, the tolerability of Namisol® in this population of patients with CP was similar to that observed in another group of CP patients (69) and healthy volunteers (47). Three patients experienced serious AEs during the study treatment that were considered by the investigator to be not related to the study drug.

Study limitations
Limitations of the current study might have contributed to the failure to show efficacy. A major limitation of the present study is the small sample size. The planned 68 patients to be included in this trial could finally not be recruited. The reasons for this are described in Section 10.1. Using the included 29 patients, with ultimately 8 evaluable patients in the Namisol® group and 15 patients in the placebo group, the possibility to obtain statistical significant results on the primary objective in such a small group is very limited and in fact only possible when a very high pain reduction of Namisol® was obtained.
The measured VAS pain group means do not deviate much from each other. Theoretically, in case the variability is low, this difference between placebo and active will not change using a larger sample size. However, the variation in the VAS pain score is substantial (both between patients and in time), indicating that a larger sample size might have affect the efficacy outcome. Taking into account that the placebo effect in clinical trials is generally high, the small number of patients tested limited the possibility to detect potentially significant pain reducing effects of Namisol®.

Patients enrolled in this study were characterized by chronic abdominal pain resulting from CP. Patients included may have received different treatments for the pain in the past, including surgery, and may have developed exocrine and/ or endocrine failure due to CP. Additionally, the severity, duration or causes of CP differ among patients. Although we assume a similar treatment effect of Namisol® across this heterogeneous patient population, other varying patient characteristics might have influenced treatment effects. On the other hand, the outcomes can be generalized towards the true clinical population.

In addition, nearly all patients were receiving analgesics before study entry. While patients still reported a high level of pain scores before study entry, it should be mentioned that these analgesics failed to provide a satisfied level of pain relief. Thus, this study included a selection of patients who did not sufficiently respond on current analgesics with proven efficacy.

Conclusion

In this phase 2 study, 8 mg TID Namisol® showed acceptable safety and tolerability profiles during a treatment period of 50-52 days, but did not significantly reduce pain scores in CP patients with chronic abdominal pain. The lack of observed efficacy regarding Namisol® might be explained by a large placebo effect, in combination with the small study population.

14. APPENDICES

A. Curriculum Vitae Principal Investigator

B. Randomization scheme

C. Study results combined population (Study HEEL-2011-02 and HEEL-2011-03)

D. Listings

- D.1. Patients demographics and clinical characteristics
- D.2. Concomitant pain medication
- D.3. Pharmacogenetics
- D.4. Pharmacokinetics
- D.5. VAS Pain
- D.6. VAS Bond&Lader
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- D.13. Izbicki
- D.14. Body weight
- D.15. Body Sway
- D.16. Heart rate
- D.17. Blood pressure
- D.18. Adverse events

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APPENDIX A

Curriculum Vitae Principal Investigator

Prof. dr. H. van Goor

PERSONAL DETAILS

Name	Harry van Goor, MD, PhD, FRCS
Date of birth	18 April 1957
Work address	Radboud University Medical Center Department of Surgery 690 P.O. Box 9101 6500 HB Nijmegen, The Netherlands Tel +31243668086, Fax +31243540501
Mobile	+3124620415961
Email address	Harry.vangoor@radboudumc.nl

MAIN ACHIEVEMENTS IN THE LAST 5 YEARS

Principal Lecturer	2009-
Principal Investigator	2012-
Founding of the Dutch Adhesion Group	2009
(Co)founding of the Regional Pancreatic Centre (PACON)	2010
Fellow of the Royal College of Surgeons of England	2010-
Professor of Surgical Education	2013-

EDUCATION/ PREVIOUS AND CURRENT EMPLOYERS	1969 – 1975	Gymnasium ß, Carolus Clusius College Zwolle
	1975 - 1983	Medical school, University Groningen
	1977 – 1979	Student-assistant, Laboratorium for Histology University Groningen
	1979 – 1980	Student-assistant Education, Department of Surgery, University Hospital Groningen (Prof dr. R.P. Zwierstra)
	1983 - 1986	Transplantcoordinator/Organ Procurement Officer University Hospital Groningen
	1986 – 1989	Surgical Training, Isala Hospitals, Zwolle (Head: Dr. W. van Rooyen)
	1989 - 1992	Surgical Training, University Hospital Groningen (Head: Prof dr. R. van Schilfgaarde
	1992 - 1994	Fellow Vascular and Transplant Surgery, University Hospital Groningen
	1994 - 1999	Senior Staff Member Abdominal Surgery Radboud University Nijmegen Medical Centre
	1999 - 2013	Associate Professor of Surgery (Surgical Education), Radboud University Nijmegen Medical Centre
	2000 - 2003	Chef de Clinique, Department of Surgery Radboud University Nijmegen Medical Centre
	2003-2008	Vice-director, surgical training program, Radboud University Nijmegen Medical Centre
	2008-	Head of Education, Department of Surgery Radboud university medical center
	2009-	Principal Lecturer, Radboud university medical center
	2010-	Fellow of the Royal College of Surgeons of England (FRCS)
	2012-	Principal Investigator, Radboud university medical center
	2012-	Head of Surgical Research Laboratory, Radboud university medical center
	2013-	Professor of Surgical Education, Radboud university medical center

Since the end of 2013 the Radboud University Nijmegen medical Centre is renamed Radboud university medical center (Radboudumc)

RESEARCH ACTIVITIES

The clinical and experimental research lines include the epidemiology, diagnosis and treatment of inflammatory and infectious surgical diseases in the abdominal cavity including early and long term postoperative healing and healing disturbances. Focus is on common surgical issues such as intra-abdominal adhesion formation, (intra-abdominal) surgical infection, anastomotic healing, incisional hernia and acute and chronic visceral pain and inflammation [BIG5A]. An important part of the research is the development and testing of new biomaterials to prevent intra-abdominal complications (e.g. adhesion formation, anastomotic healing, incisional hernia).
The educational research includes surgical skills training in the 'medical continuum'. Focus of research is on evidence based simulation, coaching in action and individual learning processes in skills training. The theme is 'Simulation Into Practice'.
Since 2014 a research line in the field of surgical innovation has started with the name 'The Surgical Journey'. This line include several programs such as 'continuous monitoring with wearable sensors', beat the pain, cheat the brain' and 'a room with a view'. The research focuses on smart, simple and cheap technological and care solutions to improve preoperative, operative and postoperative surgical care

External funding has been by surgical industry for clinical and experimental research and by European, National and Hospital grants. Total funding amount with partners is about 15 million dollars of which over 3 million is personal funding since the year 2005.

Supervision of Postdocs, PhD students, technicians, etc

A Chaturvedi	Surgery/EMCN	Msc, PHD student
M. de Vries	Surgery/Anesthesiology	Msc, PhD student
S. Bouwense	Surgery	MD, Postdoc
RP. ten Broek	Surgery	MD, Postdoc
D. Rijckevorsel	Surgery/Anesthesiology	MD, PhD student
S. Alken	Surgery/IWOO	PhD student
C. Strik	Surgery	MD, PhD student
S. Yauw	Surgery	MD, PhD student
J. Harder	Surgery	MD, PhD student
E. van de Pol	Surgery/IWOO/Pediatrics	PhD student
Y. Benthem	Surgery/IWOO/Pedriatrics	PhD student
M. Stommel	Surgery	MD, PhD student
I. van Heusden-Schotalbers	Fysiotherapy/Surgery/ÏQ Healthcare	Msc, PhD student
N. Slater	Surgery	MD, postdoc
JN Luursema	Surgery/Operating Rooms	Postdoc
T van de Belt	Reshape Innovation center	Postdoc
M Weenk	Surgery/reshape & innovation center	MD, PhD student

R Klabbers	Surgery/Univ Chicago	Bsc, PhD student
M Arron	Surgery/Univ Chicago	Bsc, PhD student
E Ozturk	Surgery/KNMG	MD, PhD student
R Lomme	Surgery/laboratory	Biotechnician

Thesis supervisor/copromotor

PhD student	**Title thesis**	**PhD defense**
MMPJ Reijnen	Effects of hyaluronan on intra-abdominal adhesion and abscess formation. An experimental study	2002
I. de Hingh	Anastomotic healing in the intestine: preclinical studies with the emphasis on the role of gelatinases and the effect of peritonitis	2005
TS de Vries Reilingh	Reconstruction of large abdominal wall defects: 'components separation technique' and prosthetic repair	2007
TJ Stefaniak (Universiteit Tilburg)	Surgical pain interventions: Evaluation and identification of determinants of success and failure	2008
OB Buyne	Fibrinolytics to prevent abscess formation in peritonitis	2009
L Posma-Bouman	The influence of ischemia and reperfusion on the healing of experimental intestinal anastomoses	2011
CJJM Sikkink	Applications of hyaluronan in abdominal surgery. An experimental study	2011
HCJL Buscher	Bilateral Thoracoscopic Splanchnicectomy for chronic pancreatitis pain	2012
RP ten Broek	The Burden of adhesions	2014
N Slater	Reconstruction of complex abdominal wall defects	2014
CS Andeweg	Changing strategies in diverticulitis	2015
SAW Bouwense	Systematic mechanism-orientated approach to chronic pancreatitis pain	2015

TEACHING ACTIVITIES/EDUCATIONAL MANAGEMENT/PAST (P) and PRESENT

Student Education	* Chairman Master curriculum Medicine Radboud University Medical Center * Educational management team 1 (P) * Examination Board Medical School (P) * 'Voortgangstoets' committee Medical School (P) * Vice-Coordinator Bachelor Course 'Stofwisseling 2' (P) * Project group Skills & Simulation Centre (P) * Member Core Group Medical education (P) * Coordinator Master Programme Surgery (P) * Coordinator Senior Clerkship Master Programme Medical School (P) * Coordinator Surgery Clerkship, Master Programme Medical School * Coordinator 'Free Choice Clerkship' Master Programme Medical School * Coordinator Clinical Orientation for 2nd year students * Teacher Bachelor course 'Infectie en Afweer' (P) * Teacher Bachelor courses 'Hoofdlijnen Functionele Morfologie', 'Stofwisseling 2' and Minor Biology (P) * Teacher in Teach the Teacher course (skills training), Radboud University Medical Center * Teacher postgraduate surgical nursing course, 'Radboud Zorg Academie' (P) * Chairman Patient Contact Team (PACT) new bachelor curriculum (2015-) * Chairman KichOff@Radboudumc congress new bachelor curriculum (2015-)
Resident Education	* Coordinator Post Graduate Courses on Surgery (PACONU) (P) * Coordinator Basic Course Operative Techniques (BOT) (P) * Coordinator Basic Course G-I Surgery (National) (P) * Coordinator Advanced Course G-I Surgery (National) * Faculty member AGC course Davos, Switzerland' * Coordinator 'Bootcamp' (CASH 1) Dutch Association of Surgeons * Coordinator skills training Department of Surgery * Teacher Post Graduate Courses on Surgery (PACONU) * Teacher National resident courses (CASH 2), Dutch Association of Surgeons * Programme director local G-I surgery differentiation
Postgraduate Education	* Coordinator and Teacher Basic Course Operative Techniques (BOT) for general practicians, nursing home specialists, anaesthetists. * Teacher Advanced International G-I surgery, Davos, Switzerland

RELEVANT EDUCATIONAL AND MANAGEMENT COURSES

IOWO, KUN, Nijmegen 1997
Train the Trainer, London 1999
Radboud Integrated Management 1998/1999
GCP exam, 2008
Human factors, Crew Resourse Management, Wings of Care, 2011
HBO management, 52.5 credits points, 2010
Creative leadership, Brussel, 2015

MEMBERSHIPS OF PROFESSIONAL SOCIETIES

Membership Societies National
Dutch Association of Surgeons
Dutch Society of Gastro-Intestinal surgery
Dutch Society of Medical Education
Dutch Pancreatitis Group
Dutch Society of Day Care and Short Stay Surgery
Dutch Hernia Society
Dutch Adhesion Group

Membership Societies International
Association of Surgical Education
Royal College of Surgeons of England
Surgical Infection Society-Europe
Peritoneal and Surgery Society
European Pancreatic Club
International Association of Pancreatology
European Hernia Society
American hernia Society

GOVERNING BOARD AND COMMITTEE ACTIVITIES

Local
Simulation Skills project group, Chairman (2002-2004)
Center for Infectious Diseases Nijmegen (2001-2006)
Day Care Surgery project, Chairman (2000-2002)
Several committees for European tenders for surgical materials such as surgical gloves, suture materials, laparoscopic instruments

National
WIP committee guidelines hand disinfection (2006).
Dutch Society of Ambulatory Surgery, Chairman (2002-2006)
Dutch Adhesion Group, Chairman (2009-)
CASH, secretary (1994-2000 and 2010-)
National examination committee, Dutch Society of Surgeons (2008-2010)
KNMG elderly program, surgical representative (2012-)
Chairman Dutch Adhesion Group (sept 2015-)

International
Treasurer PnS society (2008-2012)
President PnS Society (2012-2015)
Treasurer Surgical Infection Society-Europe (1999-2003)
Secretary Surgical Infection Society-Europe (2003-2005)
President Surgical Infection Society-Europe (2009-2012)
Faculty G-I course, Davos (2001-)
Chairman Educational Committee SIS-E (2012-)
World Surgery Advisory Board Ethicon products (2010-)

REVIEWING FOR AND EDITORSHIPS OF SCIENTIFIC JOURNALS

Editorial board
Journal of Inflammation Research

Reviewer
Annals of Surgery
British Journal of Surgery
Surgical Infections
World Journal of Surgery
Bioresearch
European Surgical Research

Clinical Reviewer for European Notifying Body (DEKRA, former KEMA) and FDA for certifying medical devices

PRIZES AND AWARDS

1.First prize category surgery at medical film festival (film title: organ donation), Parma Italy, 1984
2.Gottlieb award at John Muir medical film festival (film title: organ donation), San Francisco USA, 1985
3.Heyendael prize for outstanding contribution in Postgraduate Education, 2006
4.Student prize (6x in a row) best preparing module Masterprogramme 2008-2014 (CKO3 VOOR), Radboud University Medical Center
5.Student prize best lecturer 2010 and 2011 (docent van het 2de jaar 2010 en 2011), Radboud University Medical Center

EXPERIENCE ABROAD

1995, Pancreatic unit, University Hospital Ulm (Head Prof dr. H. Beger)
2007, Genzyme cooperation, Cambridge MA, USA, 1 months

RESULTS OF SCIENTIFIC RESEARCH

PhD Thesis
Fibrinolytic therapy in generalized peritonitis to prevent intra-abdominal abscess formation: an experimental and clinical study. Nijmegen, 2 February 1996.

Author of
233 International peer reviewed papers
29 Book chapters
4 Books (editor)

APPENDIX B

Randomization Scheme

HEEL-2011-03/ AKF1877

AKF1879 Randomisatielijst.xls/totaal

Randnr	Behandeling
1	1
2	1
3	0
4	0
5	0
6	1
7	1
8	0
9	1
10	1
11	0
12	0
13	1
14	1
15	0
16	0
17	0
18	1
19	0
20	1
21	0
22	1
23	1
24	0
25	1
26	0
27	0
28	1
29	1
30	0
31	0
32	1
33	0
34	0
35	1
36	1
37	1
38	0
39	0
40	1
41	0
42	1
43	1
44	0
45	0
46	1
47	1
48	0

0 = placebo
1 = namisol

Drs M Welzen 10 OKT. 2012 10-10-2012