BIRD
BELGIAN INFLAMMATORY BOWEL DISEASE RESEARCH AND DEVELOPMENT

Protocol Full Title:

Loss of RESponse to Ustekinumab treated by dose Escalation
The REScUE study
REScUE -BIRD2018001

EudraCT number: 2018-004269-14

Protocol Version 1.7; Feb 09, 2022

Sponsor :

Belgian IBD research and development group (BIRD)
Leuvensesteenweg 643
1930 Nossegem
BE 0465 587 924, RPR Brussel
Tel: +32 (0)499 31 70 05
Email: ingrid.arijs@birdgroup.be

Principal Investigator :

Dr. Peter Bossuyt
Imelda Ziekenhuis Bonheiden
Imeldalaan 9
2820 Bonheiden

Advisory group

Prof. Séverine Vermeire
University Hospitals Leuven
Herestraat 49
3000 Leuven

Prof. Jean-François Rahier
Service d'Hépato-gastroentérologie
CHU UCL Namur, site Godinne
5530 Yvoir

Signature page

SPONSOR: BIRD (Belgian IBD research and development)

President: Dr. Filip Baert

Signature Date

2/9/2022

DocuSigned by:
Dr. Filip Baert
03FA0978D8B749E...

PRINCIPAL INVESTIGATOR: Dr Peter Bossuyt

Signature Date

DocuSigned by:
Dr. Peter Bossuyt
322D369D70E745B...

2/9/2022

SITE INVESTIGATOR:

I will conduct the trial in compliance with GCP, with the applicable regulatory requirement(s) and with the protocol agreed to by the sponsor and given approval / favourable opinion by the IRB/IEC and competent authority. I agree to comply with procedure for data recording/reporting, especially to report all SAE to the sponsor within 24H of awareness, to permit monitoring, auditing and inspection and to retain the trial related essential document until the sponsor informs me / my institution that these documents are no longer needed.

I will conduct the trial within the time designated.

I understand that all information concerning the study supplied to me by BIRD in connection with this trial and not previously published is considered confidential information.

I agree that documents and other data pertinent of this trial are property of BIRD.

I understand that any changes in the protocol must be approved in writing by BIRD and the IRB / IEC before implementation.

By my signature below, I hereby attest that I have read, understood and agree to abide by all condition, instructions and restriction contained in the protocol.

Name _____

Signature _____ Date_____

1 Table of Contents

2 Study Synopsis

Title of clinical study	REScUE: loss of RESponse to Ustekinumab treated by dose Escalation
Protocol Short Title/Acronym	REScUE -BIRD2018001
Sponsor name	BIRD (Belgian IBD research and development group)
EudraCT number	2018-004269-14
Principal Investigator	Dr. Peter Bossuyt
Medical condition or disease under investigation	Crohn's disease
Aim of clinical study	To investigate the effect of re-induction with ustekinumab ≈6mg/kg IV followed by two different maintenance dosing regimens 90 mg SC Q8W vs 90 mg SC Q4W on clinical, biological and pharmacological outcomes in patients with Crohn's disease who show a secondary loss of response over time
Primary endpoint	Proportion of patients with steroid free clinical remission (PRO-2 remission: abdominal pain ≤ 1 AND stool frequency ≤ 3) and FCP <250µg/g at week 48. [SF: average number of liquid stools for 1 week AP: average scoring for abdominal pain for 1 week (0=none; 1=mild, 2=moderate; 3= severe)]
Secondary endpoints	Proportion of patients with complete endoscopic remission (SES-CD <3) at week 48 Proportion of patients with endoscopic remission (SES-CD <5) at week 48 Proportion of patients with endoscopic response (≥50% decrease in SES-CD) at week 48 Proportion of patients with clinical remission (PRO-2 remission: AP ≤ 1 AND SF ≤ 3) at week 48

	Proportion of patients with biomarker remission (CRP <5 mg/L and FCP <250 µg/g) at week 48 Proportion of patients with at all time points after baseline UST TC > 1.4 µg/mL Proportion of patients with SAE at week 48
Exploratory endpoints	Pharmacodynamic and pharmacokinetic evaluation. Time till clinical relapse (based on physicians discretion) after week 8. Time to clinical remission (PRO-2 remission: AP ≤ 1 AND SF ≤ 3) IBD related hospitalization. Need for IBD related intestinal resection. Improvements in quality of life based on SF-36. Pharmacoeconomic evaluation (drug cost, hospitalization, work absenteeism, surgery). Suspected Unexpected Serious Adverse Reaction (SUSAR) Serious adverse events (SAE). Extra intestinal manifestation (joint).
Study Design	Prospective double blind multicenter interventional study
Sample Size	108 patients
Number of participating sites	17 sites in Belgium
Summary of major eligibility criteria	1. ≥18 years 2. Diagnosis of Crohn's disease by endoscopic and/or radiologic examination. 3. Patient currently treated with UST, independent of previous biological exposure. 4. Patients treated with maintenance dose of UST SC 90 mg q8w 5. Documented **primary response** at any time point during induction (up to week 20) defined as a clinical response (physician discretion) **AND** confirmed by either any of the following: 1. A documented **decrease in biomarkers** based on a value during induction period compared to a value prior to UST induction (max. 3 months prior to start of UST induction)

	a. A decrease in CRP OR b. A decrease in FCP 2. A documented **endoscopic improvement** (evaluation during the induction period compared to an evaluation prior to UST induction (max. 6 months prior to start of UST induction) 6. Documented **loss of response** after induction (at any timepoint after week 16) assessed by the physician as moderate to severe active Crohn's disease. The increase in symptoms reported by the patient is defined as: PRO-2 (AP > 1 AND SF > 3) **AND** confirmed by either **any** of the following: 1. Documentation of endoscopic lesions in at least one segment of the ileum or colon as assessed by ileocolonoscopy AND a documented **increase in biomarkers** based on an increased value compared to the lowest value obtained during induction or after week 16 UST induction. a. An increase in CRP **and** >5 mg/L OR b. An increase in FCP **and** > 250 µg/mg 2. A documented **relapse on endoscopy**: Presence of mucosal ulcers in at least one segment of the ileum or colon and a SES-CD ≥6 (for patients with isolated ileitis ≥4), as assessed by ileocolonoscopy 7. Adequate contraception in female of reproductive age. 8. Have the capacity to understand and sign an informed consent form. 9. Be able to adhere to the study visit schedule and other protocol requirements. 10. All Crohn's Disease treatments stable for at least 2 weeks prior to baseline.
Period of evaluation of a subject in the study	48 weeks
Version and date of final protocol	Version 1.4, 06 Jan 2020
Version and date of protocol amendments	Version 1.7, 09 Feb2022

3 Background and rationale

Crohn's disease (CD) is an immune disorder that can involve the complete gastrointestinal tract but predominantly presents in the terminal ileum and the colon. Although the exact cause is unknown, it is assumed that it results from an inappropriate inflammatory reaction to the gut microbiome in genetically predisposed patients. Treatment goals include the achievement of sustained clinical remission, endoscopic remission and improved quality of life [1] .

The advent of anti-tumour necrosis factor (anti-TNF) agents such as infliximab and adalimumab brought a significant revolution in the therapeutic management of inflammatory bowel disease (IBD). Where conventional therapy mainly targeted symptom control, anti-TNF agents started to alter the natural history of CD. The mechanisms by which they could do this is through means of induction of mucosal healing, which in turn leads to a reduction in hospitalization and surgery rates [2]. As a consequence, anti-TNF therapy has for many years become the mainstay of therapy in CD patients refractory to corticosteroids and/or immunomodulatory agents. The therapeutic options have expanded over the last year with the introduction of anti-adhesion molecules, such as vedolizumab, targeting the addressin-integrin interaction by blocking α4β7. Furthermore, compounds targeting the IL12/23 pathway such as ustekinumab (UST) (anti body against p40 subunit of IL12/23) have entered the market. These compounds are of high importance since a significant subset of patients shows no or incomplete response to anti-TNF or loose response over time. Patients loosing response to a first anti-TNF agent, may benefit from switching to another anti-TNF agent, but the efficacy of this second anti-TNF agent has been shown to be lower than in anti-TNF naïve patients. Moreover, some patients need to stop anti-TNF therapy due to intolerance or significant side effects. Considering the life-long nature of the disease, new therapies targeting other immune pathways were needed.

Ustekinumab induces and maintains clinical response and remission in patients with moderate-to-severe Crohn's disease as demonstrated by the phase III randomized controlled UNITI program [3]. The clinical response after induction at week 6 was 34% in anti-TNF experienced and 55% in anti TNF naïve patients using ≈6mg/kg IV regime [3]. For patients responding to the induction phase and continuing maintenance treatment with UST 90mg subcutaneous every 8 or 12 weeks, clinical remission was achieved at week 44 in 53% and 49% of patients, respectively. The totality of the efficacy outcomes and certainly also the exposure–response data favour administration of UST every 8 weeks.

Ustekinumab has been approved for the treatment of patients with moderate to severe Crohn's disease (CD), following successful completion of the UNITI and IM-UNITI phase 3 programs. As described in the Stelara® SmPC, the recommended dose regimen of Stelara® is ≈6mg/kg administered by intravenous infusion at week zero. The first subcutaneous administration of 90 mg Stelara® should

take place at week 8 after the intravenous dose. After this, dosing every 12 weeks is recommended. Patients who have not shown adequate response at 8 weeks after the first subcutaneous dose, may receive a second subcutaneous dose at this time. Patients may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgment. Based on the dose response correlation and data on drug exposure in real world setting, a Q8W is preferred.

Some patients who have experienced a decrease in their response may benefit from an re-induction with ≈6mg/kg and/or an increase in dosing frequency to Stelara® 90 mg every four weeks (Q4W). Data on this dose intensification of Stelara® in patients who lose response are scarce and mainly observational or retrospective. In a Canadian cohort study in patients with CD achieving steroid-free response with UST induction, 64% of patients maintained endoscopic or radiographic response, but the cumulative probability of loss of response was 28.2% after 1 year. In this cohort dose escalation was required in 17 patients (16.3%) leading to recapturing of response in 9/17 (52.9%). The most common escalated maintenance dosing was UST 90 mg given subcutaneously every 4 or 6 weeks. Combined re-induction and escalation was effective in 4/7 (57.1%) patients [4]. The GETAID experience with UST came to similar conclusions: the UST failure-free persistence rates were 78% at 12 months, 66% at 24 months and 55% at 36 months [5]. Loss of response was also here observed in a proportion of patients and different dose intensification regimens (dose increase, interval shortening and combination) were used and resulted in overall response rates of 56%. While these real-world data used SC induction regimens, similar conclusions were reached in a Belgian cohort of refractory CD patients who received IV induction followed by 8 weekly UST 90 mg SC. In this cohort, 43% of patients reported primary non response and only very limited mucosal healing (3%) was observed [6]. When looking at UST drug levels, an association was seen between UST exposure and clinical and biological remission, suggesting that higher dosing could lead to better outcomes. A recent PK-PD analysis of the UNITI and IM-UNITI programs came to the same conclusion. UST serum levels correlate with clinical and endoscopic response and remission rates, and inversely correlate with CRP levels [7].

Similar to other biologic agents used in IBD, there also seems to be inter-individual variation in drug exposure and this will depend on the inflammatory burden, BMI, and possibly other factors. Insufficient exposure leads to lower response rates, but also to secondary loss of response over time. Optimizing drug exposure by either increasing the dose or shortening the interval between administrations, has demonstrated to be a successful strategy to regain response in anti-TNF treated patients. Although re-induction or dose intensification seem both effective in retrospective studies with UST the safety profile of dose intensification remains unknown [8]. It is furthermore unknown what the most optimal way is to restore response. Although a single UST IV re-induction seems to restore response in a considerable proportion of patients, we hypothesize that this is insufficient to maintain

clinical response and remission in the long term, since the PK change is probably limited over time and has no beneficial long term PD effect. In contrary, if the observed PD effect is longer than the expected short term PK effect of a single re-induction, it may then support the use of single re-induction followed to continuation of UST 8weekly maintenance to recover response with UST. These re-induction schemes need to be explored in both bio-naive or bio-experienced CD patients who had an objective clinical and biological response. No data exist that suggest that the mechanism of secondary loss of response to UST is different between these two groups. We suggest that the main driver of secondary loss of response is a high inflammatory burden in association with low UST exposure.

4 Study Design and objectives

4.1 Study objectives

4.1.1 Primary objective

- to assess the **clinical** effect of ustekinumab re-induction ≈6mg/kg IV followed by either 90 mg SC Q8W or 90 mg SC Q4W in patients with CD who show a secondary loss of response over time

4.1.2 Secondary objectives

- to assess the **endoscopic** effect of ustekinumab re-induction ≈6mg/kg IV followed by either 90 mg SC Q8W or Q4W in patients with CD who show a secondary loss of response over time.
- to assess the **biochemical** effect of ustekinumab re-induction ≈6mg/kg IV followed by either 90 mg SC Q8W or Q4W in patients with CD who show a secondary loss of response over time.
- to assess the **pharmacodynamic** and **pharmacokinetic** aspects of ustekinumab re-induction ≈6mg/kg IV followed by either 90 mg SC Q8W or Q4W in patients with CD who show a secondary loss of response over time
- to assess the **quality of life** of patient treated with ustekinumab re-induction ≈6mg/kg IV followed by either 90 mg SC Q8W or Q4W in patients with CD after experiencing a secondary loss of response over time.
- to assess the **safety** of ustekinumab re-induction ≈6mg/kg IV followed by either 90 mg SC Q8W or Q4W in patients with CD who show a secondary loss of response over time
- to assess **socio-economic** impact of ustekinumab re-induction ≈6mg/kg IV followed by either 90 mg SC Q8W or Q4W in patients with CD who show a secondary loss of response over time.

4.2 Study Design

4.2.1 Definitions

Clinical remission: PRO-2 remission: AP ≤ 1 AND SF ≤ 3 [SF: average number of liquid stools for 1 week AP: average scoring for abdominal pain for 1 week (0=none; 1=mild, 2=moderate; 3= severe)]

Complete endoscopic remission: SES-CD <3

Endoscopic remission: SES-CD <5

Endoscopic response: ≥50% decrease in SES-CD from baseline

Biomarker remission: CRP <5 mg/L and FCP <250 µg/g

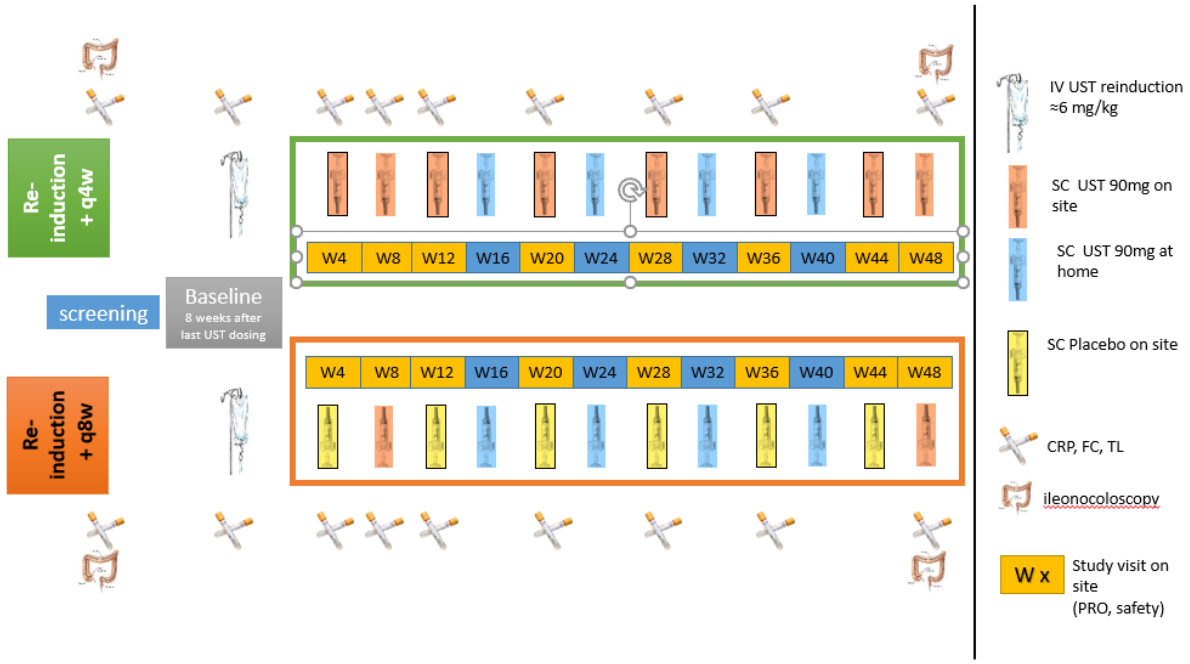
4.2.2 Description of design

The study is a prospective double blind interventional study in patients with CD treated with ustekinumab that show an objective secondary loss of response to ustekinumab after induction treatment (>W16). Patients can be screened during a four week period. The screening includes a clinical, biochemical and endoscopic assessment. A prior endoscopy (ileocolonoscopy) can be used as the screening endoscopy if this endoscopy has been performed within 10 weeks prior to the baseline visit under the following conditions: the endoscopy must have been recorded (all 5 segments must have been visualized – ensure no sensitive data are on the video) and a local SES-CD scoring must have been performed. Patients will be randomized 8 weeks after the last SC injection with ustekinumab. All patient will receive an IV re-induction with ustekinumab ≈6mg/kg at baseline (8 weeks after last SC administration). For the IV re-induction a window of maximum 3 days is authorized. After the IV re-induction, the patients receive either ustekinumab 90 mg SC Q4W or Q8W (altered with q4w placebo) till week 48. Clinical and biochemical evaluation will be planned every 8 weeks until week36 with a final evaluation at week 48. Primary endpoint will be assessed at week 48. Final assessment at week 48 will include clinical, biochemical and endoscopic evaluation. For all visits, a window of maximum 5 days is authorized.

4.2.3 Participating centers

The study is a multicenter trial conducted in Belgium. 17 centers will participate in the study. The recruitment is competitive between the different centers. As q4w weekly administration of ustekinumab is not in the label in Belgium, the only way to start extra q4w dosing of ustekinumab in patients with CD will be by inclusion in this blinded clinical trial.

4.3 Study diagram



4.4 Timelines

Q1 2020: First Patient In

Q4 2023: Last Patient In

Q1 2021: Fist Patient Out

Q4 2024: Last Patient Out

Q1 2025: final analysis

Q2 2025: submission abstract congress

Q3 2025: publication data

4.5 Study Flowchart

	Screening visit***	Baseline**	W 4*	W 8*	W 12*	W 20*	W 28*	W 36*	W 44*	W 48*	unscheduled	Early termination
Informed consent	x											
Demographics	x											
Disease characteristics	x											
Medical history	x											
Current and past treatments for CD	x	x	X	x	x	x	x	x		x	x	x
Endoscopy	x[a]									x		x
Laboratory evaluation[b,]	x	x[c]	X	x	x	x	x	x		x	x	x
pK sampling[d]		x	X	x	x	x	x	x		x	x	x
Disease activity assessment[e]	x	x[c]	X	x	x	x	x	x		x	x	x
Physical examination	x	x	X	x	x	x	x	x		x	x	x
Vital signs[f]	x	x	x	x	x	x	x	x		x	x	x
Weight	x	x	x	x	x	x	x	x		x	x	x
IV re-induction		x										
SC injection on site Q4W[g]			X	x	x	x	x	x	x	x		
SC injection on site Q8W[h]			X	x	x	x	x	x	x	x		
Drug accountability				x	x	x	x	x	x	x	x	x

Questionnaire work and quality of life[i]		x			x		x			x		
Collection of extra samples[j]		x	X	x	x	x	x	x		x	x	x
Check occurrence of (S)AE since last visit		x	x	x	x	x	x	x	x	x	x	x

[a] *A prior endoscopy (ileocolonoscopy) can be used as the screening endoscopy if this endoscopy has been performed within 10 weeks prior to the baseline visit under the following conditions: the endoscopy must have been recorded (video should not contain any sensitive data): all 5 segments (ileum, ascending colon, transverse colon, descending/sigmoid colon and rectum) must have been visualized and a local SES-CD scoring must have been performed.*

b *serum albumin, fecal calprotectin, C-reactive protein, thrombocytosis, hemoglobin. In case of doubt, a pregnancy test can be performed*

[c] *In case the laboratory evaluation was done max. 2 weeks before the baseline, this evaluation does not need to be repeated at baseline. In case the PRO-2 evaluation was done max. 2 weeks before the baseline, this evaluation does not need to be repeated at baseline*

[d] *serum to be collected pre dosing*

[e] *PRO-2: do not include the day of or day before the endoscopy (in case the bowel preparation was performed the day before the endoscopy)*

[f] *blood pressure and pulse (bpm)*

[g] *for Q4w: patients will be administrated blinded UST study labelled vials on site at week 4 and week 12 and thereafter every 8 weeks on site. The administration on the study visit of week 8 and week 48 will be done with commercial drug that the patient will bring from home. All other administrations with commercial drug will be done by the patient itself at home at weeks 16, 24, 32 and 40*

[h] *for Q8w patients: patients will be administrated blinded placebo study labelled vials on site at week 4 and week 12 and thereafter every 8 weeks on site. The administration on the study visit of week 8 and week 48 will be done with commercial drug that the patient will bring from home. All other administrations with commercial drug will be done by the patient itself at home at weeks 16, 24, 32 and 40*

[i] *36-Item Short Form Survey Instrument (SF-36) questionnaire and Work Productivity and Activity Impairment (WPAI) questionnaire*

[i] *collection of serum and whole blood to be stored locally and centralized later on – only in those patients that signed the additional ICF for the substudy*

*** *Screening period of max. 4 weeks*

** *allowed window: +/- 3 days*

* *allowed window: +/- 5 days*

5 Selection and withdrawal of subjects

5.1 Patient selection

Patients will be selected in 17 centers in Belgium.

5.2 Inclusion criteria

1. ≥18 years
2. Diagnosis of Crohn's disease for at least 3 months prior to visit 1 by endoscopic and/or radiologic examination.
3. Patient currently treated with UST, independent of previous biological exposure.

4. Patients treated with maintenance UST SC 90 mg Q8W (meaning after a minimum of 2 SC injections)
5. Documented **primary response** at any time point during induction (up to week 20) defined as a clinical response (physician discretion)
   AND confirmed by either **any** of the following:
   1. A documented **decrease in biomarkers** based on a value during induction period compared to a value prior to UST induction (max. 3 months prior to start of UST induction)
      a. A decrease in CRP
      OR
      b. A decrease in FCP
   2. A documented **endoscopic improvement** (evaluation during the induction period compared to an evaluation prior to UST induction (max. 6 months prior to start of UST induction)
6. Documented **loss of response** after induction (at any timepoint after week 16) assessed by the physician as moderate to severe active Crohn's disease. The increase in symptoms reported by the patient is defined as: PRO-2 (AP > 1 AND SF > 3)
   AND confirmed by either **any** of the following*:
   1. Documentation of endoscopic lesions in at least one segment of the ileum or colon as assessed by ileocolonoscopy AND a documented **increase in biomarkers** based on an increased value compared to the lowest value obtained during induction or after week 16 UST induction.
      a. An increase in CRP **and** >5 mg/L
      OR
      b. An increase in FCP **and** > 250µg/mg
   2. A documented **relapse on endoscopy**: Presence of mucosal ulcers in at least one segment of the ileum or colon and a SES-CD ≥ 6 (for patients with isolated ileitis ≥4), as assessed by ileocolonoscopy.
7. Adequate contraception in female of reproductive age (oral contraception, intra uterine device, sterilisation or barrier method).
8. Have the capacity to understand and sign an informed consent form.
9. Be able to adhere to the study visit schedule and other protocol requirements.
10. All Crohn's Disease treatments stable for at least 2 weeks prior to baseline.

* the criterium used to proof loss of response does not have to be identical to the one used to proof primary response: e.g. one can use an increase in biomarkers to proof primary respons and a relapse on endoscopy to proof loss of response

5.3 Exclusion criteria

1. Ongoing treatment with
    a. other concomitant biological (vedolizumab, anti-TNF)
    b. Steroids >20 mg prednisolone or equivalent at baseline (budesonide >6 mg); >5 mg beclomethasone dipropionate at baseline
    c. Q4w ustekinumab
2. Women that are pregnant, nursing, or planning pregnancy
3. Have screening laboratory test results within the following parameters:
    a. Haemoglobin < 8.5 g/dL
    b. Platelets < 100,000 /mm3
    c. Serum creatinine ≥ 1.7 mg/dL
    d. AST and ALT > 3 times the ULN range
    e. Direct (conjugated) bilirubin ≥ 3.0 mg/dL.
4. Have current signs or symptoms of infection confirmed by positive stool or blood testing (including gastrointestinal pathogens, TB, HIV, Hep B, Hep C).
5. Patients with a positive stool sample for gastrointestinal pathogen including Clostridium difficile.
6. Evidence of current or previous clinically significant disease, medical condition other than CD, finding of the medical examination, or laboratory value at the screening visit outside the reference range that is of clinical relevance, that in the opinion of the Investigator, would compromise the safety of the patient or the quality of the data.
7. Patients with an ileostomy
8. Patients that received an IV re-induction with UST within the 6 months prior to baseline.
9. Patients with an impassable stenosis even after attempt of endoscopic balloon dilation.
10. Patients with an abscess.

5.4 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study should be recorded in the case report form using the following categories.

1. Significant protocol deviation. The discovery post inclusion that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
2. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
3. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded, but patient does not need to justify its withdrawal.
4. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.
5. Significant adverse or serious adverse event, as judged by the investigator after reporting of the (S)AE.
6. Incompliance of the subject to the protocol instruction and medication administration as assessed by the investigator

5.5 Expected duration of study

The recruitment period is 45 months starting from the first patient included into the study. A total of 108 patients will be recruited. The screening period has a maximum of four weeks. The patients will be followed prospectively in the trial for 48 weeks after the baseline.

5.6 Closure of a study site

Frequent monitoring will be performed during the study period of all study sites. If during these monitoring visits important violations of the protocol or insufficient data collection are encountered than the PI and steering committee of the study can decide to exclude the site from further recruitment of patients in the study or to close the study site.

6 Randomization

A centralized online randomization system, stratified by previous exposure to anti-TNF and steroids at baseline will be implemented. The draw will be made in blocks of permutation whose size will not be disclosed to investigators. Patients will be randomized 1:1 in 2 treatment groups as described in the section below.

7 Study medication

7.1 Randomization

Randomization (allocation to treatment group 1 or 2) will be done at day 0 after the relevant information has been entered into the database. Randomization to 1 of the 2 treatment group will be stratified according to previous exposure to anti-TNF and steroids at baseline. Patients and investigators and study related personnel remain blinded to the treatment group allocation.

7.2 Dosing

All eligible subjects will receive a re-induction at baseline, with intravenous ustekinumab, in line with the EU SmPC, on a weight-tiered basis at a dose of approximately 6 mg/kg IV. Subjects with body weight ≤55 kg at Week 0 will receive 260 mg IV ustekinumab. Those subjects with body weight >55 kg and ≤85 kg will receive 390 mg IV ustekinumab. Subjects with body weight >85 kg at Week 0 will receive 520 mg IV ustekinumab. For IV administration, the study drug will be administered to each subject over a period of not less than 1 hour. The infusion should be completed within 5 hours of preparation. Patient has to stay 1 hour after finalizing the IV administration for safety surveillance. At week 4, the subjects in the Q4W arm will receive a 90 mg SC injection of ustekinumab. Subjects in the Q8W arm receive placebo at week 4. Subsequently, subjects in the Q4W arm will continue to receive 90 mg ustekinumab SC at designated 4-weekly injection times (see supply in section 7.3). The subjects in the Q8W arm will receive a 90 mg SC injection of ustekinumab every 8 weeks and placebo every 4 weeks in between (see supply in section 7.3). Subjects who have been trained how to self-inject may self-administer (in compliance with the EU SmPC) SC study drug at the times instructed by the investigator. Study-site personnel will remind subjects on how to store ustekinumab for at-home use as indicated by the SmpC, which is known practice to the subjects as they were already under ustekinumab treatment. Investigational product is stable for max. 6 hours at room temperature. For each administration of study drug, the date and hour of injection will be recorded in the CRF, whether study drug was self-administered, and if so, whether SC administration was complete

7.3 Investigational product supply

This is an investigator initiated study from the Belgian IBD research and development group. It is the only option in Belgium to treat patients with ustekinumab dose intensification after documented loss of response. Dose intensification from q8w to q4w weeks is currently not reimbursed in Belgium. For this the study has two arms. Both arms will receive an IV reinduction with approximately 6 mg/kg commercial ustekinumab. Janssens will deliver vials for the re-induction. The “q4w arm” will receive commercial available q8w ustekinumab (90 mg SC syringe) alternated with q8w double blind active ustekinumab in study labelled vials provided by Janssen. The “q8w arm” will receive commercial available q8w ustekinumab alternated with q8w double blind active placebo (NaCl 0.9%) prepared in

the pharmacy of each participating site in study. After central randomization organized by BIRD, the pharmacist will be informed on the type of syringes to prepare (ustekinumab or placebo). These blinded syringes will be delivered to the study department with subject specific labelling. Janssen will provide the 90 mg vials to the pharmacy through a third party CSM® (Clinical Supplies Management) as well as cold packs and storage devices for cooled transport of the study drugs by the patient as foreseen in the initial reimbursement request at the start of Stelara®.

7.4 Treatment compliance

Study drug will be administered as a single IV infusion (baseline) by qualified staff followed by SC injections (Week 4 investigational product or placebo and onwards every 4 weeks). Details of each administration will be recorded in the CRF, including date, time of injection, and start and stop times and volume infused (for the IV infusion). Subjects may self-administer (in compliance with the EU SmPC) SC injections of study drug under the supervision of the investigator.

7.5 Concomitant medication during the study

5-aminosalicylate: any dosing, need to be stable during the study

Steroids: prednisolone equivalent ≤ 20 mg at baseline, from week 16 tapering with 5 mg per week prednisolone equivalent is obligatory (for beclomethasone diproprionate, taper via EOD or magistral preparation). If tapering is applied, restart or increasing of the dose is allowed during the study. Initiation of steroids during the study is allowed as of week 24 .

Azathioprine/6-mercaptopurine/methotrexate: stable dosing during study, except stop for side-effects, initiation not allowed during study, switch from azathioprine to 6-mercaptopurine (and vice versa) allowed at equivalent dose.

Biologics: not allowed

Jak inhibitors: not allowed

Non registered investigational product: not allowed

Antibiotics: allowed if not started for luminal CD

8 Endpoints

8.1 Primary endpoint

- Proportion of patients with steroid free clinical remission (PRO-2 remission: AP ≤ 1 AND SF ≤ 3) and FCP <250µg/g at week 48.

8.2 Secondary endpoints (unranked)

- Proportion of patients with complete endoscopic remission (SES-CD <3) at week 48
- Proportion of patients with endoscopic remission (SES-CD <5) at week 48

- Proportion of patients with endoscopic response (≥50% decrease in SES-CD) at week 48.
- Proportion of patients with clinical remission (PRO-2 remission: AP ≤ 1 AND SF ≤ 3) at week 48.
- Proportion of patients with clinical remission (PRO-2 remission: AP ≤ 1 AND SF ≤ 3) at week 8 after IV re-induction.
- Proportion of patients with biomarker remission (CRP <5 mg/L and FCP <250 µg/g) at week 48.
- Proportion of patients with UST TC > 1.4 µg/mL at all time points (w4-8-16-24-32-40-48) after baseline in the different treatment arms.
- Proportion of patients with SAE in the different treatment arms.

8.3 Exploratory endpoints

- Pharmacodynamic and pharmacokinetic evaluation.
- Time to clinical response
- Time till clinical relapse (based on physicians discretion) after week 8.
- IBD related hospitalization.
- Need for surgery.
- Improvements in quality of life.
- Pharmacoeconomic evaluation (drug cost, hospitalization, work absenteeism, surgery).
- SUSAR
- SAE.
- Extra intestinal manifestation (joint).

9 Study Procedures

9.1 Assessments at inclusion

The following sections describe the study procedures and data to be collected. For each procedure, subjects will be assessed by the investigator. The Schedule of Study Procedures is in section 4.5.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in section 10.

Informed consent must be obtained prior to the subject entering the study, and before any protocol-directed procedures are performed.

A unique subject identification number (subject number) will be assigned to each subject at the time of screening (see section 16); this subject number will be used throughout the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include year of birth or age, sex, ethnic origin as described by the subject, smoking status, date of diagnosis of CD, and CD Montreal classification of the subject at screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study (including extra intestinal manifestations) that stopped at or prior to signing of informed consent. IBD surgeries need to be specified by number of resections, length of resections of small intestine, location of colonic resection, perianal surgical interventions. Ongoing conditions are considered concurrent medical conditions.

Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 3 months prior to signing of informed consent. Next to that, all IBD treatments in the past need to be recorded.

9.1.3 Disease Activity Measurements

Disease activity will be measured based on the patient reported outcome (PRO-2). Objective markers of disease activity will be collected locally. These markers are C-reactive protein and faecal calprotectin.

9.1.4 Physical exam

9.1.4.1 Physical Examination Procedure

A baseline physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other. All subsequent physical examinations should assess clinically significant changes from the assessment prior baseline physical examination.

9.1.4.2 Weight, Height

A subject should have weight and height measured while wearing indoor clothing and without shoes. The standard for collecting height is centimetres without decimal places and for weight it is kilograms (kg) with 1 decimal place.

9.1.4.3 Vital Sign Procedure

Vital signs will include blood pressure and pulse (bpm).

9.1.5 Documentation of Concomitant Medications

Concomitant medication is any drug given during the study. These may be prescribed by a physician or obtained by the subject over the counter. All medication used to treat IBD including vitamin supplements, over-the-counter medications, and oral herbal preparations, must also be recorded in the CRF.

9.1.6 Procedures for Clinical Laboratory Samples

All laboratory tests will be done at the local hospital labs according to standard care. The lab tests are: serum albumin, faecal calprotectin, C-reactive protein, thrombocytosis and haemoglobin. A list of normal values will be centrally collected. Furthermore, a serum sample will be collected pre-dosing, stored locally and collected for central PK analysis at the Laboratory For Therapeutic And Diagnostic Antibodies of KU Leuven.

9.1.7 Spared blood sample for biomarker research

On top of routine laboratory tests, extra serum and blood samples will be taken for biomarker research (including proteomics and genomics). At the end of the study, these tubes will be transferred and the Biobanking will be centralized at the "UZ Leuven Biobank", Herestraat 49, 3000 Leuven (wbb@uzleuven.be)

Biological samples will be kept at -80°C for 10 years. Afterwards the samples will be destroyed.

A laboratory manual will be available to define SOPs for collection, storage and the shipment procedures of the biologicals samples (in according to the procedures of the central lab).

Additional Patient Inform Consent is required and must be documented, by asking the patient to sign a specific Informed Consent Form for biological samples collection. If a patient disagree to have his samples kept for the biological collection, the physician will inform the project team so that no sample is kept after the mandatory protocol analysis. This will not affect patient follow up in anyway.

9.1.8 Endoscopy

The following aspects are required for the endoscopy and recording of the endoscopy in the study.

9.1.8.1 Preparation and recording

Bowel cleansing should be done with PEG or picosulphate solutions. Last stool before endoscopy should be water clear without faecal parts. Each ileocolonoscopy should be done with the best locally available endoscope, preferentially a high definitions endoscope. Only white light endoscopy must be performed during recording. All evaluable segments need to be recorded during withdrawal endoscopy. Five segments are recorded:

1. Ileum
2. Ascending colon

3. Transverse colon
4. Descending/sigmoid colon
5. Rectum

The complete recording time is preferentially 6 min (always <10:00 min) with a minimum of 30 and a maximum of 90 seconds per segment depending on the quality of the preparation and the presence of lesions. Images should be anonymized completely and identification of each segment must be clearly marked on the screen (ileum, ascending colon, transverse colon, descending/sigmoid colon and rectum). The transition of each segment needs to be highlighted (or by switch of the endoscopy light or by stopping the recording for 2 seconds). Each endoscopic recording is divided in 5 segments. In case of incomplete resection of a segment (ex. segmental sigmoidectomy, minor ileocecal resection) the partial segment in situ must be counted and marked on the screen. Perianal region must be documented adequately if possible by retroflexion in the rectum. Bowel wall must be cleaned sufficiently before recording. If biopsies are taken in a segment, then the segment must be filmed first and biopsies should be taken afterwards. Endoscopic pictures must be taken during endoscopy without stopping the recording. In case lesions are detected, then the lesions must be approached for more precise evaluation. A stenosis needs to be marked on the screen. A stenosis may be dilated during endoscopy after previous adequate documentation of the stenosis. The proximal (not injured by balloon dilation) segment may be recorded afterwards. If polyps are seen during endoscopy, then these can be resected according the ECCO guidelines. Polypectomy should be recorded even if performed during introduction of the scope. Chromoendoscopy is not allowed during recording but can be done afterwards.

9.1.8.2 Storing of endoscopic recording

The recording of the endoscopy will be stored locally on coded USB stick. The central storing of the images will be done on a secured web-based platform of BIRD. The image storing will be done with an adequate quality level (dpi, format). Transfer from the local data can be done by a secured data transfer system. The recording will by identified by a unique code as described in section 16. Exp: XX - XXX.

9.1.8.3 Central reading

All endoscopic videos will be scored locally with the SES-CD. After the study all endoscopic videos will be re-read by a blinded central reader. In case of discrepancy based on a sliding scale:

SES-CD range	Allowed difference
0-3	1 point
4-7	2 points
8-15	3 points
≥ 16	4 points

In case of disagreement between the local and central reader a second central reader will perform an adjudication reading. In case of agreement the average score of the agreeing scores will be used as final score. If no 2 scores were in agreement (within respective predefined confines), the average of CR 1 and CR 2 will be used.

9.2 Assessments during prospective follow up

9.2.1 Scheduled visits week 4/8/12/20/28/36 (allowed window: +/- 5 days)

9.2.1.1 Physical Examination Procedure

A baseline physical examination will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other. All subsequent physical examinations should assess clinically significant changes from the assessment prior baseline physical examination.

9.2.1.2 Weight

A subject should have weight measured while wearing indoor clothing and without shoes. The standard for collecting weight is kilograms (kg) with 1 decimal place.

9.2.1.3 Vital Sign Procedure

Vital signs will include blood pressure and pulse (bpm).

9.2.1.4 Disease Activity Measurements

Disease activity will be measured based on the PRO-2 based on the 7 days before the visit excluding the day of colon prep and day of colonoscopy if applicable. Objective markers of disease activity will be collected locally. These markers are C-reactive protein and faecal calprotectin.

9.2.1.5 Documentation of Concomitant Medications

Concomitant medication is any drug given during the study. These may be prescribed by a physician or obtained by the subject over the counter. All medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

9.2.1.6 Procedures for Clinical Laboratory Samples

All laboratory tests will be done at the local hospital labs according to standard care. The lab tests are: serum albumin, faecal calprotectin, C-reactive protein, thrombocytosis and haemoglobin. A list of normal values will be centrally collected. Furthermore, a serum sample will be collected pre-dosing, stored locally and collected for central PK analysis at the Laboratory For Therapeutic And Diagnostic Antibodies of KU Leuven.

9.2.1.7 Spared blood sample for biomarker research

On top of routine laboratory tests, extra serum and blood samples will be taken for biomarker research (including proteomics and genomics). These tubes will be transferred and the Biobanking will be centralized at the "UZ Leuven Biobank", Herestraat 49, 3000 Leuven (wbb@uzleuven.be)

Biological samples will be kept at -80°C for 10 years.

A laboratory manual will be available to define SOPs for collection, storage and the shipment procedures of the biologicals samples (in according to the procedures of the central lab).

Additional Patient Inform Consent is required and must be documented, by asking the patient to sign a specific Informed Consent Form for biological samples collection. If a patient disagree to have his samples kept for the biological collection, the physician will inform the project team so that no sample is kept after the mandatory protocol analysis. This will not affect patient follow up in anyway.

9.2.1.8 Assessment of adverse events

Any adverse or serious adverse events that occurred between two visits should be recorded and the severity as well as the correlation to the investigational product should be clarified.

9.2.1.9 Drug accountability

For each administration of study drug, the date of injection will be recorded in the CRF, whether study drug was self-administered, and if so, whether SC administration was complete.

Sites will be informed on procedures to follow to ensure product stability. Each site will receive a procedure from the sponsor to keep track of shipment, receipt, disposition, return and destruction of the IMP.

9.2.2 Visit W44 (allowed window: +/- 5 days)

Patients will be seen by the study coordinator or physician to administer the study drug (ustekinimab or placebo).

9.2.3 Unscheduled visit

Patients will be seen unscheduled in case of a disease flare or a CD related event. During the unscheduled visit, all assessments as for the scheduled visit (see section 9.2.1) needs to be done.

9.2.4 End of study visit (allowed window: +/- 5 days) and early termination visit

At the end of the study (week 48) next to the complete evaluation as described in section 9.2.1 an endoscopic evaluation will be performed according to the methodology described in section 9.1.7.

10 Informed consent procedure

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether to participate in the study. If the subject,

or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

11 Assessment of Safety

11.1 Adverse Events

Definition: An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a drug, whether or not the event is considered causally related to the use of the drug. Worsening of a pre-existing condition or illness is considered an adverse event. An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/ procedure has been pre planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event. Laboratory abnormalities judged as clinically significant should be regarded as adverse event.

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, description, severity, time course, duration and outcome, relationship of the adverse event to study drug, if known, and any action(s) taken by reporting this information in the CRF.

11.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is regarded as serious adverse event (SAE) and should be reported within 24 hours of the site being made aware of the serious adverse event to BIRD.

- **Death of Subject** An event that results in the death of a subject.
- **Life-Threatening** An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
- **Hospitalization** An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
- **Prolongation of Hospitalization** An event that occurs while the study subject is hospitalized and prolongs the subject's hospital stay.
- **Congenital Anomaly** An anomaly detected at or after birth, or any anomaly that results in fetal loss.
- **Persistent or Significant Disability/Incapacity** An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
- **Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome** An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

- **Spontaneous Abortion** Miscarriage experienced by study subject.
- **Elective Abortion** Elective abortion performed on study subject.

11.3 SUSAR reporting

A suspected unexpected serious adverse reaction (SUSAR) on the study drug(s), which **is lethal or life-threatening**, must be reported to the Competent Authority, the central Ethics Committee and the investigators within 7 days from the time-point when the responsible investigator is aware of the event. A complement of the report is sent to the authorities within a maximum of 15 days.

A suspected unexpected serious adverse reaction (SUSAR) on the study drug(s), which is **not lethal or life-threatening**, must be reported the Competent Authority, the central Ethics Committee and the investigators within 15 days from the time-point when the responsible investigator is aware of the event. A complement of the report is sent to the authorities as soon as possible.

11.4 Definitions of Adverse Event Severity

The investigator will use the following definitions to rate the severity of each adverse event:

- **Mild** The adverse event is transient and easily tolerated by the subject.
- **Moderate** The adverse event causes the subject discomfort and interrupts the subject's usual activities.
- **Severe** The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

11.5 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

- **Probably Related** An adverse event has a strong temporal relationship to study drug or recurs on re-challenge and other cause of event is unlikely or significantly less likely.
- **Possibly Related** An adverse event has a strong temporal relationship to the study drug and another cause of event is equally or less likely compared to the potential relationship to study drug.
- **Unlikely**: An adverse event for which an alternative explanation is more likely, e.g., concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal

relationship is unlikely. The patients will be specifically assessed for infection and malignancies and the incidence rates of these events will be presented as descriptive summary statistics and the number and percentage of patients who experience adverse events will be tabulated.

11.6 Notification

All adverse events as well as ustekinumab drug product quality complaints will be recorded by the investigator in the CRF.

All life-threatening adverse events and all deaths must be notified within 24 hours to the Sponsor with standard forms. A serious adverse event regarded by the investigator as related to the patient participating in the study, even if it occurred before or after study treatment administration, must be reported. Serious Adverse Event up to 60 days after the last study treatment will be reported. All Serious Adverse Events will be followed until resolution or until it is confirmed by the PI and/or the Study Responsible Physician that it is no longer necessary to do so. In case the investigator knows about a serious adverse event after the patient withdrawal from the study, he must inform the sponsor as far as he considers the serious adverse event as related to the study treatment.

For all serious adverse events, the Serious Adverse Event Report Form must be filled and sent to BIRD within 24 hours. Rules and regulations: By agreeing with this study procedures, the investigator commits himself to take these responsibilities.

SERIOUS ADVERSE EVENTS MUST BE REPORTED TO BIRD Central Office by using sae@birdgroup.be

Alternatively, notifications can also be done by phone (+32 499 31 70 05). Using the postal address (Leuvensesteenweg 643, 1930 Nossegem) is only an option for notification of additional information as the initial 24h window of reporting cannot be guaranteed.

Rules and regulations: By agreeing with this protocol, the investigator commits himself to take these responsibilities.

BIRD commits to fulfil the annual DSUR reporting to the CA and central EC. In the event of SUSAR occurrence, BIRD will comply to necessary reporting to CA and central EC as well as informing the investigators.

11.7 Pregnancy

Female subjects who become pregnant while participating in this study will be the subject of a notification to the coordinators within two weeks after notification of the pregnancy with the help of

the « Pregnancy Initial Statement ». The pregnancy will result in the patient's withdrawal from the study but a follow-up will continue until the pregnancy is carried to full term.

Male subjects whose partner becomes pregnant while participating in this study will be the subject of a notification to the coordinators within two weeks after notification of the pregnancy with the help of the « Pregnancy Initial Statement ». The pregnancy will not result in the male subject's withdrawal from the study but a follow-up will continue until the pregnancy is carried to full term on the condition that the partner has signed an ICF given permission to collect information regarding pregnancy follow-up and outcome. The pregnancy follow-up will be recorded on a « Pregnancy Follow-Up » form, which will be sent to the investigator within 6 to 8 weeks following the presumed date of term. Pregnancy is not considered as an adverse event but any complication such as spontaneous miscarriage or therapeutic interruption of the pregnancy will have to be considered as an adverse event.

11.8 Biological and other abnormalities

Biological abnormalities (biochemistry, haematology, urinalysis) or abnormal results of exams (ECG, X-Ray…) considered as clinically significant by the investigator, must, if corresponding to the definition of an adverse event (serious or not), be recorded. Biological abnormalities or abnormal exams regarded as clinically significant by the investigator are considered adverse event if they are detected after administration of the study drug or are present upon inclusion and worsen during study.

On the contrary, biological abnormalities or abnormal results of exams regarded as clinically significant by the investigator are not considered as adverse or serious adverse even if they are related to the disease under therapy (except if they are more severe than expected according to the patient's condition) or are present before inclusion (or discovered at inclusion) and did not worsen during the study.

11.9 Safety committee

A Safety Committee composed of two international IBD experts (W. Reinish and D. Laharie) not involved in the study will be constituted to consider life-threatening adverse events and fatalities occurring during the study. According to recommendations of this committee, the Principal Investigators can decide to interrupt the study as appropriate.

12 Statistics

12.1 Assumption

The proportion of patients in steroid-free clinical and biological (FCP) remission is assumed to be higher in the IV re-induction followed by Q4W maintenance arm compared to the UST IV re-induction followed by Q8W maintenance. The study will be powered to have at least 80% power detect a 30% difference between the 2 treatment groups regardless of the rate in the reference group (Q8W maintenance group).

12.2 Planned analysis

Baseline characteristics will be tabulated and differences between the two treatment groups will be examined by means of descriptive statistics.

The primary analysis set will be based on all patients randomized following the intention to treat principle. In addition, also secondary analyses in a per protocol analysis set will be performed.

Primary and secondary outcomes will be compared between treatment arms. The primary endpoint will be analysed using a stratified (on both factors on which randomisation was performed) risk difference with a 95% two-sided confidence interval. Multiple imputation will be performed to deal with missing data.

A full statistical analysis plan will be written before data base lock.

12.3 Power calculation

To achieve 80% power to detect an expected 30% difference in proportions of treatment response between the two study arms using a chi-square test with a two-sided alpha of 5%, between 64 to 86 patients in total are necessary depending on the rate in the reference group ranging from 10% to 60%. The maximum sample size of 86 patients corresponds with about a 35% vs 65% response rate and has 90% power for a reference rate of 10% or 60%. To account further for an expected attrition rate of 20%, the study therefore requires 108 patients (54 patients in each treatment arm) to achieve at least 80% power regardless of the response rate in the reference group.

13 Quality Assurance

A Monitoring Plan will be set up by the BIRD and regular monitoring will be performed centrally or at site to ensure quality of the data. Protocol deviations will be discussed with the Investigator and

retraining will be provided as appropriate. The investigator and co-investigators agree to welcome the BIRD's monitors or designee as needed for monitoring purposes. After each site visit, monitors will complete a Monitoring Visit Report (MVR) and send a follow up letter to the Investigator to address issues requiring follow up. The MVR will be kept at BIRD and is available for review by regulatory authorities as needed.

Investigator will contact BIRD immediately if they are informed of an upcoming inspection by regulatory authority for the study at their site.

14 Direct access to source data and documents

The investigator and the institution will permit study-related monitoring, audits, EC review, and regulatory inspections (where appropriate) by providing direct access to source data and other documents (i.e. patients' case sheets). Investigators agree to make themselves available for discussion on findings and corrective actions as needed.

15 Ethics and regulatory approvals

The study will be conducted in compliance with the principles of the Declaration of Helsinki (2008), the principles of GCP and in accordance with all applicable regulatory requirements. This protocol and related documents will be submitted for approval to Ethics Committee and for notification to Competent Authority according to the latest Belgian regulation.

The Study can and will be conducted only on the basis of prior informed consent by the Subjects, or their legal representatives, to participate in the Study. The Participating Site shall obtain a signed informed consent form (ICF) for all patients prior to their enrollment and participation in the Study in compliance with all applicable laws, regulations and the approval of the (local) Ethics Committee, if required. The Participating Site shall retain such ICFs in accordance with the requirements of all applicable regulatory agencies and laws.

The Investigator and the Participating Site shall treat all information and data relating to the Study disclosed to Participating Site and/or Investigator in this Study as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the performance of the Study. The collection, processing and disclosure of personal data, such as patient health and medical information is subject to compliance with applicable local law and personal data protection and the processing of personal data (Belgian law of December 8, 1992 on the Protection of the Privacy in relation to the Processing of Personal Data).

According to the European General Data Protection Regulation 2016/679, the subjects will be informed through the ICF that the sponsor will hold responsibility for the processing of their data relating to the study. This ICF will contain the contact details for the local data protection officer at the site where they have been enrolled in this study as well as contact details for the Belgian authority agency for data protection.

16 Data Management

Demographics, disease characteristics, medical history and current and past treatments for CD will be recorded on a study worksheet if not available in the patient's medical file to be used as source document and collected afterwards in an electronic CRF (eCRF) provided by BIRD. Endoscopy video images will be recorded electronically and will be stored in a secured electronic video database. The data in the eCRF and the video database will be coded with a unique code to assure anonymization of the subject included in the study. The code is a 5-digit code based consecutively number, based on the 2 digits site number and the 3 digits inclusion number. Exp: XX - XXX.

17 Data ownership

All data that will be acquired in the trial will be the property of the Belgian IBD research and development group. No use and no transmission to a third party will be made possible without its prior consent

18 Publication Policy

It is anticipated that the results of the overall Study shall be published in a multi-centre publication, involving the data of all clinical sites participating in the Study.

Participating Site is not allowed to publish any data or results from the Study prior to the multicentre publication, provided however that Participating Site can publish the results generated at the Participating Site if the multicentre publication has not occurred after 12 months from Study database lock.

Any publication by Participating Site will be submitted to the Sponsor for review at least fourteen (14) days prior to submission or disclosure. Sponsor shall have the right to delay the projected publication for a period of up to three (3) months from the date of first submission to the Sponsor to enable the Sponsor to take steps to protect its intellectual property rights and know-how.

Publications will be coordinated by the BIRD. Authorship to publications will be determined in accordance with the requirements published by the International Committee of Medical Journal Editors and in accordance with the requirements of the respective medical journal. PB will be first

author and SV will be last author on the principal paper. JFR and *** will have a significant place (second or second last) in the author list on the principal paper based on significant scientific contribution. All investigators will be mentioned as co-author on the principal paper depending on their input (number of included patients > input in data evaluation > input in the manuscript writing).

19 Insurance/Indemnity

According to Belgian Law of May 7, 2004, BIRD contracted an insurance policy with the MS AMLIN Insurance SE group covering civil liability for potential damages that could happen to any subject involved in this research in Belgium under agreement No LXX080984. The sponsor shall secure and maintain at their own expense in full force and effect through the performance of the Study (and following termination of the Study to cover any claims arising from the Study) insurance coverage in amounts appropriate to the conduct of the Study and in conformance with applicable legal and regulatory requirements as well as comprehensive and professional liability insurance of reasonable policy limits for their own country.

In accordance with the Belgian Law relating to experiments on human persons dated May 7, 2004, National Coordinator Institution shall assume, even without fault, the responsibility of any damages incurred by a Study Patient and linked directly or indirectly to the participation to the Study, and shall provide compensation therefore through its insurance."

BIRD reserves the right to terminate the study at any time for medical or administrative reasons without any compensation other than for work already performed. The investigator will be notified in this case.

20 Financial Aspects

The funding of the trial is based on an investigator initiation research funding by Janssen-Cilag NV.

21 Abbreviations

AP	abdominal pain
AST	aspartate aminotransferase
ALT	alanine aminotransferase
BIRD	Belgian IBD research and development group
BMI	body mass index
CD	Crohn's disease
CRF	clinical research file

CRP	C-reactive protein
ECG	electrocardiogram
EU	European Union
FCP	fecal calprotectin
GCP	good clinical practice
GETAID	Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif
Hep	hepatitis
HIV	Human immunodeficiency virus
IBD	inflammatory bowel disease
ICF	informed consent form
IEC	institutional ethical committee
IHC	international health council
IL	interleukin
IRB	institutional review board
IV	intravenous
MVR	Monitoring Visit Report
PD	pharmacodynamics
PK	pharmacokinetic
PRO	patient reported outcome
SAE	Serious adverse event
SC	subcutaneous
SES-CD	simple endoscopic score for Crohn’s disease
SF	stool frequency
SF-36	36-Item Short Form Survey Instrument
SmPC	Summary of the Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TC	trough concentration
TNF	tumour necrosis factor
ULN	upper limit of normal

UST	ustekinumab
WPAI	Work Productivity and Activity Impairment

22 Bibliography

1. Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L. Crohn's disease. *Lancet* 2017;**389**:1741-55.
2. Pouillon L, Bossuyt P, Peyrin-Biroulet L. Considerations, challenges and future of anti-tnf therapy in treating inflammatory bowel disease. *Expert Opin Biol Ther* 2016;**16**:1277-90.
3. Feagan BG, Sandborn WJ, Gasink C*, et al.* Ustekinumab as induction and maintenance therapy for crohn's disease. *N Engl J Med* 2016;**375**:1946-60.
4. Ma C, Fedorak RN, Kaplan GG*, et al.* Long-term maintenance of clinical, endoscopic, and radiographic response to ustekinumab in moderate-to-severe crohn's disease: Real-world experience from a multicenter cohort study. *Inflamm Bowel Dis* 2017;**23**:833-9.
5. Wils P, Bouhnik Y, Michetti P*, et al.* Long-term efficacy and safety of ustekinumab in 122 refractory crohn's disease patients: A multicentre experience. *Aliment Pharmacol Ther* 2018;**47**:588-95.
6. Verstockt, al Be. Ustekinumab induces limited mucosal healing after 6 months in a real-life, prospective cohort of patients with refractory crohn's disease. . ECCO 2018, 2018: poster 704.
7. Adedokun OJ, Xu Z, Gasink C*, et al.* Pharmacokinetics and exposure response relationships of ustekinumab in patients with crohn's disease. *Gastroenterology* 2018;**154**:1660-71.
8. Heron, al Ve. Reinduction with ustekinumab in crohn's disease patients with a loss of response to treatment. ECCO 2018 poster 438.

23 Appendices

23.1 Appendix 1: PRO-2

Variable	**Day**							**7 day average**
	1	**2**	**3**	**4**	**5**	**6**	**7**	
Number of liquid or very soft stools per day								
Abdominal pain: none=0, mild=1, moderate=2, severe=3								

23.2 Appendix 2: SES-CD

Simple endoscopic score (SES-CD)

SES Score

Variable	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

SES-CD = sum of all variables for the 5 bowel segments.
Values are given to each variable for every examined bowel segment

Source: Daperno, M. et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest. Endosc. 60, 505-512 (2004).

23.3 Appendix 3: SF-36

INSTRUCTIONS: Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by circling the number that best represents your response.

1. In general, would you say your health is?

Excellent (1)	Very Good (2)	Good (3)	Fair (4)	Poor (5)

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago

(1)	(2)	(3)	(4)	(5)

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much: (circle one number on each line)

	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
A. **Vigorous activities**, such as running, lifting heavy objects participating in strenuous sports	1	2	3
B. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
C. Lifting or carrying groceries	1	2	3
D. Climbing **several** flights of stairs	1	2	3
E. Climbing **one** flight of stairs	1	2	3
F. Bending, kneeling, or stooping	1	2	3
G. Walking **more than a mile**	1	2	3
H. Walking **several hundred yards**	1	2	3
I. Walking **one hundred yards**	1	2	3
J. Bathing or dressing yourself	1	2	3

4. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health?</u> (Circle one number on each line)

	All the time	**Most** of the time	**Some** of the time	A **little** of the time	**None** of the time
A. Cut down on the **amount of time** you spend on work or other activities	1	2	3	4	5
B. **Accomplished less** than you would like	1	2	3	4	5

C. Were limited in the **kind** of work or other activities	1	2	3	4	5
D. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2	3	4	5

5. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)? (Circle one number on each line)

	All the time	**Most** of the time	**Some** of the time	**A little** of the time	**None** of the time
A. Cut down on the **amount of time** you spend on work or other activities	1	2	3	4	5
B. **Accomplished less** than you would like	1	2	3	4	5
C. Did work or activities **less carefully than usual**	1	2	3	4	5

6. During the <u>past 4 weeks</u>, to what extent has your <u>physical health or emotional problems</u> interfered with your social activities with family, friends, neighbours, or groups? (Circle one)

Not at all (1)	Slightly (2)	Moderately (3)	Quite a bit (4)	Extremely (5)

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>? (Circle one)

None (1)	Very Mild (2)	Mild (3)	Moderate (4)	Severe (5)	Very Severe (6)

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)? (Circle one)

Not at all (1)	Slightly (2)	Moderately (3)	Quite a bit (4)	Extremely (5)

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks… (Circle one number on each line)

	All the time	**Most** of the time	**Some** of the time	**A little** of the time	**None** of the time
A. did you feel full of life?	1	2	3	4	5
B. have you been very nervous?	1	2	3	4	5
C. have you felt so down in the dumps nothing could cheer you up?	1	2	3	4	5
D. have you felt calm and peaceful?	1	2	3	4	5
E. did you have a lot of energy?	1	2	3	4	5
F. have you felt downhearted and depressed?	1	2	3	4	5
G. did you feel worn out?	1	2	3	4	5
H. have you been happy?	1	2	3	4	5
I. did you feel tired?	1	2	3	4	5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the Time (1)	Most of the Time (2)	Some of the Time (3)	A Little of the Time (4)	None of the Time (5)

11. How TRUE or FALSE is each of the following statements for you? (Circle one number on each line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
A. I seem to get sick a little easier than other people	1	2	3	4	5
B. I am as healthy as anybody I know	1	2	3	4	5
C. I expect my health to get worse	1	2	3	4	5
D. My health is excellent	1	2	3	4	5

23.4 Appendix 4:WPAI -CD

The following questions ask about the effect of your Crohn's disease on your ability to work and perform normal daily activities. Please provide answers or choose a number, as indicated.

1. Are you currently in paid employment?

   If NO, choose "NO" and skip to question 6.

   _____NO _____YES

The next questions refer to the PAST SEVEN DAYS, not including today.

2. During the past seven days, how many hours did you miss from work because of problems ASSOCIATED WITH YOUR CROHN'S DISEASE? Include hours you missed on sick days, times you went in late, left early, etc., because of your Crohn's disease. Do not include time you missed to participate in this study.

   _____HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as annual leave, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS (If "0", skip to question 6)

5. During the past seven days, how much did your Crohn's disease affect your productivity WHILE YOU WERE WORKING?

   Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If Crohn's disease affected your work only a little, choose a low number. Choose a high number if Crohn's disease affected your work a great deal.

Crohn's disease had no effect on my work	0 1 2 3 4 5 6 7 8 9 10	Crohn's disease completely prevented me from working

CHOOSE A NUMBER

6. During the past seven days, how much did your Crohn's disease affect your ability to perform your normal daily activities, excluding your job?

   By normal activities, we mean the usual activities you perform, such as working around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could perform and times you accomplished less than you would like. If Crohn's disease affected your activities only a little, choose a low number. Choose a high number if Crohn's disease affected your activities a great deal.

Crohn's disease had no effect on my daily activities	0 1 2 3 4 5 6 7 8 9 10	Crohn's disease completely prevented me from doing my daily activities

CHOOSE A NUMBER