

BMJ Open Low-dose naltrexone for the induction of remission in patients with mild to moderate Crohn's disease: protocol for the randomised, double-blinded, placebo-controlled, multicentre LDN Crohn study

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To cite: Paulides E, Lie MRKL, van der Woude CJ. Low-dose naltrexone for the induction of remission in patients with mild to moderate Crohn's disease: protocol for the randomised, double-blinded, placebo-controlled, multicentre LDN Crohn study. *BMJ Open* 2022;**12**:e058358. doi:10.1136/bmjopen-2021-058358

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-058358>).

Received 20 October 2021
Accepted 25 March 2022



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ABSTRACT

Introduction Crohn's disease (CD) is an inflammatory bowel disease (IBD). Several drugs exist to induce and maintain remission, but a significant part of the patients is refractory to current IBD drugs or experiences side effects. Whether low-dose naltrexone (LDN) is a safe and easily accessible alternative treatment option for these patients needs to be investigated. The aim of this study is to assess the efficacy of LDN for the induction of remission in patients with mild to moderate CD.

Methods and analysis The LDN Crohn study is a randomised, double-blinded, placebo-controlled multicentre trial. Patients with CD are randomised 1:1 to receive treatment with either LDN 4.5 mg once daily or placebo for 12 weeks. The primary objective is endoscopic remission at week 12, defined as Simple Endoscopic Score-CD \leq 2 and ulcerated surface subscore \leq 1 in all five segments. Secondary aims include clinical and endoscopic response, changes in laboratory measures of inflammation, adverse events and patient-reported outcomes. To have 85% power to detect a true difference in the primary outcome measure between placebo and LDN, 61 patients will be needed in both groups.

Ethics and dissemination The study is approved by the Medical Ethics Committee of the Erasmus MC, Rotterdam, the Netherlands (registration number NL69149.078.19, MEC-2019-0602). Results will be published in peer-reviewed journals and presented at international conferences.

Trial registration numbers EudraCT2019-000852-32; NL9259.

INTRODUCTION

Crohn's disease (CD) is a chronic, progressive, inflammatory disease of the gastrointestinal tract. Treatment strategies aim to induce sustained remission, by controlling inflammation and preventing complications of the disease. The last decade, an increasing number of new drugs with different mechanisms of action have been introduced to

Strengths and limitations of this study

- The low-dose naltrexone (LDN) Crohn study is the first randomised, double-blinded, placebo-controlled multicentre study that investigates the efficacy of LDN for the induction of remission of mild to moderate Crohn's disease in adults.
- The results of this study will help to decide whether LDN might be an alternative option for inducing remission in patients with mild to moderate Crohn's disease.
- LDN is cheap and has a low adverse events profile.
- The National Crohn and colitis patient's organisation is involved and patient-reported outcomes are included.
- The mechanism of action and long-term safety aspects of LDN in patients with mild to moderate Crohn's disease are not yet fully understood.

induce and/or maintain remission in CD. Although the currently available therapies are effective in many patients, all therapies have their individual safety concerns.¹ Immunosuppressive drugs or combination therapy with biologicals might induce bone marrow suppression, liver test abnormalities, malignancies and do have immunogenic risks.² Further, the introduction of biologicals resulted in increased drug and societal costs.³ The lifelong nature of CD increases the probability that patients have cycled through various therapies, leaving few approved options. Thus, alternative treatments that are less expensive and have a favourable side effect profile remain of continued interest.

A relatively unknown area of interest in the therapy of inflammatory bowel diseases (IBD) is the role of the opioid system. Available evidence suggests that the endogenous

opioid system is involved in gastrointestinal inflammation.^{4,5} Animal and human studies showed that the μ -opioid receptor (MOR) was upregulated in subjects with IBD. In addition, they demonstrated that MOR agonists can decrease inflammation through regulation of pro inflammatory cytokine release and T-cell proliferation.^{6,7} This led to the idea of new therapeutic options for the treatment of IBD by the development of selective MOR agonists. A familiar MOR agonist is naltrexone: an orally administered narcotic antagonist that is approved for the treatment of alcohol dependence by the European Medicines Agency (EMA) and Food and Drug Administration (FDA).⁸ When administered at high concentrations, for example 50 mg, this drug acts as an agonist by blocking the endogenous opioid effects. However, administered in lower doses, such as 4.5 mg, it is assumed that this lower naltrexone dose results in upregulation of endogenous enkephalin and endorphin levels and has a positive modulatory effect on the MOR, thereby controlling gut inflammation.^{9,10} Thus, the use of so called low-dose naltrexone (LDN) in the clinical settings has gained interest in IBD.

At the Erasmus MC, a pilot study was performed to evaluate the effect of LDN on the clinical, biochemical and cellular level in patients with IBD. In this study, patients not in remission and not responding to conventional therapy were offered to initiate LDN as a concomitant treatment. Among 47 patients that started LDN, 74.5% experienced clinical improvement and 25.5% clinical remission at week 12. A minority of the patients experienced side effects, but these were relatively mild and consisted of vivid dreams, drowsiness and headache. LDN therapy resulted in reduced endoplasmic reticulum stress in biopsies from inflamed mucosa, and led to improved wound healing in *in vitro* models.¹¹ To objectively define the effect of LDN on intestinal inflammation, a randomised controlled trial with endoscopic assessment is necessary. Only via an objective assessment we can elucidate the exact role of LDN in the treatment of patients with CD.

Therefore, the aim of this study is to prospectively assess the efficacy of LDN as induction therapy in patients with active CD.

METHODS

This protocol includes the standard protocol items recommended for interventional trials according to the Standard Protocol Items: Recommendations for Interventional Trials guidelines.¹² The most recent study protocol (Protocol V.4, June 2021) is presented in this manuscript. The date of the first enrolment was 14 January 2021.

Study setting

This randomised, double-blinded, placebo-controlled multi-centre trial is currently being performed at departments of Gastroenterology and Hepatology in the Netherlands, including both academic and non-academic centres. At this stage, seven hospitals are participating, and we are currently expanding the number of collaborating centres. Patients that underwent a colonoscopy and seem eligible for inclusion or patients that are interested will receive information about the study via the doctor or researcher, at the clinic or by phone. Eligible patients with active CD are randomised 1:1 to receive treatment with either LDN 4.5 mg once daily or placebo, for 12 weeks. After 12 weeks patients are invited to participate in an open label exploratory extension study until week 52. Adult patients with mild to moderately active CD, defined by endoscopy with mucosal ulcers in the ileum and/or colon and a Simple Endoscopic Score-CD (SES-CD) of 3–15, who visit the outpatient clinic of the department of Gastroenterology and Hepatology of participating hospitals are eligible.¹³ Clinical visits are planned at week 0, 4, 12 and if applicable week 24 and 52. Telephone consults are scheduled at week 2, 8 and if applicable week 36. See [figure 1](#) for the flow chart of the study design. Prior to enrolment, all patients must sign informed consent (online supplemental appendix 1).

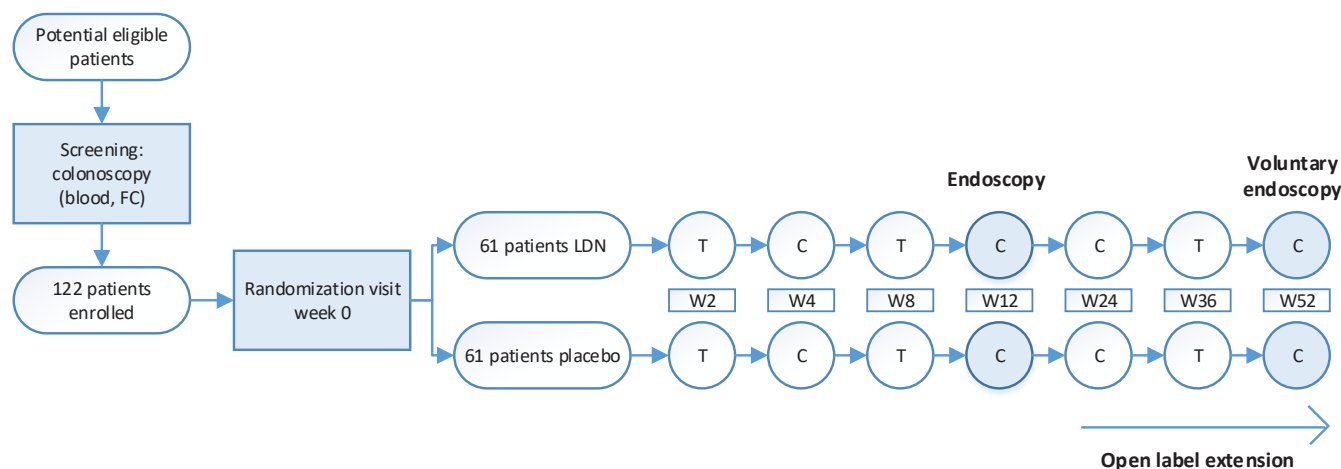


Figure 1 Flowchart of the study design, with endoscopy as primary outcome at week 12. C, clinical consult; FC, faecal calprotectine; LDN, low-dose naltrexone; T, telephone consult; W, week.

Participants

Eligibility criteria

Patients with mild to moderately active CD, defined by endoscopy with mucosal ulcers in the ileum or colon or both, and SES-CD of 3–15, aged 18 years or older who visit the outpatient clinic of the department of Gastroenterology and Hepatology of participating hospitals are eligible. Endoscopic assessment up to 2 months prior to the start of the study is mandatory. Permitted concomitant CD therapies are: aminosalicylates, azathioprine, 6-mercaptopurine, thioguanine and methotrexate provided the dose prescribed has been stable for at least 4 weeks prior to randomisation; dose must be stable for the first 10 weeks after randomisation. Oral corticosteroid therapy (prednisone prescribed at a stable dose ≤ 30 mg/day or budesonide prescribed at a stable dose of ≤ 9 mg/day) must have been stable for 2 weeks prior to randomisation, and tapering during the study is mandatory. The use of other investigational products, biologicals, Janus kinase/signal transducer and activator of transcription (JAK-STAT) inhibitors, cyclosporine, thalidomide and tacrolimus is prohibited, and these medicines need to be stopped 12 weeks prior to the start of the study. Other exclusion criteria are opioid use, drugs and/or alcohol abuse, pregnancy or lactation, stool positive for an infectious agent, and other significant medical conditions that might interfere with the study (such as a stricture causing symptoms or fistulising disease complicated by infection).

Interventions

Investigational product

In this study, the participants will be given naltrexone 4.5 mg or placebo once a day. This dose is used because of the agonistic effect of naltrexone on the MOR when administered at a low dose, and because data on efficacy and safety of this dose is already available. The active substance in the investigational medicinal product (IMP) is naltrexone hydrochloride. Naltrexone is a derivative of noroxymorphone that is the N-cyclopropylmethyl congener of naloxone. It is a narcotic antagonist that is effective orally, and longer lasting and more potent than naloxone. The placebo IMP for this trial has the same qualitative composition, except naltrexone hydrochloride. Therefore, placebo and LDN capsules are identical in appearance. The remaining ingredients are: Microcrystalline cellulose PH-102, Colloidal anhydrous silica, Magnesium stearate and lactose monohydrate 100 mesh. Naltrexone (50 mg) was approved for the treatment of alcohol dependence in June 2010 by the EMA and FDA. EU-procedure number: NL/H/1151/001/DC Registration number in the Netherlands: RVG 102900.

Patient reported outcomes

During every scheduled consult, patients are asked to fill out questionnaires online (see [table 1](#)). This includes the Patient Reported Outcome-2 (PRO2)¹⁴ and the Harvey Bradshaw Index (HBI)¹⁵ for disease activity, the short Inflammatory Bowel Disease Questionnaire (SIBDQ)¹⁶ and the 5-level EuroQol Five Dimensions Health Questionnaire (EQ5D-5L)¹⁷ for quality of life, the Work

Table 1 Schedule of study procedures, interventions and assessments

Procedures	Screening	Induction phase					Maintenance phase		
		Week 0	Week 2	Week 4*	Week 8*	Week 12	Week 24	Week 36	Week 52
Clinical visit	(X)	X		X		X	X		X
Telephone consult	(X)		X		X			X	
Eligibility screening	X								
Informed consent	X								
Colonoscopy	X					X			(X)
Laboratory tests*	X			X		X	X		X
Feecal calprotectin	X					X	X		X
Baseline information		X							
Concomitant medication		X	X	X	X	X	X	X	X
HBI, PRO2		X	X	X	X	X	X	X	X
SIBDQ, EQ-5D-5L, FACIT-F, MFI, NIH-PROMIS, WPAI		X		X		X	X		X
Adverse events			X	X	X	X	X	X	X

*Laboratory tests include: urea, creatinine, CRP, aspartate transaminase, alanine transaminase, lactate dehydrogenase, alkaline phosphatase, haemoglobin, mean corpuscular volume, thrombocytes, leucocytes
CRP, C-reactive protein; EQ5D-5L, 5-level EuroQol Five Dimensions Health Questionnaire; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F); HBI, Harvey Bradshaw Index; MFI, Multidimensional Fatigue Inventory; NIH PROMIS, sleep, anxiety and depression via the Patient-Reported Outcomes Measurement Information System; PRO2, Patient Reported Outcome-2 (PRO2); SIBDQ, short Inflammatory Bowel Disease Questionnaire; WPAI, Work Productivity and Activity Impairment Questionnaire.

Productivity and Activity Impairment Questionnaire (WPAI)¹⁸ for work productivity, fatigue via The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)¹⁹ and Multidimensional Fatigue Inventory (MFI)²⁰ and sleep, anxiety and depression via the Patient-Reported Outcomes Measurement Information System.²¹

Endoscopic assessment

A colonoscopy will be performed during screening (maximum of 8 weeks before the start of the study) and at the end of the induction phase at week 12. If patients are willing to participate in the open label follow-up study, an extra colonoscopy can be performed at week 52 (see figure 1). Colonoscopy allows for direct mucosal visualisation and the performance of biopsies. By using the SES-CD, activity, and severity of CD before and after treatment can be determined.

Serum and stool samples

Baseline blood and stool samples will be obtained from all participants, with a maximum of 8 weeks before the start of the therapy. During the study, blood will be checked at week 4 and 12 and every 3 months during the maintenance phase if applicable (see table 1). Laboratory tests include: urea, creatinine, C-reactive protein (CRP), aspartate transaminase, alanine transaminase, lactate dehydrogenase, alkaline phosphatase, haemoglobin, mean corpuscular volume, thrombocytes, leukocytes. Faecal calprotectin (FC) will be collected at week 12, and if applicable at week 24 and 52. This granulocyte-derived protein is measured in the stool and is a non-invasive, cheap and extensively studied biomarker that correlates with clinical and endoscopic disease activity.²²

Disease worsening criteria

Patients that show an increase in HBI at two consecutive visits can be discontinued from blinded treatment and can be offered the option to receive open-label therapy. If a subject experiences significant worsening of underlying CD, which requires any of the prohibited medications or surgical intervention at any point during the study, treatment discontinuation should be considered at investigator's discretion.

Outcomes

See table 1 for the schedule of study procedures and interventions.

Primary outcome

The aim of this study is to prospectively assess the efficacy of LDN for the induction of remission in patients with mild to moderate active CD. The primary objective is endoscopic remission at week 12, defined as SES-CD ≤ 2 and an ulcerated surface subscore ≤ 1 in all five segments.¹³

Secondary outcomes

Disease activity

- ▶ The proportion of patients in steroid free clinical remission defined as a HBI score of ≤ 4 and complete

tapering of systemic corticosteroids and endoscopic remission at week 12.

- ▶ Response defined by a decrease in HBI of ≥ 3 points compared with baseline and endoscopic response defined as a reduction of SES-CD score by $\geq 50\%$ vs baseline at week 12.
- ▶ Changes in laboratory measures of inflammation (CRP and FC) from baseline at week 12, 24 and 52.
- ▶ Proportion of patients in corticosteroid free clinical remission at week 52.
- ▶ Endoscopic remission and response at week 52.
- ▶ Response via the HBI and PRO2.

Quality of life

- ▶ Quality of life, via the SIBDQ and EQ5D.
- ▶ Fatigue, via the FACIT-F and MFI.
- ▶ Anxiety, depression and sleep disturbance, via the PROMIS NIH.

Healthcare costs and work

- ▶ Work productivity via the WPAI.
- ▶ Healthcare costs will be calculated and the EQ-5D utility will be used to derive a quality-adjusted life-year estimate.

Sample size

A power analysis was performed on the primary outcome of achieving endoscopic remission. Based on previous research, it was estimated that the mucosal healing rates at week 12 would be 25% for LDN and 5% for placebo, and the dropout rate 5%. To have 85% power to detect a true difference in the primary outcome measure between placebo and LDN, 61 patients will be needed in both groups. In total, we plan to recruit 122 patients to include into the study. All statistical analyses will be performed using 2-sided tests with $\alpha=0.05$.¹¹ A sample size calculation based on the data of a smaller RCT from Smith *et al*.²³, resulted in a lower sample size.²³ Because we were unsure if this patient population was representative of our population, we aim to include 122 patients.

Assignment of interventions

Eligible patients will be randomised to one of two groups (LDN or placebo) in a 1:1 ratio. The pharmacy that produced the trial medication numbered the bottles with unique package numbers, according to a randomisation schedule that was generated by a statistician. The trial medication is being stored at the pharmacy of the Erasmus MC and will be sent directly to the participant after inclusion. Patient, doctor and investigator are blinded, and if unblinding is necessary, a pharmacist from the Erasmus MC pharmacy will be asked to provide the information required.

Data management and analysis

Data of all participating centres will be collected and entered both by participants and staff in electronic case report forms of Gemstracker, an electronic database set up for clinical trials.²⁴ Data will be coded, stored and monitored by certified personnel following good clinical practice guidelines.

When subjects are withdrawn from the study, they will not be replaced. When missings are random, imputation of missing data can be carried out. Patients that are lost to follow-up will be incorporated until their lost to follow-up date only, as it is a per protocol approach. Missing and lost to follow-up patients will be described. Adverse events will be registered at every visit and in case of a serious adverse event reported to the METC of the Erasmus MC.

Statistical methods

Demographic and patient data will be described using frequencies and percentages for categorical variables. Continuous variables will be described using mean and SD, or median and IQR for non-normally distributed variables. Categorical variables will be compared between groups using χ^2 test and continuous variables using the t-test or Mann-Whitney U test for non-normally distributed variables. A $p < 0.05$ will be considered statistically significant.

The primary outcome endoscopic remission at week 12, will be compared between the LDN and placebo group using a χ^2 test. The difference between the steroid free clinical remission between the LDN and placebo group, defined by a HBI score of ≤ 4 and complete tapering of systemic corticosteroids and endoscopic remission at week 12, will be measured using a χ^2 test. Response, defined by a decrease in HBI of ≥ 3 points compared with baseline and endoscopic response defined as a reduction of SES-CD score by $\geq 50\%$ at week 12 compared with baseline, will be analysed using a χ^2 test. Proportion of patients in corticosteroid free clinical remission and endoscopic remission at week 52 will be analysed using a χ^2 test as well. Changes in laboratory measures of inflammation (CRP and FC) within each group will be analysed using a paired T-test. The evolution of different patient reported outcomes over time will be analysed using mixed models.

Ethics and dissemination

This study is approved by the METC of the Erasmus MC, Rotterdam, the Netherlands (registration number NL69149.078.19, MEC-2019-0602) on 31 January 2020. Important protocol modifications are assessed and approved by the METC, and reported to participating investigators. Results will be published in peer-reviewed journals and presented at international conferences.

Patient and public involvement statement

This study was designed in collaboration with a patient with IBD and with the Dutch Crohn's and Colitis patient organisation.²⁵ We will engage closely with the patient organisation to communicate research findings to inform patients on the effectiveness of LDN on controlling inflammation. Patient reported outcomes are included in our study to measure the impact of the intervention on the patient's life.

DISCUSSION

In this double-blinded and placebo-controlled study, the effectiveness of LDN for the induction of remission of

patients with mild to moderate CD is being investigated. The benefits of this therapy will be the anti-inflammatory effects, the low frequency and mild side-effects, the oral administration route, and low costs. Thereby, this study will have direct impact on the management of patients with CD by determining if LDN is useful in the treatment of mild to moderate CD. If LDN is capable of inducing remission, this drug might be implemented in the treatment strategies for patients with CD.

In addition to the preliminary study of the Erasmus MC, several pilot studies have been executed that investigated the effect of LDN therapy in active IBD. An open-label pilot study in 17 patients showed a clinical response in 89% and clinical remission in 67% of the participants after 12 weeks of LDN therapy. Sleep disturbance was the most common side effect, occurring in seven patients.²⁶ The same research group conducted a subsequent randomised, placebo-controlled, double blind study in 34 patients with IBD, and found a response rate of 88% in the LDN group vs 40% in the placebo group after 12 weeks of therapy. In addition, 33% of the participants achieved endoscopic remission in the LDN group vs 8% in placebo group.²³ Furthermore, LDN appeared safe and was well tolerated when investigated in a pilot RCT with 12 paediatric patients with IBD. They showed a significant reduction in PDAI scores after 8 weeks, with 25% of patients achieving clinical remission and 67% showing clinical improvement in the LDN group.²⁷ The authors from The Cochrane Database concluded in their review that there is currently insufficient evidence to allow any firm conclusions regarding the efficacy and safety of LDN, and further randomised controlled trials are required.²⁸

A quasi-experimental before-and-after study from Norway investigated whether initiation of LDN therapy by patients with IBD resulted in changes in the use of concomitant IBD medication. The investigators identified 582 patients with IBD that had at least one LDN prescription recorded in the Norwegian Prescription Database in 2013. Among the 256 patients that became persistent LDN users, there were reductions in number of users of various examined medicines. In addition, the reductions in number of users were larger in persistent LDN users compared with less frequent users for different IBD drugs. This may suggest that LDN use is associated with the use of less concurrent IBD medication in this group of patients, leading to a reduction in costs and in a lowered risk of adverse events.²⁹

A strength of this study is the double-blinded and placebo-controlled design that provides the strongest possible evidence of causation. Further, the primary outcome defined by mucosal healing, assessed by a colonoscopy before and after induction therapy, is the gold standard for evaluating disease activity. In addition, biochemical measures and self-reported disease activity are assessed to follow-up response and relapse over time. There are no evident limitations in the design of the trial, but the anti-inflammatory mechanism of action of LDN is not yet fully understood.

The efficacy signals demonstrated in the (pilot) clinical trials, as well as the beneficial findings in nonclinical models

of disease and the overall safety and tolerability of LDN that have been elucidated to date, result in a favourable benefit-risk profile for this agent in continued investigation as a treatment for CD. Therefore, this randomised, double-blinded, placebo-controlled multicentre trial will provide important insights into the anti-inflammatory effects of LDN in patients with mild to moderate active CD. If LDN is able to induce remission, this drug might be regarded as a first line therapy in the treatment of active CD because of the oral administration, affordability and anticipated low frequency of side effects.

Acknowledgements We thank Dr AC de Vries, Dr RL West, Drs S Nikkessen, T Markus, Dr E Ista for their help in designing the study. We want to thank prof. dr. E.W. Steyerberg for the statistical support.

Contributors CJvdW conceived the idea for the study, designed the protocol and supervises study execution. MRKLL designed the protocol and drafted the manuscript. EP designed the protocol, executes the study and drafted the manuscript. All authors provided critical revision of the manuscript for important intellectual content and approved the final draft of the protocol for submission.

Funding The investigator initiated LDN Crohn study is supported by the Netherlands Organisation for Health Research and Development (ZonMw, Good use of medication, grant number 848082001). ZonMw is part of the Netherlands Organisation for Scientific Research (NWO).

Competing interests Professor CJ van der Woude has served on advisory boards for Abbvie, Takeda, Pfizer and Celltrion. She is supported by research funding from ZonMw, Tramedico, and Pfizer

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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