

Janssen EMEA*

Clinical Protocol

Appendix - Guidance on Study Conduct during the COVID-19 Pandemic

**Study of Treat to Target Versus Routine Care Maintenance Strategies in Crohn's Disease
Patients Treated with Ustekinumab**

STARDUST

**Protocol CNT01275CRD3005; Phase 3b
Amendment 4**

STELARA (ustekinumab)

* Janssen EMEA is an organization in Europe, the Middle East, and Africa that operates through different legal entities in various countries. The legal entity acting as the sponsor for Janssen EMEA studies may vary, such as, but not limited to Janssen Pharmaceutica NV or Janssen-Cilag International. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

EudraCT NUMBER: 2016-002918-43

Status: Approved

Date: 14 April 2020

Prepared by: Janssen-Cilag Ltd.

EDMS number: EDMS-ERI-125725400, 6.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice and applicable regulatory requirements.

Confidentiality Statement

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	Date
Amendment 4 (COVID-19 Appendix)	14 April 2020
Amendment 3	23 November 2017
Amendment 2	13 September 2017
Amendment 1	22 March 2017
Original Protocol	04 November 2016

Amendment 4, 14 April 2020

Overall Rationale for the Amendment: To provide guidance on changes to study conduct and assessments due to restrictions and limitations during the COVID-19 pandemic.

Section Number and Name	Description of Changes and Brief Rationale
Appendix - Guidance on Study Conduct During the COVID-19 Pandemic	Description of Change: Added guidance on changes to study conduct and assessments due to restrictions and limitations during the COVID-19 pandemic. Rationale: To provide guidance on study conduct and assessments during the COVID-19 pandemic.

BACKGROUND

This document applies to all current versions of Protocol CNTO1275CRD3005.

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by subjects and/or study-site personnel; travel restrictions and limited access to public places, including hospitals; and study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study-related subject management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government guidelines or requirements or the clinical judgement of the investigator to protect the health and well-being of subjects and site staff. If at any time a subject's safety is considered to be at unacceptable risk, study drug will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely, virtually, or will be delayed until such time that on-site visits can be resumed. At each contact, subjects will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Subjects will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for subjects on study drug, including follow up. Modifications to protocol-required assessments may be permitted after consultation between the subject and investigator, and with the agreement of the sponsor (see below).

The sponsor will continue to monitor the conduct and progress of the clinical study and any changes will be communicated to the sites and health authorities according to local guidance.

If a subject has tested positive for COVID 19, the investigator should contact the sponsor's responsible medical officer or designee to discuss plans for study drug and follow-up.

GUIDANCE SPECIFIC TO THIS PROTOCOL

Study Drug and Assessments

Certain protocol-mandated visits to the study site may not be possible during the COVID-19 outbreak; therefore, temporary measures may be implemented if considered appropriate by the sponsor and investigator to maintain continuity of patient care and study integrity. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures.

- Remote (eg, by phone / telemedicine) or in-person, off-site (eg, in-home) interactions between site staff (or designees) and patients for study procedures (eg, those related to safety monitoring / efficacy evaluation / study drug storage and administration, including training where pertinent)
- Application of study drug at home and central lab assessment sample collection and efficacy assessments can also be performed by a Home Health Care service provider if agreed by the sponsor, investigator and subject.

Drug Accountability and Compliance (Protocol Section 14.5)

Notes on Shipment of Study Drug to Subjects

If it is necessary to ship the study drug directly to study subjects, shipment by the study site itself is preferred under this exception due to the COVID-19 pandemic. Shipment should be made in a manner that allows tracking of both transport and delivery. The subject should acknowledge receipt of the shipment to the site (eg, by returning a dated and signed receipt form).

In case adequate shipment by the study site is not possible (for example, owing to capacity limitations, logistics, or special transport conditions for the study drug), direct transport by the sponsor may be accepted in justified exceptional cases, provided that the sponsor appoints a suitably qualified service provider as trustee. The sponsor must contractually oblige this service provider to maintain the pseudonymization and, if necessary, blinding of study subjects to the sponsor using appropriate measures. Both the transport and handover conditions for study drug should be part of the contractual arrangements, so that pharmaceutical drug safety of study drug as well as protection of the privacy and personal data of subjects are adequately safeguarded. The study drug must be delivered directly to the subject or a person authorized by the subject and must not be given to neighbors or deposited at a storage location. Written confirmation of dose and dose regimens by the investigator should also be obtained prior to shipment.

The personnel of the service provider in charge of the transport should be trained and instructed accordingly. As personal data are transferred to the service provider, this requires a contract of assignment with the sponsor or legal representative.

For direct shipment of study drug to subjects, written instructions on storage and return of used and unused study drug should be provided to subjects. When shipped by study sites, the receipt, consumption and return of study drug must be documented in a form that allows the study site to meet its documentation requirements (ie, drug accountability), as defined in ICH GCP 4.6.3.

Study Assessments and Analyses

Safety Assessments (Protocol Section 9.6.)

Clinical laboratory safety monitoring may be performed at a certified local laboratory identified by the study site rather than at the central laboratory; for selected measures (eg, urine pregnancy), home testing may be employed.

Missed Assessments

Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study drugs and withdrawal from the study should be documented with the prefix “COVID-19-related” in the CRF.

Other relevant study data elements impacted by the COVID-19 pandemic should also be documented/labeled as “COVID-19-related” in CRFs and/or other study systems, as directed by sponsor guidance; these may include missed/delayed/modified study visits/assessments/dosing, and instances where temporary measures such as those above are implemented.

Where applicable, other study procedures may be conducted at an appropriate facility identified by the study site.

Study Analyses

The Sponsor will evaluate the totality of impact of COVID-19 on collection of key study data and additional data analyses will be outlined in the statistical analysis plan(s).

INVESTIGATOR AGREEMENT

STELARA (ustekinumab)

Clinical Protocol CNT01275CRD3005 Amendment 4
Appendix - Guidance on Study Conduct during the COVID-19 Pandemic**INVESTIGATOR AGREEMENT**

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____Signature: _____ Date: _____
(Day Month Year)**Principal (Site) Investigator:**

Name (typed or printed): _____

Institution and Address: _____

_____Telephone Number: _____
Signature: _____ Date: _____
(Day Month Year)**Sponsor's Responsible Medical Officer:**Name (typed or printed): Maciej Nazar, MD PhDInstitution: Janssen-Cilag PolskaSignature: **MACIEJ
NAZAR**

Digitally signed by MACIEJ NAZAR
DN: c=US, o=JNJ, ou=Subscribers, cn=MACIEJ
NAZAR, 0.9.2342.19200300.100.1.1-42001608
Reason: I am approving this document.
Date: 2020.04.16 17:46:29 +02'00'
Adobe Reader version: 11.0.20

Date: _____
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

CONFIDENTIAL

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Status: Approved, Date: 14 April 2020

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Clinical Protocol

**Study of Treat to Target Versus Routine Care Maintenance Strategies in Crohn's Disease
Patients Treated with Ustekinumab**

STARDUST

**Protocol CNT01275CRD3005; Phase 3b
AMENDMENT 3**

STELARA (ustekinumab)

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	04 November 2016
Amendment 1	22 March 2017
Amendment 2	13 September 2017
Amendment 3	23 November 2017

Amendments below are listed beginning with the most recent amendment.

Amendment 3 (23 November 2017)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: To extend study treatment to Week 104, to explore the effectiveness of longer-term ustekinumab treatment, and to explore de-escalation of ustekinumab dosing.

Applicable Section(s)	Description of Change(s)
Rationale: To extend the study to Week 104, and to examine the effectiveness of de-escalated ustekinumab dosing.	
Synopsis, Objectives, Endpoints and Hypothesis; 2.1 Objectives and Endpoints; 11.3.2 Secondary Endpoints	Added exploratory objectives and endpoints relating to the extension of ustekinumab treatment to Week 104, and to dose de-escalation.
Synopsis, Overview of Study Design, Dosage and Administration; 3.1 Overview of Study Design; Figure 1; 6 Dosage and Administration; 9.1.3 Open-Label Treatment Phase	Added text describing continuation of study treatment after Week 48 in an extension period up to Week 104. Modified the Schematic Overview of Study Design. Added details of ustekinumab dose de-escalation to be applied depending on endoscopic and clinical findings at Week 48, and subsequently on clinical remission and biomarker (CRP and FC) findings.
Time and Events Schedules	Added a Time and Events Schedule for the extension period. Amended the Time and Events Schedules and footnotes to allow for ustekinumab dosing at or after Week 48. Indicated that safety, efficacy, health economics, pharmacokinetic and immunogenicity assessments will be performed up to Week 104. Clarified the timing of urine pregnancy testing, and injection site evaluation.

Applicable Section(s)	Description of Change(s)
Synopsis, Objectives, Endpoints and Hypothesis, Overview of Study Design, Efficacy Evaluations; Time and Events Schedule – Extension Period; 2.1 Objectives and Endpoints; 3.1 Overview of Study Design; 3.2 Study Design Rationale; 9.1.3 Open-Label Treatment Phase; 9.2.4. Video Ileocolonoscopy; 11.3.2 Secondary Endpoints	Added ileocolonoscopic assessments at Week 104. Indicated that endoscopic endpoints at Week 104 will be explored.
Synopsis, Overview of Study Design; Time and Events Schedules, footnotes; 3.1 Overview of Study Design; 9.1.3 Open-Label Treatment Phase; 9.1.4 Posttreatment Phase (Follow Up); 10.1 Completion; 10.2 Discontinuation of Study Treatment/Withdrawal from the Study; 16.1 Study-Specific Design Considerations	Amended text to indicate a 104-week study duration, and that subjects continuing treatment to Week 104 will be considered to have completed the study. Modified reasons for discontinuation of study treatment to address discontinuations from Week 48.
3.2 Study Design Rationale; References	Added text discussing the rationale for the extension period.
Time and Events Schedule - Routine Care Arm, footnote w; 9.2.2 C-reactive Protein; 9.2.3 Fecal Calprotectin	Added text to indicate that CRP and FC may be used to guide ustekinumab dosing (eg, for demonstration of biomarker remission for second de-escalation of dosing frequency) in the extension period. Modified Time and Events Schedule footnote to align with this.
9.1.1 Overview	Amended estimated blood volume collected to accommodate assessments up to Week 104.
11.1 Subject Information; 11.3.2 Secondary Endpoints	Added text regarding the final analysis population and exploratory analyses for subjects treated during the extension period.

Applicable Section(s)	Description of Change(s)
Rationale: To add that serum collected for PK and immunogenicity analyses, and stool samples collected for FC assessments may also be used for other analyses.	
9.3 Pharmacokinetics and Immunogenicity; 9.4 Additional Biomarkers; 10.3 Withdrawal From the Use of Samples in Future Research; 16.2.4 Privacy of Personal Data. 16.2.5 Long-Term Retention of Samples for Additional Future Research	Modified the text to state that serum collected for PK and immunogenicity analyses may also be used for further characterization of immunogenicity or for the evaluation of relevant biomarkers. Added Section 9.4 (Additional Biomarkers) and specified that stool samples collected for FC assessments may also be used for testing for additional markers. Added that exploratory biomarker and immunogenicity research is not conducted under standards appropriate for the return of data to subjects. Added Section 16.2.5 to indicate that there may be long-term retention of samples for additional future research. Added Section 10.3 to indicate that subjects may withdraw consent for long-term retention of samples for additional future research.
Rationale: To update the introductory text.	
1.1 Background	Updated text regarding the approval status of ustekinumab for Crohn's disease.
Rationale: Minor editorial corrections were needed.	
Throughout the protocol	Minor editorial corrections/clarifications were added.

Amendment 2 (13 September 2017)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: To redefine the treatment target for subjects who do not have elevated CRP at baseline.

Applicable Section(s)	Description of Change(s)
Rationale: To redefine the treatment target for subjects within the treat to target arm who do not have elevated CRP at baseline, to adopt a scientifically more valid treat to target strategy in that subgroup of subjects.	
Synopsis, Overview of Study Design; 3.1 Overview of Study Design; 9.1.3 Open-label Treatment Phase, Treat to Target Arm: Weeks 16 to 48	For subjects who do not have elevated CRP at baseline in the presence of active disease, the treatment target was redefined to indicate that CRP would not be considered a biomarker target.
Rationale: To clarify that potential subjects with either ileal or colonic Crohn's disease (or both) will be eligible for inclusion.	
Synopsis, Overview of Study Design, Subject Population; 3.1 Overview of Study Design; 4.1 Inclusion Criteria	Added text to clarify that subjects with ileal and/or colonic disease will be studied.
Rationale: To inform that an ultrasound substudy will be performed at selected centers.	
Synopsis, Overview of Study Design; 3.1 Overview of Study Design	Added text to indicate that an ultrasound substudy will be performed, which will be described in a separate substudy protocol.
Rationale: To clarify that the information used to identify subjects will be in accordance with local regulations.	
17.3 Subject Identification, Enrollment, and Screening Logs	Added text to clarify that the information used to identify subjects will be as allowed by local regulations.
Rationale: Minor editorial corrections were needed.	
Throughout the protocol	Minor editorial corrections/clarifications were added.

Amendment 1 (22 March 2017)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: To redefine the treatment target according to more stringent CDAI and biomarker criteria as recommended by the study steering committee and considered scientifically more valid in the context of a treat to target strategy.

Applicable Section(s)	Description of Change(s)
Rationale: To redefine treatment targets for the treat to target arm.	
Synopsis, Overview of Study Design; Time and Events Schedule, Treat to Target Arm, footnote pp; 3.1 Overview of Study Design; 3.2 Study Design Rationale; 9.1.3 Open-label Treatment Phase, Treat to Target Arm: Weeks 16 to 48	For the treat to target arm, the treatment target was redefined to stipulate both CDAI <220 and ≥ 70 -point improvement in CDAI score from baseline (Week 0), and CRP ≤ 10 mg/L or FC ≤ 250 μ g/g.
Rationale: To correct the timing of the first serum sample for pharmacokinetic and immunogenicity assessments.	
Time and Events Schedules, footnotes y and yy; 9.3 Pharmacokinetics and Immunogenicity	Specified that a sample should be drawn prior to IV infusion at Week 0.
Rationale: To specify body weight measurement to enable CDAI assessment at the time of disease flare in the treat to target arm.	
Time and Events Schedule, Treat to Target Arm	Body weight measurement was added at the disease flare visit for the treat to target arm.
Rationale: To specify that a steering committee will provide oversight during the study.	
Synopsis, Overview of Study Design; 3.1 Overview of Study Design; 11.7 Steering committee	Text was added to state that a steering committee will act as an expert advisory group to provide consulting oversight during the study.
Rationale: To enable direct reference to the risk/benefit assessment by attaching information from the investigational medicinal product dossier (IMPD) to the protocol.	
1 Introduction; Attachment 11	A sentence referencing the risk/benefit assessment was added to the Introduction and the risk/benefit section of the IMPD was added to the Attachments.
Rationale: Minor editorial corrections were needed.	
Throughout the protocol	Minor editorial corrections/clarifications were added.

SYNOPSIS

Study of Treat to Target Versus Routine Care Maintenance Strategies in Crohn's Disease Patients Treated with Ustekinumab

Ustekinumab is a fully human immunoglobulin G1 kappa (IgG1k) monoclonal antibody to human IL-12/23p40 that binds with high affinity to the p40 subunit of human IL-12 and IL-23. Inhibition of IL-12 and IL-23 and associated inflammatory pathways via blockade of the shared p40 subunit constitutes a novel mechanism of action for the treatment of Crohn's disease.

A 'treat to target' strategy as an optimized management approach has been shown to be successful in chronic, immune-mediated inflammatory disorders. The goal of this study of adult Crohn's disease subjects treated with ustekinumab is to demonstrate that a maintenance strategy based on early endoscopy followed by regular assessment of biomarkers (fecal calprotectin [FC], C-reactive protein [CRP]) and clinical symptoms (Crohn's disease activity index [CDAI]) with subsequent adjustment of treatment in case of persistent inflammatory disease activity (failure to achieve the target) is more successful in achieving endoscopic improvement than a pragmatic maintenance strategy driven by the EU SmPC for the use of ustekinumab in Crohn's disease.

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

The endpoints listed below will be observed values at all visits assessed and at endpoint (last observation carried forward [LOCF]) and changes from baseline for continuous/ordinal variables unless otherwise specified.

Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> To evaluate the efficacy of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach in achieving endoscopic response. 	<ul style="list-style-type: none"> Endoscopic response at Week 48, defined as showing (yes or no) a reduction from baseline in simple endoscopic score for Crohn's disease (SES-CD) of $\geq 50\%$. Randomized subjects who stop treatment before reaching Week 48 due to any reason, or subjects without endoscopic data at Week 48, will be analyzed as nonresponders.
Secondary	
<ul style="list-style-type: none"> To examine the robustness of the primary endpoint analysis, sensitivity analyses of the primary endpoint will be conducted. 	<ul style="list-style-type: none"> Endoscopic response at Week 48, defined as showing (yes or no) a reduction from baseline in SES-CD score of $\geq 50\%$. Randomized subjects who stop treatment before reaching Week 48 due to reasons other than lack/loss of efficacy will be excluded from the analysis. Endoscopic response defined as a reduction from baseline in SES-CD score of $\geq 50\%$ at endpoint (LOCF).
<ul style="list-style-type: none"> To evaluate the efficacy of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach in achieving endoscopic remission. 	<ul style="list-style-type: none"> Endoscopic remission defined as SES-CD score ≤ 2 at Week 48 and endpoint (LOCF).

Objectives	Endpoints
<ul style="list-style-type: none"> To evaluate the efficacy of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach in achieving mucosal healing. 	<ul style="list-style-type: none"> Mucosal healing defined as the complete absence of mucosal ulcerations in any ileocolonic segment at Week 48 and endpoint (LOCF).
<ul style="list-style-type: none"> To evaluate the efficacy of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach in achieving clinical remission. 	<ul style="list-style-type: none"> Clinical remission defined as a CDAI score of <150 points.
<ul style="list-style-type: none"> To evaluate the efficacy of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach in achieving clinical response. 	<ul style="list-style-type: none"> Clinical response defined as a ≥ 100-point reduction from the baseline CDAI score, or a CDAI score <150.
<ul style="list-style-type: none"> To evaluate the efficacy of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach in eliminating the need for corticosteroids while maintaining disease control. 	<ul style="list-style-type: none"> Corticosteroid-free clinical remission. Corticosteroid-free endoscopic response (endoscopic response defined as a reduction from baseline in SES-CD score of $\geq 50\%$).
<ul style="list-style-type: none"> To evaluate the effect of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach on serum CRP and FC levels. 	<ul style="list-style-type: none"> Serum CRP. FC.
<ul style="list-style-type: none"> To evaluate the effect of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach on health-related quality of life (QoL), patient-reported outcomes and pharmacoeconomics. 	<ul style="list-style-type: none"> Percentage of subjects with a 16-point change from baseline for Inflammatory bowel disease questionnaire (IBDQ). Percentage of subjects with a 7-point change from baseline in work productivity and activity impairment (WPAI) scores for each domain. <p>Changes from baseline for:</p> <ul style="list-style-type: none"> IBDQ, European quality of life 5 dimensions 5 level (EQ-5D-5L), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Hospital anxiety and depression scale (HADS), WPAI, Time lost from work.

Objectives	Endpoints
<ul style="list-style-type: none"> To describe the safety of two subcutaneous (SC) ustekinumab maintenance regimens in a randomized population. 	<ul style="list-style-type: none"> Adverse events. Clinical laboratory data. Vital signs. Physical examination findings.
Exploratory	
<ul style="list-style-type: none"> To explore the effect of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach on fistula response. 	<p>For subjects with fistulas at baseline:</p> <ul style="list-style-type: none"> ≥50% reduction from baseline in the number of draining fistulas at Week 48, Week 104, and endpoint (LOCF).
<ul style="list-style-type: none"> To explore the pharmacokinetics (PK), and immunogenicity of ustekinumab therapy To explore the pharmacodynamics (PD) of ustekinumab therapy, correlating the PK with clinical outcomes, including CDAI measures, changes in CRP and FC, and endoscopic outcomes. 	<ul style="list-style-type: none"> Serum ustekinumab concentrations. Antibodies to ustekinumab.
<ul style="list-style-type: none"> To explore the benefit of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach on Crohn's disease-related hospitalizations and surgeries. 	<ul style="list-style-type: none"> Crohn's disease-related hospitalizations. Crohn's disease-related surgery.
<ul style="list-style-type: none"> To explore the effectiveness of maintenance of ustekinumab treatment up to Week 104. 	<ul style="list-style-type: none"> Endoscopic response at Week 104 and endpoint (LOCF), defined as showing (yes or no) a reduction from baseline in SES-CD of ≥50%. Randomized subjects who stop treatment before reaching Week 104 due to any reason, or subjects without endoscopic data at Week 104, will be analyzed as nonresponders. Endoscopic response at Week 104, defined as showing (yes or no) a reduction from baseline in SES-CD score of ≥50%. Randomized subjects who stop treatment before reaching Week 104 due to reasons other than lack/loss of efficacy will be excluded from the analysis. Endoscopic remission defined as SES-CD score ≤2 at Week 104 and endpoint (LOCF). Mucosal healing defined as the complete absence of mucosal ulcerations in any ileocolonic segment at Week 104 and endpoint (LOCF).

Objectives	Endpoints
	<ul style="list-style-type: none"> • Clinical remission defined as a CDAI score of <150 points. • Clinical response defined as a \geq100-point reduction from the baseline CDAI score, or a CDAI score of <150 points. • Corticosteroid-free clinical remission. • Corticosteroid-free endoscopic response (endoscopic response defined as a reduction from baseline in SES-CD score of \geq50%). • Serum CRP. • FC. • PROs and pharmacoeconomics (IBDQ, EQ-5D-5L, FACIT-F, HADS, time lost from work, WPAI). • Clinical and biomarker remission (CDAI score of <150 points, CRP \leq10 mg/L, and FC \leq250 μg/g) at Week 104 and endpoint (LOCF).
<ul style="list-style-type: none"> • To explore the effectiveness of de-escalated ustekinumab dosing after Week 48. 	<ul style="list-style-type: none"> • Durations of corticosteroid-free clinical remission and biomarker remission, • Durations of corticosteroid-free clinical remission and biomarker remission after dose de-escalation, • Duration of de-escalated doses.

Hypothesis

The hypothesis is that a ‘treat to target’ ustekinumab maintenance treatment strategy coupled with early endoscopic assessment will result in a higher endoscopic response rate (defined as the percentage of subjects achieving \geq 50% reduction in SES-CD versus baseline) after 48 weeks of treatment, compared with a pragmatic (per EU SmPC) maintenance treatment strategy in subjects with Crohn’s disease.

This study is designed to show that the percentage of subjects with endoscopic response at Week 48 in the treat to target arm is 15% higher compared with the routine care arm. Based on results of the Phase 3 IM-UNITI study, endoscopic response in the routine care arm is estimated at 30% of subjects. Endoscopic response in the treat to target arm is estimated at 45% of subjects.

OVERVIEW OF STUDY DESIGN

This is a randomized, open-label, parallel-group, multicenter, multinational, Phase 3b interventional study of ustekinumab in adult subjects with active, moderate to severe, ileal and/or colonic Crohn’s disease. The benefit of a treat to target maintenance treatment strategy versus routine care will be investigated. For the treat to target strategy, ustekinumab treatment will be adjusted based on the regular assessment of disease activity by objective clinical and biological outcome measures and clinical symptoms. Maintenance

treatment in the routine care arm will be pragmatic, in compliance with the EU SmPC for ustekinumab in Crohn's disease.

A target of 650 adult male and female subjects with endoscopic evidence of active disease will be enrolled. Subjects enrolled will have previously had an inadequate response with, lost response to, been intolerant to, or had medical contraindications to either conventional therapy, or one previous biologic therapy approved for the treatment of Crohn's disease in the countries in which the study is conducted. Study subjects may be biologic-naïve or biologic-experienced, having received no more than one prior biologic approved for the treatment of Crohn's disease.

During a screening period of up to 5 weeks, eligibility of subjects will be evaluated, and centrally-read endoscopic assessments at screening will be used for baseline evaluation. At Week 0, all eligible subjects will initiate intravenous (IV) induction treatment with ustekinumab, in line with the EU SmPC, on a weight-tiered basis at a dose of approximately 6 mg/kg IV. At Week 8, all subjects will receive a 90 mg SC injection of ustekinumab.

At Week 16, subjects who do not achieve a CDAI improvement of ≥ 70 points versus Week 0 (CDAI-70) will leave the study. Subjects who remain in the study will be randomized in a 1:1 ratio to either one of two arms for open-label maintenance treatment up to Week 48: the treat to target arm or the routine care arm. Randomized subjects will be stratified according to whether biologic-naïve at baseline versus prior exposure to 1 biologic for the treatment of Crohn's disease, and according to baseline SES-CD score ≤ 16 or SES-CD > 16 .

Routine care arm up to Week 48

In the routine care arm, assessment visits will be scheduled according to the timing of maintenance treatment injections, which will be in compliance with the EU SmPC for ustekinumab for the treatment of Crohn's disease, in which dosing every 12 weeks is recommended. At Week 16, (ie, 8 weeks after the first SC dose), subjects who have not shown adequate response based on the investigator's judgment may receive a second SC dose at that time. During the routine care maintenance treatment period up to Week 48, clinical assessments in case of disease flare will be at the investigator's discretion. Consistent with the EU SmPC for ustekinumab, subjects who lose response during 12-weekly dosing may benefit from an adjustment to 8-weekly maintenance treatment. Subjects may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgment. In contrast, those subjects previously receiving 8-weekly treatment will not be able to adjust the ustekinumab dose following disease flare and will leave the study if they would not benefit from continuing study treatment in the investigator's judgment.

Treat to target arm up to Week 48

In the treat to target arm, initial ustekinumab maintenance treatment assignment will be based on centrally-read ileocolonoscopy findings. Subjects with $< 25\%$ improvement in SES-CD score at Week 16 versus baseline will be assigned to 8-weekly maintenance treatment. Subjects with $\geq 25\%$ improvement in SES-CD score at Week 16 versus baseline will be assigned to 12-weekly treatment. Subsequently, at assessment visits (from Week 24 for subjects assigned to the 8-weekly regimen or from Week 20 for the 12-weekly group) ustekinumab maintenance treatment up to Week 48 will be directed by treat to target assessments.

Among the subgroup of subjects with elevated CRP at baseline (ie, CRP > 2.87 mg/L at Week 0), the treatment target will be the achievement of:

- CDAI < 220 and ≥ 70 -point improvement in CDAI score from baseline (Week 0)
AND
- CRP ≤ 10 mg/L or FC ≤ 250 $\mu\text{g/g}$.

For subjects who do not have elevated CRP at baseline (ie, CRP ≤ 2.87 mg/L at Week 0) in the presence of active disease, CRP would not be considered a biomarker target for dose adjustment, therefore the treatment target for these subjects will be the achievement of:

- CDAI < 220 and ≥ 70 -point improvement in CDAI score from baseline (Week 0)
AND
- FC ≤ 250 $\mu\text{g/g}$.

Subjects meeting the treatment target will continue with the same ustekinumab dosing frequency. Maintenance dosing frequency will be optimized for subjects failing to meet the treatment targets: those subjects previously on 12-weekly regimens will be adjusted to 8-weekly dosing; those previously on 8-weekly regimens will be adjusted to 4-weekly dosing. Subjects subsequently failing to meet treatment targets at the next assessment visit 4 weeks after dosing will not be able to optimize dosing further and will leave the study. In case of disease flare between scheduled assessment visits for the treat to target arm, subjects will undergo CDAI and biomarker (CRP and FC) assessments. Dosing frequency will be adjusted for subjects failing to meet the treatment target.

Extension period: Weeks 48 to 104

From Week 48, subjects will continue ustekinumab treatment in the study extension period, up to Week 104. The frequency of dosing will be based on endoscopic and/or clinical remission at Week 48, and subsequently on clinical remission and biomarker findings. From Week 48, ustekinumab dose de-escalation will be implemented for subjects with both endoscopic remission (SES-CD score ≤ 2) at Week 48 and corticosteroid-free clinical remission (CDAI score of < 150 points) of ≥ 16 weeks' duration. Among such subjects, those receiving 8-weekly ustekinumab will adjust to 12-weekly dosing, whereas those receiving 4-weekly ustekinumab will adjust to 8-weekly dosing. In the latter case, further dose de-escalation to 12-weekly ustekinumab will be applied for subjects with corticosteroid-free clinical remission (CDAI score of < 150 points) and biomarker remission (CRP ≤ 10 mg/L and FC ≤ 250 $\mu\text{g/g}$) at 2 subsequent, consecutive visits 8 weeks apart. Subjects receiving 12-weekly ustekinumab with endoscopic remission at Week 48 will maintain this 12-weekly dosing frequency.

Subjects with either clinical remission or endoscopic remission, but not both, at Week 48 will continue with the same dosing frequency. For those with only clinical remission, subsequent dosing de-escalation will be dependent on maintenance of corticosteroid-free clinical remission and demonstration of biomarker remission at 2 consecutive visits. For subjects with only endoscopic remission, subsequent dose de-escalation will be dependent on being in corticosteroid-free clinical remission and demonstrating biomarker remission at 2 consecutive visits.

Conversely, subjects with neither corticosteroid-free clinical remission nor endoscopic remission having received 12-weekly or 8-weekly ustekinumab up to Week 48 will undergo dose escalation to 8-weekly or 4-weekly dosing, respectively. After dose escalation, if neither clinical remission nor biomarker remission is evident at the next visit, subjects will leave the study. Later in the extension period, only those who achieve corticosteroid-free clinical remission of ≥ 16 weeks' duration and demonstrate biomarker remission over 2 consecutive visits will undergo dose de-escalation. Subjects with neither corticosteroid-free clinical remission nor endoscopic remission who have received ustekinumab at 4-weekly intervals up to Week 48 will not be able to adjust dosing further and will leave the study.

Among the subgroup of subjects with elevated CRP at baseline (ie, CRP > 2.87 mg/L at Week 0) disease flare during the extension period will be defined as:

- CDAI ≥ 220 and < 70 -point improvement in CDAI score from baseline (Week 0)

AND

- CRP >10 mg/L or FC >250 µg/g

Among subjects who do not have elevated CRP at baseline (ie, CRP \leq 2.87 mg/L at Week 0) disease flare during the extension period will be defined as:

- CDAI \geq 220 and <70-point improvement in CDAI score from baseline (Week 0)

AND

- FC >250 µg/g.

In case of disease flare at any time during the extension period, dosing will be escalated/re-escalated (12-weekly to 8-weekly, or 8-weekly to 4-weekly). Subjects receiving 4-weekly ustekinumab during the extension period who experience disease flare will not be able to adjust dosing further and will leave the study.

Study visits

All subjects will have study visits at Weeks 0, 8, and 16, at each assessment visit at the times scheduled for study drug administration, at Week 48 and Week 104. In cases of disease flare arising between scheduled study visits, subjects will also be assessed at the time of disease flare. Ileocolonoscopic assessments will be performed at the Week 48 and Week 104 study visits. Subjects discontinuing treatment before Week 104 will have an early termination visit at the time of discontinuation, unless consent is withdrawn. Early termination assessments should include an ileocolonoscopic assessment.

Subjects will be allowed to enter the study on oral corticosteroids at a prednisone-equivalent dose of \leq 40 mg/day or \leq 9 mg/day of budesonide. For subjects receiving corticosteroids who are randomized at Week 16 (CDAI-70 responders) corticosteroid tapering is mandatory. A recommended corticosteroid tapering schedule is specified in the protocol. Corticosteroid tapering can be initiated from Week 8 in subjects already demonstrating response (CDAI-70) to ustekinumab treatment.

For all subjects, final safety follow-up assessments will be performed 16 weeks after the last administration of ustekinumab within the study. For subjects completing the 104-week study and moving to commercially-available ustekinumab, final safety follow-up assessments should be performed before the first dose of commercially-available drug.

The study will be considered completed with the last visit for the last subject participating in the study.

A steering committee will provide consulting oversight during the study, to ensure the scientific validity of the clinical study, to identify any scientifically relevant trends, and to provide recommendations to the sponsor.

An exploratory substudy to assess changes in ultrasound parameters indicating transmural response to treatment with ustekinumab will be performed at selected study centers. Participation in the ultrasound substudy will be optional for subjects participating in the main study. The ultrasound substudy will be described in a separate substudy protocol.

SUBJECT POPULATION

Subjects enrolled will be male or female, \geq 18 years of age, with active, moderate to severe, ileal and/or colonic Crohn's disease, demonstrated by a baseline CDAI score of \geq 220 and \leq 450, and endoscopic evidence of active Crohn's disease (with a SES-CD score \geq 3, excluding the contribution of the narrowing component score). The subjects will previously have had an inadequate response with, lost response to, have been intolerant to, or have medical contraindications to either conventional therapy, or one previous biologic therapy approved for the treatment of Crohn's disease in the countries in which the study is conducted. Study subjects will not have received more than one prior biologic for the treatment of Crohn's disease. Those subjects previously treated with an anti-tumor necrosis factor (TNF) biologic

must have discontinued this at least 8 weeks prior to baseline; those treated with vedolizumab must have discontinued this at least 12 weeks prior to baseline.

DOSAGE AND ADMINISTRATION

All eligible subjects will receive induction treatment in accordance with the EU SmPC for ustekinumab. At Week 0, IV ustekinumab will be administered on a weight-tiered basis at a dose of approximately 6 mg/kg.

At Week 8, all subjects will receive a 90 mg SC injection of ustekinumab. Thereafter, subjects (CDAI-70 responders) continuing to randomization at Week 16 will receive 90 mg ustekinumab SC at designated injection times up to Week 48, enabling 12-weekly or 8-weekly treatment intervals (as per EU SmPC) and, in the treat to target arm only, the eventual opportunity to dose adjust to a 4-weekly dosing regimen (as described above; see Overview of Study Design).

After Week 8, 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.

During the extension period, subjects will receive ustekinumab at 12-weekly, 8-weekly or 4-weekly intervals. The dosing frequency will depend on the previous dosing frequency, Week 48 ileocolonoscopy and CDAI findings, and subsequent CDAI and biomarker findings (see Overview of Study Design).

EFFICACY EVALUATIONS

Video ileocolonoscopy will be used to assess SES-CD at the times indicated in the Time and Events Schedules. Centrally-read SES-CD scores will be used to evaluate endoscopic response (reduction from baseline in SES-CD score $\geq 50\%$) and endoscopic remission (SES-CD score ≤ 2) at Week 48 and Week 104 or at early termination of ustekinumab treatment. Additionally, mucosal healing will be assessed during ileocolonoscopy to determine the presence or absence of mucosal inflammation and ulceration. For subjects with fistulizing disease, fistula closure will also be assessed.

The CDAI will be used to assess disease activity. Serum CRP concentrations will be measured as a marker of the degree of inflammation. Stool samples will be collected and analyzed to evaluate changes in FC.

The wellbeing of subjects will be assessed using the IBDQ. Quality of life, fatigue, anxiety and depression will be evaluated using the EQ-5D-5L, FACIT-F, and HADS, questionnaires.

PHARMACOKINETIC EVALUATIONS

Serum samples will be analyzed to explore the PK and PD of ustekinumab.

IMMUNOGENICITY EVALUATIONS

Serum samples will be analyzed to detect and characterize anti-ustekinumab antibodies.

SAFETY EVALUATIONS

Safety evaluations will include the assessment of adverse events, targeted events (including assessment for tuberculosis (TB) and other infection), clinical laboratory tests (hematology and serum chemistry), vital signs, physical examination, observations for infusion and/or allergic reactions, and concomitant medication review. Final safety follow-up assessments will be performed 16 weeks after the last administration of ustekinumab within the study (or before the first dose of commercially-available ustekinumab after the study, if earlier).

MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Medical resource utilization data, including Crohn's disease-related hospitalizations and Crohn's disease-related surgeries will be collected in the study. Additionally, time lost from work will be collected and the potential impact of ustekinumab on subjects' work limitations, and daily productivity will be assessed through the Work Productivity and Activity Impairment Questionnaire (WPAI).

STATISTICAL METHODS

The primary endpoint of this study is endoscopic response at Week 48 of the study. Endoscopic response is defined as showing (yes or no) a reduction from baseline in the SES-CD score of $\geq 50\%$. This study is designed to show that the percentage of subjects with endoscopic response at Week 48 in the treat to target arm is 15% higher compared with the routine care arm, which is considered to be a clinically meaningful difference. Based on the results of the Phase 3 IM-UNITI study, endoscopic response in the routine care arm is estimated at 30% of subjects. Endoscopic response in the treat to target arm is estimated at 45% of subjects. A Fisher's exact test with a 0.050 two-sided significance level will have 80% power to detect the difference between the routine care arm proportion of 30% and the treat to target arm proportion of 45% when the sample size in each group is 174. With an estimated CDAI-70 response at Week 16 between 65% and 70% and a dropout rate between 10% and 17.5%, a total of 650 subjects should be enrolled.

The number and percentage of responders, and other categorical variables, will be summarized by treatment group and compared using the Fisher exact test. Changes from baseline and observed values for continuous/ordinal efficacy variables will be summarized descriptively at each assessment time point and at the subject's last efficacy evaluation (endpoint). The change from baseline at each visit and at endpoint will be analyzed using the Wilcoxon signed rank test. Between-group comparisons will be analyzed by means of the Wilcoxon 2-sample test.

An interim analysis will be performed as soon as all enrolled subjects have completed the first 16 weeks of the study or discontinued earlier. Subject characteristics and a selection of efficacy and safety endpoints will be included in this interim analysis. Endoscopic outcomes at Week 16 will be analyzed for subjects in the treat to target arm. The main analysis will be performed when all randomized subjects have completed 48 weeks of study treatment or discontinued earlier. The final analysis will be performed when all subjects have completed the last study-related visit including the follow up.

TIME AND EVENTS SCHEDULE -ROUTINE CARE ARM

Period	Screen ^a	Induction		Maintenance (Weeks 16 to 48):				ET ^e	Safety FU ^f	
		Week 0	Week 8	Week 16	Assess Visits ^c	Disease Flare Visit ^d	Week 48			
Study Procedure^b										
Screening/Administrative										
Informed consent (ICF) ^g	X									
Demographics	X									
Height	X									
Medical history requirements	X									
Inclusion/exclusion criteria ^h	X	X								
Chest radiograph ⁱ	X									
QuantiFERON-TB Gold In-Tube test ^j	X									
Stool studies to evaluate for enteric pathogens ^k	X									
Training on diary card completion	X									
Serum pregnancy test	X									
Study Drug Administration										
Administer IV ustekinumab (induction) ^l		X								
Randomization ^m				X						
Administer SC ustekinumab ⁿ			X	X ^o	X			X ^o		
Dosing frequency decision ^p				X			X			
Safety Assessments										
Detailed physical examination	X								X	X
Weight	X	X	X	X	X			X	X	
Vital signs ^q	X	X ^q	X	X	X			X	X	X
12-lead ECG	X									
Urine pregnancy test ^r		X	X	X ^o	X			X ^o		X
TB evaluation ^s /other infection assessment		X	X	X	X	X		X	X	X
Collect and review diary cards		X	X	X	X	X		X	X	
Hematology, chemistry ^t	X	X	X	X				X	X	
Study drug injection-site evaluation		X	X	X ^o	X	X		X ^o		X
Efficacy Assessments										
CDAI assessments ^u			X ^v	X	X			X	X	
Stool sample (FC) ^w			X	X	X	X		X	X	
C-reactive protein (CRP) ^w			X	X	X	X		X	X	
Video ileocolonoscopy ^u	X							X	X	
Fistula assessment			X					X	X	

Period	Screen ^a	Induction		Maintenance (Weeks 16 to 48):			ET ^e	Safety FU ^f
		Week 0	Week 8	Week 16	Assess Visits ^c	Disease Flare Visit ^d		
Study Procedure^b								
IBDQ		X		X			X	X
EQ-5D-5L		X		X			X	X
FACIT-F		X		X			X	X
HADS		X		X			X	X
Health Economics								
Time lost from work			X		X		X	X
WPAI			X		X		X	X
Pharmacokinetics and Immunogenicity								
Serum ustekinumab concentration ^x		X ^y	X	X	X		X	X
Antibodies to ustekinumab ^x		X	X	X	X		X	X
Ongoing Subject Review								
Concomitant therapy	X	X	X	X ^z	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X
Crohn's disease-related hospitalizations		X	X	X	X	X	X	X
Crohn's disease-related surgeries			X	X	X	X	X	X

Footnotes:

- The Screening period will be up to 5 weeks. A prior endoscopy may be used only if obtained within 3 months prior to baseline (Week 0), in which case the prior endoscopy must be centrally read again and SES-CD calculated based on this second, centralized read-out.
- The visit windows will be ± 10 days for all visits. At study drug injection/assessment visits, all assessments are to be completed prior to study drug administration, unless otherwise specified. It is recommended that patient-reported outcome (PRO) assessments be completed first.
- Assessment visits: the week of each visit will depend on initial maintenance dosing frequency regimen and subsequent dosing adjustments during the study.
- Disease flare assessments can be performed at any time between Week 16 and Week 48 in case of clinical worsening reported by the subject, consistent with disease flare in the investigator's judgment. Clinical assessments in case of disease flare will be at the investigator's discretion. Information on assessments of disease flare and on the reasons for dosing frequency changes will be documented in the CRF.
- Subjects who discontinue ustekinumab treatment before Week 104 will have Early Termination (ET) assessments as close as possible to the time of discontinuation, unless consent is withdrawn. ET assessments should include ileocolonoscopy.
- All subjects will have a final safety follow-up visit 16 weeks after the last administration of ustekinumab within the study (or before the first dose of commercially-available ustekinumab after the study, if earlier).
- Must be signed before first study-related activity.
- Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Section 17.4, Source Documentation. Check clinical status again before first dose of study medication.
- The screening chest radiograph may have been performed within 3 months before the Week 0 visit. Subjects who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph (see Section 9.1.3).

- j. To be performed at a central laboratory. In countries in which the QuantiFERON-TB Gold test is not considered approved/registered, a tuberculin skin test is additionally required. The QuantiFERON-TB Gold In-Tube test is not required at screening for subjects with a history of latent TB and appropriate treatment as described in the Inclusion Criteria (Section 4.1).
- k. Stool studies for enteric pathogens will be performed at the local laboratory and must include a stool culture and *Clostridium difficile* toxin assay.
- l. Induction treatment at Week 0: ustekinumab IV (weight-based dosing approximately 6 mg/kg) to be administered over a period of not less than 1 hour (see Section 6).
- m. Subjects with CDAI-70 at Week 16 will be randomized to either the treat to target arm or the routine care arm. Subjects who do not achieve CDAI-70 at Week 16 will discontinue from the study.
- n. Ustekinumab SC (90 mg prefilled syringe). After Week 8, subjects who have been trained how to self-inject may self-administer. Information documented in the CRF will include date of administration, self-administration (yes/no) and whether administration was complete based on the returned syringe.
- o. Only subjects initially assigned to 8-weekly maintenance treatment will receive ustekinumab at Week 16 (subjects initially assigned to 12-weekly treatment will have the next ustekinumab injection at Week 20). Whether dosing is required at or after Week 48 will depend on the previous dosing frequency and Week 48 ileocolonoscopy and CDAI findings, which will dictate subsequent dosing frequency during the extension period (see Section 3.1). During the maintenance period, urinary pregnancy testing and injection site evaluation will only be performed at the times scheduled for ustekinumab injection.
- p. From Week 16, subjects' ustekinumab maintenance treatment will be according to the EU SmPC for ustekinumab. After Week 16, subjects who lose response during 12-weekly SC dosing may benefit from an adjustment to 8-weekly maintenance treatment in compliance with the EU SmPC. Subjects may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgment. Subjects on an 8-weekly regimen at the time of disease flare, will not be able to dose adjust further and will leave the study if they would not benefit from continuing study treatment in the investigator's judgment.
- q. Temperature, pulse/heart rate, blood pressure. At Week 0, vital signs assessed prior to infusion, approximately every 30 minutes during infusion, and twice (approximately 30-minute intervals) after the completion of infusion.
- r. Must be performed prior to each study drug administration in females of childbearing potential. Additional pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation.
- s. If TB is suspected at any time during the study, a chest radiograph, QuantiFERON-TB Gold In-Tube test, and a tuberculin skin test (in countries in which the QuantiFERON-TB Gold test is not considered approved/registered) should be performed (see Section 9.1.3).
- t. Hematocrit to be tested at all visits indicated (for CDAI assessment). Hematology and serum chemistry panels to be tested at screening, Week 0, and Week 48/ET (Section 9.6). Hematology and clinical chemistry tests do not need to be repeated at Week 0 if the screening tests were done ≤ 2 weeks previously.
- u. Ileocolonoscopic examinations and CDAI assessment will be scheduled to avoid an impact on CDAI data. For example, if ileocolonoscopy is performed on the day of the visit, the 7 days prior to the initiation of the colonoscopy preparation should be used to calculate the CDAI score for the visit. Ileocolonoscopies will be assessed at a central facility.
- v. For calculation of CDAI at Week 0, the hematocrit value obtained during screening will be used.
- w. Analyzed at a central laboratory. During the maintenance treatment period up to Week 48, centrally-analyzed serum CRP levels and fecal calprotectin (FC) data will not be communicated to the investigator. The data will be analyzed at the end of the study. For FC testing, study site personnel will remind subjects of the need to provide stool samples.
- x. Analyzed at a central laboratory. Results available at the end of the study.
- y. For IV infusion at Week 0, a sample should be drawn before infusion and approximately 60 minutes after completion of the infusion. At all other study drug injection/assessment visits blood samples should be collected prior to study drug injection.
- z. For subjects receiving oral corticosteroids who are randomized at Week 16 (CDAI-70 Responders) corticosteroid tapering is mandatory. Corticosteroid tapering can be initiated from Week 8 in subjects already demonstrating response to ustekinumab treatment (see recommended tapering schedule in Section 8).

TIME AND EVENTS SCHEDULE -TREAT TO TARGET ARM

Period	Screen ^{aa}	Induction		Maintenance (Weeks 16 to 48):			ET ^{ee}	Safety FU ^{ff}
		Week 0	Week 8	Week 16	Assess Visits ^{cc}	Disease Flare Visit ^{dd}		
Study Procedure^{bb}								
Screening/Administrative								
Informed consent (ICF) ^{gg}	X							
Demographics	X							
Height	X							
Medical history requirements	X							
Inclusion/exclusion criteria ^{hh}	X	X						
Chest radiograph ⁱⁱ	X							
QuantIFERON-TB Gold In-Tube test ^{jj}	X							
Stool studies to evaluate for enteric pathogens ^{kk}	X							
Training on diary card completion	X							
Serum pregnancy test	X							
Study Drug Administration								
Administer IV ustekinumab (induction) ^{ll}		X						
Randomization ^{mm}				X				
Administer SC ustekinumab ⁿⁿ			X	X ^{oo}	X		X ^{oo}	
Dosing frequency decision ^{pp}				X	X	X		
Safety Assessments								
Detailed physical examination	X							X
Weight	X	X	X	X	X	X	X	
Vital signs ^{qq}	X	X ^{qq}	X	X	X	X	X	X
12-lead ECG	X							
Urine pregnancy test ^{rr}		X	X	X ^{oo}	X		X ^{oo}	X
TB evaluation ^{ss} /other infection assessment		X	X	X	X	X	X	X
Collect and review diary cards		X	X	X	X	X	X	X
Hematology, chemistry ^{tt}	X	X	X	X	X	X	X	
Study drug injection-site evaluation		X	X	X ^{oo}	X	X	X ^{oo}	X
Efficacy Assessments								
CDAI assessments ^{uu}		X ^{vv}	X	X	X	X	X	X
Stool sample (FC) ^{ww}		X	X	X	X	X	X	X
C-reactive protein (CRP) ^{ww}		X	X	X	X	X	X	X
Video ileocolonoscopy ^{uu}	X			X			X	X
Fistula assessment		X					X	X

Period	Screen ^{aa}	Induction		Maintenance (Weeks 16 to 48):			ET ^{ee}	Safety FU ^{ff}
		Week 0	Week 8	Week 16	Assess Visits ^{cc}	Disease Flare Visit ^{dd}		
Study Procedure^{bb}								
IBDQ		X		X			X	X
EQ-5D-5L		X		X			X	X
FACIT-F		X		X			X	X
HADS			X	X			X	X
Health Economics								
Time lost from work			X		X		X	X
WPAI			X	X			X	X
Pharmacokinetics and Immunogenicity								
Serum ustekinumab concentration ^{xx}		X ^{yy}		X	X	X	X	X
Antibodies to ustekinumab ^{xx}		X	X	X	X		X	X
Ongoing Subject Review								
Concomitant therapy	X	X	X	X ^{zz}	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X
Crohn's disease-related hospitalizations		X	X	X	X	X	X	X
Crohn's disease-related surgeries			X	X	X	X	X	X

Footnotes:

- aa. The Screening period will be up to 5 weeks. A prior endoscopy may be used only if obtained within 3 months prior to baseline (Week 0), in which case the prior endoscopy must be centrally read again and SES-CD calculated based on this second, centralized read-out.
- bb. The visit windows will be ± 10 days for all visits. At study drug injection/assessment visits, all assessments are to be completed prior to study drug administration, unless otherwise specified. It is recommended that patient-reported outcome (PRO) assessments be completed first.
- cc. Assessment visits: the week of the visit will depend on initial maintenance dosing frequency regimen and subsequent treat to target dosing adjustments during the study.
- dd. For subjects with evidence of disease flare between dosing visits, CDAI, CRP, and FC will be assessed at the time of disease flare.
- ee. Subjects who discontinue from the study before Week 104 will have Early Termination (ET) assessments as close as possible to the time of discontinuation, unless consent is withdrawn. ET assessments should include ileocolonoscopy.
- ff. All subjects will have a final safety follow-up visit 16 weeks after the last administration of ustekinumab within the study (or before the first dose of commercially-available ustekinumab after the study, if earlier).
- gg. Must be signed before first study-related activity.
- hh. Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Section 17.4, Source Documentation. Check clinical status again before first dose of study medication.
- ii. The screening chest radiograph may have been performed within 3 months before the Week 0 visit. Subjects who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph (see Section 9.1.3).

- jj. To be performed at a central laboratory. In countries in which the QuantiFERON-TB Gold test is not considered approved/registered, a tuberculin skin test is additionally required. The QuantiFERON-TB Gold In-Tube test is not required at screening for subjects with a history of latent TB and appropriate treatment as described in the Inclusion Criteria (Section 4.1)
- kk. Stool studies for enteric pathogens will be performed at local laboratory and must include a stool culture and *Clostridium difficile* toxin assay.
- ll. Induction treatment at Week 0: ustekinumab IV (weight-based dosing approximately 6 mg/kg) to be administered over a period of not less than 1 hour (see Section 6).
- mm. Subjects with CDAI-70 at Week 16 will be randomized to either the treat to target arm or the routine care arm. Subjects who do not achieve CDAI-70 at Week 16 will discontinue from the study.
- nn. Ustekinumab SC (90 mg prefilled syringe). After Week 8, subjects who have been trained how to self-inject may self-administer. Information documented in the CRF will include date of administration, self-administration (yes/no) and whether administration was complete based on the returned syringe.
- oo. Only subjects initially assigned to 8-weekly maintenance treatment will receive ustekinumab at Week 16 (subjects initially assigned to 12-weekly treatment will have the next ustekinumab injection at Week 20). Whether dosing is required at or after Week 48 will depend on the previous dosing frequency and Week 48 ileocolonoscopy and CDAI findings, which will dictate subsequent dosing frequency during the extension period (see Section 3.1). During the maintenance period, urinary pregnancy testing and injection site evaluation will only be performed at the times scheduled for ustekinumab injection.
- pp. Initial dosing frequency assignment will be based on SES-CD at Week 16. From Week 20 (12-weekly dosing), or Week 24 (8-weekly dosing) onwards, the decision whether to continue on the same dosing frequency or to adjust the dosing frequency (eg, to increase to 8-weekly or 4-weekly dosing) will be based on treat to target assessments (CDAI, and CRP or FC assessed at the assessment visit). For subjects with evidence of disease flare between dosing visits, CDAI, CRP, and FC will be assessed prior to dosing adjustment decisions.
- qq. Temperature, pulse/heart rate, blood pressure. At Week 0, vital signs obtained prior to infusion, approximately every 30 minutes during infusion, and twice (approximately 30-minute intervals) after the completion of infusion.
- rr. Must be performed prior to each study drug administration in females of childbearing potential. Additional pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation.
- ss. If TB is suspected at any time during the study, a chest radiograph, QuantiFERON-TB Gold In-Tube test, and a tuberculin skin test (in countries in which the QuantiFERON-TB Gold test is not considered approved/registered) should be performed (see Section 9.1.3).
- tt. Hematocrit to be tested at all visits indicated (for CDAI assessment). Hematology and serum chemistry panels to be tested at screening, Week 0 and Week 48/ET (Section 9.6). Hematology and clinical chemistry tests do not need to be repeated at Week 0 if the screening tests were done ≤ 2 weeks previously.
- uu. Ileocolonoscopic examinations and CDAI assessment will be scheduled to avoid an impact on CDAI data. For example, if ileocolonoscopy is performed on the day of the visit, the 7 days prior to the initiation of the colonoscopy preparation should be used to calculate the CDAI score for the visit. Ileocolonoscopies will be assessed at a central facility.
- vv. For calculation of CDAI at Week 0, the hematocrit value obtained during screening will be used.
- ww. Analyzed at a central laboratory. For FC testing, study site personnel will remind subjects of the need to provide stool samples.
- xx. Analyzed at a central laboratory. Results available at the end of the study.
- yy. For IV infusion at Week 0, a sample should be drawn before infusion and approximately 60 minutes after completion of the infusion. At all other study drug injection/assessment visits blood samples should be collected prior to study drug injection.
- zz. For subjects receiving oral corticosteroids who are randomized at Week 16 (CDAI-70 Responders) corticosteroid tapering is mandatory. Corticosteroid tapering can be initiated from Week 8 in subjects already demonstrating response to ustekinumab treatment (see recommended tapering schedule in Section 8).

TIME AND EVENTS SCHEDULE -EXTENSION PERIOD

	Extension Period (Weeks 48 to 104)			ET ^{ddd}	Safety FU ^{eee}
	Assess Visits ^{bbb}	Disease Flare Visit ^{ccc}	Week 104		
Study Procedure^{aaa}					
Study Drug Administration					
Administer SC ustekinumab ^{fff}	X				
Dosing frequency decision ^{ggg}	X	X			
Safety Assessments					
Detailed physical examination				X	X
Weight	X	X	X	X	
Vital signs ^{hhh}	X		X	X	X
Urine pregnancy test ⁱⁱⁱ	X				X
TB evaluation ^{jjj} /other infection assessment	X	X	X	X	X
Collect and review diary cards	X	X	X	X	
Hematology, chemistry ^{kkk}	X	X	X	X	
Study drug injection-site evaluation	X	X		X	
Efficacy Assessments					
CDAI assessments ^{lll}	X	X	X	X	
Stool sample (FC) ^{mmm}	X	X	X	X	
C-reactive protein (CRP) ^{mmm}	X	X	X	X	
Video ileocolonoscopy ^{lll}			X	X	
Fistula assessment			X	X	
IBDQ	X ⁿⁿⁿ		X	X	
EQ-5D-5L	X ⁿⁿⁿ		X	X	
FACIT-F	X ⁿⁿⁿ		X	X	
HADS	X ⁿⁿⁿ		X	X	
Health Economics					
Time lost from work	X ⁿⁿⁿ		X	X	
WPAI	X ⁿⁿⁿ		X	X	
Pharmacokinetics and Immunogenicity					
Serum ustekinumab concentration ^{ooo}	X		X	X	X
Antibodies to ustekinumab ^{ooo}	X		X	X	X
Ongoing Subject Review					
Concomitant therapy	X	X	X	X	X
Adverse events	X	X	X	X	X
Crohn's disease-related hospitalizations	X	X	X	X	X
Crohn's disease-related surgeries	X	X	X	X	X

Footnotes:

- aaa. The visit windows will be ± 10 days for all visits. At study drug injection/assessment visits, all assessments are to be completed prior to study drug administration, unless otherwise specified. It is recommended that patient-reported outcome (PRO) assessments be completed first.
- bbb. Assessment visits: the week of the visit will depend on initial maintenance dosing frequency regimen and subsequent treat to target dosing adjustments during the study. During the extension period, the dosing/visit frequency will depend on the previous dosing frequency, Week 48 ileocolonoscopy and CDAI findings, and subsequent CDAI and biomarker findings (see Section 3.1).
- ccc. For subjects with evidence of disease flare between dosing visits, CDAI, CRP, and FC will be assessed at the time of disease flare.
- ddd. Subjects who discontinue from the study before Week 104, or who discontinue ustekinumab treatment before the end of the study will have Early Termination (ET) assessments as close as possible to the time of discontinuation, unless consent is withdrawn. ET assessments should include ileocolonoscopy.
- eee. All subjects will have a final safety follow-up visit 16 weeks after the last administration of ustekinumab within the study (or before the first dose of commercially-available ustekinumab after the study, if earlier).
- fff. Ustekinumab SC (90 mg prefilled syringe). Subjects who have been trained how to self-inject may self-administer. Information documented in the CRF will include date of administration, self-administration (yes/no) and whether administration was complete based on the returned syringe.
- ggg. From Week 48, the frequency of dosing will depend on the previous dosing frequency, Week 48 ileocolonoscopy and CDAI findings, and subsequent CDAI and biomarker findings (see Section 3.1).
- hhh. Temperature, pulse/heart rate, blood pressure.
- iii. Must be performed prior to each study drug administration in females of childbearing potential. Additional pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation.
- jjj. If TB is suspected at any time during the study, a chest radiograph, QuantiFERON-TB Gold In-Tube test, and a tuberculin skin test (in countries in which the QuantiFERON-TB Gold test is not considered approved/registered) should be performed (see Section 9.1.3).
- kkk. Hematocrit to be tested at all visits indicated (for CDAI assessment). Hematology and serum chemistry panels to be tested at Weeks 48/104/ET (Section 9.6).
- lll. Ileocolonoscopic examinations and CDAI assessment will be scheduled to avoid an impact on CDAI data. For example, if ileocolonoscopy is performed on the day of the visit, the 7 days prior to the initiation of the colonoscopy preparation should be used to calculate the CDAI score for the visit. Ileocolonoscopies will be assessed at a central facility.
- mmm. Analyzed at a central laboratory. For FC testing, study site personnel will remind subjects of the need to provide stool samples.
- nnn. During the extension period, PRO assessments will be performed at Week 80 and Week 104 only.
- ooo. Blood samples should be collected prior to study drug injection. Analyzed at a central laboratory. Results available at the end of the study.

ABBREVIATIONS

5-ASA	5-aminosalicylic acid
AZA	azathioprine
BCG	Bacille Calmette-Guérin
CDAI	Crohn's Disease Activity Index
CDAI-70	≥70-point improvement versus baseline in Crohn's Disease Activity Index
CI	confidence interval
CRF	case report form(s)
CRP	C-reactive protein
ECCO	European Crohn's and Colitis Organisation
ECG	electrocardiogram
eDC	electronic data capture
EMA	European Medicines Agency
EQ-5D-5L	EuroQoL-5D Health Questionnaire (European quality of life-5 dimensions) 5 level
EU	European Union
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FC	fecal calprotectin
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HIV	human immunodeficiency virus
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IL-	interleukin-
IRB	Institutional Review Board
ITT	intent to treat
IV	intravenous
IWRS	interactive web response system
LOCF	last observation carried forward
6-MP	6-mercaptopurine
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
m2ITT	Modified intent to treat population who enter the extension phase
MTX	methotrexate
PD	pharmacodynamic(s)
PFS	prefilled syringe
PK	pharmacokinetic(s)
PQC	product quality complaint
PRO	patient-reported outcome(s)
QoL	quality of life
SC	subcutaneous
SES-CD	simple endoscopic score for Crohn's disease
SmPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
Th	T helper
TNF	tumor necrosis factor
WPAI	Work Productivity and Activity Impairment

DEFINITIONS OF TERMS

Biologic treatments:	Biological treatments including tumor necrosis factor (TNF) antagonists or vedolizumab.
Biologic-naïve	With no prior treatment with a biologic approved for the treatment of Crohn's disease in the countries in which the study is conducted.
EU SmPC:	The European Union (EU) Summary of Product Characteristics [SmPC] for ustekinumab for the treatment of Crohn's disease, which at the time of protocol writing has received positive opinion from the Committee for Medicinal Products for Human Use (CHMP) at the European Medicines Agency (EMA).
Routine care:	For the purposes of this protocol, 'routine care' refers to a pragmatic ustekinumab maintenance treatment strategy in subjects with Crohn's disease, in compliance with the EU SmPC for ustekinumab.
Treat to target:	Following initial treatment assignment based on early endoscopy, the treat to target ustekinumab maintenance strategy for this study will involve regular assessment of disease activity (CDAI and biomarkers) with subsequent adjustment of treatment in case of persistent inflammatory disease activity.

1. INTRODUCTION

Ustekinumab is a fully human immunoglobulin G1 kappa (IgG1k) monoclonal antibody to human IL-12/23p40 that binds with high affinity to the p40 subunit of human IL-12 and IL-23. By inhibiting interaction with the cell surface IL-12R β 1 receptor protein, ustekinumab effectively neutralizes all IL-12 (Th1) and IL-23 (Th17) mediated cellular responses. Abnormal regulation of IL-12 and IL-23 has been associated with multiple immune-mediated diseases including Crohn's disease.

There is a significant medical need for new safe and effective therapies for moderate to severe, active Crohn's disease. Inhibition of IL-12 and IL-23 and associated inflammatory pathways constitutes a novel mechanism of action for the treatment of Crohn's disease. The therapeutic potential of this approach is evident from nonclinical and clinical data, including the findings of recent Phase 3, double-blind, placebo-controlled studies.

For the most comprehensive nonclinical and clinical information regarding the efficacy and safety of ustekinumab, refer to the latest version of the Investigator's Brochure for ustekinumab.⁸ A risk/benefit assessment for this study is provided in Section 2 of the Investigational Medicinal Product Dossier (Attachment 11).

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

Ustekinumab (STELARA[®]) has been approved by the European Medicines Agency (EMA) and the United States Food and Drug Administration for the treatment of moderate to severe plaque psoriasis in adults or adolescent patients, and for the treatment of active psoriatic arthritis. More recently, ustekinumab has been approved for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, were intolerant to, or have medical contraindications to either: conventional therapy, or TNF α antagonist therapy.

Clinical Studies

Efficacy/Safety Studies

The efficacy and safety of ustekinumab for subjects with moderate to severely active Crohn's disease was demonstrated in 3 Phase 3, randomized, double-blind, placebo-controlled, parallel group studies. Two studies (UNITI-1 and UNITI-2) evaluated response up to Week 8 after intravenous (IV) induction of ustekinumab (130 mg or approximately 6 mg/kg by tiered, weight-based dosing). The UNITI-1 study evaluated subjects with prior failure or intolerance to at least 1 TNF antagonist, whereas the UNITI-2 study evaluated subjects who had failed conventional therapy. In both studies, a significantly greater proportion of subjects were in clinical response and remission in the ustekinumab treatment group, compared with the placebo group. The number of ustekinumab-treated subjects with a 70-point reduction from baseline in

Crohn's Disease Activity Index [CDAI] was significant compared with the placebo group as early as Week 3 and continued to improve through Week 8.⁸

In the IM-UNITI Phase 3 study, ustekinumab maintenance therapy up to Week 44 was evaluated in subjects who had participated in the UNITI-1 or UNITI-2 induction studies. Subjects who had a clinical response to induction therapy were randomized to subcutaneous (SC) treatment with either ustekinumab 90 mg every 12 weeks (n=129), or ustekinumab 90 mg every 8 weeks (n=128), or placebo (n=131). For both 12-weekly and 8-weekly maintenance dosing regimens, statistically significant maintenance of clinical remission (CDAI score <150 points) and clinical response (defined as reduction from Week 0 of the induction study in CDAI of ≥ 100 points) was demonstrated at Week 44 compared with placebo. Subjects who did not maintain response to ustekinumab when treated every 12 weeks were allowed to increase the frequency of dosing to every 8 weeks. In these cases, clinical remission was achieved in 41% of subjects 16 weeks after dosing frequency adjustment.⁵

Nonresponders to ustekinumab induction treatment received ustekinumab 90 mg SC at Week 0 of the IM-UNITI study. If clinical response was achieved after 8 weeks, ustekinumab treatment was continued at 8-weekly intervals to Week 40. More than half of the nonresponders to induction treatment attained response 8 weeks after an additional SC dose of ustekinumab; a substantial number of these subjects (68%) were in clinical response and were in clinical remission (50%) at Week 44 after continuing to receive ustekinumab 90 mg SC every 8 weeks.

Subcutaneous (SC) ustekinumab at doses of 90 mg every 8 weeks or every 12 weeks up to Week 44 was well tolerated during the IM-UNITI study, with a safety profile generally comparable with placebo. The proportions of subjects with adverse events were comparable across treatment groups with no evidence of a dose effect. Serious adverse events reported in more than 1 ustekinumab-treated subject were predominantly events of Crohn's disease, or related symptoms and complications. In addition, the proportions of subjects who discontinued due to adverse events were comparable across treatment groups with no evidence of a dose effect.

No events of anaphylaxis or other serious infusion reactions were reported during ustekinumab IV induction studies in subjects with Crohn's disease. Additionally, <3% of subjects treated with ustekinumab developed antibodies to ustekinumab. No apparent association between the development of antibodies to ustekinumab and the development of injection site reactions was observed. Subjects positive for antibodies to ustekinumab tended to have lower efficacy, however, antibody positivity did not preclude a clinical response. The majority of subjects who were positive for antibodies to ustekinumab had neutralizing antibodies.⁸

1.2. Overall Rationale for the Study

Inflammatory bowel diseases (IBD) are chronic, progressive, and disabling conditions. Most current strategies, which target control of symptoms, do not appear to significantly alter the natural course of the disease. Recent studies in Crohn's disease underscore the need to look beyond symptoms and to treat endoscopic/macrosopic lesions, ultimately with the aim of preventing structural damage and disability. Due to the invasive nature and/or cost of

endoscopies or cross-sectional imaging, frequent repetition of these procedures is not feasible; therefore, surrogate biomarkers of inflammation, including C-reactive protein (CRP) and fecal calprotectin (FC) have been increasingly studied in IBD.^{6,20,21}

A ‘treat to target’ strategy has been advocated as an optimized management approach for various diseases, by which strictly defined treatment targets facilitate decision making in clinical practice. Key to the success of this treatment strategy is the definition of appropriate treatment targets and adoption of algorithms that drive therapeutic changes within distinct time frames. This approach has been shown to be successful in chronic, immune-mediated inflammatory disorders such as rheumatoid arthritis and psoriatic arthritis. Recently, the value of such an approach in patients’ management has been suggested for IBD.^{2,16}

The goal of this study of adult Crohn’s disease subjects treated with ustekinumab is to demonstrate that a maintenance strategy based on early endoscopy followed by regular assessment of biomarkers (FC and CRP) and clinical symptoms (CDAI) with subsequent adjustment of treatment in case of persistent inflammatory disease activity (failure to achieve the target) is more successful in achieving endoscopic improvement than a pragmatic maintenance strategy based on guidance provided in the EU SmPC for the use of ustekinumab in Crohn’s disease.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

The endpoints listed below will be observed values at all visits assessed and at endpoint (last observation carried forward [LOCF]) and changes from baseline for continuous/ordinal variables unless otherwise specified.

Objectives	Endpoints
Primary <ul style="list-style-type: none"> To evaluate the efficacy of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach in achieving endoscopic response. 	<ul style="list-style-type: none"> Endoscopic response at Week 48, defined as showing (yes or no) a reduction from baseline in simple endoscopic score for Crohn’s disease (SES-CD) of $\geq 50\%$. Randomized subjects who stop treatment before reaching Week 48 due to any reason, or subjects without endoscopic data at Week 48 will be analyzed as nonresponders.

Objectives	Endpoints
Secondary	
<ul style="list-style-type: none"> To examine the robustness of the primary endpoint analysis, sensitivity analyses of the primary endpoint will be conducted. 	<ul style="list-style-type: none"> Endoscopic response at Week 48, defined as showing (yes or no) a reduction from baseline in SES-CD score of $\geq 50\%$. Randomized subjects who stop treatment before reaching Week 48 due to reasons other than lack/loss of efficacy will be excluded from the analysis. Endoscopic response defined as a reduction from baseline in SES-CD score of $\geq 50\%$ at endpoint (LOCF).
<ul style="list-style-type: none"> To evaluate the efficacy of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach in achieving endoscopic remission. 	<ul style="list-style-type: none"> Endoscopic remission defined as a SES-CD score ≤ 2 at Week 48 and endpoint (LOCF).
<ul style="list-style-type: none"> To evaluate the efficacy of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach in achieving mucosal healing. 	<ul style="list-style-type: none"> Mucosal healing defined as the complete absence of mucosal ulcerations in any ileocolonic segment at Week 48 and endpoint (LOCF).
<ul style="list-style-type: none"> To evaluate the efficacy of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach in achieving clinical remission. 	<ul style="list-style-type: none"> Clinical remission defined as a CDAI score of < 150 points.
<ul style="list-style-type: none"> To evaluate the efficacy of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach in achieving clinical response. 	<ul style="list-style-type: none"> Clinical response defined as a ≥ 100-point reduction from the baseline CDAI score, or a CDAI score < 150.
<ul style="list-style-type: none"> To evaluate the efficacy of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach in eliminating the need for corticosteroids while maintaining disease control. 	<ul style="list-style-type: none"> Corticosteroid-free clinical remission. Corticosteroid-free endoscopic response (endoscopic response defined as a reduction from baseline in SES-CD score of $\geq 50\%$).
<ul style="list-style-type: none"> To evaluate the effect of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach on serum CRP and FC levels. 	<ul style="list-style-type: none"> Serum CRP. FC.

Objectives	Endpoints
<ul style="list-style-type: none"> To evaluate the effect of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach on health-related quality of life (QoL), patient-reported outcomes (PROs) and pharmacoeconomics. 	<ul style="list-style-type: none"> Percentage of subjects with a 16-point change from baseline for Inflammatory bowel disease questionnaire (IBDQ). Percentage of subjects with a 7-point change from baseline in work productivity and activity impairment (WPAI) scores for each domain. <p>Changes from baseline for:</p> <ul style="list-style-type: none"> IBDQ, European quality of life 5 dimensions 5 level (EQ-5D-5L), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Hospital anxiety and depression scale (HADS), WPAI, Time lost from work.
<ul style="list-style-type: none"> To describe the safety of two SC ustekinumab maintenance regimens in a randomized population. 	<ul style="list-style-type: none"> Adverse events. Clinical laboratory data. Vital signs. Physical examination findings.
Exploratory	
<ul style="list-style-type: none"> To explore the effect of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach on fistula response. 	<p>For subjects with fistulas at baseline:</p> <ul style="list-style-type: none"> ≥50% reduction from baseline in the number of draining fistulas at Week 48, Week 104, and endpoint (LOCF).
<ul style="list-style-type: none"> To explore the pharmacokinetics (PK), and immunogenicity of ustekinumab therapy. To explore the pharmacodynamics (PD) of ustekinumab therapy, correlating the PK with clinical outcomes, including CDAI measures, changes in CRP and FC, and endoscopic outcomes. 	<ul style="list-style-type: none"> Serum ustekinumab concentrations. Antibodies to ustekinumab.
<ul style="list-style-type: none"> To explore the benefit of a treat to target strategy coupled with early endoscopic assessment versus a clinically driven (routine care) approach on Crohn's disease-related hospitalizations and surgeries. 	<ul style="list-style-type: none"> Crohn's disease-related hospitalizations. Crohn's disease-related surgery.

Objectives	Endpoints
<ul style="list-style-type: none"> To explore the effectiveness of maintenance of ustekinumab treatment up to Week 104. 	<ul style="list-style-type: none"> Endoscopic response at Week 104 and endpoint (LOCF), defined as showing (yes or no) a reduction from baseline in SES-CD of $\geq 50\%$. Randomized subjects who stop treatment before reaching Week 104 due to any reason, or subjects without endoscopic data at Week 104, will be analyzed as nonresponders. Endoscopic response at Week 104, defined as showing (yes or no) a reduction from baseline in SES-CD score of $\geq 50\%$. Randomized subjects who stop treatment before reaching Week 104 due to reasons other than lack/loss of efficacy will be excluded from the analysis. Endoscopic remission defined as SES-CD score ≤ 2 at Week 104 and endpoint (LOCF). Mucosal healing defined as the complete absence of mucosal ulcerations in any ileocolonic segment at Week 104 and endpoint (LOCF). Clinical remission defined as a CDAI score of < 150 points. Clinical response defined as a ≥ 100-point reduction from the baseline CDAI score, or a CDAI score of < 150 points. Corticosteroid-free clinical remission. Corticosteroid-free endoscopic response (endoscopic response defined as a reduction from baseline in SES-CD score of $\geq 50\%$). Serum CRP. FC. PROs and pharmacoeconomics (IBDQ, EQ-5D-5L, FACIT-F, HADS, time lost from work, WPAI). Clinical and biomarker remission (CDAI score of < 150 points, CRP ≤ 10 mg/L, and FC ≤ 250 $\mu\text{g/g}$) at Week 104 and endpoint (LOCF).

Objectives	Endpoints
<ul style="list-style-type: none"> To explore the effectiveness of de-escalated ustekinumab dosing after Week 48. 	<ul style="list-style-type: none"> Durations of corticosteroid-free clinical remission and biomarker remission, Durations of corticosteroid-free clinical remission and biomarker remission after dose de-escalation, Duration of de-escalated doses.

Refer to Section 9 (Study Evaluations) for evaluations related to endpoints.

2.2. Hypothesis

Initial treatment assignment for the treat to target ustekinumab maintenance treatment strategy will be based on early endoscopy, followed by regular assessment of disease activity (CDAI, FC, and CRP) with subsequent adjustment of treatment in case of persistent inflammatory disease activity. The routine care maintenance treatment strategy will be based on the guidance on posology in the EU SmPC.

The hypothesis is that a ‘treat to target’ ustekinumab maintenance treatment strategy coupled with early endoscopic assessment will result in a higher endoscopic response rate (defined as the percentage of subjects achieving $\geq 50\%$ reduction in SES-CD versus baseline) after 48 weeks of treatment, compared with a pragmatic (per EU SmPC) maintenance treatment strategy in subjects with Crohn’s disease.

This study is designed to show that the percentage of subjects with endoscopic response at Week 48 in the treat to target arm is 15% higher compared with the routine care arm. Based on the results of the Phase 3 IM-UNITI study, endoscopic response in the routine care arm is estimated at 30% of subjects. Endoscopic response in the treat to target arm is estimated at 45% of subjects.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a randomized, open-label, parallel-group, multicenter, multinational, Phase 3b interventional study of ustekinumab in adult subjects with active, moderate to severe, ileal and/or colonic Crohn’s disease. The benefit of a treat to target maintenance treatment strategy versus routine care will be investigated. For the treat to target strategy, ustekinumab treatment will be adjusted based on the regular assessment of disease activity by objective clinical and biological outcome measures and clinical symptoms. Routine care will be pragmatic, in accordance with the EU SmPC for ustekinumab in Crohn’s disease.

A target of 650 adult male and female subjects with endoscopic evidence of active disease will be enrolled. Subjects enrolled will have previously had an inadequate response with, lost response to, been intolerant to, or had medical contraindications to either conventional therapy, or one previous biologic therapy approved for the treatment of Crohn’s disease in the countries

in which the study is conducted. Study subjects may be biologic-naïve or biologic-experienced, having received no more than one prior biologic for the treatment of Crohn's disease.

During a screening period of up to 5 weeks, eligibility of subjects will be evaluated, and centrally-read endoscopic assessments at screening will be used for baseline evaluation. At Week 0, all eligible subjects will initiate IV induction treatment with ustekinumab, in line with the EU SmPC, on a weight-tiered basis at a dose of approximately 6 mg/kg IV (see Section 6). At Week 8, all subjects will receive a 90 mg SC injection of ustekinumab.

At Week 16, subjects who do not achieve a CDAI improvement of ≥ 70 points versus Week 0 (CDAI-70) will leave the study. Subjects who remain in the study will be randomized in a 1:1 ratio to either one of two arms for open-label maintenance treatment up to Week 48: the treat to target arm or the routine care arm. Randomized subjects will be stratified according to whether biologic-naïve at baseline versus prior exposure to 1 biologic for treatment of Crohn's disease, and according to baseline SES-CD score ≤ 16 or SES-CD > 16 .

Routine care arm up to Week 48

In the routine care arm, assessment visits will be scheduled according to the timing of maintenance treatment injections, which will be in compliance with the EU SmPC for ustekinumab for the treatment of Crohn's disease, in which dosing every 12 weeks is recommended. At Week 16, (ie, 8 weeks after the first SC dose) subjects continuing in the study will have demonstrated a CDAI-70 response. Nonetheless, subjects who have not shown adequate response based on the investigator's judgment may receive a second SC dose at Week 16.

Blood and stool samples will be taken at each assessment visit for central analysis but the results of CRP and FC assessments during the maintenance period up to Week 48 will not be communicated to the investigator. Overall analysis of CRP and FC data will be performed at the end of the study.

During the routine care maintenance treatment period up to Week 48, in case of clinical worsening reported by the subject, consistent with disease flare in the investigator's judgment, clinical assessments of disease flare will be performed at the investigator's discretion. In accordance with the EU SmPC for ustekinumab, subjects who lose response during 12-weekly dosing may benefit from an adjustment to 8-weekly maintenance treatment. Subjects may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgment. Information on assessments of disease flare and on the reasons for dosing frequency changes will be documented in the case report form (CRF). In contrast, subjects already receiving 8-weekly treatment will not be able to adjust the ustekinumab dose following disease flare and will leave the study if they would not benefit from continuing study treatment in the investigator's judgment.

Treat to target arm up to Week 48

In the treat to target arm, initial ustekinumab maintenance treatment assignment will be based on centrally-read ileocolonoscopy (performed at Week 16 in this arm only). Subjects with <25% improvement in SES-CD score at Week 16 versus baseline will be assigned to 8-weekly maintenance treatment and will receive ustekinumab 90 mg SC at Week 16. Only subjects assigned to 8-weekly treatment will receive ustekinumab at Week 16. In contrast, subjects with ≥25% improvement in SES-CD score at Week 16 versus baseline will be assigned to 12-weekly treatment and will receive the next ustekinumab maintenance dose (90 mg SC) at Week 20.

Subsequently, at assessment visits (from Week 24 for subjects assigned to the 8-weekly regimen or from Week 20 for the 12-weekly group) ustekinumab maintenance treatment up to Week 48 will be directed by treat to target assessments. Among the subgroup of subjects with elevated CRP at baseline (ie, CRP >2.87 mg/L at Week 0), the treatment target will be the achievement of:

- CDAI <220 and ≥70-point improvement in CDAI score from baseline (Week 0)
AND
- CRP ≤10 mg/L or FC ≤250 µg/g

For subjects who do not have elevated CRP at baseline (ie, CRP ≤2.87 mg/L at Week 0) in the presence of active disease, CRP would not be considered a biomarker target for dose adjustment, therefore the treatment target for these subjects will be the achievement of:

- CDAI <220 and ≥70-point improvement in CDAI score from baseline (Week 0)
AND
- FC ≤250 µg/g.

Subjects meeting the treatment target will continue with the same ustekinumab dosing frequency. However, maintenance dosing frequency will be optimized for all subjects failing to meet the treatment target at the assessment visit. Those subjects previously on 12-weekly regimens will be adjusted to 8-weekly dosing; those previously on 8-weekly regimens will be adjusted to 4-weekly dosing. Among those, subjects subsequently failing to meet the treatment target at the next assessment visit 4 weeks after dosing will not be able to adjust dosing further and will leave the study.

In case of disease flare between scheduled assessment visits, subjects will undergo CDAI and biomarker (CRP and FC) assessments at the time of disease flare. Dosing frequency will be adjusted as described above for subjects failing to meet the treatment target.

Extension period: dosing adjustments from Week 48

From Week 48, subjects will continue ustekinumab treatment in the study extension period, up to Week 104. The frequency of dosing will be based on endoscopic and/or clinical remission at Week 48, and subsequently on clinical remission and biomarker findings as summarized below in [Table 1](#).

From Week 48, ustekinumab dose de-escalation will be implemented for subjects with both endoscopic remission (SES-CD score ≤ 2) at Week 48 and corticosteroid-free clinical remission (CDAI score of <150 points) of at least 16 weeks' duration. Among such subjects, those receiving 8-weekly ustekinumab will adjust to 12-weekly dosing, whereas those receiving 4-weekly ustekinumab will adjust to 8-weekly dosing. In the latter case, further dose de-escalation to 12-weekly ustekinumab dosing will be applied for subjects with corticosteroid-free clinical remission (CDAI score of <150 points) and biomarker remission (CRP ≤ 10 mg/L and FC ≤ 250 μ g/g) at 2 subsequent, consecutive visits 8 weeks apart. Subjects receiving 12-weekly ustekinumab with endoscopic remission at Week 48 will maintain this 12-weekly dosing frequency.

Subjects with either clinical remission or endoscopic remission, but not both, at Week 48 will continue with the same dosing frequency. For those with only clinical remission, subsequent dosing de-escalation will be dependent on maintenance of corticosteroid-free clinical remission and demonstration of biomarker remission at 2 consecutive visits. For subjects with only endoscopic remission, subsequent dose de-escalation will be dependent on being in corticosteroid-free clinical remission and demonstrating biomarker remission at 2 consecutive visits ([Table 1](#)).

Conversely, subjects with neither corticosteroid-free clinical remission nor endoscopic remission having received 12-weekly or 8-weekly ustekinumab up to Week 48 will undergo dose escalation to 8-weekly or 4-weekly dosing, respectively. After dose escalation, if neither clinical remission nor biomarker remission is evident at the next visit, subjects will leave the study. Later in the extension period, only those who achieve corticosteroid-free clinical remission of ≥ 16 weeks' duration and demonstrate biomarker remission over 2 consecutive visits will undergo dose de-escalation ([Table 1](#)). Subjects with neither corticosteroid-free clinical remission nor endoscopic remission who have received ustekinumab at 4-weekly intervals up to Week 48 will not be able to adjust dosing further and will leave the study.

Table 1: Extension Period Ustekinumab Dosing From Week 48

Clinical remission (CDAI score of <150 points) at Week 48	Endoscopic remission (SES-CD score ≤ 2) at Week 48	Ustekinumab Dosing Strategy
Yes	Yes	<p>From Week 48, for subjects with corticosteroid-free clinical remission of ≥ 16 weeks' duration, dosing will be de-escalated from 4-weekly to 8-weekly, or from 8-weekly to 12-weekly dosing (subjects on a 12-weekly regimen at Week 48 will continue with this frequency).</p> <p>For subjects de-escalated to 8-weekly dosing and subsequently maintaining corticosteroid-free clinical remission, and demonstrating biomarker remission* over 2 consecutive visits, there will be a second de-escalation to 12-weekly dosing.</p>
No	Yes	<p>At Week 48, subjects will continue with the same dosing frequency. After Week 48, for corticosteroid-free subjects in clinical remission and demonstrating biomarker remission* over 2 consecutive visits, dosing will be de-escalated from 4-weekly to 8-weekly, or from 8-weekly to 12-weekly dosing (subjects on a 12-weekly regimen will continue with this frequency).</p>
Yes	No	<p>At Week 48, subjects will continue with the same dosing frequency. After Week 48, for subjects maintaining corticosteroid-free clinical remission for ≥ 16 weeks and demonstrating biomarker remission* over 2 consecutive visits, dosing will be de-escalated from 4-weekly to 8-weekly, or from 8-weekly to 12-weekly dosing (subjects on a 12-weekly regimen will continue with this frequency).</p>
No	No	<p>From Week 48, dosing will be escalated, from 12-weekly to 8-weekly, or from 8-weekly to 4-weekly dosing. Subjects on a 4-weekly regimen will not be able to dose adjust further and will leave the study.</p> <p>After dose escalation, if neither clinical remission nor biomarker remission is evident at the next visit, subjects will leave the study.</p> <p>For subjects continuing in the extension period who subsequently achieve corticosteroid-free clinical remission of ≥ 16 weeks' duration and demonstrate biomarker remission* over 2 consecutive visits, dosing will be de-escalated (eg, from 4-weekly to 8-weekly, or from 8-weekly to 12-weekly dosing).</p>

*Biomarker remission: CRP ≤ 10 mg/L and FC ≤ 250 μ g/g at 2 consecutive visits.

Extension period: dosing in case of disease flare

In case of disease flare at any time during the extension period, dosing will be escalated/re-escalated (12-weekly to 8-weekly, or 8-weekly to 4-weekly). Among the subgroup of subjects with elevated CRP at baseline (ie, CRP >2.87 mg/L at Week 0), disease flare during the extension period will be defined as:

- CDAI ≥ 220 and <70 -point improvement in CDAI score from baseline (Week 0)

AND

- CRP >10 mg/L or FC >250 $\mu\text{g/g}$

Among subjects who do not have elevated CRP at baseline (ie, CRP ≤ 2.87 mg/L at Week 0) disease flare during the extension period will be defined as:

- CDAI ≥ 220 and <70 -point improvement in CDAI score from baseline (Week 0)

AND

- FC >250 $\mu\text{g/g}$.

For those subjects escalated to 8-weekly dosing, further escalation to 4-weekly dosing will be implemented in case of persistent or recurring disease flare. Subjects receiving 4-weekly ustekinumab during the extension period who experience disease flare will not be able to adjust dosing further and will leave the study.

Study visits

All subjects will be evaluated at Weeks 0, 8, and 16, at each assessment visit at the times scheduled for study drug administration, and at Week 48 and Week 104. In cases of disease flare arising between scheduled study visits, subjects will also be assessed at the time of disease flare. Assessments of CDAI, CRP, and FC will be performed throughout the study at the times indicated in the Time and Events Schedules for each study arm and for the extension period. For subjects with fistulizing disease, fistula closure will also be assessed.

Blood samples for PK and immunogenicity assessments will be collected at Weeks 0, 8, and 16, at all assessment visits, and at Week 48, Week 104, or early termination. Patient-reported outcomes will include assessments of QoL and pharmacoeconomics at Weeks 0, 16, 48, 80 and 104, or upon early termination. Adverse event data and information on concomitant therapies will be collected throughout the study.

Ileocolonoscopic assessment will be performed at the Week 48 study visit for subjects in both arms, and at Week 104. A subject discontinuing treatment before Week 104 will have an early termination visit at the time of discontinuation, unless the subject withdraws consent. Early termination assessments should include an ileocolonoscopic assessment.

For subjects receiving corticosteroids, randomized at Week 16 (CDAI-70 responders) corticosteroid tapering is mandatory from Week 16. Corticosteroid tapering can be initiated from

Week 8 in subjects already demonstrating response (CDAI-70) to ustekinumab treatment (see recommended tapering schedule in Section 8).

For all subjects, final safety follow-up assessments will be performed 16 weeks after the last administration of ustekinumab within the study. For subjects completing the 104-week study and moving to commercially-available ustekinumab, final safety follow-up assessments should be performed before the first dose of commercially-available drug. For detailed information on the timing of safety and efficacy assessments throughout the study refer to the Time and Events Schedule for each study arm.

An interim analysis of efficacy and safety data will be performed when all subjects have completed the first 16 weeks of the study or discontinued earlier (Section 11.6).

A steering committee will provide consulting oversight during the study, to ensure the scientific validity of the clinical study, to identify any scientifically relevant trends, and to provide recommendations to the sponsor (Section 11.7).

A diagram of the study design is provided below in Figure 1. A diagram of the potential ustekinumab maintenance dosing frequency adjustments between Weeks 16 and 48 for the treat to target arm is shown in Figure 2.

Figure 1: Schematic Overview of the Study Design

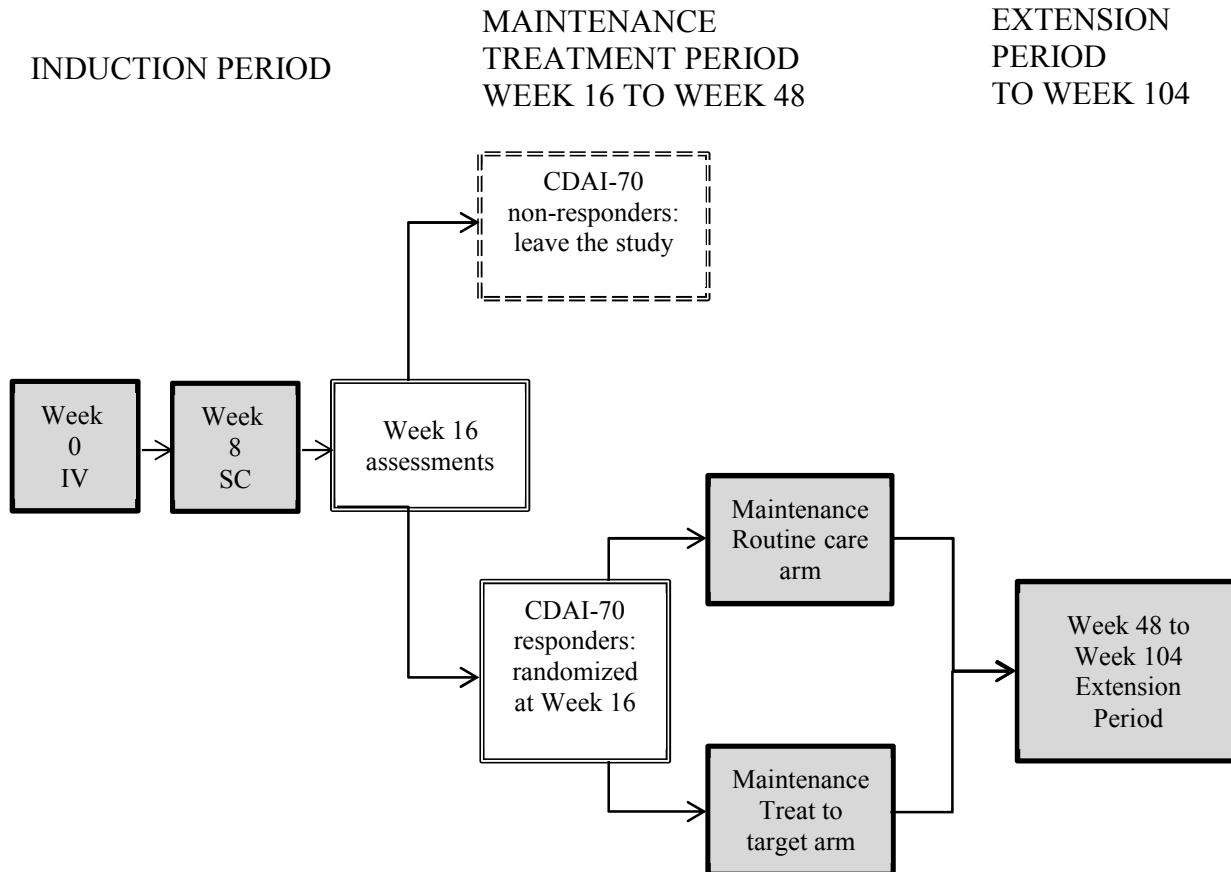
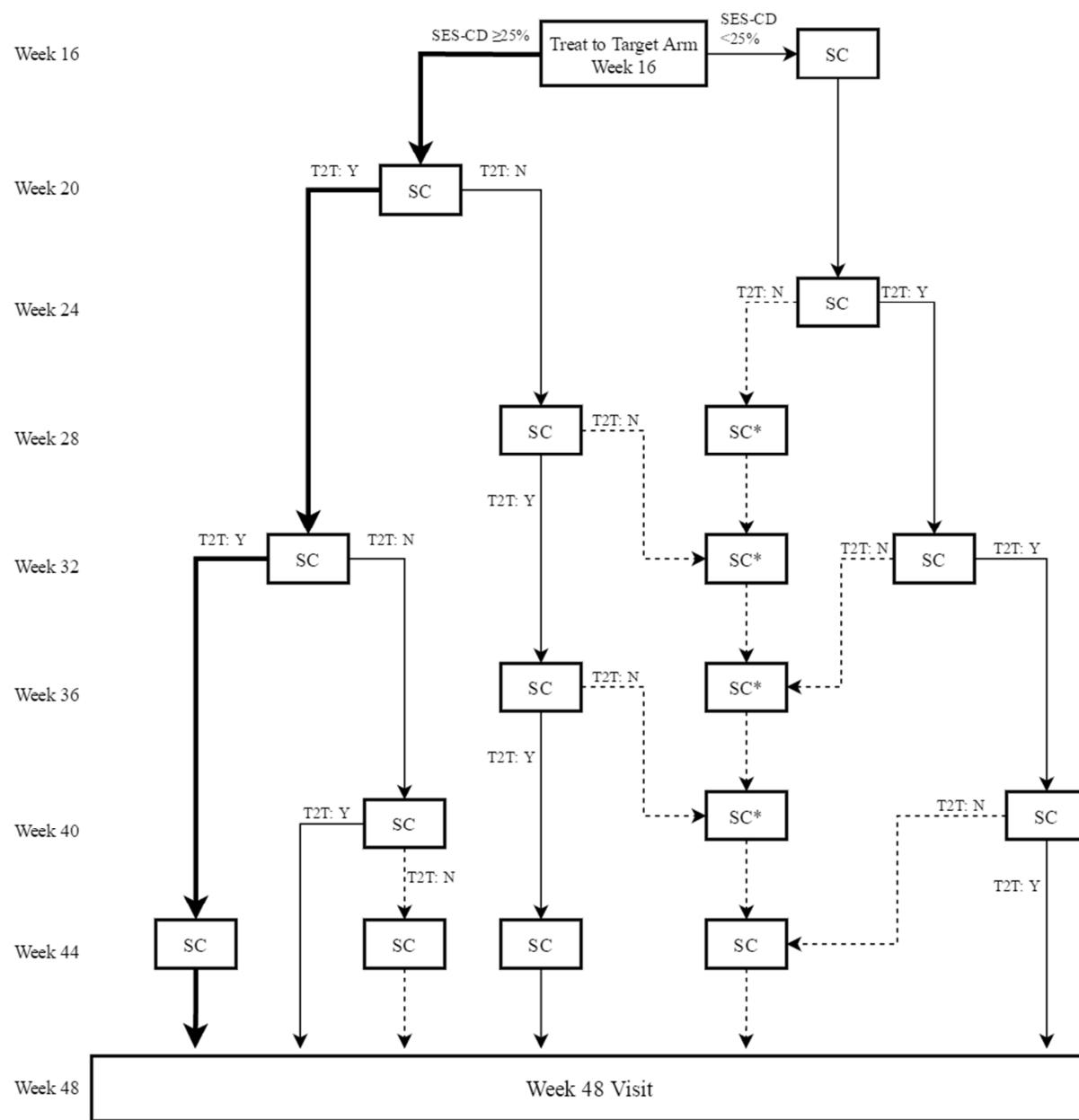


Figure 2: Ustekinumab Maintenance Dosing in the Treat to Target Arm (Week 16 to Week 48)

SES-CD $\geq 25\%$: Subjects with $\geq 25\%$ improvement in SES-CD at Week 16 versus baseline
 SES-CD $< 25\%$: Subjects with $< 25\%$ improvement in SES-CD at Week 16 versus baseline

→ 12-weekly ustekinumab maintenance dosing
 → 8-weekly ustekinumab maintenance dosing
 → 4-weekly ustekinumab maintenance dosing
 T2T: Y Subjects meeting treatment targets
 T2T: N Subjects failing to meet treatment targets at assessment visit [or evaluated between scheduled assessment visits in case of disease flare]

* Subjects meeting treatment targets following adjustment to 4-weekly dosing will continue on 4-weekly dosing. Subjects failing to meet treatment targets at the next assessment visit 4 weeks after dosing will leave the study.

An exploratory substudy to assess changes in ultrasound parameters indicating transmural response to treatment with ustekinumab will be performed at selected study centers. Participation in the ultrasound substudy will be optional for subjects participating in the main study. The ultrasound substudy will be described in a separate substudy protocol.

3.2. Study Design Rationale

Randomization

Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

Study Population

Subjects enrolled in this study may be biologic-naïve or biologic-experienced, having received no more than one prior biologic approved for the treatment of Crohn's disease in the countries in which the study is conducted. It is anticipated that approximately one third of the subjects enrolled will be biologic naïve. The UNITI-1 and UNITI-2 studies demonstrated the efficacy and safety of ustekinumab induction treatment in subjects with Crohn's disease who were respectively either previous anti-TNF α therapy failures, or conventional therapy failures (either anti-TNF α naïve [68.6%] or had previously received but not failed anti-TNF α therapy [31.4%]). Following this, the IM-UNITI study demonstrated similar maintenance treatment effects regardless of prior treatment history (ie, both in conventional therapy failures, including those naïve to prior TNF antagonists, and also in TNF antagonist-refractory subjects).⁵ To ensure balanced distribution between treatment arms in the present study, randomized subjects will be stratified according to whether biologic naïve at baseline versus prior exposure to 1 biologic for the treatment of Crohn's disease.

With the aim of balancing the distribution of baseline disease severity between treatment arms, randomized subjects will also be stratified according to baseline SES-CD. For the purposes of this study, SES-CD >16 will define subjects with severe Crohn's disease.¹¹ Thus, stratification will be according to baseline SES-CD score ≤ 16 or SES-CD >16 .

Primary Endpoint

In line with the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) consensus, an objective assessment of disease activity, endoscopic response, will be used for the primary endpoint of this study.¹⁶ An objective assessment is also considered an appropriate approach for an open-label study. The SES-CD is a standard, validated measure of endoscopic disease activity, which is simple and reproducible.⁷

Randomization at Week 16

At Week 16, CDAI-70 will be used to distinguish responding subjects who will be randomized into the maintenance treatment period. The CDAI has been widely used in clinical trials and CDAI-70 is an accepted measure of clinical response.¹⁶ Subjects will be selected on the basis of

response at Week 16 since this is considered an adequate treatment interval to demonstrate response to induction treatment. The IM-UNITI study demonstrated that more than half of the nonresponders to an IV induction dose subsequently responded 8 weeks after an additional SC dose of ustekinumab.⁸

Target Assessments in the Treat to Target Maintenance arm

For the treat to target arm, both clinical assessments (CDAI) and measures of inflammation will guide ustekinumab maintenance treatment. Although inducing and maintaining clinical remission of symptoms is an important therapeutic goal in Crohn's disease, management based on symptoms alone may be insufficient to reduce or prevent long-term bowel damage. Even asymptomatic patients may have endoscopic evidence of active bowel inflammation. Due to the inconsistent correlation between symptoms and mucosal disease activity, symptom-based treatment might lead to suboptimal therapy in a substantial proportion of patients. Inadequate control of inflammation may result in structural bowel damage, with a resultant need for surgery in many patients. Therefore, objective measures of bowel inflammation should also be considered. For this reason, early ileocolonoscopic assessment at Week 16 has been incorporated into the treat to target strategy for this study to direct initial maintenance dosing frequency.

Biomarkers such as CRP and FC are objective measures of inflammation, which are less invasive and more cost-effective than ileocolonoscopy, and can be repeated often within a predefined timeframe. Elevated CRP and FC concentrations correlate well with endoscopic and histologic evidence of inflammation, and normalization of concentrations has been associated with positive treatment outcomes.^{2,1,13,22} Therefore, for the treat to target arm, biomarkers (CRP or FC) will be used as target assessments, monitored regularly and used to guide ustekinumab maintenance treatment.

Other Endpoints

The endoscopic and clinical outcomes evaluated as secondary endpoints for this study are accepted measures of response in Crohn's disease. Endoscopic endpoints will include mucosal healing, defined as the complete absence of mucosal ulcerations in any ileocolonic segment, which is associated with better outcomes in clinical trials.¹⁶

A further goal of maintenance therapy for subjects with Crohn's disease is the ability to reduce or eliminate corticosteroid use. To assess the efficacy of ustekinumab in eliminating the need for corticosteroids while maintaining disease control, corticosteroid-free clinical remission, and corticosteroid-free endoscopic response will be evaluated at Week 48 and Week 104. To enable evaluation, subjects receiving corticosteroids with a CDAI-70 response at Week 16 will undergo mandatory steroid tapering. Tapering of corticosteroids was undertaken in the IM-UNITI study, which demonstrated greater proportions of ustekinumab subjects in remission and corticosteroid free compared with the placebo group after 44 weeks of maintenance treatment. It is also consistent with clinical practice for patients on effective treatment.

Reliable assessment of symptoms, QoL, mood, and fatigue from a patient's perspective is of recognized value, and PROs evaluating these elements are included in this study. During the

IM-UNITI study, clinically-meaningful improvements in health-related QoL (including IBDQ) were maintained over 44 weeks in ustekinumab-treated subjects.

It is of interest to determine whether ustekinumab serum levels correlate with endoscopic outcomes, CDAI measures, and changes in CRP or FC. Therefore, exploratory analyses of PK, immunogenicity and PD will be performed.

Medical Resource Utilization and Health Economics Data Collection

Medical resource utilization data including Crohn's disease-related hospitalizations and Crohn's disease-related surgeries will be collected from Week 0 to the safety follow-up visit to enable evaluation of the health economics of ustekinumab treatment. Additionally, the impact of ustekinumab treatment on work productivity will be assessed using the WPAI and time lost from work.

Dosing

Consistent with the EU SmPC for ustekinumab in Crohn's disease, all subjects will receive tiered, weight-based IV induction dosing, which was demonstrated to be well tolerated and effective in the UNITI-1 and UNITI-2 induction studies. Subsequently, subjects randomized to the routine care arm will receive an ustekinumab maintenance dosing regimen consistent with the EU SmPC, based on either 12-weekly or 8-weekly 90 mg SC dosing, the positive benefit/risk profile of which was demonstrated by the 44-week IM-UNITI study.

Maintenance treatment in the treat to target arm will also involve initial assignment to 12-weekly or 8-weekly 90 mg SC treatment, which in this arm will be based on endoscopic results at Week 16. However, within the treat to target approach, there is the potential for more intensive management, with optimization to 4-weekly dosing for subjects failing to meet treatment targets following 8-weekly dosing. Real-world experience of more intensive maintenance dosing regimens than those assessed in the IM-UNITI study has been reported for Crohn's disease patients.^{10,23} Additionally, ustekinumab 90 mg SC every 4 weeks was reported to be well tolerated in a Phase 2 study of subjects with multiple sclerosis.¹⁹

Study Period

The initial study treatment period is 48 weeks, of which 32 weeks will be the randomized maintenance treatment period. Subjects receiving study treatment up to Week 48 will receive between 3 and 7 maintenance treatment doses of study drug, depending on the treatment arm and adjustments to dosing frequency. Based on the findings of the IM-UNITI study, this treatment period is considered sufficient to evaluate the efficacy of ustekinumab maintenance treatment strategies.

Extension Period

Following Week 48 assessments, study treatment will be extended up to Week 104. This will identify subjects with sustained remission during longer-term maintenance of ustekinumab treatment. Furthermore, there is a lack of data on the impact of continuing treatment in subjects with clinical remission but not endoscopic remission, who may have persistent moderate lesions.

Previously, endoscopic evaluation of patients with sustained remission following azathioprine treatment revealed persistent lesions in a significant proportion.¹² The extension period of the present study may provide valuable information on continuation of ustekinumab treatment in subjects with persisting lesions.

Extension of ustekinumab treatment to Week 104 will also enable examination of the effectiveness of de-escalated dosing. There is interest in de-escalation strategies for biological treatment of patients with IBD, an approach that has been proposed for patients in deep remission.¹⁴ For this study, ustekinumab dosing frequency will be de-escalated from Week 48 in subjects with endoscopic remission and corticosteroid-free clinical remission of at least 16-weeks' duration, ie demonstrating stable clinical remission. Additionally, subjects de-escalated from 4-weekly to 8-weekly dosing will undergo a second de-escalation to 12-weekly ustekinumab if clinical and biomarker remission at 2 consecutive visits is confirmed, which will avoid serial, repeat endoscopies.

After Week 48, dose de-escalation will be possible for subjects with sustained corticosteroid-free clinical remission in the absence of Week 48 endoscopic remission, only if biomarker remission indicates the absence of active inflammation at 2 consecutive visits. De-escalation of dosing will also be implemented after Week 48 in subjects with endoscopic remission but not clinical remission, if they are corticosteroid-free and demonstrate biomarker remission over 2 consecutive visits. Provision for this type of subject has been made because a previous study identified a subset of Crohn's disease patients with persistent symptoms (CDAI >150) but no endoscopic lesions following treatment.¹⁵

A final ileocolonoscopy at Week 104 will allow assessment of endoscopic response, remission and mucosal healing after extended treatment, both for subjects maintaining the same dose frequency, or needing escalated doses, and for those for whom dose de-escalation is implemented.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 5 weeks before administration of the study drug.

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. Male or female ≥ 18 years of age

2. Criterion modified per Amendment 2

2.1 Have active, moderate to severe, ileal and/or colonic Crohn's disease, demonstrated by:

- Baseline CDAI score of ≥ 220 and ≤ 450 .

and

- Endoscopy with evidence of active Crohn's disease (defined as SES-CD score ≥ 3 excluding the contribution of the narrowing component score) obtained within the 5-week screening period. A prior endoscopy may be used only if obtained within 3 months prior to baseline (Week 0), in which case the prior endoscopy must be centrally read again and SES-CD calculated based on this second, centralized read-out.

3. Has had an inadequate response with, lost response to, was intolerant to, or had medical contraindications to either:

- conventional therapy, or
- one previous biologic therapy approved for the treatment of Crohn's disease in the countries in which the study is conducted.

4. Adhere to the following requirements for concomitant medication for the treatment of Crohn's disease. The following medications are permitted provided doses meeting the requirements below are stable for or have been discontinued at least 3 weeks prior to baseline (Week 0), unless otherwise specified:

- a. Oral 5-aminosalicylic acid (5-ASA) compounds.
- b. Oral corticosteroids (eg, prednisone, budesonide) at a prednisone-equivalent dose of ≤ 40 mg/day or ≤ 9 mg/day of budesonide.
- c. Antibiotics being used as a primary treatment of Crohn's disease.
- d. Subjects receiving conventional immunomodulators (ie, azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]) must have been taking them for ≥ 12 weeks, and on a stable dose for a least 4 weeks prior to baseline.

5. Are eligible according to tuberculosis (TB) infection screening criteria:
 - a. Have no history of latent or active TB prior to screening. Exceptions are made for subjects currently receiving treatment for latent TB, if there is no evidence of active TB, or who have a history of latent TB and documentation of having completed adequate treatment for latent TB within 3 years prior to the first administration of study drug. It is the responsibility of the investigator to verify the adequacy of previous TB treatment and provide appropriate documentation.

Note: The exceptions outlined above exclude subjects in countries with high multi-drug resistant TB burden (eg, South Africa, Bulgaria, and the Russian Federation), due to potential concerns for multidrug resistant TB.
 - b. Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination.
 - c. Have had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB before the first administration of study drug.
 - d. Within 2 months prior to the first administration of study drug, either have a negative QuantiFERON-TB Gold test ([Attachment 1](#)), or have a newly identified positive QuantiFERON-TB Gold test in which active TB has been ruled out, and for which appropriate treatment for latent TB has been initiated before the first administration of study drug (except in countries with high multidrug resistant TB burden [eg, South Africa, Bulgaria, and the Russian Federation], where subjects with a newly identified positive QuantiFERON-TB Gold test result are excluded). Indeterminate results should be handled as outlined in Section [9.1.2](#). A negative tuberculin skin test (see [Attachment 2](#)), or a newly identified positive tuberculin skin test in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated before the first administration of study drug, is additionally required if the QuantiFERON-TB gold test is not approved/registered in that country or the tuberculin skin test is mandated by local health authorities. The QuantiFERON-TB Gold In-Tube test or the tuberculin skin test are not required at screening for subjects with a history of latent TB and appropriate treatment as described above.
 - e. Have a chest radiograph (at least a posterior-anterior view), taken within 3 months prior to the first administration of study drug and read by a qualified radiologist, with no evidence of current active TB or old inactive TB.
6. Must sign an informed consent form (ICF) (or their legally acceptable representative if applicable must sign) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

7. A woman of childbearing potential must have a negative highly sensitive serum (β -human chorionic gonadotropin [β -hCG]) pregnancy test at screening, and a negative urine pregnancy test at Week 0.
8. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

Before randomization, a woman must be either:

- a. Not of childbearing potential defined as:
 - Premenarchal
 - Postmenopausal
 - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy, however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
 - Permanently sterile
 - Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.
- b. Of childbearing potential and
 - practicing a highly effective method of contraception (failure rate of $<1\%$ per year when used consistently and correctly)

Examples of highly effective contraceptives include

- user-independent methods:
 - implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); vasectomized partner; sexual abstinence (sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)
- user-dependent methods:
 - combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method.

- agrees to remain on a highly effective method throughout the study and for at least 15 weeks after the last dose of study drug.

Note: If the childbearing potential changes after the start of the study or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active,) a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

9. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for 15 weeks after the last study drug administration.
10. During the study and for 15 weeks after receiving the last dose of study drug, in addition to a highly effective method of contraception, a man
 - who is sexually active with a woman of childbearing potential must agree to use a barrier method of contraception (eg, condom with spermicidal foam/gel/film/cream/suppository)
 - must agree not to donate sperm.
11. Willing and able to adhere to the prohibitions and restrictions specified in this protocol.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

1. Has complications of Crohn's disease such as symptomatic strictures or stenoses, short gut syndrome, or any other manifestation that might be anticipated to require surgery, could preclude the use of the CDAI to assess response to therapy, or would possibly confound the ability to assess the effect of treatment with ustekinumab.
2. Currently has or is suspected to have an abscess. Recent cutaneous and perianal abscesses are not exclusionary if drained and adequately treated at least 3 weeks prior to baseline, or 8 weeks prior to baseline for intra-abdominal abscesses, provided there is no anticipated need for any further surgery. Subjects with active fistulas may be included if there is no anticipation of a need for surgery and there are currently no abscesses identified.
3. Has had any kind of bowel resection within 6 months prior to baseline.
4. Has a draining (ie, functioning) stoma or ostomy.

5. Has received more than one previous biologic therapy approved for the treatment of Crohn's disease in the countries in which the study is conducted.
6. Has previously received a biologic agent targeting IL-12 and/or IL-23, including but not limited to ustekinumab (CNTO 1275).
7. Has received any of the following prescribed medications or therapies within the specified period:
 - a. IV corticosteroids <3 weeks prior to baseline.
 - b. Other oral immunomodulatory agents (eg, 6-thioguanine [6-TG], cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil) <6 weeks prior to baseline.
 - c. Non-autologous stem cell therapy or biologic agents that deplete B or T cells <12 months prior to baseline.
 - d. Vedolizumab <12 weeks prior to baseline.
 - e. Anti-TNF biologic agents or other agents intended to suppress or eliminate TNF <8 weeks prior to baseline.
 - f. Any investigational drug within 4 weeks before first administration of study drug or within 5 half-lives of the investigational drug, whichever is longer.
 - g. Treatment with apheresis or total parenteral nutrition (TPN) as a treatment for Crohn's disease <3 weeks prior to baseline.
8. Has received a Bacille Calmette-Guérin (BCG) vaccination within 12 months or any other live bacterial or live viral vaccination within 12 weeks of baseline.
9. Have a stool culture or other examination positive for an enteric pathogen, including *Clostridium difficile* toxin, in the last 4 months unless a repeat examination is negative and there are no signs of ongoing infection with that pathogen.
10. Has a history of, or ongoing, chronic or recurrent infectious disease, including but not limited to, chronic renal infection, chronic chest infection, recurrent urinary tract infection (eg, recurrent pyelonephritis or chronic nonremitting cystitis), or open, draining, or infected skin wounds or ulcers.
11. Has current signs or symptoms of infection. Established nonserious infections (eg, acute upper respiratory tract infection, simple urinary tract infection) need not be considered exclusionary at the discretion of the investigator.
12. Has a history of serious infection (eg, sepsis, pneumonia, or pyelonephritis), including any infection requiring hospitalization or IV antibiotics, for 8 weeks prior to baseline.

13. Has evidence of a herpes zoster infection \leq 8 weeks prior to baseline.
14. Has a history of latent or active granulomatous infection, including histoplasmosis or coccidioidomycosis, prior to screening. Refer to inclusion criteria for information regarding eligibility with a history of latent TB.
15. Has evidence of current active infection, including TB, or a nodule suspicious for lung malignancy on screening or any other available chest radiograph, unless definitively resolved surgically or by additional imaging and with source document confirmation.
16. Has or ever has had a nontuberculous mycobacterial infection or serious opportunistic infection (eg, cytomegalovirus colitis, *Pneumocystis carinii*, aspergillosis).
17. Is known to be infected with HIV, hepatitis B, or hepatitis C.
18. Has severe, progressive, or uncontrolled renal, hepatic, hematological, endocrine, pulmonary, cardiac, neurologic, cerebral, or psychiatric disease, or signs and symptoms thereof.
19. Has a transplanted organ (with exception of a corneal transplant $>$ 12 weeks prior to screening).
20. Has a known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly.
21. Has any known malignancy or has a history of malignancy (with the exception of basal cell carcinoma; squamous cell carcinoma in situ of the skin; or cervical carcinoma in situ that has been treated with no evidence of recurrence; or squamous cell carcinoma of the skin that has been treated with no evidence of recurrence within 5 years prior to screening).
22. Has previously undergone allergy immunotherapy (administration of an antigen) for prevention of anaphylactic reactions.
23. Has known allergies, hypersensitivity, or intolerance to ustekinumab or its excipients, or an allergy to latex (refer to Investigator's Brochure).⁸
24. is a woman who is pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 15 weeks after the last dose of study drug
25. is a man who plans to father a child while enrolled in this study or within 15 weeks after the last dose of study drug.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such

that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. Refer to Section 8 PRESTUDY AND CONCOMITANT THERAPY for details regarding prohibited and restricted therapy during the study.
2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).
3. Subjects must agree not to receive a live virus or live bacterial vaccination, including a BCG vaccination, during the study or for 15 weeks after receiving study drug.
4. Subjects must not receive ustekinumab outside the protocol or participate in any other clinical study with an investigational agent while in this study, and must terminate study participation if they do. If they intend to receive ustekinumab or participate in any other clinical study with an investigational agent, this should be preceded by an early termination visit.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Up to Week 16, all enrolled subjects will receive ustekinumab induction therapy. At Week 16, subjects achieving CDAI improvement of ≥ 70 points versus baseline (Week 0), will be randomized in a 1:1 ratio to one of two ustekinumab maintenance treatment arms: the treat to target arm or the routine care arm.

Procedures for Randomization and Stratification

Central randomization will be implemented in this study. Subjects will be randomly assigned to one of two treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by whether the subject was biologic-naïve at baseline/had prior exposure to 1 biologic for treatment of Crohn's disease, and according to baseline SES-CD score ≤ 16 or SES-CD > 16 . The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then give the relevant subject details to uniquely identify the subject.

Blinding

As this is an open-label study, blinding procedures are not applicable.

6. DOSAGE AND ADMINISTRATION

All eligible subjects will receive induction treatment in accordance with the EU SmPC for ustekinumab. At Week 0, IV ustekinumab will be administered on a weight-tiered basis at a dose of approximately 6 mg/kg. Subjects with body weight \leq 55 kg at Week 0 will receive 260 mg IV ustekinumab. Those subjects with body weight $>$ 55 kg and \leq 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.

At Week 8, all subjects will receive a 90 mg SC injection of ustekinumab. Subsequently, subjects continuing to randomization at Week 16 (CDAI-70 responders) will receive 90 mg ustekinumab SC at designated injection times, enabling 12-weekly, 8-weekly or 4-weekly treatment intervals depending on the study arm and response (see Section 3.1).

After Week 8, 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 instruct subjects on how to store study drug for at-home use as indicated for this protocol. 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 (based on the returned syringe). Detailed instructions on the administration of study drug are provided in the Site Investigational Product Procedures Manual.

Routine care arm up to Week 48

In the routine care arm, the timing of maintenance injections up to Week 48 will be in compliance with the EU SmPC for ustekinumab for the treatment of Crohn's disease, in which dosing every 12 weeks is recommended. At Week 16, (ie, 8 weeks after the first SC dose), subjects who have not shown adequate response based on the investigator's judgment may receive a second SC dose at that time. During the routine care maintenance treatment period, clinical assessments in case of disease flare will be at the investigator's discretion. Consistent with the EU SmPC for ustekinumab, subjects who lose response during 12-weekly dosing may benefit from an adjustment to 8-weekly maintenance treatment. Subjects may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgment. Information on assessments of disease flare and on the reasons for dosing frequency changes will be documented in the CRF. Those subjects previously receiving 8-weekly treatment will not be able to adjust the ustekinumab dose following disease flare and will leave the study if they would not benefit from continuing study treatment in the investigator's judgment.

Treat to target arm up to Week 48

In the treat to target arm, initial ustekinumab maintenance treatment assignment will be based on centrally-read endoscopy findings. Subjects with $<$ 25% improvement in SES-CD score at

Week 16 versus baseline will be assigned to 8-weekly maintenance treatment and will receive the next ustekinumab 90 mg SC injection at Week 16. Subjects with $\geq 25\%$ improvement in SES-CD score at Week 16 versus baseline will be assigned to 12-weekly treatment and will receive the next ustekinumab maintenance dose (90 mg SC) at Week 20.

Subsequently, at assessment visits for the treat to target arm (from Week 24 for subjects assigned to the 8-weekly regimen or from Week 20 for the 12-weekly group) ustekinumab maintenance treatment up to Week 48 will be directed by treat to target assessments (CDAI, and CRP or FC). Subjects meeting the treatment target will continue on the same ustekinumab dosing frequency. Maintenance dosing frequency will be optimized for subjects failing to meet the treatment target: those subjects previously on 12-weekly regimens will be adjusted to 8-weekly dosing; those previously on 8-weekly regimens will be adjusted to 4-weekly dosing. Among those, subjects subsequently failing to meet the treatment target at the next assessment visit 4 weeks after dosing will not be able to optimize dosing further and will leave the study.

In case of disease flare between scheduled assessment visits for the treat to target arm, subjects will undergo CDAI, CRP and FC assessments. Dosing frequency will be adjusted as described above for subjects failing to meet the treatment target.

Extension period: dosing adjustments from Week 48

From Week 48, subjects will continue ustekinumab treatment in the study extension period, up to Week 104. The frequency of dosing will be based on endoscopic and/or clinical remission at Week 48, and subsequently on clinical remission and biomarker findings (refer to Section 3.1, [Table 1](#)).

From Week 48, ustekinumab dose de-escalation will be implemented for subjects with both endoscopic remission (SES-CD score ≤ 2) at Week 48 and corticosteroid-free clinical remission (CDAI score of < 150 points) of at least 16 weeks' duration. Among such subjects, those receiving 8-weekly ustekinumab will adjust to 12-weekly dosing, whereas those receiving 4-weekly ustekinumab will adjust to 8-weekly dosing. In the latter case, further dose de-escalation to 12-weekly ustekinumab will be applied for subjects with corticosteroid-free clinical remission (CDAI score of < 150 points) and biomarker remission (CRP ≤ 10 mg/L and FC ≤ 250 μ g/g) at 2 subsequent, consecutive visits 8 weeks apart. Subjects receiving 12-weekly ustekinumab with endoscopic remission at Week 48 will maintain this 12-weekly dosing frequency.

Subjects with either clinical remission or endoscopic remission, but not both, at Week 48 will continue with the same dosing frequency. For those with only clinical remission, subsequent dosing de-escalation will be dependent on maintenance of corticosteroid-free clinical remission and demonstration of biomarker remission at 2 consecutive visits. For subjects with only endoscopic remission, subsequent dose de-escalation will be dependent on being in corticosteroid-free clinical remission and demonstrating biomarker remission at 2 consecutive visits (Section 3.1, [Table 1](#)).

Conversely, subjects with neither corticosteroid-free clinical remission nor endoscopic remission having received 12-weekly or 8-weekly ustekinumab up to Week 48 will undergo dose escalation to 8-weekly or 4-weekly dosing, respectively. After dose escalation, if neither clinical remission nor biomarker remission is evident at the next visit, subjects will leave the study. Later in the extension period, only those who achieve corticosteroid-free clinical remission of ≥ 16 weeks' duration and demonstrate biomarker remission over 2 consecutive visits will undergo dose de-escalation (Table 1). Subjects with neither corticosteroid-free clinical remission nor endoscopic remission who have received ustekinumab at 4-weekly intervals up to Week 48 will not be able to adjust dosing further and will leave the study.

Disease flare during the extension period will be defined according to the CDAI, CRP and FC criteria provided in Section 3.1. In case of disease flare at any time during the extension period, dosing will be escalated/re-escalated (12-weekly to 8-weekly, or 8-weekly to 4-weekly). For those subjects escalated to 8-weekly dosing, further escalation to 4-weekly dosing will be implemented in case of persistent or recurring disease flare. Subjects receiving 4-weekly ustekinumab during the extension period who experience disease flare will not be able to adjust dosing further and will leave the study.

7. TREATMENT COMPLIANCE

Study drug will be administered as a single IV infusion (Week 0) by qualified staff followed by SC injections (Week 8 onwards). 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).

After Week 8, subjects may self-administer (in compliance with the EU SmPC) SC injections of study drug at the times instructed by the investigator. When study drug is self-administered by subjects the amount of study drug dispensed will be recorded and compared with the amount returned, whether as empty syringes or syringes containing study drug.

8. PRESTUDY AND CONCOMITANT THERAPY

Prestudy Therapies

Disallowed prestudy therapies, with specified intervals before baseline (Week 0) are listed in the study exclusion criteria (Section 4.2). Prestudy therapies documented at screening will include any previous biologic therapies, therapies for Crohn's disease (including those for extraintestinal manifestations), or therapies for other immune-mediated conditions. For previous biologic therapies approved for the treatment of Crohn's disease in the countries in which the study is conducted, the reason for stopping treatment (eg, inadequate response or loss of response, intolerance, contraindications, or other reasons) will be documented in the CRF.

Concomitant Therapies

Concomitant medication will be reviewed at each visit. Concomitant therapies must be recorded throughout the study from signing of consent to last study visit. Recorded information will

include a description of the type of the drug, treatment period, dosing regimen, route of administration, and its indication.

Subjects are permitted to receive oral 5-ASA compounds, the immunomodulators AZA, 6-MP, and MTX, oral corticosteroids, and/or antibiotics for the treatment of Crohn's disease during the study provided the subject was on a stable dose for a specified period prior to baseline (as defined in the inclusion criteria in Section 4.1). Subjects receiving these medications at baseline should maintain a stable dose throughout this study, with the exception of oral corticosteroids for subjects with CDAI-70 response (see tapering schedule for oral corticosteroids below).

Enrolled subjects should not initiate any of the following concomitant Crohn's disease-specific medical therapies during the study:

- Oral or rectal 5-ASA compounds.
- Immunomodulators (AZA, 6-MP, or MTX).
- Oral, parenteral, or rectal corticosteroids.
- Antibiotics as a treatment of Crohn's disease.
- Total parenteral nutrition as a treatment of Crohn's disease.

If the above medications are initiated or doses/regimens modified, subjects should continue to attend all study visits and have all assessments. If, due to medical necessity in the opinion of the investigator, the above medications are initiated or increased, this does not represent a deviation from the study protocol.

Subjects may transiently use (ie, for <4 weeks) increased doses of corticosteroids for reasons other than loss of response to treatment for Crohn's disease (eg, stress doses of corticosteroids for surgery, asthma, adrenocortical insufficiency, etc).

Oral Corticosteroids

Subjects will be allowed to enter the study on oral corticosteroids at a prednisone-equivalent dose of ≤ 40 mg/day or ≤ 9 mg/day of budesonide. For subjects receiving corticosteroids, randomized at Week 16 (CDAI-70 Responders) corticosteroid tapering is mandatory. Corticosteroid tapering can be initiated from Week 8 in subjects already demonstrating response (CDAI-70) to ustekinumab treatment.

If subjects experience a worsening in their disease activity while tapering corticosteroids, further dose decreases may be suspended, and/or their oral corticosteroid dose may be temporarily increased if deemed necessary by the investigator. The oral corticosteroid dose, however, may not be increased above the baseline dose unless due to medical necessity. For subjects whose corticosteroid taper is interrupted on this basis, investigators are encouraged to resume tapering within 4 weeks.

Recommended tapering schedule for oral corticosteroids (other than budesonide):

- Dose >15 mg/day prednisone or equivalent: taper daily dose by 5 mg/week until receiving 10 mg/day, then continue tapering at 2.5 mg/week until 0 mg/day.
- Dose 11 to 15 mg/day prednisone or equivalent: taper daily dose to 10 mg/day for 1 week, then continue tapering at 2.5 mg/week until 0 mg/day.
- Dose \leq 10 mg/day prednisone or equivalent: taper daily dose by 2.5 mg/week until 0 mg/day.

Recommended tapering schedule for oral budesonide:

- Subjects receiving budesonide should have their daily dose tapered by 3 mg every 3 weeks until 0 mg/day.

Prohibited Medications

Enrolled subjects must not initiate any of the following Prohibited Medications during the study. If prohibited medications are initiated at any time during the study, treatment with study drug will be discontinued and subjects will complete early termination assessments and the final safety follow-up visit.

- Immunomodulatory agents other than 6-MP/AZA or MTX.
- Immunomodulatory biologic agents.
- Experimental Crohn's disease medications.

Note: Subjects must not receive ustekinumab outside of the protocol or participate in any other clinical study with an investigational agent while in this study, and must terminate study participation if they do. If they intend to receive ustekinumab or participate in any other clinical study with an investigational agent, an early termination visit should occur beforehand.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The Time and Events Schedules summarize the frequency and timing of efficacy, PK, immunogenicity, health economic, and safety measurements applicable to this study.

All study-specific PRO assessments should be conducted/completed before any tests, procedures, or other consultations for that visit to prevent influencing subject perceptions. The PRO instruments will be provided in the local language in accordance with local guidelines.

Study site personnel will remind subjects of the need to provide stool samples at the visits indicated in the Time and Events Schedules.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

Medical resource utilization and health economics data will be collected. Refer to Section 9.5, Medical Resource Utilization and Health Economics for details.

The total blood volume to be collected from each subject during this study will be approximately 348 mL.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1.2. Screening Phase

The eligibility of subjects will be assessed during a 5-week screening period. At screening, written informed consent must be obtained from the subject for this study by the investigator or designee prior to conducting any protocol-specific procedure.

Procedures to be performed at screening are outlined in the Time and Events Schedules. The requirements regarding prestudy therapies are detailed in Section 4.

During the screening period subjects will receive training in diary card completion for CDAI and for recording information on adverse events. Subjects' height and weight will be recorded. For calculation of CDAI by the investigator or appropriate site personnel at Week 0, the hematocrit value obtained during screening will be used.

A baseline, centrally-read, ileocolonoscopic evaluation will be performed during screening. A previous video ileocolonoscopy may be used, provided this has been obtained within 3 months prior to baseline (Week 0), in which case the prior ileocolonoscopy must be read again at a central facility and SES-CD calculated based on this second, centralized read-out.

Women of childbearing potential must have a negative serum β -hCG pregnancy test at screening. Subjects are to be reminded that they are required to use an acceptable method of contraception during the study and must continue taking such precautions for 15 weeks after receiving the study drug (Sections 4.1 and 4.3). The method(s) of contraception used by each subject must be documented.

Subjects must have a chest radiograph during screening or have had a chest radiograph within 3 months prior to Week 0, with no evidence of current active TB or old inactive TB (see Section 4.1). Additionally, subjects must undergo testing for TB ([Attachment 1](#) and [Attachment 2](#)) and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. The subject should be asked about past testing for TB, including chest radiograph results and responses to tuberculin skin or other TB testing.

Subjects with a negative QuantiFERON-TB Gold test result (and a negative tuberculin skin test result in countries in which the QuantiFERON-TB Gold test is not approved/registered or the tuberculin skin test is mandated by local health authorities) are eligible to continue with screening procedures. Subjects with a newly identified positive QuantiFERON-TB Gold (or tuberculin skin) test result must undergo an evaluation to rule out active TB and initiate appropriate treatment for latent TB. Appropriate treatment for latent TB is defined according to local country guidelines for immunocompromised patients. If no local country guidelines for immunocompromised patients exist, the ECCO guidelines must be followed, or the subject will be excluded from the study.¹⁷

Note: Subjects in countries with high multidrug-resistant TB burden (eg, South Africa, Bulgaria, and the Russian Federation) identified with latent TB at screening will be excluded from participating in the study.

A subject whose first QuantiFERON-TB Gold test result is indeterminate should have the test repeated. In the event that the second QuantiFERON-TB Gold test result is also indeterminate, the subject may be enrolled without treatment for latent TB if active TB is ruled out, his/her chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB) and the subject has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the sponsor's medical monitor and recorded in the subject's source documents and initialed by the investigator. Note: Subjects in countries with high multidrug-resistant TB burden (eg, South Africa, Bulgaria, and the Russian Federation) with a repeat indeterminate QuantiFERON-TB Gold test result will be excluded from participating in the study, unless their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB), they have no additional risk factors for TB as determined by the investigator and medical monitor, and they have a negative tuberculin skin test result within the 2 months prior to baseline, in which case they may be enrolled without treatment for latent TB.

An assessment of all screening laboratory test results, clinical data, and concomitant medication data will be made by the principal investigator or designee to confirm that the subject satisfies all inclusion criteria and does not violate any exclusion criteria.

9.1.3. Open-Label Treatment Phase

Subjects will visit the study sites for efficacy and safety evaluations at the times scheduled for study drug administration. Procedures to be performed at those assessment visits are outlined in the Time and Events Schedules. All procedures are to be conducted prior to administration of study drug, unless otherwise specified.

Each study visit will have a window of ± 10 days.

Subjects will be instructed to complete diary cards for CDAI or adverse event information daily up to Week 104.

Ileocolonoscopic examinations and CDAI assessments will be scheduled to avoid an impact on CDAI data. For example, if ileocolonoscopy is performed on the day of the visit, the 7 days prior

to the initiation of the ileocolonoscopy preparation should be used to calculate the CDAI score for the visit.

After Week 8, 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. Information documented in the CRF will include date of administration, self-administration (yes/no) and whether administration was complete based on the returned syringe.

Throughout the study, women of childbearing potential must have a negative urine pregnancy test, tested at assessment visits, prior to study drug administration.

Study drug should not be administered to a subject with a clinically important, active infection. Investigators are required to evaluate subjects for any signs or symptoms of infection, and also review subjects' diary cards for signs of infection, at scheduled visits (refer to the Time and Events Schedules). If a subject develops a serious infection, including but not limited to sepsis or pneumonia, discontinuation of study treatment must be considered. For active varicella-zoster infection or a significant exposure to varicella-zoster infection in a subject without history of chickenpox, study treatment should be interrupted until the symptoms have resolved and no active infection is present.

If a subject has a clinically important, active infection at the time of a scheduled injection, which cannot be controlled within 10 days, the subjects should be discontinued from the study (Section 10.2).

Early Detection of Active Tuberculosis

To aid in the early detection of TB reactivation or new TB infection during study participation, subjects must be evaluated for signs and symptoms of active TB at scheduled visits (refer to Time and Events Schedules). The following series of questions is suggested for use during the evaluation:

- “Have you had a new cough of >14 days’ duration or a change in a chronic cough?”
- “Have you had any of the following symptoms:
 - Persistent fever?
 - Unintentional weight loss?
 - Night sweats?”
- “Have you had close contact with an individual with active TB?” (If there is uncertainty as to whether a contact should be considered “close,” a physician specializing in TB should be consulted.)

If the evaluation raises suspicion that a subject may have TB reactivation or new TB infection, study drug administration should be interrupted and an immediate and thorough investigation should be undertaken, including, where possible, consultation with a physician specializing in TB.

Investigators should be aware that TB reactivation in immunocompromised subjects may present as disseminated disease or with extrapulmonary features. Subjects with evidence of active TB must immediately discontinue study drug and should be referred for appropriate treatment.

Subjects who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph, a repeat QuantiFERON TB Gold test, a repeat tuberculin skin test in countries in which the QuantiFERON-TB Gold test is not approved/registered or the tuberculin skin test is mandated by local health authorities, and, if possible, referral to a physician specializing in TB to determine the subject's risk of developing active TB and whether treatment for latent TB is warranted. Study drug administration should be interrupted during the investigation. A positive QuantiFERON TB Gold (or tuberculin skin) test result should be considered detection of latent TB. If the QuantiFERON TB Gold Test is indeterminate, the test should be repeated as outlined in Section 9.1.2. If recommended, treatment for latent TB must be initiated before the administration of further study drug. Subjects who discontinue treatment for latent TB prematurely or who are noncompliant with therapy must immediately discontinue further administration of study drug and undergo early termination assessments (Section 10). Refer to [Attachment 1](#) and [Attachment 2](#) for details regarding QuantiFERON-TB Gold and tuberculin skin testing during the study.

Weeks 0 to 8

At Week 0, the investigator will review the inclusion/exclusion criteria to confirm subjects' continuing eligibility for study. Following the assessments indicated in the Time and Events Schedules, all eligible subjects will receive ustekinumab IV induction treatment at Week 0 and then ustekinumab 90 mg SC at Week 8.

Week 16 Randomization

At Week 16, subjects who do not achieve CDAI-70 versus baseline (Week 0) will leave the study. Subjects who remain in the study will be randomized in a 1:1 ratio to either one of two arms for open-label maintenance treatment up to Week 48: the routine care arm or the treat to target arm.

Routine Care Arm: Weeks 16 to 48

In the routine care arm, the timing of maintenance treatment injections will be in compliance with the EU SmPC for ustekinumab for the treatment of Crohn's disease, in which dosing every 12 weeks is recommended. At Week 16, (ie, 8 weeks after the first SC dose), subjects who have not shown adequate response based on the investigator's judgment may receive a second SC dose at that time.

Blood and stool samples will be taken at each maintenance assessment visit. Biomarkers will be assessed in a centralized manner at the end of the study.

During the routine care maintenance treatment period, in case of clinical worsening reported by the subject, consistent with disease flare in the investigator's judgment, clinical assessments of disease flare will be performed at the investigator's discretion. In accordance with the EU SmPC

for ustekinumab, subjects who lose response during 12-weekly dosing may benefit from an adjustment to 8-weekly maintenance treatment. Subjects may subsequently be dosed every 8 weeks or every 12 weeks according to clinical judgment. Information on assessments of disease flare and on the reasons for dosing frequency changes will be documented in the CRF. In contrast, those subjects previously receiving 8-weekly treatment will not be able to adjust the ustekinumab dose following disease flare and will leave the study if they would not benefit from continuing study treatment in the investigator's judgment.

Assessments including video ileocolonoscopy at Week 48 will be performed for all subjects as indicated in the Time and Events Schedules.

Treat to Target Arm: Weeks 16 to 48

In the treat to target arm, all subjects will undergo ileocolonoscopic evaluation at Week 16. Subsequent study assessments will be scheduled according to injection timing, which will be determined by the dosing frequency assigned to subjects. Initial ustekinumab maintenance treatment assignment will be based on centrally-read ileocolonoscopy findings. Subjects with <25% improvement in SES-CD score at Week 16 versus baseline will be assigned to 8-weekly maintenance treatment and will receive ustekinumab 90 mg SC at Week 16. Subjects with $\geq 25\%$ improvement in SES-CD score at Week 16 versus baseline will be assigned to 12-weekly treatment and will receive the next ustekinumab maintenance dose (90 mg SC) at Week 20.

At subsequent assessment visits (ie, from Week 24 for the 8-weekly regimen or from Week 20 for the 12-weekly regimen) ustekinumab maintenance treatment will be directed by treat to target assessments. Among the subgroup of subjects with elevated CRP at baseline (ie, CRP >2.87 mg/L at Week 0) the treatment target will be the achievement of:

- CDAI <220 and ≥ 70 -point improvement in CDAI score from baseline (Week 0)
AND:
 - CRP ≤ 10 mg/L or FC ≤ 250 $\mu\text{g/g}$.

For subjects who do not have elevated CRP at baseline (ie, CRP ≤ 2.87 mg/L at Week 0) in the presence of active disease, CRP would not be considered a biomarker target for dose adjustment, therefore the treatment target for these subjects will be the achievement of:

- CDAI <220 and ≥ 70 -point improvement in CDAI score from baseline (Week 0)
AND
 - FC ≤ 250 $\mu\text{g/g}$.

Subjects meeting the treatment target will continue with the same ustekinumab dosing frequency. However, maintenance dosing frequency will be optimized for all subjects failing to meet the treatment target at the assessment visit. Those subjects previously on 12-weekly regimens will be adjusted to 8-weekly dosing; those previously on 8-weekly regimens will be adjusted to 4-weekly dosing. Among those, subjects subsequently failing to meet the treatment target at the

next assessment visit 4 weeks after dosing will not be able to optimize dosing further and will leave the study.

In case of disease flare between scheduled assessment visits for the treat to target arm, subjects will undergo CDAI and biomarker (CRP and FC) assessments. Dosing frequency will be adjusted as described above for subjects failing to meet the treatment target.

Assessments including video ileocolonoscopy at Week 48 will be performed for all subjects as indicated in the Time and Events Schedules.

Extension Period: Weeks 48 to 104

From Week 48, the frequency of dosing and associated assessment visits will depend on the previous dosing frequency, Week 48 ileocolonoscopy and CDAI findings, and subsequent CDAI and biomarker findings (see Section 3.1, Table 1). In case of disease flare, dosing frequency may be escalated (Section 3.1). Subjects will undergo the assessments indicated in the Time and Events Schedule for the extension period.

Completion of Treatment

For all subjects, Week 104 visit assessments including video ileocolonoscopy will be performed as indicated in the Time and Events Schedule for the extension period.

End of Treatment/Early Withdrawal

In both arms, subjects discontinuing from the study before Week 104 will have the early termination assessments indicated in the Time and Events Schedules, to be performed as close as possible to the time of discontinuation, unless consent is withdrawn. Early termination assessments should include video ileocolonoscopy.

9.1.4. Posttreatment Phase (Follow Up)

All subjects should complete a final safety follow-up visit 16 weeks after their last study drug administration within the study, as outlined in the Time and Events Schedules. Subjects discontinuing from the study will be instructed that study drug will not be made available to them after they have discontinued study drug and that they should return to their primary physician to determine standard of care. For subjects completing the 104-week study and continuing to respond to ustekinumab, it is anticipated that ustekinumab will be commercially available for the treatment of Crohn's disease at the time of study completion. In this case, final safety follow-up assessments should be performed before the first dose of commercially-available ustekinumab. In the event of ustekinumab not being available for some subjects, alternative options will be discussed based on country-specific requirements and regulations (Section 16.1).

Information on subsequent therapies for Crohn's disease, including commercially-available ustekinumab if applicable, will be documented at the final safety follow-up visit.

9.2. Efficacy Evaluations

9.2.1. Crohn's Disease Activity Index

The CDAI will be assessed at the visits indicated in the Time and Events Schedules by collecting information on 8 different Crohn's disease-related variables ([Attachment 3](#) and [Attachment 4](#)). These 8 variables are: extra-intestinal manifestations, abdominal mass, weight, hematocrit, total number of liquid stools, abdominal pain/cramping, use of antidiarrheal drug(s) and/or opiates, and general wellbeing.³ The last 4 variables are scored over 7 days by the subject on a diary card.

9.2.2. C-reactive Protein

Serum CRP has been demonstrated to be useful as a marker of inflammation in patients with IBD. In Crohn's disease, elevated CRP concentrations have been associated with severe clinical activity, elevated sedimentation rate, and active disease as detected by colonoscopy.^{20,21} Blood samples for the measurement of CRP will be collected from all subjects at the visits indicated in the Time and Events Schedules. The serum CRP will be assayed using a validated, high sensitivity CRP assay at a central laboratory.

In the routine care arm, the results of CRP testing during the maintenance period up to Week 48 will not be communicated to the investigator during the study; these data will be analyzed at the end of the study.

In the treat to target arm, CRP will be assessed at every assessment visit to be used by investigators as part of treat to target assessments for the adjustment of maintenance dosing frequency up to Week 48, and in cases of disease flare between assessment visits.

During the extension period, regardless of the original treatment arm, CRP data may be used to guide ustekinumab dosing (eg, for demonstration of biomarker remission in cases requiring a dosing de-escalation, see Section [3.1](#), or in case of disease flare requiring dose escalation).

9.2.3. Fecal Calprotectin

Fecal calprotectin (FC) has been demonstrated to be a sensitive and specific marker in identifying intestinal inflammation and response to treatment in patients with IBD.⁶ Stool samples for FC concentrations will be collected from all subjects at the visits indicated in the Time and Events Schedules. The assay for FC concentration will be performed using a validated method at a central laboratory.

In the routine care arm, the results of FC testing during the maintenance period up to Week 48 will not be communicated to the investigator during the study; these data will be analyzed at the end of the study.

In the treat to target arm, FC will be tested at every assessment visit to be used by investigators as part of treat to target assessments for the adjustment of maintenance dosing frequency up to Week 48, and in cases of disease flare between assessment visits.

During the extension period, regardless of the original treatment arm, FC data may be used to guide ustekinumab dosing (eg, for demonstration of biomarker remission in cases requiring a dosing de-escalation, see Section 3.1, or in case of disease flare requiring dose escalation).

9.2.4. Video Ileocolonoscopy

Ileocolonoscopy will be used to assess SES-CD at the times indicated in the Time and Events Schedules. The SES-CD is a simple, reproducible, and easy-to-use endoscopic scoring system for Crohn's disease, by which endoscopic parameters (ulcer size, ulcerated and affected surfaces, stenosis) are scored from 0 to 3.⁷ In the treat to target arm, initial ustekinumab maintenance treatment assignment will be based on centrally-read ileocolonoscopy findings at Week 16 (Section 3.1). For all subjects, centrally-read SES-CD scores will be used to evaluate endoscopic response (reduction from baseline in SES-CD score $\geq 50\%$) and endoscopic remission (SES-CD score ≤ 2) at Week 48, at Week 104, or at early termination of ustekinumab treatment.

Mucosal healing will be assessed during ileocolonoscopy to determine the presence or absence of mucosal inflammation and ulceration. Video ileocolonoscopies will be assessed by a central facility.

9.2.5. Fistula Assessment

All subjects will be assessed for fistulas at the times indicated in the Time and Events Schedules. For subjects with fistulizing disease, fistula closure will be assessed. Enterocutaneous fistulas (eg, perianal and abdominal) will be considered no longer draining (ie, closed) when there is absence of drainage despite gentle compression. Rectovaginal fistulas will be considered closed based on either physical examination or absence of relevant symptoms (eg, passage of rectal material or flatus from the vagina).

9.2.6. Inflammatory Bowel Disease Questionnaire

The IBDQ ([Attachment 5](#)) is a 32-item self-report questionnaire for subjects with IBD to evaluate the PROs across 4 dimensions: bowel symptoms (loose stools, abdominal pain), systemic symptoms (fatigue, altered sleep pattern), social function (work attendance, need to cancel social events), and emotional function (anger, depression, irritability). Scores range from 32 to 224 with higher scores indicating better outcomes.⁹ The IBDQ questionnaires will be completed at the times indicated in the Time and Events Schedules.

9.2.7. EQ-5D-5L

The EuroQoL-5D-5L Health Questionnaire (EQ-5D-5L; [Attachment 6](#)) is a validated quality-of-life instrument to be completed by the subject. The EQ-5D-5L provides a visual analogue scale to integrate many aspects of the subject's disease process into a single assessment along with targeted quality-of-life questions. It is a non-disease-specific measure of health status that provides a simple descriptive profile and a single index value that can be used in the clinical and economic evaluation of health care and in population health surveys. The EQ-5D-5L questionnaires will be completed at the times indicated in the Time and Events Schedules.

9.2.8. Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)

The FACIT-F scale ([Attachment 7](#)) is a 13-item fatigue scale with a 7-day recall period. It measures the level of fatigue during the usual daily activities. The level of fatigue is measured on a 4-point Likert scale (0=very much fatigued to 4=not at all fatigued). It has been validated in studies of patients with IBD in correlating severity of fatigue with overall health-related QoL as well as disease-specific QoL.¹⁶ The FACIT-F data will be collected at the times indicated in the Time and Events Schedules.

9.2.9. Hospital Anxiety and Depression Scale (HADS)

The HADS ([Attachment 8](#)) is a validated 14-item scale with 7 of the items relating to anxiety and 7 relating to depression. Each item is scored from 0 to 3, with higher scores indicating greater likelihood of depression or anxiety. Cases of anxiety or depression are each defined by subscale scores of 8 or greater, and categorized as normal (score of 0 to 7), mild (score of 8 to 10), moderate (score of 11 to 14), and severe (score of 15 to 21). The recall period is the past week. The HADS takes approximately 2 to 5 minutes to complete.^{4,24} The HADS data will be collected at the times indicated in the Time and Events Schedules.

9.3. Pharmacokinetics and Immunogenicity

Serum samples will be used to evaluate the PK of ustekinumab, as well as the detection and characterization of anti-ustekinumab antibodies. Serum collected for PK and immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period, for further characterization of immunogenicity or for the evaluation of relevant biomarkers. Genetic analyses will not be performed on these serum samples. Subject confidentiality will be maintained.

For IV infusion at Week 0, a sample should be drawn before infusion and approximately 60 minutes after completion of the infusion. At all other assessment visits, blood samples should be collected prior to study drug injection. At visits where serum concentration and antibodies to ustekinumab will be evaluated, 1 blood draw of sufficient volume can be used. Venous blood samples will be collected and each serum sample will be divided into 3 aliquots (1 each for PK, antibodies to study drug, and a backup). Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

9.4. Additional Biomarkers

Additional tests may be performed on the stool samples taken for FC assessments, to test for additional markers related to intestinal inflammation and treatment response such as the microbiome. Genetic analyses will not be performed on biological samples obtained for this study.

9.4.1. Analytical Procedures

Pharmacokinetics

Serum samples will be analyzed to determine concentrations of ustekinumab using a validated, specific, and sensitive method by or under the supervision of the sponsor.

Immunogenicity

The detection and characterization of anti-ustekinumab antibodies will be performed using a validated assay method by or under the supervision of the sponsor. All samples collected for detection of anti-ustekinumab antibodies will also be evaluated for ustekinumab serum concentration to enable interpretation of the antibody data.

9.4.2. Pharmacokinetic Parameters

Serum samples will be used to evaluate various PK parameters.

9.4.3. Immunogenicity Assessments (Anti-ustekinumab antibodies)

Anti-ustekinumab antibodies will be evaluated in serum samples collected from all subjects according to the Time and Events Schedules. Additionally, serum samples should be collected at the final visit from subjects who are discontinued from treatment or withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

Serum samples will be screened for antibodies binding to ustekinumab and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterize the immunogenicity of ustekinumab.

9.5. Medical Resource Utilization and Health Economics

Medical resource utilization, including Crohn's disease-related hospitalizations and Crohn's disease-related surgeries will be collected. Additionally, time lost from work will be collected and the potential impact of ustekinumab on subjects' work and activities, and on daily productivity will be assessed through the Work Productivity and Activity Impairment Questionnaire (WPAI).

9.5.1. Work Productivity and Activity Impairment (WPAI)

The Work Productivity and Activity Impairment (WPAI) questionnaire is a well-validated instrument to measure impairments in work and activities ([Attachment 9](#)).¹⁸ It is a 6-item questionnaire with a 7-day recall period. The WPAI produces 4 types of scores: absenteeism (work time missed), presenteesism (impairment at work/reduced on-the-job effectiveness), work productivity loss (overall work impairment/absenteeism plus presenteeism), and activity impairment. The WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, ie, worse outcomes.

9.5.2. Time Lost From Work

Time lost from work will be collected by asking the subjects a single question, "How many days did you miss from work due to your Crohn's disease in the last 4 weeks?"

9.6. Safety Evaluations

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the CRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the Time and Events Schedules:

Adverse Events

Subjects will complete diary cards during the study to record information on adverse events. Diary cards will be collected and reviewed by the investigator at the times indicated in the Time and Events Schedules. Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. The laboratory reports must be filed with the source documents.

Hematocrit will be tested by the local laboratory at the times indicated in the Time and Events Schedules to enable CDAI evaluations.

At screening, Week 0, Week 48, and Week 104 (or for early termination assessments, if applicable) the following tests will be performed by the local laboratory:

- Hematology Panel
 - hemoglobin
 - hematocrit
 - white blood cell (WBC) count with differential
 - platelet count
- Serum Chemistry Panel
 - sodium
 - potassium
 - chloride
 - blood urea nitrogen (BUN)/urea
 - creatinine
 - aspartate aminotransferase (AST)
 - alanine aminotransferase (ALT)
 - total and direct bilirubin
 - alkaline phosphatase
 - calcium
 - phosphate
 - albumin
 - total protein

Hematology and clinical chemistry tests do not need to be repeated at Week 0 if the screening tests were done \leq 2 weeks previously.

For women of childbearing potential, serum pregnancy testing will be performed at screening and urine pregnancy testing will be performed before each dose of study drug and at the safety follow-up visit.

Electrocardiogram (ECG)

A 12-lead ECG will be performed at screening.

Vital Signs

Vital signs (temperature, pulse/heart rate, blood pressure [systolic and diastolic]) will be assessed at screening and at the times indicated in the Time and Events Schedules. At Week 0, vital signs will be assessed prior to infusion, approximately every 30 minutes during infusion, and twice (at approximately 30-minute intervals) after the completion of infusion.

Physical Examination

While assessment of the subjects' for safety and efficacy requires some physical examination by an investigator at all visits, a more complete, detailed physical exam will be performed at the visits specified in the Time and Events Schedules. Body weight will be assessed at the visits indicated in the Time and Events Schedules.

Concomitant Medication Review

Concomitant medication will be reviewed at each visit.

Infusion Reactions

An infusion reaction is defined as an adverse event that occurs during or within 1 hour following the infusion of study drug, with the exception of laboratory abnormalities. Minor infusion reactions may be managed by slowing the rate of the IV infusion and/or treating with antihistamines and/or acetaminophen (paracetamol) as clinically indicated. If an IV infusion of study drug is stopped because of an infusion reaction and the reaction, in the opinion of the investigator, is not severe or does not result in a serious adverse event (see Section 12.1.1), the infusion may be restarted with caution.

Injection Site Reaction

A study drug injection-site reaction is any adverse reaction at a study drug injection site. The injection sites will be evaluated for reactions and any injection site reactions will be recorded as an adverse event.

Allergic Reactions

Before IV infusion, appropriately trained personnel and medications to treat allergic reactions, including anaphylaxis, must be available. Appropriate medical personnel must be in attendance at the time of the infusion and for at least 1 hour after the start of the IV infusion.

Appropriate medical personnel must remain in close proximity to the infusion center for the remaining duration of the infusion, and for 1 hour after the end of the infusion in the event that emergency resuscitation is required. All subjects must be observed carefully for symptoms of an

allergic reaction (eg, urticaria, itching, hives). If a mild or moderate allergic reaction is observed, acetaminophen, NSAIDs, and/or diphenhydramine may be administered.

In the case of a severe allergic reaction (eg, anaphylaxis), SC aqueous epinephrine, corticosteroids, respiratory assistance, and other proper resuscitative measures are essential and must be available at the study site where the infusion or injections are being given.

Subjects who experience serious adverse reactions related to either an injection or infusion should be discontinued from further study injections. For severe reactions related to the injection or infusion, the subject may be permanently discontinued from further study injections at the discretion of the investigator (refer to Section 10.2).

Subjects who experience reactions following an injection or infusion that result in bronchospasm with wheezing and/or dyspnea that requires ventilatory support, or symptomatic hypotension with a decrease in systolic blood pressure greater than 40 mmHg, will not be permitted to receive additional injections.

Infections

Study drug should not be administered to a subject with a clinically important, active infection. Investigators are required to evaluate subjects for any signs or symptoms of infection, and also review subjects' diary cards for signs of infection, at scheduled visits (refer to the Time and Events Schedules).

If a subject develops a serious infection, including but not limited to sepsis or pneumonia, discontinuation of study treatment must be considered. For active varicella-zoster infection or a significant exposure to varicella-zoster infection in a subject without history of chickenpox, study treatment should be interrupted until the symptoms have resolved and no active infection is present.

Additional Assessments

Assessments for TB and infection will be performed at the visits specified in the Time and Events Schedules. Refer to [Attachment 1](#) and [Attachment 2](#) for details regarding QuantiFERON-TB Gold In-Tube and tuberculin skin testing and to Section 9.1.2 and Section 9.1.3 for additional details regarding TB testing and infections during the study.

9.7. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form. Refer to the Time and Events Schedules for the timing and frequency of all sample collections. Instructions for the collection, handling, and shipment of samples are found in the laboratory manual.

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

10.1. Completion

A subject will be considered to have completed the study if he or she has completed assessments at Week 104.

Subjects who discontinue study treatment for any reason before Week 104 will not be considered to have completed the study.

10.2. Discontinuation of Study Treatment/Withdrawal from the Study

Discontinuation of Study Treatment

If a subject's study treatment must be discontinued before Week 104, the subject should not terminate their study participation. Instead, subjects should return for a final safety visit 16 weeks after the last study drug administration.

A subject's study treatment must be discontinued if:

- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment
- The subject fails to meet the protocol-specified response criteria for continuation of study treatment as described in Section 3.1:
 - A subject fails to demonstrate CDAI improvement of 70 points versus baseline (Week 0) at Week 16
 - Up to Week 48: a subject in the routine care arm, receiving 8-weekly ustekinumab maintenance treatment, experiences disease flare and would not benefit from continuing study treatment in the investigator's judgment
 - Up to Week 48: a subject in the treat to target arm, scheduled to receive 4-weekly ustekinumab maintenance treatment, fails to meet the treatment target (CDAI, and CRP or FC) at the next assessment visit 4 weeks after dosing.
 - At Week 48, a subject receiving 4-weekly ustekinumab treatment demonstrates neither clinical remission nor endoscopic remission.
 - A subject whose dosing was escalated from Week 48 demonstrates neither clinical remission nor endoscopic remission at the next visit.
 - During the extension period, a subject receiving 4-weekly ustekinumab treatment experiences disease flare.
- The subject becomes pregnant or plans a pregnancy within the study period or within 15 weeks after the last study drug administration.
- The subject is deemed ineligible according to the following TB screening criteria:
 - A diagnosis of active TB is made

- A subject has symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination, or has had recent close contact with a person with active TB, and cannot or will not continue to undergo additional evaluation.
- A subject undergoing continued evaluation has a chest radiograph with evidence of current active TB and/or a positive QuantiFERON-TB Gold test result (and/or a positive tuberculin skin test result in countries in which the QuantiFERON-TB Gold is not approved/registered or the tuberculin skin test is mandated by local health authorities) unless active TB can be ruled out and appropriate treatment for latent TB can be initiated before the next administration of study drug and continued to completion. Indeterminate QuantiFERON TB Gold test results should be handled as described in Section 9.1.2. Subjects with persistently indeterminate QuantiFERON-TB Gold test results may continue without treatment for latent TB, if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB) and the subject has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the sponsor's medical monitor and recorded in the subject's source documents and initialed by the investigator.
- A subject receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy.
- The subject has an injection site or infusion reaction resulting in bronchospasm with wheezing and/or dyspnea requiring ventilatory support, or symptomatic hypotension with a >40 mmHg decrease in systolic blood pressure.
- The subject has a malignancy including squamous cell skin cancer. Consideration may be given to allow subjects who develop ≤ 2 basal cell skin cancers that are adequately treated with no evidence of residual disease to continue to receive study drug.
- The subject initiates the following prohibited medications during the study:
 - Immunomodulatory agents other than 6-MP/AZA or MTX
 - Immunomodulatory biologic agents
 - Experimental Crohn's disease medications
- The subject receives ustekinumab outside of the protocol or participates in any other clinical study with an investigational agent.
- The subject has a clinically important active infection at the time of a scheduled injection, which cannot be controlled within 10 days.
- The subject withdraws consent for administration of study drug.
- The subject has Crohn's disease-related surgery (with the exception of drainage of an abscess or seton placement).

If a subject discontinues study treatment for any reason before Week 48, the early termination assessments indicated in the Time and Events Schedules should be performed as close as possible to the time of discontinuation.

Withdrawal From the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow up
- Withdrawal of consent
- Death
- Sponsor decision.

Subjects who terminate study participation will not be required to return for any follow-up assessments; however, these subjects should complete the Early Termination assessments specified in the Time and Events Schedules at the time they terminate study participation.

If a subject is lost to follow up, every reasonable effort must be made by the study-site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced.

10.3. Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for future research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the ICF.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

All statistical tests will be 2-sided at a significance level of 0.05 unless otherwise specified.

Baseline for all analyses will be the day of the start of study treatment unless otherwise specified.

An interim analysis will be performed as soon as all enrolled subjects have completed the first 16 weeks of the study or discontinued earlier. Further details of the interim analyses are provided in Section 11.6.

The main analysis will be performed when all randomized subjects have completed 48 weeks of study treatment or discontinued earlier.

The final analysis will be performed when all subjects have completed the last study-related visit including the follow up.

11.1. Subject Information

The intent-to-treat (ITT) population will be defined as all subjects who sign informed consent and who are not screening failures. The interim analysis will be based on this ITT population.

The main analysis population will be the modified intent-to-treat (mITT) population defined as all subjects in the ITT population randomized to one of the 2 maintenance treatment arms. Efficacy analysis for the 48-week treatment phase will be performed for this mITT population. Safety analysis for the 48-week treatment phase will be based on subjects in the mITT who receive at least one dose of study treatment in the maintenance period.

The final analysis population will be based on all subjects in the mITT population who enter the extension phase (m2ITT). Efficacy analysis for the 104-week treatment phase will be based on this m2ITT population. Safety analysis for the 104-week treatment phase will also be based on subjects in the m2ITT population who receive at least one dose of study treatment in the extension period.

If there are a substantial number of protocol violators that affect efficacy outcomes (eg, >10%), an additional per protocol analysis may be performed and will be pre-specified in the Statistical Analysis Plan.

11.2. Sample Size Determination

The primary endpoint of this study is endoscopic response at Week 48 of the study. Endoscopic response is defined as showing (yes or no) a reduction from baseline in the SES-CD score of $\geq 50\%$.

This study is designed to show that the percentage of subjects with endoscopic response at Week 48 in the treat to target arm is 15% higher compared with the routine care arm, which is considered to be a clinically meaningful difference. Based on the results of the Phase 3 IM-UNITI study, endoscopic response in the routine care arm is estimated at 30% of subjects. Endoscopic response in the treat to target arm is estimated at 45% of subjects.

A Fisher's exact test with a 0.050 two-sided significance level will have 80% power to detect the difference between the routine care arm proportion of 30% and the treat to target arm proportion of 45% when the sample size in each group is 174. With an estimated CDAI-70 response at Week 16 between 65% and 70%, and a dropout rate between 10% and 17.5%, a total of 650 subjects should be enrolled.

11.3. Efficacy Analyses

11.3.1. Primary Endpoint

The primary efficacy endpoint is endoscopic response at Week 48, defined as showing (yes or no) a reduction from baseline in SES-CD score of $\geq 50\%$. Randomized subjects who stop treatment before reaching Week 48 due to any reason, or subjects without endoscopic data at Week 48 will be analyzed as nonresponders. The number and percentage of responders will be summarized by treatment group and compared using the Fisher exact test.

11.3.2. Secondary Endpoints

The endpoints listed below will be observed values at all visits assessed and at endpoint (last observation carried forward [LOCF]) and changes from baseline for continuous/ordinal variables unless otherwise specified.

The following secondary efficacy endpoints will be analyzed within each arm and compared between the 2 arms:

- Endoscopic response at Week 48, defined as showing (yes or no) a reduction from baseline in SES-CD score of $\geq 50\%$. Randomized subjects who stop treatment before reaching Week 48 due to reasons other than lack/loss of efficacy will be excluded from the analysis.
- Endoscopic response defined as a reduction from baseline in SES-CD score of $\geq 50\%$ at endpoint (LOCF).
- Endoscopic remission defined as SES-CD score ≤ 2 at Week 48 and endpoint (LOCF).
- Mucosal healing defined as the complete absence of mucosal ulcerations in any ileocolonic segment at Week 48 and endpoint (LOCF).
- Clinical remission defined as CDAI score of < 150 points.
- Clinical response defined as ≥ 100 -point reduction from the baseline CDAI score, or a CDAI score < 150 .
- The following will be analyzed both for the whole mITT population, and for those subjects who were receiving corticosteroids at baseline:
 - Corticosteroid-free clinical remission.
 - Corticosteroid-free endoscopic response (endoscopic response defined as a reduction from baseline in SES-CD score of $\geq 50\%$).
- Serum CRP.
- FC.

In addition, changes from baseline for the following health-related QoL, PROs and pharmacoeconomic endpoints will be analyzed:

- IBDQ (also the percentage of subjects with a 16-point change from baseline).
- EQ-5D-5L.
- FACIT-F.
- HADS.
- Time lost from work.
- WPAI (also the % subjects with a 7-point change from baseline for each domain).

For subjects with fistulas at baseline, exploratory analyses will include fistula response (defined as $\geq 50\%$ reduction from baseline in the number of draining fistulas) at Week 48, Week 104, and endpoint (LOCF).

Exploratory analyses of Crohn's disease-related hospitalizations and Crohn's disease-related surgery will be performed.

Exploratory analyses for subjects treated beyond Week 48 in the extension period will include:

- Endoscopic response at Week 104 and endpoint (LOCF), defined as showing (yes or no) a reduction from baseline in SES-CD score of $\geq 50\%$. Randomized subjects who stop treatment for any reason before reaching Week 104, or subjects without endoscopic data at Week 104, will be analyzed as nonresponders. A separate analysis will exclude subjects who stop treatment before reaching Week 104 due to reasons other than lack/loss of efficacy.
- Endoscopic remission defined as SES-CD score ≤ 2 at Week 104 and endpoint (LOCF).
- Mucosal healing defined as the complete absence of mucosal ulcerations in any ileocolonic segment at Week 104 and endpoint (LOCF).
- Clinical remission defined as a CDAI score of < 150 points.
- Clinical response defined as a ≥ 100 -point reduction from the baseline CDAI score, or a CDAI score of < 150 points.
- Corticosteroid-free clinical remission.
- Corticosteroid-free endoscopic response (endoscopic response defined as a reduction from baseline in SES-CD score of $\geq 50\%$).
- Serum CRP.
- FC.
- Changes from baseline for health-related QoL and pharmacoeconomic endpoints (IBDQ, EQ-5D-5L, FACIT-F, HADS, time lost from work, WPAI).
- Clinical and biomarker remission (CDAI score of < 150 points, CRP ≤ 10 mg/L, and FC ≤ 250 $\mu\text{g/g}$) at Week 104 and endpoint (LOCF).
- Durations of corticosteroid-free clinical remission and biomarker remission, durations of remission after dose de-escalation, and time from first de-escalation to first re-escalation.

The exploratory analyses for subjects treated in the extension period will be based on the total group. If the two arms (treat to target and routine care) contain substantial numbers of subjects, an additional descriptive analysis per arm (without between-group comparison) might be considered. Subsequently, results from the extension period might also be explored per dosing regimen at the start of the extension period.

Changes from baseline throughout the study and observed values for continuous/ordinal efficacy variables (eg, PRO data) will be summarized descriptively at each assessment time point and at the subject's last efficacy evaluation (endpoint). The change from baseline at each visit and at endpoint will be analyzed using the Wilcoxon signed rank test. When applicable, between-group comparisons will be analyzed by means of the Wilcoxon 2-sample test. Summary tabulations will display the number of observations, mean, standard deviation, median, minimum, maximum and 95% confidence interval (CI) overall and, if applicable by treatment group.

For categorical variables (eg, response rates), the number and percentage per category will be summarized overall, and if applicable by treatment group including between-group comparison using the Fisher exact test.

11.4. Pharmacokinetic/Immunogenicity/Pharmacodynamic Analyses

Exploratory analyses of the PK, immunogenicity, and PD of study treatment will include:

- Characterization of the PK and immunogenicity of ustekinumab in subjects with Crohn's disease
- Assessment of the relationship between systemic ustekinumab exposure and:
 - clinical outcomes, including CDAI measures.
 - changes in CRP and FC.
 - endoscopic outcomes.

11.5. Safety Analyses

Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are adverse events with onset during the treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported adverse events will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate.

Analyses of adverse events in this study will include:

- Frequency and type of adverse events.
- Frequency and type of serious adverse events.
- Frequency and type of reasonably related adverse events.
- Frequency and type of adverse events leading to discontinuation of study drug.
- Frequency of infusion reactions
- Frequency of injection-site reactions.
- Frequency and type of infections, including infections requiring oral or parenteral antimicrobial treatment.
- Frequency and type of serious infections.

Information evaluated for the above events of interest will include: time of onset, duration of events, time to resolution, concomitant therapies, and relationship to ustekinumab.

Listings of subjects with serious adverse events and adverse events leading to discontinuation of study drug will also be provided. Any deaths, malignancies, or major cardiovascular events will either be presented in a listing or described in the clinical study report.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Changes from baseline results will be presented in pre- versus post-treatment cross-tabulations (with classes for below, within, and above normal ranges). A listing of subjects with any laboratory results outside the reference ranges will be provided.

Vital Signs

Descriptive statistics of temperature, pulse/heart rate, and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits will be summarized.

Physical Examination

Frequency tabulations of the abnormalities will be made at each scheduled time point.

11.6. Interim Analysis

When all subjects have completed the first 16 weeks of the study or discontinued earlier an interim analysis will be performed for publication purposes. This analysis will provide relevant information on the benefit:risk of ustekinumab in subjects who have received their first ustekinumab IV injection (approximately 6 mg/kg) at the start of the study (Week 0) and the second ustekinumab SC injection (90 mg) at Week 8. In addition, a subgroup of subjects (those randomized to the treat to target arm) will undergo endoscopy at Week 16 per protocol. These data will also be analyzed, further expanding the knowledge of the effect of ustekinumab on endoscopic outcomes.

The Interim population will consist of all subjects enrolled in the study who receive at least one study treatment. Results will be presented for the entire population. Subject characteristics and a selection of efficacy and safety endpoints will be included in this interim analysis. Endoscopic outcomes at Week 16 will be analyzed for subjects in the treat to target arm.

11.7. Steering Committee

A steering committee provided consulting oversight during protocol development and will do so during the course of the study to ensure the scientific validity of the clinical study, to identify any scientifically relevant trends, and to provide recommendations to the sponsor. The steering committee serves as an expert advisory group. Any final strategic decision will belong to the sponsor.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product (definition per International Conference on Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to Section 12.3.1, All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
(The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For ustekinumab, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

Adverse Event Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section [12.1.2](#), Attribution Definitions.

12.1.2. Attribution Definitions

Not Related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest on a sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Accidental or occupational exposure to a sponsor study drug
- Any failure of expected pharmacologic action (ie, lack of effect) of a sponsor study drug
- Unexpected therapeutic or clinical benefit from use of a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)
- Exposure to a sponsor study drug from breastfeeding

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

12.3. Procedures

12.3.1. All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure, which may include contact for follow up of safety. Serious adverse events, including those spontaneously reported to the investigator within 16 weeks after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Anticipated events will be recorded and reported as described in [Attachment 10](#).

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology

(eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

For all studies with an outpatient phase, including open-label studies, the subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Any other information that is required

12.3.2. Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be made by facsimile (fax).

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available

- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

The cause of death of a subject in a study, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

12.3.3. Events of Special Interest

Any newly identified malignancy or case of active TB occurring after the first administration of study drug(s) in subjects participating in this clinical study must be reported by the investigator according to the procedures in Section 12.3.2. Investigators are also advised that active TB is considered a reportable disease in most countries. These events are to be considered serious only if they meet the definition of a serious adverse event.

12.3.4. Pregnancy

All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must discontinue further study treatment.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

Solution for Intravenous Infusion

Ustekinumab for IV injection is supplied as a sterile solution in a single-use glass vial. Each vial contains 130 mg ustekinumab in 26 mL. The solution is clear, colorless to light yellow. The aqueous medium contains L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate 80, L-methionine and EDTA disodium salt dihydrate at a pH of 6.0. No preservatives are present.

Ustekinumab for IV injection should only be used for the IV induction dose at Week 0 of the study (Section 6).

Solution for Injection for Subcutaneous Administration

The ustekinumab for SC injection supplied for this study is a sterile solution in a single-use prefilled syringe (PFS). Each PFS contains 90 mg ustekinumab in 1.0 mL of liquid. The solution is clear to slightly opalescent, colorless to light yellow. The aqueous medium contains L-histidine, L-histidine hydrochloride, sucrose, and polysorbate 80 at a pH of 6.0. No preservatives are present. The needle cover on the PFS contains dry natural rubber.

Details regarding the study drug are provided in the Pharmacy Manual/Site Investigational Product and Procedures Manual.

14.2. Packaging

The study drug will be uniquely packaged to ensure that it is appropriately managed throughout the supply chain process.

14.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

All study drug must be stored at controlled temperatures ranging from 2°C to 8°C, not frozen, and protected from light. The solution in the vial or PFS should not be shaken. Prior to administration, the solution should be inspected visually for particulate matter and discoloration. The solution should not be used if it is discolored or cloudy, or if foreign particulate matter is present.

Study drug in glass vials and PFS will be ready to use. The pharmacist (or designated personnel) will prepare the required volume of study drug using the appropriate vials or PFS.

Aseptic procedures must be used during the preparation and administration of the ustekinumab solution for IV injection.

After Week 8, following proper training in SC injection technique, subjects may self-administer ustekinumab for SC injection at the times instructed by the investigator. Study site personnel will instruct subjects on how to store study drug for at-home use as indicated for this protocol.

Refer to the Pharmacy Manual/Site Investigational Product and Procedures Manual for additional guidance on study drug preparation, handling, and storage.

14.5. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The study drug administered to the subject, or dispensed to the subject, and the return of study drug from the subject (if applicable), must be documented on the drug accountability form. Subjects must be instructed to return all original containers, whether empty or containing study drug. All study drug will be stored and disposed of according

to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug must be available for verification by the sponsor's study site monitor during on-site monitoring visits. If applicable, the return to the sponsor of unused study drug, will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator's Brochure
- EU SmPC for ustekinumab for the treatment of Crohn's disease
- Pharmacy Manual/Site Investigational Product and Procedures Manual
- Laboratory Manual
- IWRS Manual
- Manual for electronic data capture (eDC)
- Sample ICF
- Paper PRO questionnaires
- Contact information page
- Subject diaries
- Subject study card

Samples of the following assessments are included as attachments to the protocol:

- CDAI
- IBDQ

- EQ-5D-5L
- FACIT-F
- HADS
- WPAI

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the World Health Organisation (450 mL once every 2 months, up to a maximum of 3 L over 12 consecutive months for blood donation).

This study will be conducted only in those countries where ustekinumab has been submitted for registration for the treatment of Crohn's disease and where the intent is to make ustekinumab available in the market. It is anticipated that ustekinumab will be commercially available for the treatment of Crohn's disease in subjects continuing to respond to ustekinumab at the time of study completion. Nevertheless, ustekinumab may not be available for some subjects completing the 104-week study, depending on regulatory approval and reimbursement timelines. In this event, alternative options will be discussed based on country-specific requirements and regulations.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation.

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study

- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB.

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent

Each subject (or a legally acceptable representative if applicable) must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects or their legally acceptable representatives if applicable the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her Crohn's disease. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject or legally acceptable representative is authorizing such access. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed.

The subject or legally acceptable representative will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent

should be appropriately recorded by means of either the subject's or his or her legally acceptable representative's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

If the subject or legally acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject or legally acceptable representative is obtained.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject (or his or her legally acceptable representative) includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory biomarker, PK, and immunogenicity research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand ustekinumab, to understand Crohn's disease, to understand differential intervention responders, and to develop tests/assays related to ustekinumab and Crohn's disease. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.3, Withdrawal From the Use of Samples in Future Research).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study drug to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license).

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth (as allowed by local regulations). In cases where the subject is not enrolled into the study, the date seen and date of birth (as allowed by local regulations) will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

An electronic source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. These data are electronically extracted for use by the sponsor. If an electronic source is utilized, references made to the CRF in the protocol include the electronic source system but information collected through the electronic source may not be limited to that found in the CRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documents. Data must be entered into CRF in English. The CRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review CRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The study is considered completed with the last visit for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject visit at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study drug development

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding ustekinumab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of ustekinumab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Results of exploratory analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish

information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

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Attachment 1: QuantiFERON-TB Gold Testing

The QuantiFERON-TB Gold test is one of the interferon- γ (IFN- γ) based blood assays for TB screening (Cellestis, 2016). It utilizes the recently identified *M. tuberculosis*-specific antigens ESAT-6 and CFP-10 in the standard format, as well as TB7.7 (p4) in the In-Tube format, to detect in vitro cell-mediated immune responses in infected individuals. The QuantiFERON-TB Gold assay measures the amount of IFN- γ produced by sensitized T-cells when stimulated with the synthetic *M. tuberculosis*-specific antigens. In *M. tuberculosis*-infected persons, sensitized T lymphocytes will secrete IFN- γ in response to stimulation with the *M. tuberculosis*-specific antigens and, thus, the QuantiFERON-TB Gold test should be positive. Because the antigens used in the test are specific to *M. tuberculosis* and not found in BCG, the test is not confounded by BCG vaccination, unlike the tuberculin skin test. However, there is some cross-reactivity with the 3 Mycobacterium species, *M. kansasii*, *M. marinum*, and *M. szulgai*. Thus, a positive test could be the result of infection with one of these 3 species of Mycobacterium, in the absence of *M. tuberculosis* infection.

In a study of the QuantiFERON-TB Gold test (standard format) in subjects with active TB, sensitivity was shown to be approximately 89% (Mori et al, 2004). Specificity of the test in healthy BCG-vaccinated individuals has been demonstrated to be more than 98%. In contrast, the sensitivity and specificity of the tuberculin skin test was noted to be only about 66% and 35% in a study of Japanese patients with active TB and healthy BCG-vaccinated young adults, respectively. However, sensitivity and specificity of the tuberculin skin test depend on the population being studied, and the tuberculin skin test performs best in healthy young adults who have not been BCG-vaccinated.

Data from a limited number of published studies examining the performance of the QuantiFERON-TB Gold assay in immunosuppressed populations suggest that the sensitivity of the QuantiFERON-TB Gold test is better than the tuberculin skin test even in immunosuppressed patients (Ferrara et al, 2005; Kobashi et al, 2007; Matulis et al, 2008). The ability of IFN- γ -based tests to detect latent infection has been more difficult to study due to the lack of a gold standard diagnostic test; however, several TB outbreak studies have demonstrated that the tests correlated better than the tuberculin skin test with the degree of exposure that contacts had to the index TB case (Brock et al, 2004; Ewer et al, 2003). In addition, TB contact tracing studies have shown that patients who had a positive QuantiFERON-TB Gold test result and were not treated for latent TB infection were much more likely to develop active TB during longitudinal follow up than those who had a positive tuberculin skin test and a negative QuantiFERON-TB Gold test result (Higuchi et al, 2007; Diel et al, 2008).

Although the performance of the new IFN- γ -based blood tests for active or latent *M. tuberculosis* infection have not been well validated in the immunosuppressed population, experts believe these new tests will be at least as, if not more, sensitive, and definitely more specific, than the tuberculin skin test (Barnes, 2004; personal communication, April, 2008 TB Advisory Board).

Performing the QuantiFERON-TB Gold Test

The QuantiFERON-TB Gold test In-Tube format will be provided for this study. The In-Tube format contains 1 additional *M. tuberculosis*-specific antigen, TB7.7 (p4), which is thought to increase the specificity of the test.

To perform the test using the In-Tube format, blood is drawn through standard venipuncture into supplied tubes that already contain the *M. tuberculosis*-specific antigens. Approximately 3 tubes will be needed per subject, each requiring 1 mL of blood. One tube contains the *M. tuberculosis*-specific antigens, while the remaining tubes contain positive and negative control reagents. Thorough mixing of the blood with the antigens is necessary prior to incubation. The blood is then incubated for 16 to 24 hours at 37°C, after which tubes are centrifuged for approximately 15 minutes at 2000 to 3000 g. Following centrifugation, plasma is harvested from each tube, frozen, and shipped on dry ice to the laboratory. The laboratory will perform an ELISA to quantify the amount of IFN- γ present in the plasma using spectrophotometry and computer software analysis.

The laboratory will analyze and report results for each subject, and sites will be informed of the results. Subjects who have an indeterminate result should have the test repeated.

Adherence to Local Guidelines

Local country guidelines for immunocompromised patients should be consulted for acceptable antituberculous treatment regimens for latent TB. If no local country guidelines for immunocompromised patients exist, ECCO guidelines must be followed.

In countries in which the QuantiFERON-TB Gold test is not considered approved/registered, a tuberculin skin test is recommended but not additionally required if tuberculin is not available.

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Attachment 2: Tuberculin Skin Testing**Administering the Mantoux Tuberculin Skin Test**

The Mantoux tuberculin skin test (CDC, 2000) is the standard method of identifying persons infected with *Mycobacterium tuberculosis*. Multiple puncture tests (Tine and Heaf) should not be used to determine whether a person is infected because the amount of tuberculin injected intradermally cannot be precisely controlled. Tuberculin skin testing is both safe and reliable throughout the course of pregnancy. The Mantoux tuberculin test is performed by placing an intradermal injection of 0.1 mL of tuberculin into the inner surface of the forearm. The test must be performed with tuberculin that has at least the same strength as either 5 tuberculin units (TU) of standard purified protein derivative (PPD)-S or 2 TU of PPD-RT 23, Statens Serum Institut, as recommended by the World Health Organization. PPD strengths of 1 TU or 250 TU are not acceptable (Menzies, 2000). Using a disposable tuberculin syringe with the needle bevel facing upward, the injection should be made just beneath the surface of the skin. This should produce a discrete, pale elevation of the skin (a wheal) 6 mm to 10 mm in diameter. To prevent needle-stick injuries, needles should not be recapped, purposely bent or broken, removed from disposable syringes, or otherwise manipulated by hand. After they are used, disposable needles and syringes should be placed in puncture-resistant containers for disposal. Institutional guidelines regarding universal precautions for infection control (eg, the use of gloves) should be followed. A trained health care worker, preferably the investigator, should read the reaction to the Mantoux test 48 to 72 hours after the injection. Subjects should never be allowed to read their own tuberculin skin test results. If a subject fails to show up for the scheduled reading, a positive reaction may still be measurable up to 1 week after testing. However, if a subject who fails to return within 72 hours has a negative test, tuberculin testing should be repeated. The area of induration (palpable raised hardened area) around the site of injection is the reaction to tuberculin. For standardization, the diameter of the induration should be measured transversely (perpendicular) to the long axis of the forearm. Erythema (redness) should not be measured. All reactions should be recorded in millimeters, even those classified as negative.

Interpreting the Tuberculin Skin Test Results

In many countries, the most conservative definition of positivity for the tuberculin skin test is reserved for immunocompromised patients, and this definition is to be applied in this study to maximize the likelihood of detecting latent TB, even though the subjects may not be immunocompromised at baseline.

An induration of 5 mm or greater in response to the intradermal tuberculin skin test is considered to be a positive result and evidence for either latent or active TB.

Country-specific guidelines **for immunocompromised patients** should be consulted for the interpretation of tuberculin skin test results. If no local country guidelines for immunocompromised patients exist, the ECCO guidelines must be followed.

Treatment of Latent Tuberculosis

Local country guidelines **for immunocompromised patients** should be consulted for acceptable antituberculous treatment regimens for latent TB. If no local country guidelines for immunocompromised patients exist, ECCO guidelines must be followed.

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Attachment 3: Crohn's Disease Activity Index (Sample)

<u>DISEASE ACTIVITY INDEX</u>	<u>SUM</u>	<u>X FACTOR</u>	<u>SUBTOTAL</u>
Total number of liquid or very soft stools in the previous 7 days	<u> </u>	<u>x 2</u>	<u> </u>
Sum abdominal pain/cramps ratings (total for previous 7 days):	<u> </u>	<u>x 5</u>	<u> </u>
0 = none 2 = moderate 1 = mild 3 = severe			
General well being (total for previous 7 days): 0 = generally well 3 = very poor 1 = slightly under par 4 = terrible 2 = poor	<u> </u>	<u>x 7</u>	<u> </u>
Categories currently present and <u>presumed to be related to Crohn's disease</u> : 0 = no; 1 = yes			
<input type="checkbox"/> = arthritis/arthralgia	<u> </u>	<u>x 20</u>	<u> </u>
<input type="checkbox"/> = iritis/uveitis	<u> </u>	<u>x 20</u>	<u> </u>
<input type="checkbox"/> = erythema nodosum/pyoderma gangrenosum/aphthous stomatitis	<u> </u>	<u>x 20</u>	<u> </u>
<input type="checkbox"/> = anal fissure, fistula or abscess	<u> </u>	<u>x 20</u>	<u> </u>
<input type="checkbox"/> = other fistula	<u> </u>	<u>x 20</u>	<u> </u>
<input type="checkbox"/> = fever over 100° F (37.8° C) during the previous 7 days.	<u> </u>	<u>x 20</u>	<u> </u>
During the previous 7 days has subject received antidiarrheal therapy at least once:			
OR	<u> </u>	<u>x 30</u>	<u> </u>
During the previous 7 days has subject received opiate therapy on each of the 7 days:			
0 = no 1 = yes			
Abdominal mass:	<u> </u>	<u>x 10</u>	<u> </u>
0 = none 2 = questionable 5 = definite			
Hematocrit:	<u> </u>	<u>x 6</u>	<u> </u>
Males: (47-Hct) = SUM	(add or subtract by sign)		
Females: (42-Hct) = SUM			
*			
<u>(Standard Weight - Actual Body Weight)</u> x 100 =	<u> </u>	<u>x 1</u>	<u> </u>
Standard Weight	(add or subtract by sign, round to 3 decimal places)		

* If this value is less than -10 then enter -10 here.

Standard weight and actual weight must be in same units (kg or lb)

TOTAL =
(round total to integer)

Attachment 4: Standard Weight Table (Sample)

Actual Height Inches (cm)	Standard Weight in Pounds Men (kg)	Standard Weight in Pounds Women (kg)
58.0 (147.3)		115.0 (52.2)
58.5 (148.6)		116.0 (52.6)
59.0 (149.9)		117.0 (53.1)
59.5 (151.1)		118.3 (53.6)
60.0 (152.4)		119.5 (54.2)
60.5 (153.7)		120.8 (54.8)
61.0 (154.9)		122.0 (55.3)
61.5 (156.2)		123.5 (56.0)
62.0 (157.5)	136.0 (61.7)	125.0 (56.7)
62.5 (158.8)	137.0 (62.1)	126.5 (57.4)
63.0 (160.0)	138.0 (62.6)	128.0 (58.0)
63.5 (161.3)	139.0 (63.0)	129.5 (58.7)
64.0 (162.6)	140.0 (63.5)	131.0 (59.4)
64.5 (163.8)	141.3 (64.1)	132.5 (60.1)
65.0 (165.1)	142.5 (64.6)	134.0 (60.8)
65.5 (166.4)	143.8 (65.2)	135.5 (61.4)
66.0 (167.6)	145.0 (65.8)	137.0 (62.1)
66.5 (168.9)	146.5 (66.4)	138.5 (62.8)
67.0 (170.2)	148.0 (67.1)	140.0 (63.5)
67.5 (171.5)	149.5 (67.8)	141.5 (64.2)
68.0 (172.7)	151.0 (68.5)	143.0 (64.9)
68.5 (174.0)	152.5 (69.2)	144.5 (65.5)
69.0 (175.3)	154.0 (69.8)	146.0 (66.2)
69.5 (176.5)	155.5 (70.5)	147.5 (66.9)
70.0 (177.8)	157.0 (71.2)	149.0 (67.6)
70.5 (179.1)	158.5 (71.9)	150.5 (68.3)
71.0 (180.3)	160.0 (72.6)	152.0 (68.9)
71.5 (181.6)	161.8 (73.4)	153.5 (69.6)
72.0 (182.9)	163.5 (74.1)	155.0 (70.3)
72.5 (184.2)	165.3 (75.0)	
73.0 (185.4)	167.0 (75.7)	
73.5 (186.7)	169.0 (76.6)	
74.0 (188.0)	171.0 (77.5)	* Height in shoes with one-inch heels
74.5 (189.2)	172.8 (78.4)	* Indoor clothing weighing 5 pounds for men and 3 pounds for women
75.0 (190.5)	174.5 (79.1)	
75.5 (191.8)	176.8 (80.2)	* Centimeters x 0.3937 = inches
76.0 (193.0)	179.0 (81.2)	* Pounds x 0.4535 = kilograms

Attachment 5: Inflammatory Bowel Disease Questionnaire (IBDQ)**For Regulatory Submissions Only**INSTRUCTIONS FOR SELF-ADMINISTERED IBDQ

This questionnaire is designed to measure the effects of your inflammatory bowel disease on your daily function and quality of life. You will be asked about symptoms you have been having as a result of your bowel disease, the way you have been feeling in general, and how your mood has been.

There are two versions of this questionnaire - IBDQ and IBDQ-Stoma. If you have a colostomy or ileostomy, you should complete the IBDQ-Stoma. Questions 1, 5, 17, 22, 24 and 26 are slightly different in each version. Be sure you have the correct questionnaire.

On this questionnaire there are 32 questions. Each question has a graded response numbered from 1 through 7. Please read each question carefully and answer the number which best describes how you have been feeling in the past 2 weeks.

EXAMPLE

How often have you felt unwell as a result of your bowel problem in the past 2 weeks?

- 1 **ALL OF THE TIME**
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME

If you are having trouble understanding a question, **STOP** for a moment! Think about what the question means to you. How is it affected by your bowel problem? Then answer the question as best you can. You will have the chance to ask the nurse questions after completing the questionnaire. This takes only a few minutes to complete.

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For Regulatory Submissions Only**QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)**

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.

1. How frequent have your bowel movements been during the last two weeks? Please indicate how frequent your bowel movements have been during the last two weeks by picking one of the options from

- 1 BOWEL MOVEMENTS AS OR MORE FREQUENT THAN THEY HAVE EVER BEEN
- 2 EXTREMELY FREQUENT
- 3 VERY FREQUENT
- 4 MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
- 5 SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
- 6 SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
- 7 NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME

3. How often during the last 2 weeks have you felt frustrated, impatient, or restless? Please choose an option from

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME

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For Regulatory Submissions Only

IBDQ

4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

5. How much of the time during the last 2 weeks have your bowel movements been loose? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

6. How much energy have you had during the last 2 weeks? Please choose an option from

1 NO ENERGY AT ALL
2 VERY LITTLE ENERGY
3 A LITTLE ENERGY
4 SOME ENERGY
5 A MODERATE AMOUNT OF ENERGY
6 A LOT OF ENERGY
7 FULL OF ENERGY

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For Regulatory Submissions Only

IBDQ

7. How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem? Please choose an option from

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME

8. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME

9. How often during the last 2 weeks have you been troubled by cramps in your abdomen? Please choose an option from

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME

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For Regulatory Submissions Only

IBDQ

10. How often during the last 2 weeks have you felt generally unwell? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

11. How often during the last 2 weeks have you been troubled because of fear of not finding a washroom? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from

1 A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE
2 A LOT OF DIFFICULTY
3 A FAIR BIT OF DIFFICULTY
4 SOME DIFFICULTY
5 A LITTLE DIFFICULTY
6 HARDLY ANY DIFFICULTY
7 NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES

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For Regulatory Submissions Only

IBDQ

13. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME

14. How often during the last 2 weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night? Please choose an option from

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME

15. How often during the last 2 weeks have you felt depressed or discouraged? Please choose an option from

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME

16. How often during the last 2 weeks have you had to avoid attending events where there was no washroom close at hand? Please choose an option from

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME

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For Regulatory Submissions Only	
6	HARDLY ANY OF THE TIME
7	NONE OF THE TIME

IBDQ

17. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of gas? Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

18. Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to the weight you would like to be at? Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

19. Many patients with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. In general, how often during the last 2 weeks have you felt worried or anxious? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

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IBDQ

20. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating? Please choose an option from

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME

21. How often during the last 2 weeks have you felt relaxed and free of tension? Please choose an option from

- 1 NONE OF THE TIME
- 2 A LITTLE OF THE TIME
- 3 SOME OF THE TIME
- 4 A GOOD BIT OF THE TIME
- 5 MOST OF THE TIME
- 6 ALMOST ALL OF THE TIME
- 7 ALL OF THE TIME

22. How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements? Please choose an option from

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME

23. How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem? Please choose an option from

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME

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For Regulatory Submissions Only	
6	HARDLY ANY OF THE TIME
7	NONE OF THE TIME

IBDQ

24. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

25. How much of the time during the last 2 weeks have you felt tearful or upset? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

26. How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

27. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME

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b A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

IBDQ

28. To what extent has your bowel problem limited sexual activity during the last 2 weeks?
Please choose an option from

1 NO SEX AS A RESULT OF BOWEL DISEASE
2 MAJOR LIMITATION AS A RESULT OF BOWEL DISEASE
3 MODERATE LIMITATION AS A RESULT OF BOWEL DISEASE
4 SOME LIMITATION AS A RESULT OF BOWEL DISEASE
5 A LITTLE LIMITATION AS A RESULT OF BOWEL DISEASE
6 HARDLY ANY LIMITATION AS A RESULT OF BOWEL DISEASE
7 NO LIMITATION AS A RESULT OF BOWEL DISEASE

29. How much of the time during the last 2 weeks have you been troubled by nausea or feeling sick to your stomach? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

30. How much of the time during the last 2 weeks have you felt irritable? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

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For Regulatory Submissions Only

IBDQ

31. How often during the past 2 weeks have you felt a lack of understanding from others?
Please choose an option from

- 1 ALL OF THE TIME
- 2 MOST OF THE TIME
- 3 A GOOD BIT OF THE TIME
- 4 SOME OF THE TIME
- 5 A LITTLE OF THE TIME
- 6 HARDLY ANY OF THE TIME
- 7 NONE OF THE TIME

32. How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks? Please choose one of the following options from

- 1 VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
- 2 GENERALLY DISSATISFIED, UNHAPPY
- 3 SOMEWHAT DISSATISFIED, UNHAPPY
- 4 GENERALLY SATISFIED, PLEASED
- 5 SATISFIED MOST OF THE TIME, HAPPY
- 6 VERY SATISFIED MOST OF THE TIME, HAPPY
- 7 EXTREMELY SATISFIED, COULD NOT HAVE BEEN MORE HAPPY OR PLEASED

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Attachment 6: EuroQoL-5D-5L Health Questionnaire (EQ-5D-5L) – Sample UK English Version



Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about	<input type="checkbox"/>
I have slight problems in walking about	<input type="checkbox"/>
I have moderate problems in walking about	<input type="checkbox"/>
I have severe problems in walking about	<input type="checkbox"/>
I am unable to walk about	<input type="checkbox"/>

SELF-CARE

I have no problems washing or dressing myself	<input type="checkbox"/>
I have slight problems washing or dressing myself	<input type="checkbox"/>
I have moderate problems washing or dressing myself	<input type="checkbox"/>
I have severe problems washing or dressing myself	<input type="checkbox"/>
I am unable to wash or dress myself	<input type="checkbox"/>

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

I have no problems doing my usual activities	<input type="checkbox"/>
I have slight problems doing my usual activities	<input type="checkbox"/>
I have moderate problems doing my usual activities	<input type="checkbox"/>
I have severe problems doing my usual activities	<input type="checkbox"/>
I am unable to do my usual activities	<input type="checkbox"/>

PAIN / DISCOMFORT

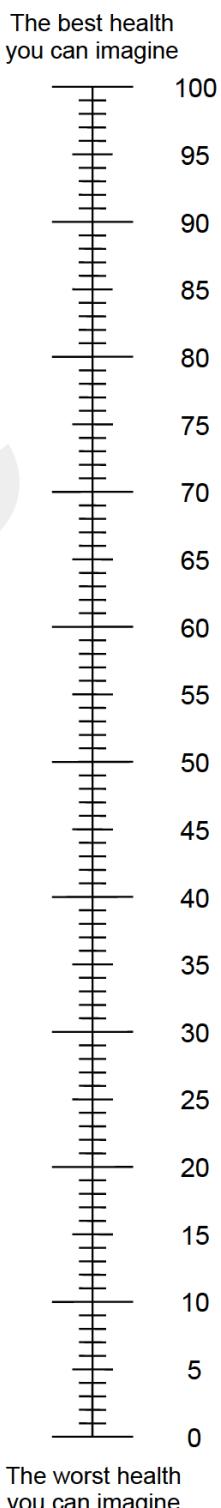
I have no pain or discomfort	<input type="checkbox"/>
I have slight pain or discomfort	<input type="checkbox"/>
I have moderate pain or discomfort	<input type="checkbox"/>
I have severe pain or discomfort	<input type="checkbox"/>
I have extreme pain or discomfort	<input type="checkbox"/>

ANXIETY / DEPRESSION

I am not anxious or depressed	<input type="checkbox"/>
I am slightly anxious or depressed	<input type="checkbox"/>
I am moderately anxious or depressed	<input type="checkbox"/>
I am severely anxious or depressed	<input type="checkbox"/>
I am extremely anxious or depressed	<input type="checkbox"/>

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =



Attachment 7: Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) [Sample]**Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale (Version 4)**

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

		Not At All	A Little Bit	Somewhat	Quite a Bit	Very Much
1	I feel fatigued	0	1	2	3	4
2	I feel weak all over	0	1	2	3	4
3	I feel listless ("washed out")	0	1	2	3	4
4	I feel tired	0	1	2	3	4
5	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
6	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
7	I have energy	0	1	2	3	4
8	I am able to do my usual activities	0	1	2	3	4
9	I need to sleep during the day	0	1	2	3	4
10	I am too tired to eat	0	1	2	3	4
11	I need help doing my usual activities	0	1	2	3	4
12	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
13	I have to limit my social activity because I am tired	0	1	2	3	4

Scoring: Items are scored as follows: 4=Not At All; 3=A Little Bit; 2=S somewhat; 1=Quite A Bit; 0=Very Much, EXCEPT items #7 and #8 which are reversed scored. Score range 0-52. A score of less than 30 indicates severe fatigue. The higher the score, the better the quality of life.

Item Number	Reverse Item?		Item Response	Item Score
1	4	-	-	-
2	4	-	-	-
3	4	-	-	-
4	4	-	-	-
5	4	-	-	-
6	4	-	-	-
7	0	+	-	-
8	0	+	-	-
9	4	-	-	-
10	4	-	-	-
11	4	-	-	-
12	4	-	-	-
13	4	-	-	-

Sum individual item scores: _____

Multiply by 18: _____

Divide by number of items answered: _____

Source: <http://www.facit.org/FACITOrg/Questionnaires>

Attachment 8: Hospital Anxiety and Depression Scale (HADS) [Sample]**Hospital Anxiety and Depression Scale (HADS)**

Instructions: Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he or she will be able to help you more. This questionnaire is designed to help your doctor know how you feel. Read each item and circle the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.

I feel tense or 'wound up':	A	I feel as if I am slowed down:	D
Most of the time	3	Nearly all of the time	3
A lot of the time	2	Very often	2
Time to time, occasionally	1	Sometimes	1
Not at all	0	Not at all	0
I still enjoy the things I used to enjoy:	D	I get a sort of frightened feeling like 'butterflies in the stomach':	A
Definitely as much	0	Not at all	0
Not quite so much	1	Occasionally	1
Only a little	2	Quite often	2
Not at all	3	Very often	3
I get a sort of frightened feeling like something awful is about to happen:	A	I have lost interest in my appearance:	D
Very definitely and quite badly	3	Definitely	3
Yes, but not too badly	2	I don't take as much care as I should	2
A little, but it doesn't worry me	1	I may not take quite as much care	1
Not at all	0	I take just as much care as ever	0
I can laugh and see the funny side of things:	D	I feel restless as if I have to be on the move:	A
As much as I always could	0	Very much indeed	3
Not quite so much now	1	Quite a lot	2
Definitely not so much now	2	Not very much	1
Not at all	3	Not at all	0
Worrying thoughts go through my mind:	A	I look forward with enjoyment to things:	D
A great deal of the time	3	A much as I ever did	0
A lot of the time	2	Rather less than I used to	1
From time to time but not too often	1	Definitely less than I used to	3
Only occasionally	0	Hardly at all	2
I feel cheerful:	D	I get sudden feelings of panic:	A
Not at all	3	Very often indeed	3
Not often	2	Quite often	2
Sometimes	1	Not very often	1
Most of the time	0	Not at all	0

I can sit at ease and feel relaxed:	A	I can enjoy a good book or radio or TV programme:	D
Definitely	0	Often	0
Usually	1	Sometimes	1
Not often	2	Not often	2
Not at all	3	Very seldom	3

Questions relating to anxiety are indicated by an 'A' while those relating to depression are shown by a 'D'. Scores of 0-7 in respective subscales are considered normal, with 8-10 borderline and 11 or over indicating clinical 'caseness'

Attachment 9: Work Productivity and Activity Impairment (WPAI) [Sample]**Work Productivity and Activity Impairment Questionnaire:
CROHN'S DISEASE (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 fill in the blanks or circle a number, as indicated.*

1. Are you currently in paid employment? _____ NO _____ YES
NO, tick "NO" and skip to question 6.

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?

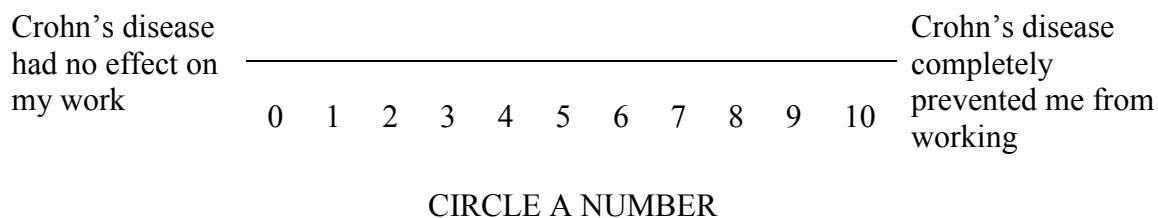
_____ HOURS

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

_____ HOURS *(If "0", skip to question 6)*

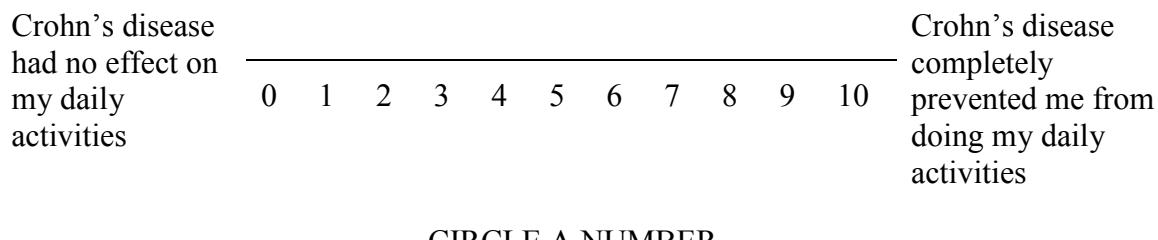
5. During the past seven days, how much did your Crohn's disease affect your productivity while you were working?

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.



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.



WPAI-CD (UK English)

Attachment 10: Anticipated Events**Anticipated Event**

An anticipated event is an adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease-related) or background regimen.

For the purposes of this study the following events will be considered anticipated events:

Adverse Events Associated with the Study Population

- Adverse events related to symptoms of Crohn's disease
- Adverse events related to worsening or progression of Crohn's disease

Reporting of Anticipated Events

All adverse events will be recorded in the CRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described in Section 12.3.1, All Adverse Events. Any anticipated event that meets serious adverse event criteria will be reported to the sponsor as described in Section 12.3.2, Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the sponsor will report these events in an expedited manner.

Serious adverse events relating to lack of efficacy (eg, events attributed to Crohn's disease or related symptoms such as abdominal pain, diarrhea, nausea, vomiting, fistula, and rectal bleeding) or progression of the disease under study (ie, stenosis, stricture, ileus, or bowel obstruction) will not be reported as 15 day SUSARs (with the exception of fistula complications or fistula events that are indicated by the investigator to represent infections).

Anticipated Event Review Committee (ARC)

An Anticipated Event Review Committee (ARC) will be established to perform reviews of prespecified anticipated events at an aggregate level. The ARC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The ARC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study drug.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan (ASMP).

Attachment 11: Risk/Benefit Assessment of the Investigational Medicinal Product Dossier

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2. OVERALL RISK AND BENEFIT ASSESSMENT**2.1. Overall Rationale for the study**

Inflammatory bowel diseases (IBD) are chronic, progressive, and disabling conditions. Most current strategies, which target control of symptoms, do not appear to significantly alter the natural course of the disease. Recent studies in Crohn's disease underscore the need to look beyond symptoms and to treat endoscopic/macrosopic lesions, ultimately with the aim of preventing structural damage and disability. Due to the invasive nature and/or cost of endoscopies or cross-sectional imaging, frequent repetition of these procedures is not feasible; therefore, surrogate biomarkers of inflammation, including CRP and fecal calprotectin (FC) have been increasingly studied in IBD.^{3,9,10}

A 'treat to target' strategy has been advocated as an optimized management approach for various diseases, by which strictly defined treatment targets facilitate decision making in clinical practice. Key to the success of this treatment strategy is the definition of appropriate treatment targets and adoption of algorithms that drive therapeutic changes within distinct time frames. This approach has been shown to be successful in chronic, immune-mediated inflammatory disorders such as rheumatoid arthritis and psoriatic arthritis. Recently, the value of such an approach in patients' management has been suggested for IBD.^{1,7}

The goal of this study of adult Crohn's disease subjects treated with ustekinumab is to demonstrate that a maintenance strategy based on early endoscopy followed by regular assessment of biomarkers (FC and CRP) and clinical symptoms (CDAI) with subsequent adjustment of treatment in case of persistent inflammatory disease activity (failure to achieve the target) is more successful in achieving endoscopic improvement than a pragmatic maintenance strategy based on guidance provided in the EU SmPC for the use of ustekinumab in Crohn's disease.

2.2. Summary of Data and Guidance for Investigators

For a summary of the important nonclinical and clinical data and the description of specific tests, observations, and precautions that may be required for a clinical study with Stelara, please refer to Section 5 of the current Stelara IB.

2.3. Study STARDUST (CNTO1275CRD3005)

The sponsor plans to conduct the STARDUST (CNTO1275CRD3005) study titled: "Study of Treat to Target Versus Routine Care Maintenance Strategies in Crohn's Disease Patients Treated with Ustekinumab". For the most comprehensive information on the STARDUST (CNTO1275CRD3005) study, please refer to the study protocol.

2.3.1. Dose Justification

Consistent with the approved EU SmPC¹⁰ for ustekinumab in Crohn's disease, all subjects will receive tiered, weight-based IV induction dosing, which was demonstrated to be well tolerated and effective in the UNITI-1 and UNITI-2 induction studies. Subsequently, subjects randomized to the routine care arm will receive an ustekinumab maintenance dosing regimen consistent with the approved EU SmPC, based on either 12-weekly or 8-weekly 90 mg SC dosing, the positive benefit/risk profile of which was demonstrated by the 44-week IM-UNITI study. Maintenance

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treatment in the treat to target arm will also involve initial assignment to 12-weekly or 8-weekly 90 mg SC treatment, which in this arm will be based on endoscopic results at Week 16. However, within the treat to target approach, there is the potential for more intensive management, with optimization to 4-weekly dosing for subjects failing to meet treatment targets following 8-weekly dosing. Real-world experience of more intensive maintenance dosing regimens than those assessed in the IM-UNITI study has been reported for Crohn's disease patients.^{1,5,12} For example, the GETAID experience from France, reported a quite heterogeneous pattern of maintenance schedules including about 15% of patients on 4-weekly dosing with an overall clinical benefit at 6 months of 65% and a good safety profile.¹² Similarly, in the Spanish cohort about 12% of patients were on 4-weekly dosing and 4% on 2-weekly dosing with an overall clinical benefit at 12 months of 64%; adverse events were reported in 9.5% of cases but none required ustekinumab withdrawal.⁵ Another example comes from Canada where after more than 6 months of treatment, 78% (n=59) of patients were on 4-weekly dosing with no safety issues.¹ Additionally, ustekinumab 90 mg SC every 4 weeks was reported to be well tolerated in a Phase 2 study of patients with multiple sclerosis.⁸

After Week 8, 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.

2.4. Potential Benefits of STELARA (ustekinumab) in the Treatment of Crohn's Disease

The benefit of ustekinumab in the treatment of adult patients with moderately to severely active Crohn's disease has been established based on the results of the 3 Phase 3 studies (UNITI-1 and UNITI-2 induction studies and the 44-week IM-UNITI study). Ustekinumab has been recently approved in Europe and the U.S. for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, were intolerant to, or have medical contraindications to either: conventional therapy, or TNF α antagonist therapy.

A 'treat to target' strategy as an optimized management approach has been shown to be successful in chronic, immune-mediated inflammatory disorders.

The goal of this study of adult Crohn's disease subjects treated with ustekinumab is to demonstrate that a maintenance strategy based on early endoscopy followed by regular assessment of biomarkers (fecal calprotectin [FC], C reactive protein [CRP]) and clinical symptoms (Crohn's disease activity index [CDAI]) with subsequent adjustment of treatment in case of persistent inflammatory disease activity (failure to achieve the target) is more successful in achieving endoscopic improvement than a pragmatic maintenance strategy driven by the EU SmPC for the use of ustekinumab in Crohn's disease.

The sponsor believes that a maintenance strategy based on early endoscopy followed by regular assessment of biomarkers and clinical symptoms with subsequent adjustment of treatment in case of persistent inflammatory disease activity may provide a significant addition to the therapeutic options for the treatment of moderate to severe Crohn's disease in adults.

2.5. Risk Management

The risk profile of ustekinumab is well-established, with the product having been approved for more than 8 years and the cumulative worldwide exposure to ustekinumab from launch to 31 December 2015 is 551,966 person-years. There are some (potential) risks associated with ustekinumab, and the product is labeled accordingly. These risks include infections, malignancies and hypersensitivity reactions. Subjects in this study will be subject to these same risks, but there is no reason to believe the magnitude of risk would be higher in these subjects than in any other Crohn's disease patients receiving ustekinumab.

The potential risks indicated above will be mitigated by a program that includes the following:

- Judicious inclusion/exclusion criteria.
- Guidelines for subject management.
- Prohibited concomitant medications
- Comprehensive medical monitoring of data by the Sponsor during the conduct of the trial

The known risks of ustekinumab, as described in the Stelara SmPC sections 4.4 and 4.8, are addressed in the protocol in line with the precautions described in section 4.4 of the ustekinumab SmPC. Additionally, ustekinumab 90 mg SC every 4 weeks was reported to be well tolerated in a Phase 2 study of patients with multiple sclerosis and in real world use.

2.6. Conclusion: Overall Benefit and Risk Assessment

Inflammatory bowel diseases (IBD), such as Crohn's Disease, are chronic, progressive, and disabling conditions. Most current strategies, which target control of symptoms, do not appear to significantly alter the natural course of the disease. There is a significant medical need for new safe and effective therapies for moderate to severe, active Crohn's disease.

Inhibition of IL-12 and IL-23 and associated inflammatory pathways constitutes a novel mechanism of action for the treatment of Crohn's disease. The therapeutic potential of this approach is evident from nonclinical and clinical data of ustekinumab, including the findings of recent Phase 3, double-blind, placebo controlled studies. Ustekinumab has been recently approved in Europe and the U.S. for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, were intolerant to, or have medical contraindications to either: conventional therapy, or TNF α antagonist therapy.

Recent studies in Crohn's disease underscore the need to look beyond symptoms and to treat endoscopic/macroscopic lesions, ultimately with the aim of preventing structural damage and disability. Due to the invasive nature and/or cost of endoscopies or cross sectional imaging, frequent repetition of these procedures is not feasible; therefore, surrogate biomarkers of inflammation, including CRP and fecal calprotectin (FC) have been increasingly studied in IBD.

The sponsor believes that a maintenance strategy based on early endoscopy followed by regular assessment of biomarkers (FC and CRP) and clinical symptoms (CDAI) with subsequent

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adjustment of treatment in case of persistent inflammatory disease activity may provide a significant addition to the therapeutic options for the treatment of moderate to severe Crohn's disease in adults.

Ustekinumab is a drug with known risks and extensive experience has been gained over the past 8 years in delineating these risks, and learning how to evaluate and manage them. Using this approach, the benefit-risk profile of ustekinumab has remained positive in appropriately selected patients. Any potential safety risks associated with the use of ustekinumab are managed in this study by appropriate protocol eligibility criteria, subject management procedures, and careful safety monitoring (Section 2.5). The Sponsor believes that the extensive safety database of ustekinumab, the judicious inclusion/exclusion criteria and the established risk mitigation measures largely support the safe use of ustekinumab in the proposed CNTO1275CRD3005 study.

In conclusion, the evaluation of the "treat to target" strategy of ustekinumab in the treatment of moderate to severe Crohn's disease in the proposed study is deemed reasonable based on the overall benefit-risk profile observed to date in the clinical studies completed in adult moderate to severe Crohn's disease, the safety data from the approved indications in adult psoriasis, PsA and adolescent psoriasis, and data from clinical studies in various other immunologic indications.

4. REFERENCES

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INVESTIGATOR AGREEMENT

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____
Institution and Address: _____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____
Institution and Address: _____

Telephone Number: _____
Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): Valentina Tornatore MD
Institution: PPD Janssen-Cilag Italy PPD _____
Signature: PPD _____ Date: 30.11.2017
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.