Final protocol

Discontinuation of infliximab therapy in patients with Crohn's disease during sustained complete remission: A national multi-center, double blinded, randomized, placebo controlled study

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October 19, 2015

Discontinuation of infliximab therapy in patients with Crohn's disease during sustained complete remission:

A Nordic multi-center, double blinded, randomized, placebo controlled study

Study Title:	Discontinuation of infliximab therapy in patients with Crohn's disease during sustained complete remission: A Nordic multi-center, double blinded, randomized, placebo controlled study
Short Study Title:	STOP IT
Protocol number:	010951201207
EUDRACT number:	2012-002702-51
Sponsor/ Principal investigator:	Mark A. Ainsworth, M.D., Ph.D., DMSc Department of Medical Gastroenterology Copenhagen University Hospital, Herlev Herlev Ringvej 75 2730 Herlev Denmark
Date:	19.10.2015
Version:	3.6 (DK)
This study will be conducted according to the principles of Good Clinical Practice and the World Medical Association's Declaration of Helsinki (Tokyo 2004 update)	

PROTOCOL APPROVAL AND INVESTIGATOR AGREEMENT

Discontinuation of infliximab therapy in patients with Crohn's disease during sustained complete remission: A national multi-center, double blinded, randomized, placebo controlled study

I have read this protocol, including its appendices, and will carry out the clinical study as described. The study will be performed in accordance with Good Clinical Practice (ICH-GCP).

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STUDY SYNOPSIS

Study Title:	Discontinuation of infliximab therapy in patients with Crohn's disease during sustained complete remission: A Nordic multi-center, double blinded, randomized, placebo controlled study
Objectives:	Primary Objective: The aim of the study is to investigate if infliximab (IFX) can safely and favourably be discontinued in patients with Crohn's disease in sustained complete remission on IFX maintenance therapy. Secondary Objectives: Further we will examine the clinical utility of measuring levels/activity of IFX and activity of anti-IFX Ab in patients in sustained complete remission, in order to investigate whether pharmacoimmunological data can predict the clinical outcome and rationalize therapeutic management of these patients with respect to continuation or discontinuation of IFX therapy. Additional, we will investigate the optimal time-point, out of three, to measure this activity.
Study Design:	Prospective, double-blinded, randomized, placebo-controlled, Nordic study. Patients, treating physicians and treating nurses are blinded for the type of intervention.
Number of patients & Location of investigative site:	It is planned to include 136 patients in the study. For further details se sample size calculations section 4.2 The locations: Dept. of gastroenterology, Herlev Hospital, Denmark. Dept. of Endokrinology / Gastroenterology I, Bispebjerg Hospital, Denmark. Dept. of Medical diseases, Nykøbing F. Sygehus, Denmark. Dept. of Medical Gastroenterology S, Odense University Hospital, Denmark. Department of Medical Hepato-Gastroenterology V. Aarhus University Hospital /Århus Sygehus, Denmark Department of gastroenterology, The National Hospital of the Faroe Islands, Faroe Islands. Diagnostic center, Silkeborg Regional Hospital, Denmark. Department of Medical Gastroenterology and Hepatology, Horsens Regional Hospital, Denmark. Department of Medical Diseases, Herning Regional Hospital, Denmark. Department of Medical Gastroenterology, Medical Section 360, Hvidovre Hospital, Denmark. Center of Abdominal diseases, Clinic of Gastroenterology, Helsinki University Central Hospital Meilahti, Finland. Center of Abdominal diseases, Clinic of Gastroenterology. Helsinki University Central Hospital Peijas, Finland. Department of gastroenterology, Lund University Hospital, Sweden. Department of Medicine, Gastroenterology Unit, Karolinska University Hospital, Sweden.

Study Population:	Primary inclusion criteria: • Luminal Crohn's disease defined according to standardized diagnostic criteria. • Age ≥ 18 years. • IFX treatment length minimum 12 months (minimum 365 days from first IFX administration to last IFX administration prior to inclusion). Episodic therapy with IFX pause > 12 weeks is not accepted within the last year. The treatment interval in the last three months has to be of 6-10 weeks. • Complete remission defined as: o Crohn's Disease Activity Index (CDAI) score < 150,[22] and o Biochemical remission, and o No other signs of disease activity as evaluated by endoscopic examination, by magnetic resonance imaging (MRI) and / or capsule endoscopy. • Stable remission, judged by the treating physician, at two consecutive treatments visits corresponding 2 scheduled IFX infusions. Thus, the first visit is during IFX maintaining therapy (screening visit). The second visit is at time of inclusion corresponding time of next scheduled IFX infusion (i.e. after ≈ 8 weeks). • No use of oral steroids within 3 months prior to inclusion. • Concomitant therapy with other immune suppressants, except steroids, is allowed. The dosage and frequency must have been stable three months prior to inclusion and must remain stable throughout the study period. Primary exclusion criteria: • Initial indication for IFX being predominantly fistulizing perianal disease. • Active fistulizing disease • Any contraindications for continuing IFX treatment, including prior acute or delayed infusion reaction to a TNF- inhibiting agent, any active infection requiring parenteral or oral antibiotic treatment, known infection with tuberculosis, human immunodeficiency virus (HIV) or hepatitis virus. • Any condition including physician finds incompatible with participation in the study or the patient being unwilling or unable to follow protocol requirements.
Study treatment and study drug administration:	Patients are randomized to either continue IFX therapy at an unchanged dosage, or alternatively to receive matching placebo. IFX therapy at an unchanged dosage (as before inclusion) or matching placebo will be administered as a 1 hour intravenous infusion every eight weeks.

Study Procedures:	See also study flow chart (Figure 2) and Table 1. All patients will be graded for disease activity by CDAI, WPAI, IBDQ, biochemical parameters, endoscopy, and/or MRI) at baseline. Following screening and inclusion patients are seen after four weeks, and then every eight weeks. CDAI score, WPAI, IBDQ, and biochemical parameters: every eight weeks throughout the study period and at four weeks after inclusion.
Study Assessments:	Endpoints are assessed at 48 weeks. Primary endpoint The primary endpoint of this study is the proportion of patients who maintain remission, i.e. CDAI <150. Secondary endpoints Patients who continue IFX and patients who discontinue IFX are compared with respect to the following at 48 weeks after inclusion: • Proportion of patients who maintain complete remission. • Proportion of patients experiencing relapse. • The proportion of patients, who are no longer in remission, but are not in relapse. • Median time to relapse after discontinuation of IFX. • Change from baseline in disease activity evaluated by: CDAI as assessed by CDAI score, quality of life (QoL) as assessed by short-IBDQ, work productivity and activity as assessed by WPAI, biochemical markers assessed by, i.e. C-reactive protein (CRP), albumin, platelets, white blood cell (WBC) count, Hemoglobin (Hb) and fecal calprotectin and colonoscopy (scored by the SES-CD) / MR imaging. • Economical expenses in the to groups.
Initiation Date:	November 9, 2012
Completion Date:	May 1, 2017.

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LIST OF ABBREVIATIONS

Ab	Antibody
ADA	adalimumab
AE	Adverse Event
5-ASA	5-Amino Salicylic Acid
C_1	Concentration one hour after end of infusion
CDAI	Crohn's Disease Activity Index
CRF	Case Record Form
CRP	C-reactive protein
DKMA	Competent Authorities in Denmark
ECCO	European Crohn's and Colitis Organisation
EU	European Union
GCP	Good Clinical Practice
Hb	Hemoglobin
HIV	Human Immunodeficiency Virus
IBDQ	Inflammatory Bowel Disease Questionnaire
IEC	Independent Ethics Committee
IFX	infliximab
i.v.	Intravenously
6-MP	6-Mercaptopurine
MRI	Magnetic Resonance Imaging
NYHA	New York Heart Association
p.n.	Pro necessitate – when necessary
p.o.	Per os, oral administration
QoL	Quality of Life
RADS	Rådet for Anvendelse af Dyr Sygehusmedicin
SAE	Serious Adverse Event
SC	Subcutaneously
SES-CD	Simple Endoscopic Score for Crohn's Disease
SUSAR	Suspected unexpected serious adverse reaction
TNF	Tumor necrosis factor
TNFi	TNF-inhibitor
US	United States of America
WBC	White Blood cell count
WPAI	Work Productivity and Activity Impairment

1. BACKGROUND

Crohn's disease is a chronic inflammatory condition of the gastrointestinal tract, which is thought to arise from a disordered immune response. [1] Time of disease onset, is most common between the age of 15 to 30 years. The prevalence is about 200 pr. 100.000 citizens in Western countries. [2,3] Even though patients experience periods with both high and low disease activity, the course of disease is progressive with a large fraction of patients developing complications such as fistulas, abscesses, strictures, and extra intestinal manifestations, and ultimately resulting in a substantial reduction in quality of life, with, among others, severe daily stomach pains, surgery, malnutrition and sick leave days.[1,4]

Biologic agents targeting tumor necrosis factor (TNF)-alpha such as infliximab (IFX), adalimumab (ADA) and certolizumab pegol are effective in inducing and maintaining remission in patients with moderate to severe luminal Crohn's disease. [1,5-7] The chronic nature of Crohn's disease necessitates TNF-inhibitor (TNFi) maintenance treatment in a large proportion of patients. This, along with potential severe side effects such as infections, infusion reactions and risk of neoplasia,[6] and high economic expenses, warrants exploration of strategies for discontinuing TNFi in patients in long-term sustained remission. While it is generally accepted, albeit yet unproven, that IFX and ADA should not be discontinued in patients who respond, but have not yet obtained full remission (partial remission), recent guidelines, for the management of Crohn's disease (European Crohn's and Colitis Organisation ECCO), conclude that currently available data are insufficient to make firm recommendations on when and in whom to stop IFX or ADA treatment after having obtained clinical remission. [6-10] Of note, however, the most recent British guidelines suggest that all patients preferably should have their disease re-evaluated after one year of therapy, to determine if the treatment is still indicated. [11]

Recently published prospective data from the STORI study of 115 patients with luminal Crohn's disease showed that 56% maintained remission one year after discontinuation of IFX. [12] A few minor studies have explored relapse rates in patients with Crohn's disease having discontinued IFX while being in a state of clinical remission. Sustained remission one year after withdrawal has been reported in 55-85% of patients with luminal disease. [9,13] Consistent with these data, we have recently reported that 61% of patients with Crohn's disease, who discontinued IFX while in steroid free IFX induced remission, maintained remission after one year; and half the patients were still in remission after nearly two years (median 680 [412-948] days). [14] Taken together, these data indicate that approximately 40% of patients with Crohn's disease relapse within the

first year after discontinuing IFX treatment, suggesting that patients who discontinue IFX while in clinical remission follow the natural disease course of disease. [4] Thus, prior effective treatment with IFX does not seem to impose a subsequent disease modifying effect. A prospective randomized study is necessary to confirm and extend these outcome findings.[5] It has been suspected that the response to retreatment with IFX in case of relapse after IFX withdrawal may be lost.[15] However data from the STORI study and from our center suggest, that patients may respond well to retreatment with IFX at relapse. [12,14]

Complete remission: The term 'remission' is not well uniformly defined and may incorporate one or more features such as clinical remission, as assessed by Crohn's Disease Activity Index (CDAI) score, biochemical remission, endoscopic remission etc. Patients who respond to TNFi therapy, both clinical, biochemical and endoscopic are considered to be in complete remission (typically defined as CDAI score < 150 [22] and no other signs of disease activity). In line with this the STORI study identified predictors of relapse including certain features as well as objective biochemical and endoscopical markers of disease activity. Following risk factors were associated with relapse: 1) Male sex; 2) absence of surgical resection; 3) corticosteroid use between 6 and 12 months before discontinuation of IFX; 4) IFX trough level ≥ 2 µg/ml at time of discontinuation of IFX; 5) Crohn's disease endoscopic index score (CDEIS) > 0; 6) leukocyte counts > 6.0 x10^9/L; 7) CRP ≥ 5.0 mg/L; 8) Hemoglobin ≤ 145 g/l; and 9) fecal calprotectin ≥ 300 µg/g.[12] A complete model and a simplified model describing the risk of relapse with respect to the number of risk factors present was proposed. Interestingly, patients with ≤ 3 risk factors in the complete model, and ≤ 2 risk factors in the simplified model, had a very low risk of relapse of approximately 10% at 1 year after IFX discontinuation, as compared to a relapse rate of approximately 60% in those patients with a higher number of risk factors. Relapse rates in patients during ongoing IFX therapy are 13% per year in a recent review by Gisbert et al.[33] Thus very similar to the relapse rate observed in patients with only a few risk factors in the STORI study. Indicating that the degrees of remission might predict the outcome after discontinuation of IFX.

Decision of discontinuation of TNFi is typically made on the basis of an individual judgment of benefits versus risks. [8,9] A number of concerns relate to cessation of TNFi in this subgroup of patients: Risk of relapse, risk of infusion reactions at re-initiation, and limited future medical treatment options. [8,13,16,17] However, in a real life clinical setting with limited economic resources and the fact that long time safety of TNFi has been questioned, make it highly unlikely that IFX

or ADA can be continued throughout the lives of all patients with Crohn's disease who have obtained clinical remission. Further TNFi are introduced in patients with Crohn's disease earlier and earlier, as well as in a wider variety of patients. Consequently, there is a need for new and evidence based therapeutic strategies.

TNFi and anti-TNFi antibody (Ab) activities: Serum concentrations of TNFi in individual patients vary despite the same dosing. [18,19] This is partly caused by individual differences in drug consumption and degradation. [19] At initiation of treatment, high concentrations of TNFi immediately prior to the next administrations, i.e. trough levels of the drug, are associated with maintenance of clinical remission, whereas low trough levels are associated with loss of response.[15,18-20] In addition, repeated infusions/injections of TNFi might result in the patient forming Ab against the drug (anti-TNFi Ab). Development of anti-IFX Ab is generally associated with loss of response,[15,18,19] though transient expression may also occur [21] Thus, monitoring patients for circulating levels of functional TNFi as well as for anti-TNFi Ab is warranted to allow optimal individual treatment. Due to methodological limitations, e.g. cross-binding of drug and anti-drug Ab in commonly used binding assays such as ELISA, levels are conventionally measured as trough levels. However, it is highly likely that this is not the optimal time point for assessments of rational therapeutic management.

As described above, there is a need to investigate how to manage patients with Crohn's disease in long-term sustained complete remission. Data, however only from a small number of patients, suggest that most patients in complete remission can safely discontinue TNFi treatment; it remains to be examined in a prospective, placebo-controlled study. Generally, treatment evaluations are based on clinical and paraclinical signs of disease activity. This study aims to investigate if the clinician, in addition, can use assessment of the drug and anti-drug antibody activity in the decision process. A prospective controlled trial is suitable to investigate the optimal tailored management in individual patients.

2. OBJECTIVE

The aim of the study is to investigate if IFX can safely and favourably be discontinued in patients with Crohn's disease, in sustained complete remission on IFX maintenance therapy.

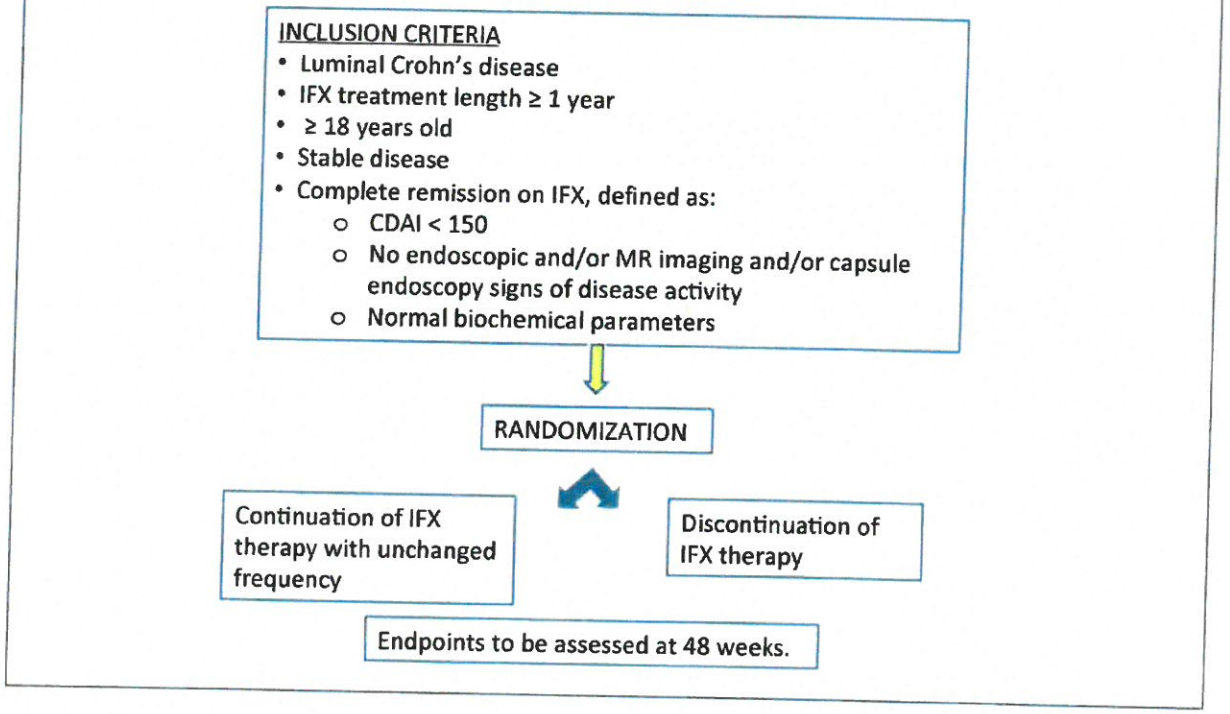
Further we will examine, the clinical utility of measuring levels/activity of IFX and activity of anti-IFX Ab in patients in sustained complete remission, in order to investigate whether pharmacoimmunological data can predict the clinical outcome and rationalize therapeutic management of these patients, with respect to continuation or discontinuation of IFX therapy. Additional, we will investigate the optimal time-point, out of three, to measure this activity.

3. METHODS

3.1 STUDY DESIGN

Prospective, double-blinded (patient, physician and treating nurse), randomized, placebo controlled, Nordic multicenter study. Patients with luminal Crohn's disease in sustained complete remission on IFX are randomized, to either continue IFX treatment or alternatively to receive matching placebo. All patients will be graded for disease activity at time of enrolment. The study duration is 48 weeks. Study overview is displayed in the Flow-chart below (**Figure 1**).

Figure 1: Flow-chart
STOP IT - Discontinuation of IFX therapy in patients with Crohn's disease during sustained complete remission



3.2 STUDY POPULATION

3.2.1 Inclusion criteria

- Luminal Crohn's disease defined according to standardized diagnostic criteria.[3]
- Age ≥ 18 years.
- IFX treatment length ≥ 12 months (minimum 365 days from first IFX administration to last IFX administration prior to inclusion). Episodic therapy with IFX pause > 12 weeks is not

accepted within the last year. The treatment interval, in the last three months, must be 6-10 weeks.

- Complete remission defined as:
  - Crohn's Disease Activity Index (CDAI) score < 150,[22]

    and
  - Biochemical remission, i.e. normal C- Reactive Protein (CRP), White Blood Cell (WBC) count, Hemoglobin (Hb) and Albumin. (Hb (female) ≥ 7,3 mmol/L, Hb (male) ≥ 8,3 mmol/L, Leucocyte ≤ 8,8 x 10^9/L, CRP ≤ 10 mg/L, Albumin (age 18-69 year) ≥36 g/L and (age >70 year) ≥34 g/L.

    and
  - No other signs of disease activity, as evaluated by endoscopic examination, by magnetic resonance imaging (MRI) or by capsule endoscopy.
    i. Endoscopic remission is defined as SES-CD score 0 – 2. [23,24]
    ii. Remission on MRI as defined by no or minimal signs of disease activity when evaluated by a trained radiologist.[25,26]
    iii. Remission on capsule endoscopy as defined as mucosal healing (few aphthous ulcers is allowed) when evaluated by a trained gastroenterologist.[27,28]
- Stable remission, judged by the treating physician at two consecutive treatment visits, corresponding 2 scheduled IFX infusions. Thus, the first visit is during IFX maintaining therapy (screening visit). The second visit is at time of inclusion corresponding time of next scheduled IFX infusion (i.e. after ≈ 8 weeks).
- No use of oral steroids within 3 months prior to inclusion.
- Concomitant therapy with other immune suppressants, except steroids, is allowed (Azathioprine (Aza), 6-Mercaptopurinitol (6-MP), Methotrexate (MTX)). The dosage and frequency must have been stable three months prior to inclusion, and must remain stable throughout the study period.
- Sexually active females of child-producing potential must use adequate contraception (intrauterine device or hormonal contraceptives (contraceptive pills, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release)) for the study duration and at 6 months (according to summary of product characteristics) after the last IFX infusion. (Sterilized or infertile subjects are exempt from the requirement to use contraception. In order to be considered sterilized or infertile, subjects must generally have undergone surgical sterilization (bilateral tubectomy, hysterectomy and bilateral

ovariectomy) or be postmenopausal defined as 12 months or more with no menses prior to enrolment).

- Patient must understand the investigational nature of this study and sign an independent ethical committee approved written informed consent form prior to any study related activities.

3.2.2 Exclusion criteria

- Initial indication for IFX being predominantly fistulizing perianal disease.
- Active fistulizing perianal disease.
- Any contraindications for continuing IFX treatment, including prior acute or delayed infusion reaction to a TNF- inhibiting agent, former malignancy, moderate to severe heart disease (New York Heart Association (NYHA) 3-4), any active infection requiring parenteral or oral antibiotic treatment, known infection with tuberculosis, human immunodeficiency virus (HIV) or hepatitis virus. (Testing for tuberculosis, HIV and hepatitis B / C must be taken if it has not been tested prior to induction of treatment, or if it is judged that the patient subsequent has been exposed).
- Alcohol or drug abuse within the last year.
- Any condition including physician finds incompatible with participation in the study.
- Female patients who are pregnant or breast-feeding (pregnancy test with a positive result before study entry).
- Unwilling or unable to follow protocol requirements.

3.2.3 Withdrawal criteria

Patients are free to withdraw from the study at any time, and withdrawal will not have any consequences for their future medical care.

Investigators must withdraw patients if:

1. The patient's clinical condition necessitates the withdrawal (e.g. pregnancy, concomitant diseases).
2. The patient fails to comply with the protocol.

For patients who withdraw / are withdrawn from the study, an early termination is scheduled as soon as possible. At this visit the investigator, determines CDAI score, WPAI score, Short- IBDQ score, and register other relevant information such as reason for withdrawal, adverse events and changes in concomitant diseases and treatment.

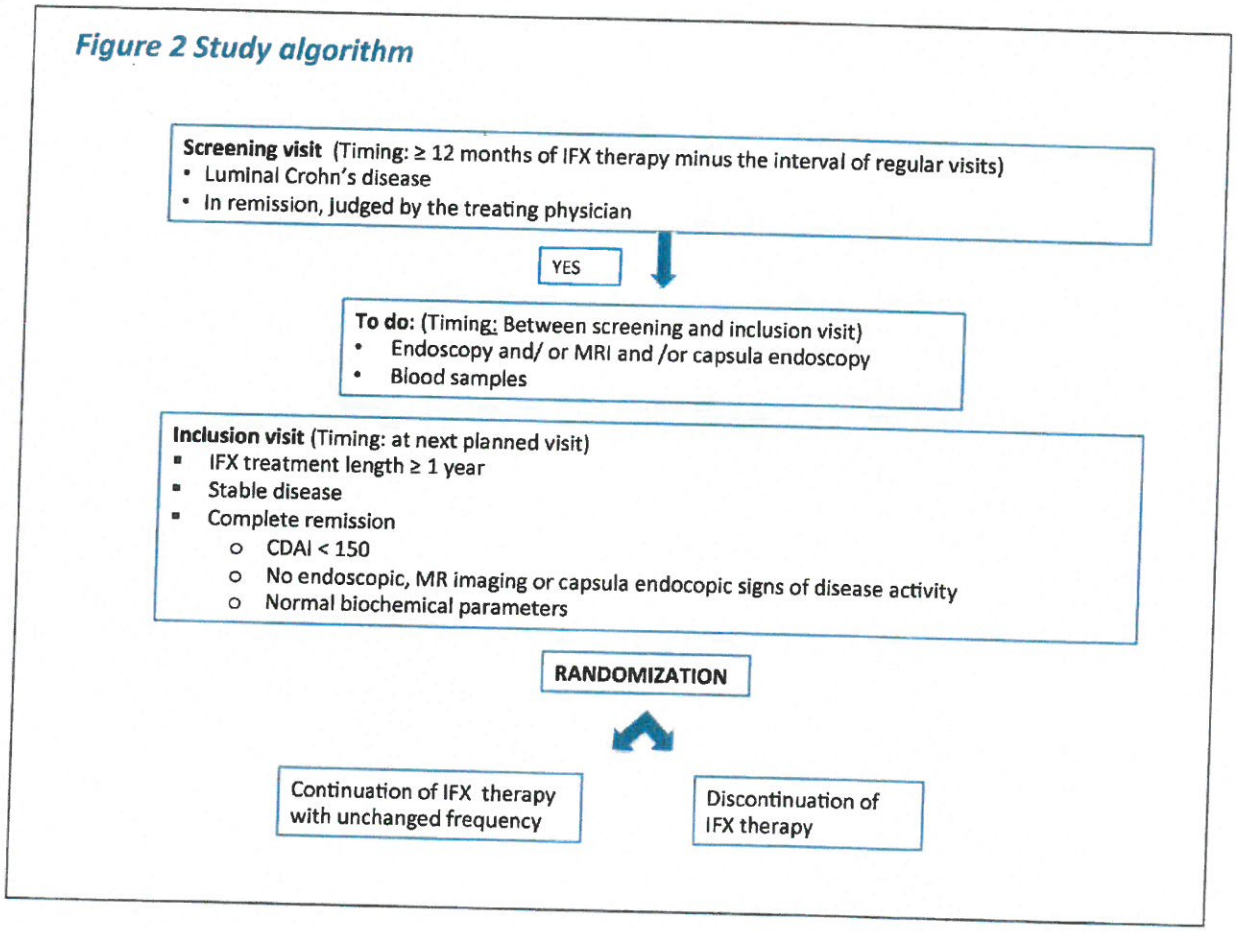
3.3 NUMBER OF PATIENTS AND INCLUSION PERIOD

A total number of 136 patients will be included in the study. See sample size calculations in section 4.2. The inclusion period is from September 1, 2012 until November 1, 2015. The study is planned as a Nordic multicenter study including 14 centers. If needed we will apply for additional participating centers in a later amendment.

3.4 INTERVENTION

The study algorithm is given in **Figure 2**.

Figure 2 Study algorithm



3.5 RANDOMIZATION

Patients are randomized to either continue IFX treatment at an unchanged dosage, or alternatively to receive matching placebo at the time of the inclusion visit (i.e. visit 2). We will use blocked randomization and an allocation ratio of 1:1. Further, to make sure that there is an equal distribution of patients with fistulizing disease in each group and an equal distribution of patients receiving concomitant immune suppressants in each group (control and intervention) we will stratify for these factors. Thus, randomization will be stratified for

fistulizing disease/ not-fistulizing disease and for concomitant immune suppressants (AZA,MP,MTX)/ no- concomitant immune suppressants.

On A4-size paper is written: either "The patient is randomized to the control group (continuation of infliximab treatment)" or "The patient is randomized to the intervention group (discontinuation of infliximab treatment)". Each paper will be placed in a sealed solid envelope on which it is stamped: "For use in the clinical randomized study: *Discontinuation of infliximab therapy in patients with Crohn's disease during sustained complete remission*". The envelopes are placed in blocks in each stratification group and for each participating center, with an equal number in each group (e.g. 5 in the intervention group and 5 in the control group). The blocks are thoroughly mixed by a person not related to the experiment, thus subjects are allocated randomly within each block.

Overview randomization blocks				
Center 1	No-concomitant Non-fistulising	No-concomitant Fistulising	Concomitant Non-fistulising	Concomitant Fistulising
Center 2	No-concomitant Non-fistulising	No-concomitant Fistulising	Concomitant Non-fistulising	Concomitant Fistulising
Center 3	No-concomitant Non-fistulising	No-concomitant Fistulising	Concomitant Non-fistulising	Concomitant Fistulising
Etc.				

No randomization code will be used. The envelopes will be kept in a locked cupboard at the Research Laboratory, Department of Medical Gastroenterology, Herlev Hospital, to which only the unblinded laboratory technicians has access. The randomization procedure takes place at Herlev Hospital. The unblinded nurse from participating centers must contact the Research Laboratory, Department of Medical Gastroenterology, Herlev Hospital phone 38 68 34 18 (8-14.30 Monday to Friday) for randomization.
Information about the patient must be given and a copy of the randomization note must be faxed to Herlev Hospital (fax. Number: xx xx xx xx) or information must be mailed to gaslab@regionh.dk. For randomization note see appendix XII.
The non-blinded nurse, receives the allocation result and subsequently prepares and labels IFX or placebo medication accordingly. The allocation sequence is double controlled by two non-blinded persons (eg, two non-blinded nurses).

3.6 BLINDING

All included patients continue to receive scheduled infusions every eight weeks, throughout the study period. Patients who are randomized to discontinue IFX are treated with infusions of physiological saline. Patients in both groups will receive premedication in accordance with current local guidelines.

Patients, treating nurses and treating physicians are blinded for type of intervention (IFX infusion versus placebo). After 48 weeks the blindings are lifted.

3.6.1 Blinding procedure

A non-blinded nurse, whom does not treat the patient, will do preparation and labelling of infliximab and placebo. It will not be possible for the patient, treating nurse or treating physician to see if the study treatment is infliximab or placebo.

Preparation of infusion; infliximab is supplied as a concentrate for infusion and the calculated volume for infusion must be diluted in sterile isotonic sodium chloride, 0.9 % NaCl (aq), solution to 250 ml. Placebo infusion consist of 250 ml sterile isotonic sodium chloride solution, 0.9 % NaCl (aq). Aseptic technique must be strictly observed. Infusions are given from a bag system; one bag will be used for each treatment. The bag will be labelled with the patients ID study title and with a treatment number. Infliximab and placebo will be labelled identical as study treatment. See labelling example in Appendix X.

3.7 COURSE OF STUDY

The course of this study is given in **Table 1** and **2** together with the study algorithm **Figure 2.** Endpoints are assessed at 48 weeks. Total study length is 48 weeks. *The screening visit* is defined as clinical remission and 12 months of scheduled IFX therapy minus the interval of regular visits. *The inclusion visit* is defined as time of next scheduled IFX infusion after the screening visit, thus resulting in an inclusion date after minimum 12 months of IFX maintenance therapy. Following screening- and inclusion- visits, the patients are seen after four weeks, and the next consultations will be undertaken as part of the regular visits related to control, every eight weeks. Recruitment of participants will occur at one of the regularly visits of control.

3.7.1 Informed consent

No study related activities will be performed until informed consent has been obtained. All eligible patients will be completely informed – verbally and in writing - of the potential benefits

and risks of participating in the study and are free to withdraw at any time without influencing further treatment.

Prior to obtaining informed consent, the purpose and nature of the study, as well as possible adverse effects resulting from discontinuing or maintaining infliximab therapy, will be explained to each patient in quiet and undisturbed surroundings. The patient will have amble time to consider, be allowed to ask questions, and read the information and other relevant documents and be informed that participation is voluntary, that not participating in the trial will have no influence on the usual treatment option for the disease. The patient will be informed that she/he is welcome to bring a family member, friend or companion and that we will set up an extra meeting, if she/he need more time to consider. The investigator is responsible for obtaining written consent from each patient. Informed consent must be obtained using the approved informed consent form, before any study specific procedures (including screening procedures) are performed.

Patients are handed out written information materials in the form of: Informed consent form, the brochure; "Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt" (only in Denmark) as well as written information (skriftlig deltager information). This will provide all information that must be given to the patient, explaining the study to the patient, providing him/her with information such as the expected efficacy, safety and possible side effects, including a statement to clarify the aim of the study, and that refusal to participate will not influence further options for therapy.

The patient should also be made aware that by signing the consent form, processing of sensitive clinical study data and transfer to our collaborating laboratory in California, US, for further processing is allowed. The signed consent form must be in the CRF. At any stage, the patient may withdraw from the study and such a decision will not affect any further treatment options.

3.7.2 Grading for disease activity

All patients will be graded for disease activity in accordance with CDAI, Work Productivity and Activity Index (WPAI),[29] life quality score (IBDQ short),[30,31] endoscopy (Simple Endoscopic Score for Crohn's disease (SES-CD)) [23,24] MRI, [25,26] or capsula endoscopy[27,28] and biochemical parameters at time of inclusion. Disease activity will be assessed at every study related visit by; CDAI, WPAI, IBDQ, and by biochemical parameters. When using the scoring systems, the clinician will take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the scores and make any adjustments they consider appropriate. For the scoring forms see Appendix I, II, III and IV.

CDAI score:

Patients will fill in a diary card daily in the seven days before each study visit. Data from the patient diary card, the last seven days prior to a visit, together with the clinical assessment will be used to calculate the CDAI score. In case of relapse, the CDAI calculation will be made using the diary data for the seven days prior to the termination visit.

IBDQ. Inflammatory Bowel Disease Questionnaire:

Patients will be asked to answer 10 questions relating to the condition of their Crohn's disease over the 2 weeks prior to their study visit using the Inflammatory Bowel Disease Questionnaire (IBDQ). The 10 questions cover four domains; bowel symptoms, systemic symptoms, emotional function and social function.

WPAI:

The WPAI:CD assesses the impact of Crohn's Disease (CD) on work and activity during the past 7 days. The specificity of WPAI:CD is achieved by replacing "health problems" in the general health version of the WPAI with "CD." It consists of 6 questions, which elicit the following information: employment status; hours missed due to CD; hours missed due to other reasons; hours actually worked; the degree to which CD affected productivity while working from 0 (no effect) to 10 (maximum impairment); and the degree to which CD affected regular activities (from 0-10). The sum of work time missed and impairment at work yields the overall work impairment (productivity loss) score; scores are expressed as percent of impairment/productivity loss, with higher scores indicating greater impairment.

SES-CD:

The treating physician, who does the endoscopic examination, will calculate the SES-CD. The calculation consists of scoring in five predefined segments (ileocolonic segment, the right colon segment, the transverse colon segment, the left colon segment and the rectum segment). The scoring will be made for four variables: ulcers, proportion of the surface covered by ulcers, proportion of the surface with any other lesions, and stenosis. Each variable has to be scored from 0 to 3 in each segment.

3.7.3 Assessments of Biochemical Parameters

All patients will on the day of each infusion, have blood samples drawn three times; just before infusion, right after the infusion (obtained from the other arm) and after one hour after the end of

infusion. In these samples, taken before infusion, we will measure biochemical parameters and levels of IFX and anti-IFX Ab. In the two samples drawn after infusion, we will measure levels of IFX and anti-IFX Ab. The assessed biochemical parameters are; Hemoglobin, leucocyte count, platelets, CRP, ALAT, creatinine, ALAT, bilirubin and albumin.
Patients must submit stool samples (at all study visits) for determination of fecal calprotectin.
Excess blood material is stored in a biobank for 10 years for potential subsequent analyzes (no later analyzes will be done unless approved by Danish Health and Medicines Authority and The Regional Committee on Health Research Ethics subsequent to a new application). See section 13, for further details about the biobank.

3.7.4 Study treatment

Patients are randomized to either continue IFX treatment at an unchanged dosage, or alternatively to receive matching placebo. IFX or matching placebo will be administered as a one-hour intra-venous (i.v.) infusion every eight weeks. The treatment dose of IFX for patients randomized to continue IFX are the same as, before entering the study (between 5 and 10 mg /kg) and has to remain stable throughout the study period.

Since patients receive the study medication as an i.v. infusion at the hospitals, we will know the exact dose and frequency of the study medication. At every study visit the primary investigator will ask the patient if he or she have taken their concomitant medication regularly and normally to address optimal compliance.

3.7.4.1 Procedures to register study medication

The non-blinded nurse will as described in 3.6, do packaging and labelling of infliximab and placebo. It will not be possible for the patient, treating nurse or treating physician to see if the study medication is infliximab or placebo. Infliximab are administered routinely in the participating centers.
It will be registered that the patient are receiving study medication according to the protocol. The non-blinded nurse will for every patient, at every study treatment write in a confidential form the date and register the treatment as either: Saline infusion or infliximab infusion (incl. BATCH number) according to the randomization. The forms will be kept confidential and physically away from both patients, treating nurses and treating physicians. Further the treating physician or the treating nurse will describe in the journal that the patient received study medication.

3.7.5 Concomitant therapy

Concomitant therapy may include medication and surgery.

Concomitant medication with other immune suppressants, except steroids, is allowed (Azathioprine (Aza), 6-Mercaptopurinitol (6-MP), Methotrexate (MTX)). The dosage and frequency must be stable throughout the study period.

Other concomitant medications, administered at the start of the study should preferably not be changed during the study. Additional supportive medications are allowed throughout the study (i.e. antibiotics, paracetamol etc.). Increase of Crohn's disease related symptoms requiring surgery will be considered as disease relapse and patients will go off study.

3.7.6 Screening visit

No study related activities will be performed before informed consent has been obtained (se above in section 3.7.1.

- Informed consent
- Check inclusion and exclusion criteria
- Order endoscopy and /or MRI and/or capsule endoscopy
- Assessment of Biochemical Parameters See section 3.7.3.
- Testing for HIV, hepatitis B and C serology and for tuberculosis if indicated see section 3.2.2.
- Pregnancy test
- CDAI scorecards will be issued for the patients.

3.7.7 Inclusion visit

- Check inclusion and exclusion criteria
- Patient's disease history, all current medical treatment, duration of Crohn's disease, date of first infliximab treatment, and demographics (date of birth, gender, height, body weight, smoking status etc.).
- Focused physical examination (including abdominal examination)
- Assessments of Biochemical Parameters, see section 3.7.3.
- Grading for disease activity, see section 3.7.2.
- Randomization and administration of medication according to randomization
- Study card (CDAI) for next visit will be issued

3.7.8 Visit 2 – 8:

- Focused physical examination (including abdominal exam).
- Grading for disease activity, see section 3.7.2.
- Assessments of Biochemical Parameters see section 3.7.3.
- Recording of any changes in concomitant diseases and/or medication.
- Adverse events.
- Administration of medication according to randomization.
- Study card (CDAI) for next visit will be issued.
- At visit 8; order endoscopy, MRI or capsule endoscopy (If the treating physician finds it indicated before visit 8, another endoscopy, MRI or capsule endoscopy must be made close to visit 9).

3.7.9 Visit 9:

- Focused physical examination (including abdominal exam).
- Grading for disease activity, including the results of endoscopy and/or MRI and/or capsule endoscopy. see section 3.7.2.
- Assessments of Biochemical Parameters, see section 3.7.3.
- Recording of any changes in concomitant diseases and/or medication.
- Adverse events.

3.7.10 Course of study at relapse

Patients who experience relapse (defined in section 3.8.1) will not subsequently be followed in the study and the study medication will be unblinded for these patients. All the patients will be treated at the discretion of the treating physician. Patients who were randomized to discontinue infliximab, and after relapse are retreated with infliximab, will be offered participation in a rescue study where we will examine response to retreatment. (We have not applied for approval of this study yet, and the study will only take place when approved by The Regional Committee on Health Research Ethics, subsequent to an application). In case of re-initiation of treatment we recommend to start up maintenance therapy, without new induction.

All patients with relapse will, if clinically indicated, have a colonoscopy and / or MRI done at time of relapse. An early termination visit is scheduled as soon as possible. At this visit the investigator, determines CDAI score, WPAI score, Short- IBDQ score, biochemical parameters

(Hb, CRP, etc.) and register other relevant information such as surgery, adverse events and changes in concomitant diseases and treatment.

Table 1

Visit number	1 Scree -ning	2 Inclu-sion[1]	3	4	5	6	7	8	9
Week (from inclusion)	-	0	4	8	16	24	32	40	48
Informed Consent[2]	☐								
Study medication		☐		☐	☐	☐	☐	☐	
Colonoscopy and / or MR imaging and / or capsule endoscopy	☐[3]								☐[3]
Colono-scopy SES-CD	☐								☐
Colono-scopy Biopsi	☐								☐
Focused physical examination		☐	☐	☐	☐	☐	☐	☐	☐
CDAI score, WPAI score and short-IBDQ score		☐	☐	☐	☐	☐	☐	☐	☐
Biochemical parameters[4] - Blood sample - Fecal sample	☐	☐	☐	☐	☐	☐	☐	☐	☐
Blood sample before infusion Biobank	☐#	☐	☐[5]	☐	☐	☐	☐	☐	☐
Blood sample after infusion (other arm) and one hour after the end of infusion Biobank	☐#	☐		☐	☐	☐	☐	☐	☐
Pregnancy test	☐								
Registration of Demographics and Medical History		☐							
Registration of Adverse events and changes in concomitant medication	☐	☐	☐	☐	☐	☐	☐	☐	☐

[1]Defined as time of next scheduled treatment
[2]Acquire a signed Written Informed Consent prior to conducting any study related procedures
[3] Colonoscopy and / or MR between visit 1 and 2, and at - 4 to 0 weeks before visit 9.
[4] CRP, Hb, WBC counts, Platelets, Albumin, creatinine, ALAT, bilirubuin and fecal-calprotectin
[5] Blood sample for determination of IFX and anti-IFX Ab, note there are study medication at this visit.
Normally scheduled infliximab therapy, not study medication.

Table 2

Visit 2-8	Day of study medication		
	÷ 15 minutes	0h +1h	+2h
Infliximab or placebo		X----------X	
Blood sample	X	X	X
Observation (from infusion start until one hour after ended infusion)		X----------X	

3.7.11 Follow-up

No follow-up, after the end of study period (48 weeks) is planned.

3.8 EFFICACY ASSESSMENT

3.8.1 Definitions

Remission is defined as CDAI < 150

Complete remission defined as: (see 3.2.1)

- Crohn's Disease Activity Index (CDAI) score < 150[22] and
- Biochemical remission, i.e. normal C- Reactive Protein (CRP), White Blood Cell (WBC) count, Hemoglobin (Hb), and albumin and
- No other signs of disease activity, either from endoscopic examination or MR imaging.

Relapse is defined as a CDAI score > 150 and a greater than 70 point increase from inclusion over two consecutive weeks. [12,32] Alternatively, if symptoms and findings are judged so severe, by the treating physician, that immediate intervention is needed, and a two week observation period is unreasonable, then the patient is also in relapse.

Assessment of secondary endpoints: See **Table 3**

Table 3

Endpoint	How to assess
CDAI	CDAI score (Appendix I)
Work productivity and activity	WPAI score (Appendix II)
Quality of life (QoL)	Short-IBDQ score (Appendix III)
Biochemical parameters	CRP, WBC, Hb, Albumin, Platelets and fecal calprotectin
IFX concentration/activity.	Common solid- and fluid phase assays for this purpose, e.g. Reporter Gene Assay (RGA).[15,19,33,34]
Anti-IFX Ab	As above.
Endoscopic disease activity	Colonoscopy, biopsi and SES-CD (Appendix IV)
Radiologically disease activity	MR imaging
Economical expenses	Directly Crohn's disease related health care costs (medication, surgery, hospitalization etc.)

3.8.2 Endpoints

Primary endpoint

The primary endpoint of this study is the proportion of patients who maintain remission, i.e. CDAI <150 as defined above in section 3.8.1.

Secondary endpoints

Patients who continue IFX and patients who discontinue IFX are compared with respect to the following at 48 weeks after inclusion:

- Proportion of patients who maintain complete remission as defined above in section 3.8.1.
- Proportion of patients experiencing relapse, as defined above (section 3.8.1) and as defined by a CDAI score over > 150 and a greater than 100 point increase from inclusion over two consecutive weeks.
- The proportion of patients, who are no longer in remission (as defined above in section 3.8.1), but are not in relapse (as defined above in section 3.8.1).
- Median time to relapse after discontinuation of IFX.
- Change from baseline in disease activity evaluated by: CDAI as assessed by CDAI score, quality of life (QoL) as assessed by short-IBDQ, work productivity and activity as assessed by WPAI, biochemical markers assessed by, i.e. C-reactive protein (CRP), platelets, albumin, white blood cell (WBC) count, Hemoglobin (Hb) and fecal calprotectin and colonoscopy (scored by the SES-CD) / MR imaging.

- Economical expenses in the to groups.

3.8.3 Explorative analyses

Based on disease activity after one year, (48 weeks) patients are categorised as either in complete remission or not in complete remission (complete remission defined in section 3.8.1). In patients who maintain IFX therapy, results of IFX (and anti-IFX Ab) trough concentrations, and concentrations just after infusions (peak), and concentrations one hour after the end of infusion (C_1), in each of the two groups (remitters versus non-remitters) will be compared. In patients who receive placebo, results of IFX and anti-IFX Ab concentrations at screening visit in the two groups (remitters versus non-remitters) will be compared. This will allow an assessment of which of the three time-points (i.e. trough versus peak versus C_1) and which assay is the best predictor of clinical effect of continued/ discontinued IFX therapy.

3.8.4 Treatment after termination of the study

The study is terminated after 48 weeks, after which patients are treated in accordance with the department's usual guidelines. The treating physician and the patient will after termination of the study, corresponding to week 48, be informed about whether the patient have continued IFX or received placebo.

3.8.5 Interruption of trial

The trial will be terminated if scientific findings from other research groups eliminate the trial. The trial will also be disrupted if there are serious, not yet known side effects to the drugs used.

4. STATISTICAL CONSIDERATIONS

4.1 STATISTICAL ANALYSIS

Descriptive statistics are calculated as percentages for discrete variables, and median with interquartile range (IQR) or mean with standard error of the mean (SEM) for continuous variables, as appropriate. Fisher's exact or Chi2 test, as appropriate, is used for univariate analysis of discrete variables. Unpaired t-test / paired t-test or Mann-Whitney U-test / Wilcoxon signed-rank test is used for univariate analysis of continuous variables, as appropriate. Time until relapse is estimated using survival statistics, i.e. the Kaplain-Meier method and log-rank test. Association of demographical, clinical, and biochemical variables with relapse is estimated using univariate and multivariabel Cox proportional hazard regression analysis. P-values are two sided, and $p < 0.05$ is considered significant.

Any changes in the original statistical analysis plan will be reported to The Danish Health and Medicine Authority.

4.2 SAMPLE SIZE

Calculations are based on the assumption that remission rates are higher in patients maintaining IFX treatment compared to patients receiving placebo. Relapse rates in patients during ongoing IFX therapy was estimated to 13% per year in a recent review by Gisbert et al.[35] As we will include a selected group of patients who already have received treatment for a year with good response, we expect the remission rate in patients who continue IFX maintenance therapy to be 90%. In the STORI study, the subgroup with the best prognostic markers had a similar proportion of patients maintaining remission. However, it is unknown if this can be extrapolated to other populations, especially because no control group was included in STORI study[12]. Thus, remission rates upon discontinuation may be somewhat lower. A difference between patients continuing and patients stopping IFX of 20 percentage points is considered clinically relevant. Based on this minimally clinically relevant difference of 20 % and α set at 0.05 (two sided) and β set at 0.2, (IBM SPSS Sample Power ver.3) a total of 62 patients in each group are needed to demonstrate a clinically relevant difference of continuing versus discontinuing IFX therapy. To correct for dropouts it is planned to include 136 patients in the study.

4.3 MISSING DATA

Data are analyses as both per-protocol (PP) and intension to treat (ITT).

Missing values: Missing values will be replaced by the average of the available values just before and after the missing values. If no values are available after the missing values the last-observation-carried-forward (LOCF) method and will be used for imputation of missing values. However other methods of inputting missing values will be applied in several sensitivity analyses.

5. SCHEDULE

The trial started November 9, 2012 when the necessary permissions from the Research Ethics Committees, the Danish Data Protection Agency and the Danish Medicines Agency were obtained.

The study protocol is submitted to a clinical trial registry (www.clinicaltrials.org) and will also comply with ICH-GCP (Good Clinical Practice) rules.

6. RISKS, SIDE EFFECTS AND INCONVENIENCES

There are risks, discomfort and inconvenience associated with all clinical scientific investigations. The drugs used in this experiment are all licensed and used for registered indications in registered dosages. Issues relating to reporting of adverse events (AE) to the Danish Health and Medicines Authority therefore follow the usual guidelines for registered drugs. After termination of the study patients are followed in the department's usual regimens. Record of any late occurring adverse events will also follow usual guidelines for registered drugs.

6.1 DEFINITIONS

Adverse Events: An AE is any untoward medical occurrence in a patient administered a pharmaceutical product that may or may not have a causal relationship with this treatment. An AE can, therefore, be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product. AEs include toxicities, which are related to study drug, to the disease, to study-related procedures, or to other unknown causes.

Serious Adverse Events or Serious Adverse reaction: A serious adverse event (SAE) or serious adverse reaction is defined; any untoward medical occurrence or effect that at any dose results in any of the following serious outcome criteria:

1. Is fatal.
2. Is life-threatening, meaning the patient was, in the view of the Investigator, at immediate risk of death from the reaction as it occurred; it does not include a reaction that, had it occurred in a more serious form, might have caused death.
3. Requires or prolongs inpatient hospitalisation.
4. Results in significant or persistent disability/incapacity, i.e., the event cause a substantial disruption of a person's ability to conduct normal life functions.
5. Is a congenital anomaly or birth defect.

6. Is an important medical event, based on appropriate medical judgment, that may jeopardize the patient or the patient may require medical or surgical intervention to prevent one of the other outcomes above.

Adverse reaction: Adverse reaction is an untoward and unintended responses to an investigational medicinal product related to any dose administered.

Unexpected adverse reaction: An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. summary of product characteristics).

Suspected unexpected serious adverse reactions: (SUSARs)

6.2 ADVERSE EVENTS ATTRIBUTED TO INFLIXIMAB

Adverse events during infliximab therapy are generally mild to moderate, and consist of nausea, vomiting, dyspepsia, fatigue, headache, fever, abdominal pain, and sinusitis. Hematological reactions with; pancytopenia, leucopenia, neutropenia and thrombocytopenia have been observed. For all known side effect see summary of product characteristics.
Severe adverse events are; risk of infections (viral, fungus, bacteria), suspected higher risk of lymphoma and other malignant diseases, demyelinisering, heart failure, and infusion reactions during the administration. In order to prevent infusion-related complications (e.g. allergic reaction) prophylactic medicines will be administered before each infusion and the patients are observed until one hour after the end of infusion. In order to prevent serious infection, all patients has been screened, at the time of infliximab induction, for infections such as tuberculosis, HIV, and viral hepatitis. The treating physician must be alert to the risk of malignant disease, and examine clinically for any signs of a malignant disease, in line with the normal care of patients. In this study the treating physician is required to be alert to these potential risks also in patients who receive additional immunomodulators.

6.2.1 Risk of lymphoma and other malignant diseases

The long-term risk of malignancy during IFX treatment is unknown. The risk of malignancies during shorter periods of IFX treatments seems to be low, but both solid organ cancers and lymphomas may occur. A meta-analysis from 2009, examined the rate of non-Hodgkin's lymphoma in adults with Crohn's disease who have received anti-TNF therapy. They found a risk of 6.1 out of 10.000 patient year (13 cases was reported out of 8905 patients) the expected rate was 1.9 out of 10.000 patient years. Similar rates of solid cancers have been observed

elsewhere.[11] These observations have, however, not been reproduced in other prospective studies.[11] A meta-analysis of 21 studies with 5356 individuals revealed no overall increased risk of malignancy during IFX therapy in patients with Crohn's disease.[36] Of note, the majority of patients who develop malignancies during IFX treatment, have also been exposed to other immunomodulators (which is in itself associated with increased risk of malignancy) and it is thus difficult to determine the relative influence of IFX versus conventional immunomodulators on the risk of malignancies. It has been speculated, that a combination of a TNF-inhibitor and of a conventional immunosuppressant (e.g. azathioprine) may increase the risk. In a study of paediatric patients, treated with such combination therapy, cases of the fatal hepatosplenic T-cell lymphoma have been described.[6,37]

6.3 RISKS BY DISCONTINUATION OF INFLIXIMAB

As discussed in section 1, the evidence-based knowledge about the risk of relapse, in the selected patients group included in this study, is sparse. Patients whom discontinue infliximab treatment might be in higher risk of relapse, than patients who continue treatment. We will examine the patients very closely at every study visit, for any signs of exacerbation. In case of any suspicion of relapse, the patient will be followed as closely as the treating physician finds optimal and safe. In case of relapse, data from our previous study and from the STORI study, suggest that the patient will respond very well to retreatment with infliximab. Of notice, recent guides from "Rådet for Anvendelse af Dyr Sygehusmedicin" (RADS) advise that patients should discontinue IFX, after 26./52. weeks of treatment if they are in remission. At Herlev Hospital we have already begun to implement the recommendations, thus patients participating in this study, will not necessarily be more likely to have to stop treatment.

6.4 RISKS BY STUDY RELATED PROCEDURES

Blood tests: Participation in this study will include extra blood tests. It takes approximately three additional blood sample for each study visit. For most people drawing blood gives no serious problem. However fainting, bleeding, bruising, discomfort, dizziness, infections and / or pain at the injection site may occur.

Stool samples: Subjects will be asked to submit a stool sample (ca. 100 g) at each study visit. There are no known side effects or risks associated with the submission of stool samples, though it might be inconvenient.

Endoscopy, MR imaging and capsule endoscopy:

Patients will undergo endoscopy and / or MR imaging and / or capsule endoscopy as often as they would if they were not included in the study and in accordance with current guidelines. Therefore there is no increased risk, due to these procedures, associated with participation in the trial. However, there are risks associated with the endoscopic procedure (such as; perforation). Before any MR scanning a checklist form have to be fulfilled in accordance with usual guidelines. All three examinations are inconvenient for the patient and can lead to discomfort and pain, however this will cease shortly after the examination.

Colon and rectum must be completely empty for the endoscopy to be thorough and safe, thus the patient must drink only clear liquids for 12 to 24 hours beforehand. This includes bouillon or broth, gelatin, strained fruit juice, water, plain coffee, plain tea, or diet soft drinks. The patient receives laxative and enema. The endoscopy (sigmoideoscopi, colonoscopy) is performed by an experienced physician and lasts approximately 30-60 minutes. Biopsies will be taken during the procedure. Side effects; it is possible to experience bloating and abdominal pain. There is a slight risk of the endoscope tearing, or perforating, the colon. This happens to 1 in 1,000 patients.

To visualize the intestine during the MR scanning patient must drink per oral contrast medium 45 minutes before the MR scan, and immediately before the scan, i.v. contrast medium is injected. The oral contrast medium can cause reversible nausea, diarrhea and gas. In rare cases during the injection, the needle (catheter) slips out of the vein. Thereby the injected contrast medium leaks into the tissue and may cause local pain. This is usually treated with compression. Reversible metallic taste in mouth, nausea, vomiting and hives may happen. Very rarely breathing problems, decreased blood pressure and dizziness which requires treatment occurs. Adverse reactions resulting in death, is extremely rare.

To do a capsule endoscopy the patient swallows a vitamin-sized capsule with a tiny wireless camera. As the capsule travels through the digestive tract and the camera takes thousands of pictures. Capsule endoscopy is generally a safe procedure that carries few risks for adults who are able to swallow the capsule. In most cases, the capsule leaves the body within hours to days. Occasionally, the capsule can become lodged in the digestive tract. The risk is under 1.5 percent for most people who have capsule endoscopy, though the risk may be higher in people diagnosed with Crohn's disease (5 to 13 percent). If the patient has symptoms of intestinal blockage, further examination is indicated (e.g. barium X-ray, CT, MRI or test soluble capsule) before the capsule endoscopy. If the capsule is retained, the capsule will often eventually leave the body. It's very

unusual for a retained capsule to cause any symptoms. However, if the capsule continues to be retained surgery may be considered.

7. ASSESSMENT OF SAFETY AND REPORTING

The condition of the subject will be monitored throughout the study. At each visit, adverse events (AEs) will be elicited using a standard non-leading question such as "How did you feel since last visit?" In addition, any signs or symptoms will be observed.

All AEs will be collected as:

- The patient's positive response to questions about their health
- Symptoms spontaneously reported by the patient
- Clinically relevant changes and abnormalities observed by the investigator (e.g. local and systemic tolerability, laboratory measurements (ALAT, creatinine, CRP, WBC, Hb etc.) results of physical examinations)

In case of any AEs the following will be recorded:

- Description of the adverse event
- Relevant clinical findings
- Date/Time of onset (the date when the first sign(s) or symptom(s) were noted)
- Date/Time of recovery
- Intensity*
- Action taken on study drug
- Other action taken to treat the event (if medication initiated, this should be entered in the concomitant medication log)
- Causal Relationship to study drug**
- Seriousness of the AE
- Outcome

*Intensity

The following 3-point rating scale will be used for rating of the intensity of each AE:

Mild: Awareness of signs or symptoms, but no disruption of usual activity

Moderate: Event sufficient to affect usual activity (disturbing)

Severe: Inability to work or perform usual activities (unacceptable)

**Causality

The following 4-point scale will be used for rating the causal relationship of the AE to the investigational product:

Unrelated: Clearly and incontrovertibly due to extraneous causes and does not meet a criterion listed under unlikely, possible or probable.

Unlikely: Does not follow a reasonable temporal sequence from administration. May have been produced by the patient's clinical state, by environmental factors or by other therapies administered.

Possible: Follows as reasonable temporal sequence from administration. May have been produced by the patient's clinical state, by environmental factors or other

Probable: Clear-cut temporal association with improvement on cessation of investigational medicinal product or reduction in dose. Reappears upon retreatment. Follows a known pattern of response to the investigational medicinal product.

The sponsor (principal investigator Mark Ainsworth) must inform the Danish Medicines Agency immediately if suspected unexpected serious adverse reactions (SUSARs) occur during the trial: The sponsor must ensure that all relevant information about suspected unexpected serious adverse reactions (SUSAR), which are fatal or life-threatening, is recorded and reported to the Danish Medicines Agency as soon as possible, and no later than 7 days after the sponsor is informed of such a suspected adverse reaction. No later than 8 days after the reporting, must the sponsor inform the Danish Medicines Agency of relevant follow-up information on the sponsor's and the investigator's follow-up action to the reporting. Any other suspected unexpected serious adverse reactions must be reported to the Danish Medicines Agency no later than 15 days from the time when the sponsor is informed about them. All serious and unexpected side effects of drugs must be reported immediately by the sponsor to Danish Health and Medicines Authority. In case of a SAE or SUSAR, the blinding for the involved patient is ceased. At the end of the trial, all adverse reactions and events must be reported to the Danish Medicines Agency.

The investigator must immediately report all serious incidents to the sponsor (Marain01@heh.regionh.dk). Reporting must be followed-up by a detailed report, and in both the immediate report and the subsequent report, the investigator must identify the trial subjects with a personal code number. Moreover, the investigator must report to the sponsor any incidents and/or irregular analysis results that are critical to the trial patients safety. The Summary of

product characteristics must be used, when assessing whether a suspected adverse reaction (SAR) is unexpected/expected and thereby may be a SUSAR.

Interim analysis: No formal interim analysis is planned.

8. DATA COLLECTION AND CASE REPORT FORM MONITORING

The study will be monitored after Good Clinical Practic (GCP). Monitoring of the trial according to GCP including quality control and quality assurance (kvalitetskontrol og kvalitetssikring) is carried out by:

GCP-enheden Københavns Universitets Hospital
Bispebjerg Hospital, Bygning 51, 3.sal
Bispebjerg Bakke 23
2400 København NV
Tlf: 3531 3890

GCP-enheden ved Aarhus Universitetshospital
Aarhus Universitet,
Olof Palmes Allé 15
8200 Aarhus N
Tlf: 7841 3950

GCP-enheden ved Odense Universitetshospital
Afdeling for Klinisk Biokemi og Farmakologi
GCP-enheden - Odense Universitetshospital
J. B. Winsløws Vej 19, 2. sal
5000 Odense C
Tlf: 6550 4360

The unit at Bispebjerg Hospital will be coordinating the monitoring of the study and must approve the study start, before any study related activities begins.
All study data, with relevance for the study (se section 3.7) must be recorded on the Case Report Forms (CRFs) provided by the sponsor (principal investigator). The data will be recorded as

soon as possible after they are generated. All sections of each CRF must be completed and each page identified with the patient's assigned registration number. All data must be in accordance with patient's records. An explanation for the omission of any required data should appear on the appropriate page. Any corrections to the CRF must be made in a way that does not obscure the original entry. The correct data must be inserted with the reason for the correction (if appropriate) and the change dated and initialled by the Investigator or authorised designee.

The monitor or primary investigator will be available between visits if the investigators(s) or other staffs need information and advice.

8.1 MONITORING

On-site monitoring visits will be performed frequently during the study. First monitoring visit will be performed after the first patient has been included. Also monitoring visits will be performed by need.

8.2 SOURCE DOCUMENTATION

At a minimum, source documentation must be available to substantiate: subject identification, eligibility, and participation; proper informed consent procedures; dates of visits; adherence to protocol procedures; records of safety and efficacy parameters; (serious) adverse events; administration of concomitant medication; study drug administration information; and date of subject completion, or withdrawal from the study, and the reason if appropriate. Any data that will be recorded directly in the CRFs which will be considered as source data (e.g., assessment scores, quality-of-life instruments) must be described here. Otherwise, it will be expected for these data to be recorded in the source document.

Direct access to paper source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. This will require direct access to all original records for each patient (e.g. clinic charts, patient files, laboratory results and CT-scans). During monitoring visits, the relevant investigational staff needs to be available and the source documentation must be available.

Source data and CRFs are available to the relevant authorities in connection with monitoring, audit and / or inspection. CRFs are stored according to applicable laws for 5 years after the trial is ended, hereafter the data will be made anonymous.

During the study a confidential identification list of patients are kept by the investigator. The identification list contains information on name, cpr.nr, trial number, initials and date of screening and inclusion. All other records relating to the study will only identify patients with a number, initials and birthday. Patient's full name will not appear on publicly available material on trial.

9. ETHICS

It is essential to determine optimal strategies for discontinuation of IFX therapy in patients with Crohn's disease. Withdrawal of IFX therapy must not cause the patient unnecessarily high risk of disease flare. On the other hand the possible risk for development of lymphoma, including hepatosplenic T-cell lymphoma, which is often fatal, and other malignancies cannot be excluded. In particular young patients and patients who have received prolonged treatment are at risk. In addition, though seldom, severe side effects to IFX are a danger for patient safety.

This study examines patients with Crohn's disease in sustained complete remission on IFX. To date there is little evidence concerning whether IFX can be discontinued favourably and safely, in this selected patient group. In prior studies patients in remission who discontinued infliximab therapy faced higher risk of relapse than patients who continued therapy. However, data suggest that patients with very few risk factors (i.e. in complete remission) might have similar relapse rates as if IFX therapy is maintained. The intention of the study is to examine whether IFX can be discontinued safely in the complete-remission patient group. To form a rational and efficient management algorithm, we will seek predictors of outcomes after discontinuation. Further, we hypothesize that incorporation of measurements of blood levels of TNFi and anti-TNFi Ab is clinically relevant. A prospective controlled trial is suitable to investigate the optimal tailored management in individual patients.

The decision to discontinue/ continue TNFi is typically made on the basis of an individual judgment of benefits versus risks. However, new recommendations from "Rådet for Anvendelse af Dyr Sygehusmedicin (RADS)" prescribe cessation after 26 /52 weeks of treatment if the disease is in remission. However, this recommendation albeit based on sound common clinical sense, is not evidence-based. Thus it is justified to deviate from these guidelines in order to provide solid evidence for the correct treatment strategy for these patients. Thereby making the

treatment guidelines more evidence-based and improve treatment strategy, which will benefit patients and society.

Often the patient at inclusion in our study will not miss any medication she/he would otherwise obtain, because the standard would be "no treatment" according to the RADS guidelines. Patients participating in this study may potentially benefit from the discontiuation if they are able to tolerate cessation. The cessation can continue after the study period, as long as they experience low disease activity. In case of relapse, after discontinuation of IFX, data from our study and from the STORI study suggest that the patient will respond very well to retreatment. Patients, who have been randomly selected to continue IFX therapy are subjected to the same side effects as they would have faced before entering the study.
Participation in the trial should provide new data and information to benefit future patients.

During the experiment, the patients will be monitored closely and every reasonable precaution will be taken to ensure patients' safety. Patients will be informed if there are changes to the experiment, or if new risks of the product are discovered. Infliximab is a registered drug and is administered following the current instructions for administering the drug. Facilities for resuscitation and intensive therapy will be immediately at hand and patients should be under observation during the infusion. Patients may experience risks related to the side effects from IFX treatment. For total risks see section 6 and summary of product.

In summary, the project will provide new knowledge regarding how to optimally handle patients with Crohn's disease in sustained remission on a TNFi, and will help develop new therapeutic strategies for this patient group. The study will provide information about the value of measuring concentrations of TNFi and antibodies against TNFi in an every day clinical decision-making setup. In addition, anti-TNF treatment plays an important role in many inflammatory diseases (e.g. rheumatoid arthritis, spondylarthritis, and psoriasis).[38,39] As is the case in patients with Crohn's disease, discontinuation of TNFi in patients with other inflammatory diseases - after achievement of low disease activity - is important for reasons of safety and economy.[40] Thus, the study results might inspire similar research studies in other inflammatory diseases impacting patient safety of TNFi therapies. It is estimated that the knowledge acquired about how to handle patients with Crohn's disease in sustained complete remission on infliximab therapy is proportionate to the outlined risks and inconveniences to which patients are exposed to by voluntarily participating in the project.

The study is executed in accordance with the Helsinki Declaration. Approval by the Ethical Committee (Region Hovedstaden), the Data Protection Agency and the Danish Health and Medicines Authority must be obtained before any study related activity starts. The study will be performed with respect for patient integrity and autonomy and in accordance with the protocol and applicable regulatory requirements.

10. BUDGET, INTERESTS AND INSURANCE

All expenses for own patients at each center, including medication, study medication (infliximab/placebo), laboratory tests (except for analysis for IFX and anti- IFX Ab), endoscopy, capsule endoscopy and MRI will be covered by the center itself. The medication and investigations are part of the standard clinical care of the patients. Expenses related to measuring IFX and anti-IFX Ab levels will be covered by Mark Ainsworths research fond. This is an investigator initiated trial. The sponsor, primary investigators, investigators or patients included in the trial, will not receive any fees related to the study. Sine Schnoor Buhl, will as this is part of a PhD -project, receive salary according to the current agreement for PhD students at Herlev Hospital (Region Hovedstaden). To pay for economic expenses throughout the study we will apply different funds, private and public, and any funding will be paid to Mark Ainsworths research fond. See Appendix XI for the detailed budget. Any excess amount will be used for other research projects.

10.1 STATEMENT OF INTEREST

Within the last three years, Casper Steenholdt has served as speaker for MSD and Abbott, and as a consultant for MSD; Ole Østergaard Thomsen has served as speaker and consultant for Schering-Plough, USB, and Zealand pharma. Klaus Bendtzen has served as a speaker for Pfizer, Wyeth, Roche, Novo-Nordisk, Bristol-Meyers Squibb, and Biomonitor A/S, and own stocks in Biomonitor A/S. Sine Schnoor Buhl, Mark Ainsworth, and Jørn Brynskov have no interest to declare.

10.2 INSURANCE

Each center is responsible for insurance of own patients.

11. CONFIDENTIALITY

All research records associated with the trial will only identify the patient by their initials, date of birth and study number except the patient consent forms. The patient's name will not be used in any public report of the study.
All information, materials and data obtained during the study will be available to the principal investigator and its nominees and may be used for inspection from the appropriate regulatory authorities. The investigator is responsible for the retention of the patient log and patient records; although personal information may be reviewed by authorized persons, that information will be treated as strictly confidential and will not be made publicly available.
All information about the patients, including non-clinical data, protocols, CRFs and verbal and written information, are protected under the act concerning the processing of personal data and the Danish health law (Lov om behandling af personoplysninger og sundhedsloven).

12. PUBLICATION

It is the intension that any results will be published, positive, negative or inconclusive in a relevant English language scientific journal/conference. Sine Schnoor Buhl will be first author. Last author will be Mark Ainsworth, Second author will be Casper Steenholdt. Jørn Brynskov; Ole Østergaard Thomsen and Klaus Bendtzen will be 3., 4., and 5. Author. Hereafter, investigators from other sites; the order of which will depend upon number of included patients. In addition information of the study will be available on the international public database for clinical studies at the website: www.clinicaltrials.gov

It is possible to have a maximum of 2 co-authors from each participating center. (Except from the main center, Herlev Hospital). Required is, in addition to participation in manuscript preparation, a minimum of 5 patients enrolled for the first co-authorship and a total of 7 patients enrolled for two co-authorships.

13. BIOBANK

In this study we will store biological material in the form of blood from the patients. The project is reported to the Data Protection Agency.

At every study visit blood samples is drawn three times (6 mL x 3 venous blood/ pr. blood sample). The samples are stored in the form of serum, plasma, and buffy coat (white blood cells). If later in the trial, it is deemed necessary, the concentration of infliximab and anti-infliximab Ab will be determined. Fecal samples are stored for analyses of f-calprotectin. The fecal samples are destroyed after determination of f-calprotectin.

The samples are stored for up to 10 years after the termination of the study, after which all samples and leftover material will be destroyed immediately.

If further or other investigations of biological material is needed, this will only take place after renewed application and approval.
Our collaborating laboratories will do determination of IFX and anti-IFX Ab levels, thus samples will be sent out of Herlev Hospital to Biomonitor A/S (Copenhagen, Denmark) and to Prometheus (San Diego, USA). After determination of IFX and anti-IFX Ab, the remaining material will be either destroyed or sent back for storage in the Biobank at Herlev Hospital. Any sent material will be completely anonymous.

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15. APPENDICES- List of appendices

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