Statistical Analysis Plan (SAP)

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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Statistical Analysis Plan

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TRIAL STATISTICIAN	Tobias Wirenfeldt Klausen
TRIAL CHIEF INVESTIGATOR	Mark A. Ainsworth MD, PhD, DMSc
SAP AUTHOR	Sine Buhl MD, PhD

1 SAP Signatures

I give my approval for the attached SAP entitled "Discontinuation of infliximab therapy in patients with Crohn's disease during sustained complete remission" dated 01.10.2020

Chief Investigator

Name: Mark A. Ainsworth

Signature:

Date: 02/10/2020

Statistician

Name: Tobias Wirenfeldt Klausen

Signature:

Date: 02/10/2020

Author

Name: Sine Buhl Næss Schmidt

Signature: SinSBuhN

Date: 02/10/2020

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3 Abbreviations and Definitions

Ab	Antibodies
AZA	Azathioprine
AE	Adverse Event
cLDA	Constrained Longitudinal Data Analysis
CRF	Case Report Form
CRP	C-reactive protein
CDAI	Crohn's Disease Activity Index
Hb	Haemoglobin
IBDQ	Inflammatory Bowel Disease Questionnaire
IFX	Infliximab
IMP	Investigational Medical Product
MMRM	Mixed Model Repeated Measures
MP	Mercaptopurine
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
SAP	Statistical Analysis Plan
SES-CD	Simple Endoscopic Activity Score in Crohn's Disease
TNF	Tumour Necrosis Factor
WBC	white blood cell count
WPAI	Work Productivity and Activity Index

4 Introduction

4.1 Preface

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 ages 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 tumour necrosis factor (TNF)-alpha such as infliximab (IFX), adalimumab 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 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 TNF-inhibitor in patients in long-term sustained remission. While it is generally accepted, albeit yet unproven, that IFX 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 TNF-inhibitor 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]

5 Study Objectives and Endpoints

5.1 Study Objectives

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. Additionally, we will investigate the optimal time-point, out of three, to measure this activity.

5.2 Endpoints

5.2.1 Primary endpoint

Time to relapse defined as Crohn's Disease Activity Index CDAI >150 and an increase in CDAI from baseline > 70 point increase from inclusion over two consecutive weeks or definitive relapse (judged by treating physician).

5.2.2 Secondary endpoints

- Time to loss of remission defined as CDAI > 150
- Proportion of patients who maintain remission, i.e. CDAI <150 as defined in section 3.8.1 of the protocol.
- Proportion of patients who maintain complete remission as defined above in section 3.8.1 of the protocol.
- Proportion of patients experiencing relapse, as defined above (section 3.8.1 of the protocol) and as defined by a CDAI score over > 150 and a greater than 100 point increase from inclusion over two consecutive weeks.
- Proportion of patients experiencing relapse, as defined above (section 3.8.1 of the protocol) and as defined by a CDAI score over > 150 and a greater than 70 point increase from inclusion over two consecutive weeks
- The proportion of patients, who are no longer in remission (as defined in section 3.8.1 of the protocol), but are not in relapse (as defined above in section 3.8.1 of the protocol).
- 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, Haemoglobin (Hb) and faecal calprotectin and colonoscopy (scored by the SES-CD) / MR imaging.
- Economical expenses in the two groups.

5.2.3 Explorative endpoints

- IFX (and anti-IFX Ab) trough concentrations
- IFX concentrations just after infusions (peak)
- IFX concentrations one hour after the end of infusion (C1)
- Subgroup analyses of time to relapse, as defined above, in:
    - Patients with fistula disease / patients not having fistulae disease
    - Patients receiving concomitant immunosuppressive therapy / patients not receiving concomitant immunosuppressive therapy

- Patients with a prior IFX discontinuation episode / patients with no prior IFX discontinuation episodes
- Patients with SES-CD score <1 (at inclusion endoscopy) / Patients with SES-CD score =1 or 2.
- Patients with CDAI < 100 (at inclusion) / Patients with CDAI ≥ 100 (at inclusion)

The sample size may impact the power of these subgroup analyses.

6 Study Methods

6.1 General Study Design and Plan

Prospective, double-blinded (patient, physician and treating nurse), randomized, placebo controlled, Nordic multicentre 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).

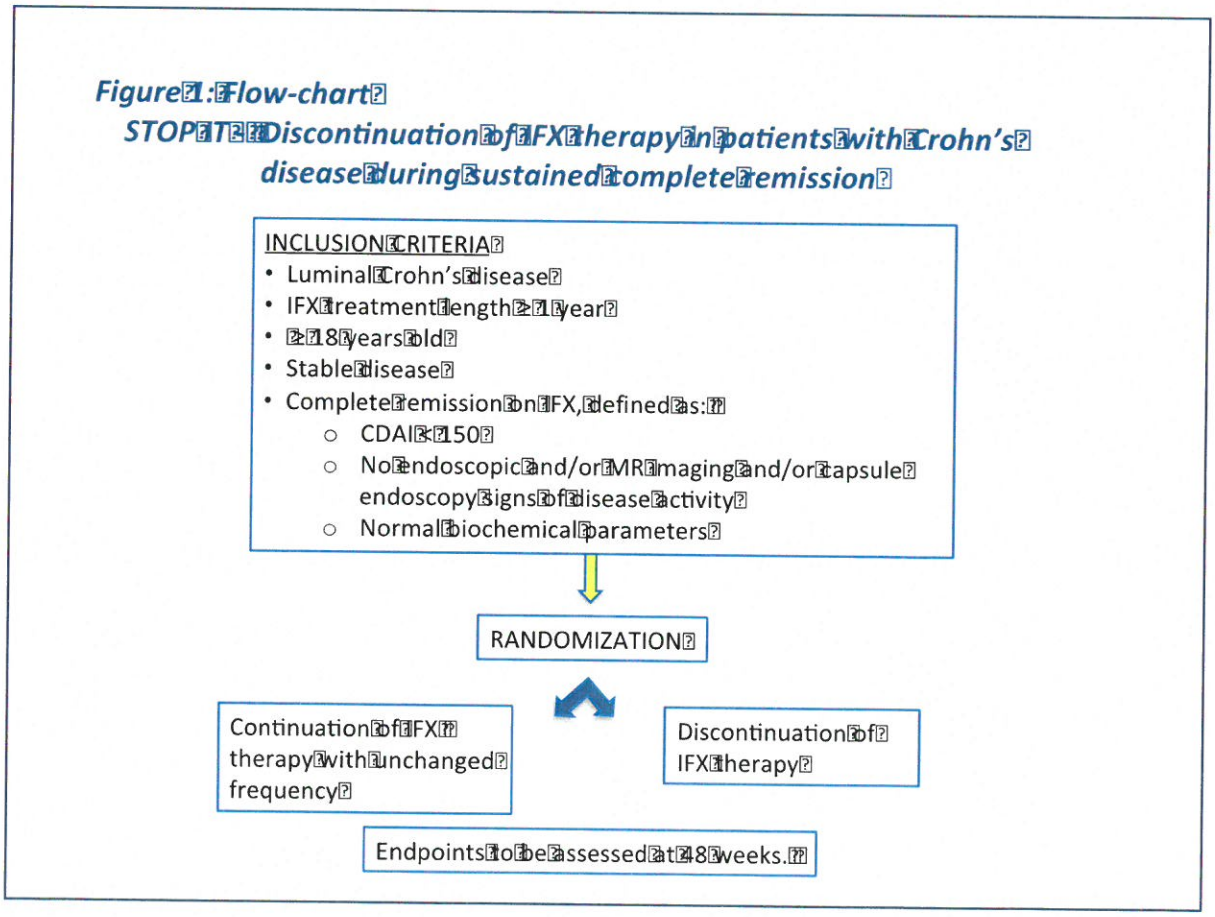

Figure 1: Flow-chart STOP IT – Discontinuation of IFX therapy in patients with Crohn's disease during sustained complete remission

7 Inclusion-Exclusion Criteria and General Study Population

7.1 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:
    - CDAI score < 150,[12]

      And
    - Biochemical remission, i.e. normal CRP, WBC count, 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. [13, 14]
        ii. Remission on MRI as defined by no or minimal signs of disease activity when evaluated by a trained radiologist.[15, 16]
        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.

7.2 Exclusion criteria

- Initial indication for IFX being predominantly fistulising perianal disease.
- Active fistulising 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.

7.3 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.

7.4 Randomisation and Blinding

7.4.1 Randomisation

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 fistulising 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 fistulising disease/ not-fistulising disease and for concomitant immune suppressants (AZA, MP, and 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 centre, 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				
Centre 1	No-concomitant Non-fistulising	No-concomitant Fistulising	Concomitant Non-fistulising	Concomitant Fistulising
Centre 2	No-concomitant Non-fistulising	No-concomitant Fistulising	Concomitant Non-fistulising	Concomitant Fistulising
Centre 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 centres 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 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 (e.g., two non-blinded nurses).

7.4.2 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 blinding is lifted.

7.4.2.1 Blinding procedure

A non-blinded nurse, whom does not treat the patient, will do preparation and labelling of IFX and placebo. It will not be possible for the patient, treating nurse or treating physician to see if the study treatment is IFX or placebo.
Preparation of infusion; IFX 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. IFX and placebo will be labelled identical as study treatment. See labelling example in Appendix X.

7.5 Study Variables

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	Biopsy	☐								☐
Focused physical examination			☐	☐	☐	☐	☐	☐	☐	☐
CDAI score, WPAI score and short-IBDQ score			☐	☐	☐	☐	☐	☐	☐	☐
Biochemical parameters[4] - Blood sample - Faecal 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, bilirubin and faecal-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.

CDAI score

Variable	Description		Multiplier
Number liquid stools	Sum of 7 days		x2
Abdominal pain	Sum of 7 days ratings	0 = none 1 = mild 2 = moderate 3 = severe	x5
General well being	Sum of 7 days ratings	0 = generally well 1 = slightly under par 2 = poor 3 = very poor 4 = terrible	x7
Extra intestinal complications	Number of listed complications	Arthritis/arthralgia, iritis/uveitis, erythema nodosum, poyderma gangrenosum, aphtous stomatitis, anal fissure/fistula/abscess, fever >37.8°C	x20
Antidiarrheal drugs	Use in the previous 7 days	0 = no 1 = yes	x30
Abdominal mass		0 = no 2 = questionable 5= definite	x10
Haematocrit	Expected-observed Hct	Males: 47-observed Females: 42-observed	x6
Body weight	Ideal / observed ratio	[1 – (ideal/observed)] x 100	x1 (not < -10)

In case of missing elements of a single assessment of the CDAI score, the following rules will be applied:

For elements that are calculated as sum of assessments on each of the 7 days (Number liquid stools, abdominal pain, and General well-being) missing values will be replaced by the average of the days for which data are available.

For elements that are only assessed once (Abdominal mass, Haematocrit, Body weight) the whole CDAI assessment is considered missing at that time point.

SES-CD

Variable	Score			
	0	1	2	3

Size of ulcers(cm)	None	Aphthous ulcers (diameter 0.1-0.5)	Large ulcers (diameter 0.5-2)	Very large ulcers (diameter >2)
Ulcerated surface (%)	None	< 10	10-30	> 30
Affected surface (%)	Unaffected segment	< 50	50-75	> 75
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Segment / Variable	Ileum	Right Colon	Transverse colon	Left colon	Rectum	Total
Presence and size of ulcers (0-3)						
Extent of ulcerated surface (0-3)						
Extent of affected surface (0-3)						
Presence and type of narrowings (0-3)						
					SES-CD=	*

Total SES-CD: sum of the values of the 4 variables for the 5 bowel segments. Values are given to each variable and for every examined bowel segment. [14]

In case of missing elements of a single assessment of the SES-CD score, the whole SES-CD assessment is considered missing at that time point. In case of patients with limited distal disease being evaluated by sigmoidoscopy alone, the total score is corrected to account for the segments not assessed.

MR imaging.

MR images (of the small bowel) are assessed according to the following. 1. No signs of inflammation; 2 Uncertainty of signs of inflammation 3. Definite signs of inflammation

QoL (short-IBDQ)

Short version of the Inflammatory Bowel Disease Questionnaire (IBDQ) in relevant Nordic language.

Up to one missing item of the short IBDQ is replaced by the median score of the respective domain. If more than one item to a domain in the short-IBDQ at a given time point is missing, the whole short-IBDQ assessment is considered missing at that time point. [17] Missing values at a single

time point will be handled as described in section 9.5. The IBDQ score will be used as it is, and no transformations will be performed.

WPAI (work productivity and activity as assessed)

Work Productivity and Activity Impairment Questionnaire (CROHN'S DISEASE (WPAI-CD)) in relevant Nordic language

In case of missing answers to single questions in the WPAI-CD at a given time point, the whole WPAI-CD assessment is considered missing at that time point. Missing values at a single time point will be handled as described in section 9.5. The WPAI-CD score will be used as it is, and no transformations will be performed.

Biochemical parameters (C-reactive protein (CRP), Platelets, Albumin, White blood cell (WBC) count, Haemoglobin (Hb), Faecal calprotectin

The distribution of biochemical parameters will be investigated by histogram and QQ-plots. Outlying values will be checked. It is expected Albumin and Hb will be used as it is and CRP, platelets, WBC and Faecal calprotectin will be log transformed unless other indicated. Missing values will be handled as described in section 9.5.

8 Sample Size

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 study12. 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.

We successfully included 115 patients in the study. Because of slow inclusion rate the last year, we had to terminate the study before we reached the planned 136 patients.

9 General Considerations

9.1 Timing of Analyses

The analyses will be done after last patient last visit and after monitoring and cleaning of data gathered from all patients and after the finalisation and approval of this SAP document.

9.2 Analysis Populations

9.2.1 Full Analysis Population (ITT)

All subjects who received any study drug and who participated in at least one post-baseline assessment

9.2.2 Per Protocol Population (PP)

All subjects who adhere to the major criteria in the protocol (e.g. all subjects who completed at least two efficacy analyses, whose study drug compliance was between 75% and 100% and who did not take any rescue medication). This includes patients who, according to protocol experienced a relapse and was withdrawn from the study but does not include patients who were withdrawn from study without experiencing a relapse.

9.2.3 Safety Population

All subjects who received any study treatment (including control) but excluding subjects who drop out prior to receiving any treatment.

9.3 Covariates and Subgroups

We expected that two covariates could have an important influence on the endpoints and therefore we stratified for fistulising disease and concomitant immunosuppressive therapy.

For explorative subgroup analyses please see 5.2.3

9.4 Intercurrent events

Rescue medication:

Patients who, during the study, receive rescue treatment for their Crohn's disease, including steroids, immunosuppressants or other biologics are considered treatment failures and thus considered to have had relapse.

Discontinuation of study medication:

Patients experiencing relapse as defined above are considered to have met the endpoint.

As regards the time to event endpoints, patients who prior to the scheduled end of study, discontinued study treatment, irrespective of reason for doing so (except for relapse), will be censored.

For the non-time to event endpoints (secondary), patients withdrawn for other reasons than relapse are excluded from the analysis.

In analyses using mixed effect models, all available observations are used for the included patients.

9.5 Missing Data

As regards the secondary endpoints related to CDAI, short-IBDQ, WPAI, biochemical markers (C-reactive protein (CRP), platelets, albumin, white blood cell (WBC) count, Haemoglobin (Hb) and faecal calprotectin) all will be analysed using mixed models for repeated measures (MMRM). These models estimate treatment and time effects using all available data and do not requires prior imputation of missing values. MMRM is considered to give unbiased estimates if data is missing complete at random or missing at random. [18] No further imputations will be performed for these models. Missing values of covariates in multiple analyses will be imputed by multiple imputations.

9.6 Interim Analyses and Data Monitoring

N/A

9.7 Multi-centre Studies

In this multi-centre study, it is intended to analyse data as a whole. Patients eligible for inclusion in this study are limited, and therefore it was necessary to do the study as a multicentre study. In order to avoid selection bias we used block randomization see section 6.3.1.

The "center-factor" will not be considered in statistical models or for subgroup analyses due to the high number of participating centres in relation to the small number of patients randomized at each centre.

9.8 Multiple Testing

Only if the primary objective of the study is met, formal claims on statistical significance of the key secondary endpoint (Proportion of patients who maintain complete remission until end of study) will be made. The statistical level will be set at 0.05 as no correction for multiplicity is necessary when testing is performed in this hierarchical order. Should the primary objective not be met, the key secondary endpoint will be analysed without making formal claims of statistical significance.

Subsequent secondary endpoints and exploratory endpoints are tested at 0.05 level without correction for multiplicity.

10 Sensitivity analyses

Sensitivity analyses will be performed regarding missing values of outcomes and loss to follow up. Missing outcomes will be replaced with values in a best-case worst-case scenario. We may during analyses add additional sensitivity analyses

11 Summary of Study Data

All continuous variables will be summarised using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, IQR. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted by treatment group, and when appropriate by visit number. All summary tables will be structured with a column for each treatment in the order (Control, Experimental) and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

11.1 Subject Disposition

The consort 2010 diagram for patient disposition will be followed. Total number of patients screened and included will be stated. Reasons for non-inclusion will be noted. Number of patients included who received at least one dose of study medication will be stated. The CRF section on medication will be used for determining if at least one dose of study medication was received. Number of patients discontinuing study medication (except for patients who meet the primary endpoint) will be noted.

11.2 Derived variables

The primary endpoint as well as a number of secondary endpoints are based on CDAI score which is calculated based on clinical data entered in a diary as part of the CRF. See 6.4

11.3 Protocol Deviations

Major protocol deviation considered to have a significant impact on the analyses include

a. Not fulfilling the diagnostic criteria for inclusion

b. Not fulfilling the criteria for remission at inclusion (except for deviations considered minor by investigator)

c. Use of non-permitted medication for treatment of Crohn's disease

All important/major protocol deviations will be reported

11.4 Demographic and Baseline Variables

Demographic and baseline variables are shown in Table 1 (section 17). The summary statistics will be produced in accordance with section 11.

11.5 Concurrent Illnesses and Medical Conditions

Concurrent illnesses and medical conditions (according to WHO ICD-10) will be noted.

11.6 Prior and Concurrent Medications

Prior (not administered at time of screening) and concurrent (administered at time of screening) will be noted. Specifically, it is noted if patients are on concomitant immunosuppressants.

11.7 Treatment Compliance

Treatment compliance is based on the CRF section on study drug. As study drug is administered as an intravenous infusion during study visit, this is considered evidence of study drug received.

12 Efficacy Analyses

The null hypothesis is: Time to relapse does not differ between patients continuing infliximab and patients discontinuing infliximab

Time to event (e.g. relapse) will be depicted in Kaplan Meier plots. Analysis will be performed using Log rank Test comparing patients receiving infliximab and patients receiving placebo. Association of demographical, clinical, and biochemical variables with the event is estimated using univariate and multivariable Cox proportional hazard regression analysis. Multivariate analyses will include all variables with $p<0.20$ in the univariate analysis.

For binary endpoints, fraction of patients achieving the endpoint in the two groups will be compared using chi square test/Fisher's exact test.

P-values are two sided, and $p < 0.05$ is considered statistically significant.

Summary tables will be grouped by treatment group (placebo, treatment). See Table 1 for summary statistics that will be produced for continuous and categorical data. Descriptive data will be presented as number/counts and percentages for discrete variables, and as medians with IQR for continuous variables. Statistical uncertainties are expressed in 95% two-sided confidence intervals.

For handling of missing data please see section 7.5 and 9.5

12.1 Primary Efficacy Analysis

Time to relapse will be depicted in a Kaplan Meier plot. Relapse rates at specific time points will be deducted from the Kaplan-Meier curves and presented with 95% confidence intervals. The primary efficacy analysis will be performed using Log rank Test comparing patients receiving infliximab and patients receiving placebo. Association of demographical, clinical, and biochemical variables with relapse is estimated using univariate and multivariable Cox proportional hazard regression analysis. P-values are two sided, and $p < 0.05$ is considered statistically significant.

12.2 Secondary Efficacy Analyses

Time to event endpoints will be depicted in Kaplan Meier plots and differences in median time to event will be analysed using Log rank Test. Association of demographical, clinical, and biochemical variables with relapse is estimated using univariate and multivariable Cox proportional hazard regression analysis. P-values are two sided, and $p < 0.05$ is considered significant. As regards control of inflation of P, please see section 8.8.

For binary endpoint, fraction of patients achieving the endpoint in the two groups will be compared using chi square test/Fisher's exact test. P-values are two sided, and $p < 0.05$ is considered significant.

For normally distributed continuous variables, unpaired t-test is used for univariate analysis. For continuous variables not normally distributed Mann-Whitney U-test is used for univariate analysis. The summary statistics will be produced in accordance with section 11.

For analysing changes over time in continuous variables (secondary endpoints related to CDAI, short-IBDQ, WPAI, biochemical markers (C-reactive protein (CRP), platelets, albumin, white blood cell (WBC) count, Haemoglobin (Hb) and faecal calprotectin)) a mixed model for repeated measures (MMRM). A constrained longitudinal data analysis (cLDA) method where baseline means in the two arms are constrained to be equal will be used. Furthermore, an unstructured covariance matrix will be used.[18] Changes in values over visits and differences between the randomisation groups including 95% confidence intervals will be extracted from the mixed models.

The distribution of the variables and residual errors will be inspected. If analyses of the residual errors indicate a mis specified model the sources for this will be investigated and non-parametric alternatives will be presented as sensitivity analyses.

For cox-regression analyses and the proportional hazard assumption will be evaluated by scaled Schoenfeld residuals. If the treatment effect violates the proportional hazard assumption the analyses will be kept but conclusions will specify that the treatment effect is for the specific follow-up time in this trial.

12.3 Exploratory Efficacy Analyses

For normally distributed continuous variables, Paired/Unpaired t-test is used for univariate analysis. For continuous variables not normally distributed Mann-Whitney U-test/Wilcoxon Matched Pairs Signed Ranks test is used for univariate analysis.

13 Safety Analyses

Safety data included Adverse Events collected during study visits and as spontaneous reports. For each event assessment of severity, seriousness and causality was/ is performed. Please refer to section 6 for details including definitions and specification of the different categories. Number of events in each category, irrespective of repeated events, is listed for each treatment group. Incidence of adverse events is based on calculation of number of events per 100 patients. In this calculation, the same event reported several times will only be counted as one event. Incidence of adverse events will also be corrected for duration of exposure.

13.1 Extent of Exposure

Duration of exposure for each patient is calculated based on days/weeks in study.

13.2 Deaths, Serious Adverse Events and other Significant Adverse Events

Please see above

13.3 Pregnancies

Please see above

13.4 Clinical Laboratory Evaluations

The summary statistics will be produced in accordance with section 11. Please also see section 11.1 as clinical laboratory parameters are considered part of the efficacy evaluation.

- Hgb unit differs in Sweden as compared to other study sites. Normal hgb in Sweden is defined as: >117g/L (female), >134 g/L (male). Normal range or unit for biochemical parameters (CRP, leucocytes, platelets) do not differ between study centres.
- Summaries are only provided over scheduled laboratory tests.

13.5 Other Safety Measures

N/A

14 Pharmacokinetics

Samples for analysis of IFX levels as well as antibodies against infliximab will be drawn at previously specified time points for all patients. However, only samples from patients who after breaking the blind are identified as having received receiving infliximab will subsequently be analysed (except inclusion trough levels, corresponding trough level of last IFX infusion prior to inclusion). Patients maintaining remission will be compared to patients not maintaining remission in terms of levels of infliximab and antibodies against infliximab at all time points using unpaired t-test without correction for multiplicity.

15 Reporting Conventions

Unless other required by publishing journal, P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

Figures and Tables see 17.

16 Technical Details

At the time of writing it is expected that analyses will be performed using IBM SPSS 26.0 (Mac) or newer or GraphPad Prism version 8 (Mac) or newer.

All calculations will be done by the investigators. A second review statistician will independently reproduce all analyses. These calculations will be performed using SAS version 9.4M5 or newer or R version 3.6.1 or newer.

To allow reproduction of the analysis a log will be done for any output including information of the population used, the date and time, the name of the code file that produced the analysis (or for SPSS the syntax name), the author, version of the software and any external add-on code used.

17 Summary of Changes to the Protocol

Compared to the most recently approved protocol the statistical analysis has been changed. Whereas the approved protocol stipulated fraction of patients who maintain remission at the end of one year treatment, the primary endpoint in the present version of the SAP is time to relapse. The justification for the changes are based on the following considerations. Using the originally proposed primary endpoint does not utilize all data collected as patients discontinuing treatment for other reasons than relapse are not included in the analysis thus making this less powerful. This is considered important as number of patients included fell slightly short of the number calculated to achieve appropriate power (please see sample size calculation). By changing to a time to event analysis including all patients (but censoring patients discontinuing due to other causes than relapse all available data are included in the analysis improving power. As the changes are performed prior to analysis of data, it is considered justified.

18 Listing of Tables and Figures

Table: Baseline Characteristics

	Infliximab	Placebo	p-value
Male sex – no. (%) Missing	X (%) N	X (%) N	x
Age – yr. median (IQR)			
Current smoker – no. (%)			
Age at diagnosis – y median (IQR)			
Disease duration – y median (IQR)			
Gastrointestinal area involved – no./total no. (%) - Ileocoecal - Colon only			
Fistulising Crohn's disease – no. (%)			
Crohn's Disease Activity Index (CDAI) – score (IQR)			
WPAI			
IBDQ			
IFX therapy characteristics			
Age at 1st IFX infusion – yr. median (IQR)			
Total IFX infusions (in current series) – median (IQR)			
IFX dose 5mg/kg (no (%).			
Age at start of IFX -y median (IQR)			
Concomitant immunosuppression* – no. (%) Immunosuppresives (AZA, 6-MP, MTX) Topical therapy Antibiotics			
CRP – mg/ml median /mean			
Leucocytes			
Albumin			
Haemoglobin			
SES-CD			

Figure: Study overview

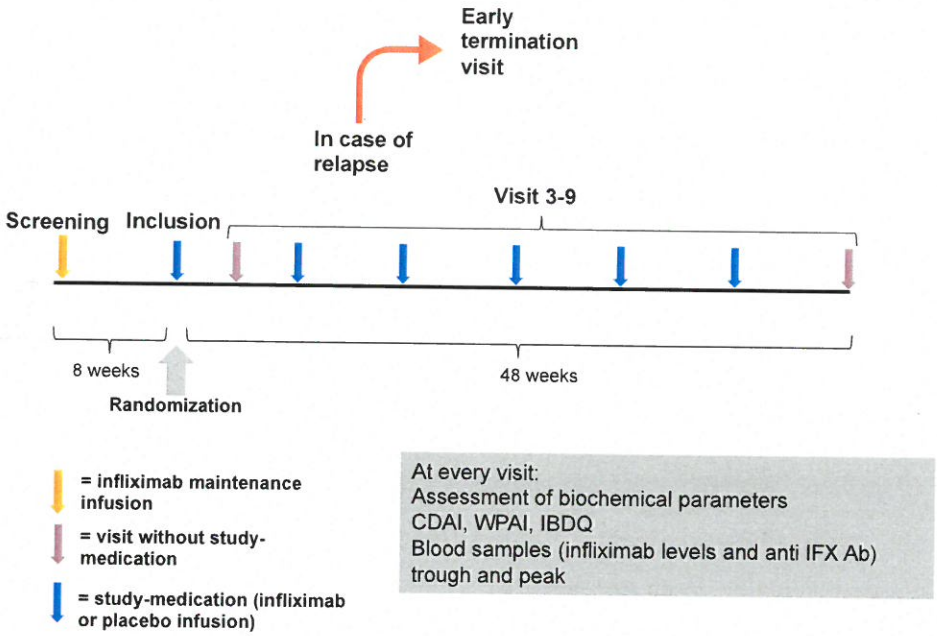

Figure: Patient disposition

(content described in 11.1)

Figure: (primary outcome)
Time to relapse (survival curve) placebo and infliximab group
Y-axis: Proportion of patients in remission. X-axis: time from last infliximab infusion prior to inclusion

Figure: Remission rates in the intervention and control group at week 48
Y-axis: % of patients in remission X-axis: Infliximab group and placebo group

Figure: CDAI score for patients from time of inclusion to week 4, 8, 16, 24, 32, 40, and 48
Y-axis: CDAI score estimated from MMRM including 95% CI. X-axis: week 0 (placebo and infliximab), week 4 ((placebo and infliximab), week 8 (placebo and infliximab) etc.

Figure: WPAI score for patients from time of inclusion to week 4, 8, 16, 24, 32, 40, and 48
Y-axis: WPAI score estimated from MMRM including 95% CI. X-axis: week 0 (placebo and infliximab), week 4 ((placebo and infliximab), week 8 (placebo and infliximab) etc.

Figure: IBDQ score for patients from time of inclusion to week 4, 8, 16, 24, 32, 40, and 48
Y-axis: IBDQ score estimated from MMRM including 95% CI. X-axis: week 0 (placebo and infliximab), week 4 ((placebo and infliximab), week 8 (placebo and infliximab) etc.

Figure: Biochemical parameters (Haemoglobin (Hb), C-Reactive Protein (CRP), albumin for patients from time of inclusion to week 4, 8, 16, 24, 32, 40, and 48
Y-axis: Biochemical parameter estimated from MMRM including 95% CI. X-axis: week 0 (placebo and infliximab), week 4 ((placebo and infliximab), week 8 (placebo and infliximab) etc.

Figure: Endoscopic/MRI remission rates in the intervention and control group
Y-axis: % of patients in endoscopic /MRI remission X-axis: Infliximab group and placebo group

Figure: Complete (clinical (CDAI) endoscopic and biochemical) remission rates in the intervention and control group
Y-axis: % of patients in complete remission X-axis: Infliximab group and placebo group

19 References

1. Talley, N.J., et al., *An evidence-based systematic review on medical therapies for inflammatory bowel disease.* Am J Gastroenterol, 2011. **106 Suppl 1**: p. S2-25; quiz S26.
2. Cosnes, J., et al., *Epidemiology and natural history of inflammatory bowel diseases.* Gastroenterology, 2011. **140**(6): p. 1785-94.
3. Munkholm, P., et al., *Incidence and prevalence of Crohn's disease in the county of Copenhagen, 1962-87: a sixfold increase in incidence.* Scand J Gastroenterol, 1992. **27**(7): p. 609-14.
4. Solberg, I.C., et al., *Clinical course in Crohn's disease: results of a Norwegian population-based ten-year follow-up study.* Clin Gastroenterol Hepatol, 2007. **5**(12): p. 1430-8.
5. Clark, M., et al., *American gastroenterological association consensus development conference on the use of biologics in the treatment of inflammatory bowel disease, June 21-23, 2006.* Gastroenterology, 2007. **133**(1): p. 312-39.
6. Dignass, A., et al., *The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management.* J Crohns Colitis, 2010. **4**(1): p. 28-62.
7. Travis, S.P.L., et al., *European evidence-based Consensus on the management of ulcerative colitis: Current management.* J Crohns Colitis, 2008. **2**(1): p. 24-62.
8. D'Haens, G.R., et al., *The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organization: when to start, when to stop, which drug to choose, and how to predict response?* Am J Gastroenterol, 2011. **106**(2): p. 199-212; quiz 213.
9. Louis, E., J. Belaiche, and C. Reenaers, *Anti-TNF and Crohn's disease: when should we stop?* Curr Drug Targets, 2010. **11**(2): p. 148-51.
10. Danese, S., et al., *Review article: infliximab for Crohn's disease treatment--shifting therapeutic strategies after 10 years of clinical experience.* Aliment Pharmacol Ther, 2011. **33**(8): p. 857-69.
11. Mowat, C., et al., *Guidelines for the management of inflammatory bowel disease in adults.* Gut, 2011. **60**(5): p. 571-607.
12. Sostegni, R., et al., *Crohn's disease: monitoring disease activity.* Alimentary Pharmacology and Therapeutics, 2003. **17**(s2): p. 11-17.
13. Sipponen, T., et al., *Endoscopic evaluation of Crohn's disease activity: Comparison of the CDEIS and the SES-CD.* Inflammatory Bowel Diseases, 2010. **16**(12): p. 2131-2136.
14. Daperno, M., et al., *Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD.* Gastrointest Endosc, 2004. **60**(4): p. 505-12.
15. Grand, D.J., et al., *MR enterography correlates highly with colonoscopy and histology for both distal ileal and colonic Crohn's disease in 310 patients.* Eur J Radiol, 2012.
16. Tolan, D.J.M., et al., *MR enterographic manifestations of small bowel Crohn disease.* Radiographics, 2010. **30**(2): p. 367-84.
17. Häuser, W., et al., *Validation of the inflammatory bowel disease questionnaire IBDQ-D, German version, for patients with ileal pouch anal anastomosis for ulcerative colitis.* Z Gastroenterol, 2004. **42**(2): p. 131-9.
18. Coffman, C.J., D. Edelman, and R.F. Woolson, *To condition or not condition? Analysing 'change' in longitudinal randomised controlled trials.* BMJ Open, 2016. **6**(12): p. e013096.