Janssen Research & Development *

Clinical Protocol

A Phase 4, Multicenter, Open-label Study of Serum Infliximab Concentrations and Efficacy and Safety of Dose Escalation in Pediatric Patients with Inflammatory Bowel Disease

ADAPT

Protocol C0168IBD4020; Phase 4
Amendment 3

Remicade® (infliximab)

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

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	03 August 2015
Amendment 1	25 January 2016
Amendment 2	07 December 2016
Amendment 3	20 February 2018

Amendment 3 (20 February 2018)

This amendment is considered 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 reasons for the amendment are to:

- Clarify several entry criteria
- Extend the screening period
- Add details for corticosteroid tapering
- Include complete instructions to ensure safety procedures related to any potential cases of hepatotoxicity
- Update text describing informed consent procedures

Edits and additions to original text are noted in bold, and deletions are noted in strikeout.

Applicable Section(s)	Description of Change(s)
Rationale: The Screening period has been extended from 14 ± 7 days to 28 days to ensure time for screening laboratory tests to be returned, to assess eligibility.	
4, Patient Population (also reflected in the Time and Events Schedule, Screening column and Note 1); 9.2, Study Procedures	Screening for eligible patients will be performed within **28** ~~14 ± 7~~ days before the Week 0 administration of infliximab. The maximum acceptable visit window for all visits ~~including~~ **after the** Screening **visit** is ± 7 days.
Rationale: The inclusion criterion pertaining to prior use of infliximab is being modified to align with standard of care.	

Applicable Section(s)	Description of Change(s)
4.1, Inclusion Criteria, #10; 2 sub-bullets added for (both) Patients in the Dose Escalation Group and Patients in the Reference Group Also reflected in 3.1, Overview of Study Design for (both) Patients in the Dose Escalation Group and Patients in the Reference Group	**Patients who have received an induction regimen with doses greater than 6 mg/kg must have received at least 2 maintenance doses of 5 mg/kg q8wk (the last 2 doses occurring at least 48 days, but no more than 64 days, apart, with allowable dose range of 4.5 to 6 mg/kg) and have demonstrated a clinical response for at least 28 days after the most recent (second or later) 5 mg/kg maintenance dose according to the criteria in Attachment 3 for CD patients or Attachment 4 for UC patients** **Patients who have received maintenance doses greater than 6 mg/kg within the past 6 months must have received at least 2 maintenance doses of 5 mg/kg q8wk (the last 2 doses occurring at least 48 days, but no more than 64 days, apart, with allowable dose range of 4.5 to 6 mg/kg) and have demonstrated a clinical response for at least 28 days after the most recent (second or later) 5 mg/kg maintenance dose according to the criteria in Attachment 3 for CD patients or Attachment 4 for UC patients**
Synopsis, Patient Population; 4.1, Inclusion Criteria, #10d for Patients in Dose Escalation Group	Must have lost clinical response, according to the criteria in **Attachment 3** for CD patients or **Attachment 4** for UC patients, after the first or subsequent q8wk maintenance dose of infliximab 5 mg/kg, **for patients who have completed the recommended infliximab induction dosing regimen (5 mg/kg at weeks 0, 2, and 6) or, after the most recent (second or later) q8wk maintenance dose of infliximab 5 mg/kg for patients with an induction regimen with doses >6 mg/kg or for patients with previous maintenance doses >6 mg/kg**
Rationale: The exclusion criterion pertaining to prior medications is being clarified.	
4.2, Exclusion Criteria, #11d	Any **immunosuppressant biologic** ~~investigational~~ drug (**approved or investigational** ~~including investigational vaccines, vedolizumab, ustekinumab, etc.~~) within 4 weeks prior to first administration of infliximab or within 5 half-lives of the investigational agent, whichever is longer, or is currently enrolled in an **interventional** ~~investigational~~ study
Rationale: Since corticosteroid tapering is permitted in this study, a recommended corticosteroid dose tapering schedule is being added to the protocol to ensure uniform treatment for all patients.	

Applicable Section(s)	Description of Change(s)
8, Prestudy and Concomitant Therapy	**For patients in *both* the Dose Escalation and the Reference Group:** **Treatment with and tapering of corticosteroids (including budesonide) is at the discretion of the investigator. For those patients whom the investigator determines it is appropriate to taper the use of corticosteroids and budesonide, the following tapering schedule is recommended:** **<u>Recommended tapering schedule for oral corticosteroids (other than budesonide)</u>** • **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 at 2.5 mg/week until 0 mg/day.** • **Dose ≤ 10 mg/day prednisone or equivalent: taper daily dose by 2.5 mg/week until 0 mg/day.** **<u>Recommended tapering schedule for oral budesonide</u>** **Patients receiving budesonide should have their daily dose tapered by 3 mg every 3 weeks until 0 mg/day.**
Rationale: Details for recording stools for the PCDAI are being clarified to ensure accurate PCDAI scores are collected.	
9.1, Screening, 5th paragraph	**CD patients (or their legally acceptable representatives) will be instructed to ensure that liquid stools reported on the PCDAI are indeed loose or watery.**
Rationale: An endpoint is being added to specify the analyses that will be performed for clinical and pharmacokinetic results.	
9.3.2, Endpoints, Secondary Endpoints	**Other pharmacokinetic and clinical remission secondary endpoint: The relationship between trough infliximab levels and clinical remission at Week 16 will be analyzed with the Reference Group and the Dose Escalation Group patients in a combined analysis**
11.4, Serum Infliximab Concentrations and Antibodies to Infliximab, new 5th paragraph	**The relationship between trough infliximab levels and clinical remission at Week 16 will be analyzed with the Reference Group and the Dose Escalation Group patients in a combined analysis.**
Rationale: To ensure patient safety, detailed instructions for the management of patients with elevated hepatic enzymes at screening or during the study are being added.	
4.1, Inclusion Criteria, #6e	Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels not exceeding 2.0 times the upper limit of normal. **If patients have ALT or AST levels between the ULN and 2x the ULN, clinically appropriate evaluations must be performed (and documented in the record) prior to enrollment to rule out etiologies that would contraindicate treatment with infliximab.**

Applicable Section(s)	Description of Change(s)
9.5.2, Clinical Laboratory Tests	• **Abnormal liver function tests. If laboratory testing for a patient who is enrolled in the study and receiving study drug reveals an increase of serum aminotransferases (ALT or AST) to >3 x ULN and an increase of bilirubin to >2 x ULN, study agent administration should be suspended immediately. In addition, laboratory tests for ALT, AST, alkaline phosphatase, and total bilirubin should be confirmed by a retest within 24 hours if possible, but no later than 72 hours after notification of test results. See** Attachment 5 **(Liver Safety: Suggested Actions and Follow-up Assessments) for additional information on monitoring and assessment of abnormal liver function tests.** **During the study, all abnormal laboratory values will require further explanation from the investigator. Clinically significant abnormal laboratory values should be repeated until they return to normal or are otherwise explained by the investigator.**
10.2, Discontinuation of Study Treatment (new bullet)	• **Severe hepatic function abnormalities, as described in Section 9.5 and** Attachment 5
Attachment 5 added: (Liver Safety: Suggested Actions and Follow-up Assessments)	The Guideline Algorithm for Monitoring, Assessment, and Evaluation of Abnormal Liver Tests in Participants with No Underlying Liver Disease and Normal Baseline ALT, AST, Alkaline Phosphatase, and Bilirubin was added along with instructions for procedures to be followed in cases of potential lover toxicity. This information is based on the FDA Guidance for Industry, "Drug Induced Liver Injury: Premarketing Clinical Evaluation".
Rationale: To ensure consistency with screening procedures, instructions are being added to ensure that both informed consents and assents are obtained for all patients.	
16.2.4, Privacy of Personal Data, 3rd paragraph	**Written informed consent must be obtained from the patient's parent or legal guardian, and assent must be obtained from the patient. Informed consent and assent must be obtained for this study by the principal investigator or designee prior to conducting any protocol-specific procedure.**
Rationale: The table for enrollment eligibility based on hepatitis B and C status (in Attachment 2) is being updated (and reformatted) to provide additional clarity.	
Attachment 2: Table for "Eligibility based on hepatitis C and B virus test results"	(added): **Not eligible: Seropositive for antibodies to hepatitis C virus**.
Rationale: The screening procedure regarding PCDAI and Mayo scores is being updated to align with the standard of care and to acknowledge that disease status may change slightly between screening and Week 0.	
Time and Events Schedule, footnote r; and footnote w added	For calculation of PCDAI at **Screening and/or** Week 0….. **The Week 0 PCDAI or partial Mayo score should be the highest of any values obtained during a period of up to 28 days prior to, or including, Week 0.**
Rationale: All references to the Investigator's Brochure are being changed to references to the local label since the sponsor is now using the local labels rather than the Investigator's Brochure for all trials involving Remicade.	

Applicable Section(s)	Description of Change(s)
Throughout the protocol	….~~Investigator's Brochure~~ **local label**….

Amendment 2 (07 Dec 2016)

This amendment is considered 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: The overall reasons for the amendment are to:

- Modify the inclusion criteria (for PCDAI and partial Mayo score) to ensure adequate disease severity
- Define loss of response
- Obtain history of infliximab treatment at initiation, time of response and loss of response, including number of infliximab doses, for the Dose Escalation group
- Define "initial response"
- Add 2 secondary endpoints (and the corresponding analyses), to evaluate any association between *clinical remission/response*
- Revise wording for several entry criteria, for clarity
- Correct or clarify inadvertent errors

Changes reflect feedback from the Food and Drug Administration (FDA) received in August 2016. Edits and additions to original text are noted in bold, and deletions are noted in strikeout.

Applicable Section(s)	Description of Change(s)
Rationale: In line with the FDA Type C meeting Written Response Only (WRO) feedback received on 26 August 2016, clinical response has been more clearly defined in the newly added Attachment 3 (for patients with Crohn's disease [CD]) and Attachment 4 (for patients with ulcerative colitis [UC]). The conditions and evidence of response for both CD and UC are defined using clinical signs and symptoms, eg, an assessment by the patient's physician.	
Synopsis, Patient Population, Patients in the Dose Escalation Group; and a similar change in Section 3.1, Overview of Study Design, Dose Escalation Group	a. Must have completed the recommended infliximab induction dosing regimen …. and have demonstrated a clinical response according to ~~the investigator's assessment~~ **the criteria in** Attachment 3 **for CD patients or** Attachment 4 **for UC patients** b. Must have lost clinical response, according to ~~the investigator's assessment~~ **the criteria in** Attachment 3 **for CD patients or** Attachment 4 **for UC patients…**
Synopsis, Patient Population, Patients in the Reference Group; and Section 3.1, Overview of Study Design, Reference Group	a. Must have completed the recommended infliximab induction dosing regimen of 5 mg/kg at weeks 0, 2, and 6 and have **achieved and** maintained a stable clinical response* to infliximab after at least 1 maintenance dose of 5 mg/kg q8wk **according to the criteria in** Attachment 3 **for CD patients or** Attachment 4 **for UC patients** …. * Patients with a stable clinical response to infliximab are defined as those patients who have achieved clinical response **according to criteria in** Attachment 3 **for CD patients or** Attachment 4 **for UC patients** and who did not initiate or receive increased doses of 5-aminosalicylic acid (5-ASA), corticosteroids, immunomodulators or antibiotics for the treatment of IBD for 4 weeks prior to screening.

Applicable Section(s)	Description of Change(s)
Section 4.1 Inclusion Criterion #10,	
Patients in the Dose Escalation Group:	a. Must have completed the recommended infliximab induction dosing regimen … and have demonstrated a clinical response according to ~~the investigator's assessment~~ **the criteria in** Attachment 3 **for CD patients or** Attachment 4 **for UC patients**. b. Must have lost clinical response, according to ~~the investigator's assessment~~ **the criteria in** Attachment 3 **for CD patients or** Attachment 4 **for UC patients**…..
Patients in the Reference Group:	a. Must have completed the recommended infliximab induction dosing regimen… and have maintained a stable clinical response* **according to the criteria in** Attachment 3 **for CD patients or** Attachment 4 **for UC patients**…. * Patients with a stable clinical response to infliximab are defined as those patients who have achieved clinical response **according to criteria in** Attachment 3 **for CD patients or** Attachment 4 **for UC patients** and who did not initiate or receive increased doses of 5-aminosalicylic acid (5-ASA), corticosteroids, immunomodulators or antibiotics for the treatment of IBD for 4 weeks prior to screening.
Rationale: In line with the FDA Type C Meeting WRO feedback received on 26 August 2016, baseline assessments will include assessment and collection of qualitative and quantitative signs and symptoms present at initiation of on-study infliximab therapy.	
Synopsis, Overview of Study Design, Paragraph 2, Sentence 1; and Section 3.1, Overview of Study Design, Paragraph 4, Sentence 1	After obtaining informed consent/assent, detailed demographic and medical history, **including qualitative and quantitative signs and symptoms present at initiation of infliximab therapy and the time of response,** will be collected on all patients meeting inclusion and exclusion criteria at the time of enrollment.
Rationale: Per discussions between the Sponsor and the FDA, the Sponsor is modifying the inclusion criteria for the PCDAI and partial Mayo score in lieu of the requirement of ileocolonoscopy, for the Dose Escalation Group.	
Synopsis, Patient Population, Patients in the Dose Escalation Group; Section 4.1, Inclusion Criterion #10, Patients in Dose Escalation Group	f. Must have a PCDAI of > 30 points **with both an abdominal pain and stool frequency sub-score of ≥ 5** (patients with CD) g. Must have a partial Mayo score of ≥ 5 points **with both stool frequency and rectal bleeding sub-scores of ≥ 1** (patients with UC)
Rationale: Screening procedures for the Dose Escalation group are being revised to also account for infliximab concentrations.	
Time and Events Schedule, footnote i; and added to Section 4.1, Inclusion Criteria as footnote for Inclusion criterion #10e and 10h for the Dose Escalation group	For patients undergoing screening for the Dose Escalation Group, those who do not meet entry criteria based on **infliximab concentration and/or** fecal calprotectin and/or CRP levels may have repeat **infliximab concentration and/or** fecal calprotectin and/or CRP levels performed during the screening process, provided that all entry criteria are met within 14 days prior to administration of the first 10 mg/kg dose of infliximab.

Applicable Section(s)	Description of Change(s)
Rationale: Per the FDA Type C Meeting WRO received on 26 August 2016, the Sponsor is adding 2 secondary endpoints (and the corresponding analyses), to evaluate any association between Wong-Baker FACES scale results with abdominal pain PCDAI sub-score in patients with Crohn's disease, and with clinical response.	
Synopsis, Secondary Endpoints, Other secondary efficacy endpoints; Section 9.3.2 Endpoints, Secondary Endpoints, Other Secondary Efficacy Endpoints	**3. Correlates of Wong-Baker FACES scale with clinical remission and response at Week 16** **4. The association between abdominal pain PCDAI sub-score and the Wong-Baker FACES scale for CD patients**
Section 11.3.2 Analyses for the Secondary Endpoints, Paragraphs 3 and 4	**The Sponsor will analyze how the Wong-Baker FACES scale correlates with clinical remission/response by performing a logistical regression to evaluate the association between Wong-Baker FACES scale and clinical response at Week 16.** **In a secondary analysis, an ordinary regression model will be used to evaluate the association between abdominal pain PCDAI sub-score and Wong-Baker FACES scale for CD patients.**
Rationale: A clarification to the full body, physical examination is being made.	
Time and Events Schedule, Row for Physical Examination	Physical examination ~~(including skin examination)~~
Time and Events Schedule, footnote g; Section 9.5.3, Physical Examination and Vital Signs, Paragraph 1	Complete physical examinations (~~excluding genitourinary examination but~~ including skin **and genitourinary** examination) are to be conducted.
Rationale: Consent for the collection of the stool sample has been clarified.	
Time and Events Schedule, footnote d added for Informed consent/assent	**Pre-screening stool sample consent may be obtained prior to the screening visit per local or site requirements.**

Applicable Section(s)	Description of Change(s)
Time and Events Schedule, row for Stool Culture; footnote h added	h. **Sample to be collected at or up to 24 hours prior to screening visit (with completion of appropriate stool sample consent), however, if not done, patient/caregiver may collect at home and return to the site within 24 hours of collection. The following medications should be avoided for 48 hours prior to the sample collection: antacids, barium, bismuth, antidiarrheal medication, and oily laxatives. Please refer to the Covance laboratory manual for further instructions.**
Section 9.1, Screening Procedures	**Pre-screening stool sample consent may be obtained prior to the screening visit per local or site requirements.**
Section 17.4, Source Documentation	At a minimum, source documentation must be available for the following to confirm data collected in the CRF: patient identification, eligibility, and study identification; study discussion and date of signed study **and (if applicable) pre-screening stool sample collection** informed consents;….
Rationale: A correction to the entry criteria regarding prior maintenance doses is being made, that was erroneous in Protocol Amendment 1.	
Synopsis, Patient Population, Patients in the Dose Escalation Group; Section 4.1, Inclusion Criteria, #10 - Patients in Dose Escalation Group	b. Must have lost clinical response, according to the criteria in Attachment 3 for CD patients or Attachment 4 for UC patients, after the **first** ~~second~~ or subsequent q8wk maintenance dose of infliximab 5 mg/kg
Rationale: An entry criterion regarding immunization is being changed to avoid unnecessary blood draws if proof of prior immunization is available.	
Section 4.1, Inclusion Criteria, #8	~~Must have positive protective antibody titers to varicella and measles prior to the first administration of infliximab at Week 0~~ **Must have acceptable evidence of immunity to measles and varicella prior to the administration of infliximab at Week 0, including any of the following:** **(a) Documentation of age-appropriate vaccination for varicella and/or measles (that includes two doses of each vaccine), or** **(b) Verification of past varicella and/or measles infection by a healthcare provider (school or occupational clinic nurse, nurse practitioner, physician assistant, or physician), or** **(c) In the absence of (a) or (b) for varicella and/or measles, must have documentation of positive protective antibody titers (performed prior to or during screening) to varicella and/or measles.**
Time and Events Schedule, rows for "Varicella antibody titers", "Measles antibody titers"	Added footnote m: **Varicella and measles titers do not need to be obtained if proof of age-appropriate immunization or proof of prior infection is obtained.**
Rationale: Text for laboratory assessments is being clarified.	
Time and Events Schedule, Footnote o, Sentence 2	~~Note that at these visits, routine hematology and chemistry laboratory studies are not obtained; therefore, h~~Hematocrit and albumin laboratory studies must be performed **at each of these visits** in order to calculate PCDAI.

Applicable Section(s)	Description of Change(s)
Rationale: Clarification is being added for the 7-day window allowed for the screening visit.	
Section 4, Patient Population, Paragraph 1	Screening for eligible patients will be performed within 14 ± **7** days before the Week 0 administration of infliximab.
Rationale: Clarification is being made for the entry criterion related to prior discontinuation of infliximab.	
Synopsis, Patient Population, Dose Escalation Group (bullet c) and Reference Group (bullet b) Section 4.1, Inclusion Criteria, #10c for Dose Escalation Group and #10a for Reference Group	Must not have discontinued infliximab therapy **(discontinuation defined as period of ≥ 6 months without receiving a dose)**
Rationale: Clarification is being made for timing of ileocolonoscopy	
Synopsis, Patient Population, Dose Escalation Group, bullet h.iii.	The ileocolonoscopy must have occurred within **6 weeks prior to the first infliximab 10 mg/kg dose**
Section 3.1, Overview of Study Design (last paragraph)	If a UC patient in the Dose Escalation Group undergoes optional ileocolonoscopy ~~at screening and at least 24 weeks after dose escalation or later~~, Mayo scores will also be obtained.
Section 9.3.1.5, Optional Evaluations; Time and Events Schedule, footnote f	For patients in the Dose Escalation Group, investigators may perform optional ileocolonoscopy during screening~~, unless ileocolonoscopy was performed~~ **or as standard care within 6 weeks prior to the first infliximab 10 mg/kg dose** ~~within 4 weeks prior to screening,~~ and again at Week 24 or later.
Rationale: Clarifications are being made to several entry criteria.	
Section 4.2, Exclusion Criteria, #8-9, #11, #27	8. **Patients with UC** must not have a history of extensive colonic resection….. 9. Must not have a history of **dysplasia or** adenomatous colonic polyps that were not removed 11. Has previously received: a. Natalizumab ~~or vedolizumab~~ within 12 months of first infliximab administration d. Any investigational drug (including investigational vaccines, **vedolizumab, ustekinumab, etc.**) within 4 weeks…. 27. Must not have had a fever of unknown origin for longer than 3 weeks duration within 3 months prior to screening**, unless thought likely to be associated with IBD**

Applicable Section(s)	Description of Change(s)
Rationale: Text for TB screening is being revised for clarity.	
Time and Events Schedule, footnote l (shortened)	~~Unless country or site guidelines do not recommend a chest radiograph as a necessary screening process prior to initiation of anti-TNF therapies, a chest radiograph (both posterior-anterior and lateral views) must have been performed within 3 months prior to infliximab administration at Week 0 and read by a qualified radiologist; the results of which must show no evidence of current active TB or old inactive TB.~~
Section 4.1, Inclusion Criteria, #4g	….a chest radiograph (both posterior-anterior and lateral views) must have been performed within 3 months prior to infliximab initiation **or during treatment** and read by a qualified radiologist; the results of which must show no evidence of current active TB or old inactive TB. Chest radiographs (both posterior-anterior and lateral views) must be performed as part of the screening process in all cases when either the tuberculin skin test and/or QFT-TB Gold test results for TB are positive **or proof of previously performed negative chest radiograph cannot be obtained**.
Section 9.5.4, Screening Chest Radiograph, Paragraph 1	Unless country or site guidelines do not recommend a chest radiograph as a necessary screening process prior to initiation of anti-TNF therapies, a chest radiograph (both posterior-anterior and lateral views) must have been performed within 3 months prior to infliximab **initiation or during the pre-study infliximab treatment** ~~administration at Week 0~~ and read by a qualified radiologist;….
Section 9.5.4, Screening Chest Radiograph, Paragraph 2	Chest radiographs (both posterior-anterior and lateral views) must be performed as part of the screening process in all cases when either the tuberculin skin test and/or QFT-TB Gold test results for TB are positive **or proof of negative chest radiograph performed prior to initiation of infliximab cannot be obtained**.
Rationale: Text in the Time and Events Schedule for TB testing is being clarified to match instructions elsewhere in the protocol.	
Time and Events Schedule, row for QFT-TB Gold test	QFT-TB Gold test (or tuberculin skin test in countries where the QFT-TB Gold test is not ~~accepted/required~~ **approved/registered** or is not required per local guidelines)
Rationale: Clarification is being added for the time period to which the dose range for prior induction and maintenance doses applies.	
Synopsis, Patient Population, Patients in the Dose Escalation Group *and* Patients in the Reference Group; Section 4.1, Inclusion Criteria, #10, Patients in the Dose Escalation Group *and* Patients in the Reference Group	a. ….(~~allowable dose range of 4.5 to 6 mg/kg with a ± 7 day window for induction and maintenance doses)~~ and have demonstrated a clinical response according to the criteria in Attachment 3 for CD patients or Attachment 4 for UC patients **(the last 2 doses occurring at least 48 days, but no more than 64 days, apart, with allowable dose range of 4.5 to 6 mg/kg)**
Paragraph 3, Sentence 1	Upon meeting enrollment criteria for the Reference Group, patients will ~~continue to~~ receive 5 mg/kg q8wk.
Section 3.1, Overview of Study Design, Dose Escalation Group *and* Reference Group	…. (~~allowable dose range of 4.5 to 6 mg/kg with a ± 7 day window for induction and maintenance doses~~ the last 2 doses occurring at least 48 days, but no more than 64 days, apart, with allowable dose range of 4.5 to 6 mg/kg).

Applicable Section(s)	Description of Change(s)
Rationale: Clarifications are made related to the timing of infliximab administration.	
Section 4.1, Inclusion criteria #4d - #5	…first **on-study** administration of infliximab…
Section 9.2 Study Procedures, Paragraph 2	All visit-specific assessments should be completed before administration of infliximab. The maximum acceptable visit window for all visits **including screening** is ± 7 days. Patients must meet all enrollment criteria **prior to the first on-study administration of infliximab at Week 0** ~~for the Week 0 visit prior to the administration of infliximab~~.
Rationale: Clarification is being made for the major secondary efficacy endpoint.	
Synopsis, Secondary Endpoints Section 9.3.2, Secondary Endpoints	*Major secondary efficacy endpoint:* Sustained clinical response **through** 56 weeks after dose escalation
Rationale: Text for infliximab treatment at study entry is being deleted as it was erroneously included in this section.	
Synopsis, Dosage and Administration Section 6, Dosage and Administration	~~At the time of enrollment in the trial, patients must be receiving infliximab at a dose of 5 mg/kg q8wk (allowable dose range of 4.5 to 6 mg/kg with a ± 7 day window for maintenance doses) as described in Section 3.1.~~
Rationale: Clarification for the study evaluations is being added.	
Section 9.1, Screening Procedures, Paragraph 5	At screening and subsequent visits, PCDAI and Mayo diary cards will be distributed for patients to use over the course of the study. Patients (or their legally-acceptable representatives) will be instructed ~~on how~~ to complete the diary cards…
Section 9.3.1, Evaluations	**The disease activity assessments listed below should be performed for both Reference and Dose Escalation Group patients.**
Section 9.3.1.1, PCDAI, Paragraph 1, Sentence 2	The PCDAI is a validated clinical tool used to assess disease severity in pediatric patients with CD.[10] **This assessment should be performed for all study visits at which infliximab is administered (Week 0 - Week 56/End of Treatment).**
Section 9.3.1.2, Mayo and Partial Mayo Score, Paragraph 1, Sentence 2	The Mayo score is a validated clinical tool used to assess disease activity in patients with UC.[11] **This assessment should be performed for all study visits at which infliximab is administered (Week 0 - Week 56/End of Treatment).**
Rationale: Clarification is being made to differentiate between patients with UC and CD, for possible discontinuation of study treatment.	
Section 10.2, Discontinuation of Study Treatment	• If, in the opinion of the patient and the investigator, **a UC** ~~the~~ patient requires a colectomy (partial or total)

Applicable Section(s)	Description of Change(s)
Rationale: Clarification is being made to the statistical analysis section, for secondary efficacy analyses.	
Section 11.3.2, Analyses for the Secondary Endpoints	**The analysis will be performed for both the Dose Escalation and Reference groups.**
Rationale: Clarification is being added regarding additional study-specific documents being provided to sites.	
Section 15, STUDY-SPECIFIC MATERIALS, Additions	• **CDC Growth Charts** • **Wong-Baker FACES Pain Scale** • **Stool frequency questionnaire**

Amendment INT-1 (25 January 2016)

This amendment is considered 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. No patient was enrolled at the time of this amendment.

The overall reason for the amendment: The overall reasons for the amendment are to revise entry criteria regarding prior maintenance doses of infliximab and time of loss of response, and to correct or clarify inadvertent errors.

Edits and additions to original text are noted in bold, and deletions are noted in strikeout.

Applicable Section(s)	Description of Change(s)
Rationale: The wording for age at entry was clarified.	
Section 4.1, Inclusion criterion #1; Synopsis, Patient Population	[Patients] must be male or female at least 6 years of age and less than 17 years of age~~, inclusive,~~ at the time of enrollment.
Rationale: Text mentioning situations where the QFT-TB Gold test for tuberculosis may not be done was clarified to account for local guidelines.	
Section 4.1, Inclusion criterion #4e; Time and Event Schedule	If the QFT-TB Gold test is not approved/registered in that country **or is not required per local guidelines**,….
Rationale: The criterion regarding the number of maintenance doses received prior to enrollment was changed based on the investigators' feedback that modifying criteria to include patients after 1 maintenance dose, rather than 2, will potentially increase enrollment. This change was made everywhere prior maintenance doses were mentioned in the protocol.	
Synopsis, Patient Population, Patients in the Dose Escalation Group, criterion a.	Must have completed the recommended infliximab induction dosing regimen of 5 mg/kg at weeks 0, 2, and 6 and at least ~~2~~**1** maintenance dose~~s~~ of 5 mg/kg q8wk (allowable dose range of 4.5 to 6 mg/kg with a ± 7 day window for induction and maintenance doses) and have demonstrated a clinical response according to the investigator's assessment.
Synopsis, Patient Population, Patients in the Reference Group, criterion a; Section 4.1, Inclusion Criteria, Criterion #10.a for Patients in the Reference Group	Must have completed the recommended infliximab induction dosing regimen of 5 mg/kg at weeks 0, 2, and 6 and have maintained a stable clinical response* to infliximab after at least ~~2~~**1** maintenance dose~~s~~ of 5 mg/kg q8wk (allowable dose range of 4.5 to 6 mg/kg with a ± 7 day window for induction and maintenance doses).
Section 3.1, Overview of Study Design, Dose Escalation Group and Reference Group	Pediatric patients with IBD …. the recommended infliximab induction dosing regimen of 5 mg/kg at weeks 0, 2, and 6, followed by at least ~~2~~**1** maintenance dose~~s~~ of 5 mg/kg q8wk

Applicable Section(s)	Description of Change(s)
Section 4.1, Inclusion Criteria, Criterion # 10a for Patients in the Dose Escalation group	Must have completed the recommended infliximab induction dosing regimen of 5 mg/kg at weeks 0, 2, and 6, and at least ~~2~~**1** maintenance dose~~s~~ of 5 mg/kg q8wk (allowable dose range of 4.5 to 6 mg/kg with a ± 7 day window for induction and maintenance doses) and have demonstrated a clinical response according to the investigator's assessment.
Figure 1	≥ ~~2~~**1** maintenance dose~~s~~
Rationale: Criterion was changed based on the investigators' feedback that inclusion of patients with loss of response 4-10 weeks, rather than 6-10 weeks, after the last infliximab dose in the Dose Escalation will potentially increase enrollment.	
Synopsis, Patient Population, Patients in the Dose Escalation Group, criterion d; Section 4.1, Inclusion Criteria, Dose Escalation Group, #10d.	Must have received the last maintenance dose of infliximab at least ~~6~~**4** weeks but not more than 10 weeks **prior to** ~~at the time of~~ screening.
Rationale: The time period for donation of eggs for assisted reproduction was clarified and made consistent with prior protocols.	
Section 4.1, Inclusion Criterion 13	A female patient must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction **for a period of 6 months after last dose of study medication**.
Rationale: Details for effective birth control for female patients were added, for completeness.	
Section 4.3, Prohibitions and Restrictions	If sexually active, female patients must be practicing a highly effective method of birth control **(eg, prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method [eg, condoms, diaphragm, or cervical cap, with spermicidal foam, cream, or gel], or male partner sterilization) as local regulations permit,** during the study and for 6 months after receiving the last administration of infliximab
Rationale: Instructions were clarified regarding how baseline PCDAI and Mayo score criteria will be collected.	
Section 9.1, Screening Procedures	At screening and subsequent visits, ~~information needed for the PCDAI or partial Mayo scores with respect to questions such as stool frequency or quality, abdominal pain, and general well-being will be obtained from recall. At that visit, diary cards will be distributed for patients to use over the course of the study.~~ **PCDAI and Mayo diary cards will be distributed for patients to use over the course of the study.** Patients (or their legally-acceptable representatives) will be instructed on how to complete the diary cards daily and will be reminded to bring the diary cards to each visit for data collection and review by the investigator/study coordinator. **Information needed for the PCDAI or partial Mayo scores with respect to questions such as stool frequency or quality, abdominal pain, and general well-being will be obtained from the patient diary and/or recall at Week 0 and subsequent visits.**

Applicable Section(s)	Description of Change(s)
Rationale: Footnote "h" referring to the Fecal Calprotectin Test in the Time and Events Schedule was updated for clarity.	
Time and Events Schedule, Footnote "h"	At screening, only to be performed for **patients in** the Dose Escalation Group **or for patients in the Reference Group prior to crossing over to the Dose Escalation Group**.
Rationale: In inclusion criterion #6-f, the youngest age range presented in the protocol is not applicable for this study and was removed.	
Section 4.1, Inclusion Criterion #6-f	Modified Text: Serum creatinine not to exceed: – ~~2 to 5 years of age: 0.5 mg/dL (SI: 44 µmol/L)~~ – 6 to 10 years of age: 0.7 mg/dL (SI: 62 µmol/L) – 11 to 12 years of age: 1.0 mg/dL (SI: 88 µmol/L) – ≥ 13 years of age: 1.2 mg/dL (SI: 106 µmol/L)
Rationale: Antibiotics for the treatment of IBD were inadvertently omitted from the list of allowed prior and concomitant medications. Antibiotics for the treatment of IBD have been added to the list of accepted prior and concomitant medications, throughout the protocol.	
Synopsis, Patient Population, Patients in the Reference Group, note (*) to criterion a	Patients with a stable clinical response to infliximab are defined as those patients who did not initiate or receive increased doses of 5-aminosalicylic acid (5-ASA), corticosteroids, ~~or~~ immunomodulators **or antibiotics for the treatment of IBD** for 4 weeks prior to screening.
Section 3.1, Overview of Study Design, Reference Group, (*)	Patients with a stable clinical response to infliximab are defined as those patients who did not initiate or receive increased doses of 5-aminosalicylic acid (5-ASA), corticosteroids, ~~or~~ immunomodulators**, or antibiotics for the treatment of IBD** for 4 weeks prior to screening.
Section 4.1, Inclusion Criteria, * note to Criterion #10.a for patients in the Reference Group	A stable clinical response to infliximab is defined as those patients who did not initiate or receive increased doses of 5-ASA, corticosteroids, **antibiotics for the treatment of IBD,** or immunomodulators for 4 weeks prior to screening.

Applicable Section(s)	Description of Change(s)
Section 8, PRESTUDY AND CONCOMITANT THERAPY	….(eg, 5-ASAs; corticosteroids; immunomodulators, including thiopurines; biologics**; antibiotics**)
Section 8, PRESTUDY AND CONCOMITANT THERAPY	The following concomitant medications for IBD are allowed in this study: 5-ASAs, corticosteroids, ~~and~~ immunomodulators (ie, 6-MP, AZA, MTX)**, and antibiotics**.
Section 8, Bullets 1 and 2 for patients in the Dose Escalation Group; and Bullet 4	… 5-ASAs, and/or corticosteroids, and/or immunomodulators**, and/or antibiotics** …. For patients receiving immunomodulators (ie, 6-MP, AZA, or MTX), ~~or~~ corticosteroids, **or antibiotics** at baseline, the immunomodulators **and antibiotics** may be **tapered or** may be discontinued at any time during the study, and corticosteroids may be tapered beginning at Week 0
Section 8, Bullets 1 and 2 for patients in the Reference Group who cross over to the Dose Escalation Group; and Bullet 4	… (ie, 5-ASAs, and/or corticosteroids, and/or immunomodulators**, and/or antibiotics…** For patients receiving immunomodulators (ie, 6-MP, AZA, or MTX), ~~or~~ corticosteroids, **or antibiotics** at the time of dose escalation, the immunomodulators **and antibiotics** may be **tapered or** may be discontinued at any time during the study, and corticosteroids may be tapered beginning at the time of dose escalation
Rationale: The instructions for infusion preparation and administration were clarified, per investigators' request.	
14.4, Preparation, Handling, and Storage	Aseptic procedures must be used during the preparation and administration of the study material. **The infusion must be administered over a period of not less than 2 hours and must use an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2 µm or less). The vials do not contain antibacterial preservatives. Therefore, any unused portion of the infusion solution should not be stored for reuse.** Additional details for the preparation and administration of infliximab are provided in the site investigational product manual.

Applicable Section(s)	Description of Change(s)
Rationale: Other secondary efficacy endpoints were revised to include the addition of the Wong-Baker FACES pain scale and stool frequency in absolute values.	
Synopsis, Other Secondary Efficacy Endpoints; Section 9.3.2, Other Secondary Efficacy Endpoints; Section 11.3.2, Analyses for the Secondary Endpoints	~~1. Changes from baseline at Week 16 and at Week 56 in abdominal pain and loose/watery stool frequency sub scores of the PCDAI in CD patients~~ ~~2. Changes from baseline at Week 16 and at Week 56 in stool frequency and rectal bleeding sub scores of the Mayo score for UC patients~~ **1. For CD patients changes from baseline at Week 16 and at Week 56 in:** • **Abdominal pain and loose/watery stool frequency sub-scores of the PCDAI** • **Abdominal pain using the Wong-Baker FACES scale** • **Absolute stool frequency** **2. For UC patients changes from baseline at Week 16 and at Week 56 in:** • **Stool frequency and rectal bleeding sub-scores of the partial Mayo score** • **Abdominal pain using the Wong-Baker FACES scale** • **Absolute stool frequency**
Time and Event schedule, FACES (Wong-Baker pain scale) and Stool Frequency	Added Row/Timing, to indicate are to be collected at Weeks 0, 16, 56/End of Treatment, with explanatory footnotes: **p. For cross over patients, the Wong-Baker FACES pain scale will be administered prior to the administration of the first and the third dose of 10 mg/kg infliximab.** **q. For cross over patients stool frequency data will be collected prior to the administration of the first and the third dose of 10 mg/kg infliximab.**
Rationale: Instructions for performing the Wong-Baker FACES Pain scale (with a description and reference) and the stool frequency measurement were added.	
Sections 9.3.1.3 and 9.3.1.4 were added.	**9.3.1.3.The Wong-Baker FACES Pain Scale** **The Wong-Baker FACES Pain Scale is a pain scale that combines pictures and numbers to allow pain to be rated by children over the age of 3.[4] The scale shows a series of faces ranging from a happy face at 0, "No hurt" to a crying face at 10 "Hurts worst". The patient must choose the face that best describes how they are feeling.** **The Wong-Baker FACES Pain Scale should be completed prior to infliximab administration at Week 0, Week 16 and Week 56 visits for the Dose Escalation Group and Reference Group or prior to the administration of the first and third 10 mg/kg dose for patients crossing over from the Reference Group. In addition, all patients who discontinue treatment will complete the Wong-Baker FACES pain scale at the time of treatment discontinuation visit.** **9.3.1.4. Stool Frequency (absolute value)** **Absolute stool frequency values will be recorded from patients' recall prior to infliximab administration at Week 0, Week 16 and Week 56 visits for the Dose Escalation Group and Reference Group or prior to the administration of the first and third 10 mg/kg dose for patients crossing over from the Reference Group. In addition, stool frequency information should be obtained from all patients who discontinue treatment at the time of treatment discontinuation visit.**

Applicable Section(s)	Description of Change(s)
Rationale: The timing of screening and follow-up endoscopy was clarified, including allowing it to be performed at least 24 weeks after dose escalation.	
Synopsis, Overview of Study Design; Section 3.1, Overview of Study Design	If a UC patient in the Dose Escalation Group undergoes optional ileocolonoscopy at screening and **at least** 24 weeks after dose escalation **or later**, Mayo scores will also be obtained.
Synopsis, Patient population; Section 4.1, Inclusion Criterion 10.h.iii	The ileocolonoscopy must have occurred within 4 weeks prior to **the initiation of, or during, the** screening **process**.
Section 9.3.1.5, Optional Evaluations (renumbered from 9.3.1.3)	For patients in the Dose Escalation Group, investigators may perform optional ileocolonoscopy during screening, **unless ileocolonoscopy was performed within 4 weeks prior to screening,** and again at Week 24 **or later** ~~(allowable window of +1 week)~~. For patients who cross over from the Reference Group to the Dose Escalation Group, investigators may perform optional ileocolonoscopy within 2 weeks prior to the first 10 mg/kg infliximab dose and **at least** 24 weeks after dose escalation ~~(allowable window of +1 week)~~.
Time and Events Schedule, Footnote "e"	Optional repeat ileocolonoscopy may be performed **at least** 24 weeks after dose escalation **or later**; refer to Section 9.3.1.5 for further details.
Time and Events Schedule, Ileocolonoscopy	"X" mark **from** ~~at~~ week 24 **through 56** for Ileocolonoscopy
Time and Events Schedule, Mayo score (only for UC patients in Dose Escalation Group having optional ileocolonoscopy)	"X" mark ~~at week 16~~ **from Week 24 through 56** for Mayo score (only for UC patients in Dose Escalation Group having optional ileocolonoscopy), with associated **Footnote "o" added: For patients who discontinue treatment prior to Week 56 information needed for the PCDAI or partial Mayo scores with respect to questions such as stool frequency or quality, abdominal pain, and general well-being will be obtained from patient diary and/or recall.**
Rationale: The time window for reporting serious adverse events was revised to be more consistent with the Sponsor's standard post-trial reporting guidelines.	
Section 12.3.1, All Adverse Events	Serious adverse events, including those spontaneously reported to the investigator within ~~16~~**8** weeks after the last dose of infliximab, must be reported using the Serious Adverse Event Form.
Rationale: Clarification added to the Time and Events Schedule regarding assessments to be performed at the time of treatment discontinuation, or early study discontinuation.	
Time and Events Schedule	Modified Column Heading: (Week) 56/**End of Treatment**; Week 64 (Final Safety Visit) [c] **/Early Study Discontinuation**
Rationale: Wording pertaining to the screening visit was corrected in the bullets for "New Malignancy" and "New Autoimmune Disorder".	
Section 12.1.1, Adverse Event Definitions and Classifications	…(including during the ~~enrollment~~ **screening** visit)

Applicable Section(s)	Description of Change(s)
Rationale: Text regarding sample storage for future research is not applicable and was corrected.	
Section 16.2.5, Long-Term Retention of Samples for Additional Future Research	~~Samples collected in this study may be stored according to local regulations for additional research. However, no genetic analyses will be performed. 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. Patients may withdraw their consent for their samples to be stored for research.~~ **No samples will be stored for additional future research.**
Rationale: Minor grammatical and formatting errors were noted and corrected in the protocol. These changes do not impact the conduct of the protocol and therefore are not listed here.	

SYNOPSIS

Title

A Phase 4, Multicenter, Open-label Study of Serum Infliximab Concentrations and Efficacy and Safety of Dose Escalation in Pediatric Patients with Inflammatory Bowel Disease

Remicade® (infliximab)

Remicade® (infliximab), a recombinant immunoglobulin G (IgG) 1-κ human-murine chimeric monoclonal antibody, is an antagonist of the cytokine tumor necrosis factor alpha (TNFα) that specifically binds and neutralizes both the soluble TNFα homotrimer and its membrane-bound precursor. Infliximab is indicated for treatment of several autoimmune diseases in which TNFα plays a major role.

OBJECTIVES AND HYPOTHESIS

Primary Objective

The primary objective of this study is to evaluate whether trough serum infliximab concentrations at the time of loss of clinical response will identify pediatric patients with inflammatory bowel disease (IBD) who would benefit (regain clinical response) from dose escalation above the currently approved dose (5 mg/kg every 8 weeks [q8wk]).

Overall safety will be assessed throughout the duration of the study.

Secondary Objectives

Secondary objectives of this study are to:

- Identify disease characteristics associated with maintenance of sustained clinical response in patients after dose escalation
- Evaluate the rate of serious adverse events in patients who receive an increased dose of infliximab due to loss of response (Dose Escalation Group) relative to the rate of serious adverse events in those patients in response who are maintained on infliximab 5 mg/kg q8wk (Reference Group)

Hypothesis

In pediatric IBD patients with loss of response, trough serum infliximab concentrations will be associated with regaining of response after dose escalation.

OVERVIEW OF STUDY DESIGN

This is a multicenter, prospective, open-label study in pediatric patients with IBD who are receiving infliximab therapy. The study will include 2 groups, a Dose Escalation Group (n=80) and a Reference Group (n=50). Both the Dose Escalation and Reference Groups will include 60% Crohn's disease (CD) patients and 40% ulcerative colitis (UC) patients at enrollment, to ensure a clinically meaningful number of patients by IBD diagnosis. Patients in both groups will receive infliximab q8wk through Week 56, with a Final Safety Visit occurring 8 weeks after the last dose of infliximab. Patients in the Reference Group who lose clinical response may cross over to the Dose Escalation Group provided they meet all entry criteria for the Dose Escalation Group (as described under PATIENT POPULATION below). Investigators may discontinue patients who have not regained clinical response after receiving 2 doses of 10 mg/kg infliximab.

After obtaining informed consent/assent, detailed demographic and medical history, including qualitative and quantitative signs and symptoms present at initiation of infliximab therapy and the time of response, will be collected on all patients meeting inclusion and exclusion criteria at the time of enrollment. Review of concomitant medications as well as safety and efficacy assessments (Pediatric Crohn's Disease Activity Index [PCDAI] scores or partial Mayo scores) will be conducted at every study visit through Week 56. Samples will be collected for measurement of serum concentrations of infliximab and antibodies to infliximab (ATI) at screening for patients in the Dose Escalation Group, prior to each infusion during the study for patients in each group, and at the time of loss of clinical response for patients in each group. If a UC patient in the Dose Escalation Group undergoes optional

ileocolonoscopy, Mayo scores will also be obtained. The end of the study will occur on the date of the last visit of the last patient participating in the study.

An internal Safety Monitoring Committee will be established to monitor safety data on an ongoing basis to ensure the continuing safety of patients enrolled in this study.

PATIENT POPULATION

Patients must be male or female at least 6 years of age and less than 17 years of age at the time of enrollment. He/she must have a biopsy-confirmed diagnosis of CD or UC prior to study entry. In addition, group-specific inclusion criteria include the following:

Patients in the Dose Escalation Group:

a. Must have completed the recommended infliximab induction dosing regimen of 5 mg/kg at weeks 0, 2, and 6 and at least 1 maintenance dose of 5 mg/kg q8wk and have demonstrated a clinical response according to the criteria in Attachment 3 for CD patients or Attachment 4 for UC patients (the last 2 doses occurring at least 48 days, but no more than 64 days, apart, with allowable dose range of 4.5 to 6 mg/kg); or, an induction regimen with doses >6 mg/kg and have received at least 2 maintenance doses of 5 mg/kg q8wk (the last 2 doses at least 48, but no more than 64, days apart with allowable dose range of 4.5 to 6 mg/kg) and have demonstrated clinical response for at least 28 days after the most recent (second or later) 5 mg/kg maintenance dose; or, maintenance doses >6 mg/kg within the past 6 months and at least 2 maintenance doses of 5 mg/kg q8wk (the last 2 doses occurring at least 48 days, but no more than 64 days, apart, with allowable dose range of 4.5 to 6 mg/kg) and have demonstrated a clinical response for at least 28 days after the most recent (second or later) 5 mg/kg maintenance dose

b. Must have lost clinical response, according to the criteria in Attachment 3 for CD patients or Attachment 4 for UC patients, after the first or subsequent q8wk maintenance dose of infliximab 5 mg/kg, for patients who have completed the recommended infliximab induction dosing regimen (5 mg/kg at weeks 0, 2, and 6) or, after the most recent (second or later) q8wk maintenance dose of infliximab 5 mg/kg for patients with an induction regimen with doses >6 mg/kg or for patients with previous maintenance doses >6 mg/kg

c. Must not have discontinued infliximab therapy (discontinuation defined as period of ≥ 6 months without receiving a dose)

d. Must have received the last maintenance dose of infliximab at least 4 weeks but not more than 10 weeks prior to screening

e. Must have an infliximab C_{trough} < 7 µg/mL and ATI titers ≤ 12,800 at the time of loss of response

f. Must have a PCDAI of > 30 points with both an abdominal pain and stool frequency sub-score of ≥ 5 (patients with CD)

g. Must have a partial Mayo score of ≥ 5 points with both stool frequency and rectal bleeding sub-scores of ≥ 1 (patients with UC)

h. Must meet one of the following criteria:

   i. Have serum CRP > 0.287 mg/dL

   ii. Have fecal calprotectin > 50 µg/g

   iii. Have evidence of active disease (ulcerations) on ileocolonoscopy. The ileocolonoscopy must have occurred within 6 weeks prior to the first 10 mg/kg dose.

Patients in the Reference Group:

a. Must have completed the recommended infliximab induction dosing regimen of 5 mg/kg at weeks 0, 2, and 6 and have achieved and maintained a stable clinical response* to infliximab after at least 1 maintenance dose of 5 mg/kg q8wk according to the criteria in Attachment 3 for CD patients or Attachment 4 for UC patients (the last 2 doses occurring at least 48 days, but no more than 64 days, apart, with allowable dose range of 4.5 to 6 mg/kg) ; or, an induction regimen with doses >6 mg/kg and have received at least 2 maintenance doses of 5 mg/kg q8wk (the last 2 doses at least 48, but no more than 64, days apart with allowable dose range of 4.5 to 6 mg/kg) and have demonstrated clinical response for at least 28 days after the most recent (second or later) 5 mg/kg maintenance dose; or, maintenance doses >6 mg/kg within the

past 6 months and at least 2 maintenance doses of 5 mg/kg q8wk (the last 2 doses occurring at least 48 days, but no more than 64 days, apart, with allowable dose range of 4.5 to 6 mg/kg) and have demonstrated a clinical response for at least 28 days after the most recent (second or later) 5 mg/kg maintenance dose.

* Patients with a stable clinical response to infliximab are defined as those patients who have achieved clinical response according to criteria in Attachment 3 for CD patients or Attachment 4 for UC patients and who did not initiate or receive increased doses of 5-aminosalicylic acid (5-ASA), corticosteroids, immunomodulators or antibiotics for the treatment of IBD for 4 weeks prior to screening.

b. Must not have discontinued infliximab therapy (discontinuation defined as period of ≥ 6 months without receiving a dose).

Refer to the full protocol for a list of all entry criteria.

DOSAGE AND ADMINISTRATION

Upon meeting enrollment criteria for the Dose Escalation Group, patients will receive infliximab 10 mg/kg q8wk at Week 0. Patients will be eligible to receive 56 weeks of therapy with infliximab at the escalated dose with a Final Safety Visit at Week 64.

Upon meeting enrollment criteria for the Reference Group, patients will receive 5 mg/kg q8wk. Those who lose clinical response during participation in the study will be eligible, if they meet the enrollment criteria for the Dose Escalation Group, to cross over to the Dose Escalation Group.

Patients in the Reference Group who lose response and cross over to the Dose Escalation Group must complete screening for the Dose Escalation Group and receive the first 10 mg/kg dose of infliximab within 40 weeks of enrollment into the study.

Patients who cross over from the Reference Group to the Dose Escalation Group will be eligible to receive a total of 56 weeks of therapy with infliximab, which includes duration of therapy while in the Reference Group prior to dose escalation.

EFFICACY EVALUATIONS/ENDPOINTS

Efficacy will be evaluated using the PCDAI and partial Mayo score.

Primary Endpoint

The primary efficacy endpoint is clinical response at Week 16 after dose escalation, defined as:

- CD patients: A decrease from baseline in PCDAI of ≥ 15 points with total score of ≤ 30 points
- UC patients: A decrease from baseline in partial Mayo score of ≥ 2 points and ≥ 30% and a decrease in the rectal bleeding sub-score by ≥ 1 point or achievement of an absolute sub-score of ≤ 1point

Secondary Endpoints

Major secondary efficacy endpoint: Sustained clinical response through 56 weeks after dose escalation

Other secondary efficacy endpoints:

1. For CD patients changes from baseline at Week 16 and at Week 56 in:
   - Abdominal pain and loose/watery stool frequency sub-scores of the PCDAI
   - Abdominal pain using the Wong-Baker FACES scale
   - Absolute stool frequency

2. For UC patients changes from baseline at Week 16 and at Week 56 in:
   - Stool frequency and rectal bleeding sub-scores of the partial Mayo score

- Abdominal pain using the Wong-Baker FACES scale
- Absolute stool frequency

3. Correlates of Wong-Baker FACES scale with clinical remission and response at Week 16

4. The association between abdominal pain PCDAI sub-score and the Wong-Baker FACES scale for patients with CD

Secondary safety endpoint: The incidence of serious adverse events

SERUM INFLIXIMAB CONCENTRATIONS AND ANTIBODIES TO INFLIXIMAB

Venous blood samples will be collected for measurement of serum concentrations of infliximab and ATI titers. Serum infliximab concentrations will be determined using a validated, enzyme-linked immunosorbent assay. Serum ATI titers will be determined using a validated, drug-tolerant electrochemiluminescence immunoassay (ECLIA) method.

SAFETY EVALUATIONS

Safety evaluations during the study include adverse events, clinical laboratory tests, physical examinations including vital signs, and screening for tuberculosis.

STATISTICAL METHODS

Sample Size Calculation

Both the Dose Escalation and Reference Groups will be composed of 60% CD patients and 40% UC patients. Accordingly, the proposed study will enroll 80 (48 CD and 32 UC) patients in the Dose Escalation Group and 50 (30 CD and 20 UC) patients in the Reference Group, with the conservative assumption that approximately 10 patients (20%) in the Reference Group may dose escalate. [1,2] Thus, the final sample size in the Dose Escalation Group is estimated to be 90 patients, with 54 CD patients and 36 UC patients.

The sample size estimation was calculated based on precision estimates for clinical response rates after dose escalation from 5 mg/kg q8w to 10 mg/kg q8w at Week 16, the primary efficacy endpoint. It is anticipated the dropout rate due to loss to follow up and other non-efficacy related reasons by Week 16 will be about 5% of patients, based on the Phase 3 pediatric infliximab trials in CD and UC patients.[1,2] Adjusting for dropout rate, a sample size of 76 - 85 patients (without or with cross over) will provide precision estimates between ± 8.5 – 11.2% for expected response rates between 20 - 50%, based on a 2-sided 95% confidence interval (CI).

A response rate of 5% was assumed for patients with loss of clinical response not receiving dose escalation. At a significance level of 0.05 (2-sided), the statistical power is greater than 90% to detect at least a 15% increase in clinical response after dose escalation, for the overall Dose Escalation Group (N=76 – 85, without or with cross over). For the CD subgroup (N = 46 - 51, without or with cross over), the power is between 84% - 90%. For the UC subgroup (N = 30 - 34, without or with cross over), the power is between 70% - 74%.

When testing the association between infliximab concentration and regain of clinical response after dose escalation, using logistic regression to test the null hypothesis of no association between infliximab serum concentrations and clinical response, ie, $\beta = 0$ ($\alpha = 0.05$, 2-sided), a sample size of 76 - 85 patients (without or with cross over) will provide statistical power between 66% and 85% to detect β of 0.916, assuming the response rate is between 20 – 50%.

Statistical Analyses

For the primary analysis, the clinical response rate at 16 weeks after dose escalation and the surrounding 2-sided 95% confidence interval will be estimated for the entire Dose Escalation Group, as well as for subgroups of CD and UC patients. For the patients who cross over from the Reference Group to the Dose Escalation Group, their clinical response at 16 weeks after dose escalation will be included in the primary endpoint analysis. For the Dose Escalation Group, including patients who cross over from the Reference Group, logistic regression will be performed to evaluate the relationship between serum infliximab concentration prior to dose escalation and clinical response at Week 16 after dose escalation.

Safety data will be summarized for both the Dose Escalation Group and the Reference Group.

References

1. Hyams J, Crandall W, Kugathasan S, et al, and the REACH Study Group. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. Gastroenterol. 2007;132:863–873.

2. Hyams J, Damaraju L, Blank M, et al, for the C0168T72 Study Group. Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis. Clin Gastroenterol Hepatol. 2012;10:391–399.

TIME AND EVENTS SCHEDULE

Study Procedures [a, b]	Screening (Day -28)	Week 0	Week 8	Week 16	Week 24	Week 32	Week 40	Week 48	Week 56/ End of Treatment	Week 64 (Final Safety Visit) [c] / Early Study Discontinuation
Informed consent/assent [d]	X									
Distribute patient PCDAI or partial Mayo diary and study cards	X									
Medical history and demographics	X									
Review of inclusion/exclusion criteria	X	X								
Prior medication review [e]	X	X								
Concomitant medication review	X	X	X	X	X	X	X	X	X	X
Ileocolonoscopy [f]	X				X----------					
Physical examination [g]	X					X				X
Vital signs and Weight	X	X	X	X	X	X	X	X	X	X
Height	X	X				X				X
Stool culture for enteric pathogens, including *Clostridium difficile* toxins [h]	X									
Fecal calprotectin [h, i, j]	X									
Tuberculosis evaluation [k]	X	X	X	X	X	X	X	X	X	X
QFT-TB Gold test (or tuberculin skin test in countries where the QFT-TB Gold test is not approved/registered or is not required per local guidelines)	X									
Chest radiograph [l]	X									
Hepatitis B testing	X									
Hepatitis C testing	X									
Varicella antibody titers [m]	X									
Measles antibody titers [m]	X									

Study Procedures [a, b]	Screening (Day -28)	Week 0	8	16	24	32	40	48	56/ End of Treatment	Week 64 (Final Safety Visit) [c] / Early Study Discontinuation
Urine pregnancy test [n]	X	X	X	X	X	X	X	X	X	X
Hematology and chemistry	X	X		X		X		X		X
Hematocrit			X [o]		X [o]		X [o]		X [o]	
Albumin			X [o]		X [o]		X [o]		X [o]	
ESR	X [j, p]	X [p]	X [p]	X [p]	X [p]	X [p]	X [p]	X [p]	X [p]	
CRP	X [j]	X	X	X	X	X	X	X	X	
Infliximab concentration [i, q]	X [j]	X	X	X	X	X	X	X	X	X
Antibodies to infliximab [q]	X [j]	X	X	X	X	X	X	X	X	X
ANA and anti-dsDNA antibodies		X								X
PCDAI score or partial Mayo score [r]	X [w]	X [w]	X	X	X	X	X	X	X [s]	
FACES (Wong-Baker pain scale) [t]		X		X					X	
Stool Frequency [u]		X		X					X	
Mayo score (only for UC patients in Dose Escalation Group having optional ileocolonoscopy)		X			X----------					
Adverse event review	X	X	X	X	X	X	X	X	X	X [v]
Infliximab administration		X	X	X	X	X	X	X	X	

[a] All assessments are to be completed prior to infliximab administration.

[b] If a patient discontinues study participation, he/she will be requested to return for a follow-up safety visit 8 weeks following the final administration of infliximab. During the follow-up safety evaluation, the procedures and evaluations indicated at Week 64 will be performed, prior to withdrawal of consent. If a patient withdraws consent, no further study procedures are to be performed.

[c] The Final Safety Visit for those patients completing the treatment portion of the study is to occur 8 weeks after the last administration of infliximab at Week 56.

[d] Pre-screening stool sample consent may be obtained prior to the screening visit per local or site requirements.

[e] The name, dose, frequency, route of administration, the start and stop dates, and duration of any therapy taken by the patient for CD or UC at any time in the past (eg, 5-ASAs; corticosteroids; immunomodulators, including thiopurines; biologics) will be recorded in the case report form. For biologics, brand (trade) names will be recorded. In addition, any other prestudy therapies administered up to 30 days before the first dose of infliximab at Week 0 must be recorded at screening.

[f] An ileocolonoscopy is an optional evaluation for patients in the Dose Escalation Group and for patients crossing over to the Dose Escalation Group; it is not applicable to patients in the Reference Group. Optional repeat ileocolonoscopy may be performed during screening or as standard care within 6 weeks prior to the first infliximab 10 mg/kg dose and again at least 24 weeks after dose escalation or later; refer to Section 9.3.1.5 for further details.

[g] Complete physical examinations (including skin and genitourinary examination) are to be conducted.

[h] Sample to be collected at or up to 24 hours prior to screening visit (with completion of appropriate stool sample consent), however, if not done, patient/caregiver may collect at home and return to the site within 24 hours of collection. The following medications should be avoided for 48 hours prior to the sample collection: antacids, barium, bismuth, antidiarrheal medication, and oily laxatives. Please refer to the Covance laboratory manual for further instructions.

[i] For patients undergoing screening for the Dose Escalation Group, those who do not meet entry criteria based on infliximab concentration and/or fecal calprotectin and/or CRP levels may have repeat infliximab concentration and/or fecal calprotectin and/or CRP levels performed during the screening process, provided that all entry criteria are met within 14 days prior to administration of the first 10 mg/kg dose of infliximab.

[j] At screening, to be performed for patients in the Dose Escalation Group or for patients in the Reference Group prior to crossing over to the Dose Escalation Group.

[k] See Section 9.5.5 for TB evaluations. If TB is suspected at any time, follow-up is required as described in Section 9.5.5.

[l] Chest radiographs (both posterior-anterior and lateral views) must be performed as part of the screening process in all cases when either the tuberculin skin test and/or QFT-TB Gold test results for TB are positive or proof of negative chest radiograph performed prior to initiation of infliximab cannot be obtained.

[m] Varicella and measles titers do not need to be obtained if proof of age-appropriate immunization or proof of prior infection is obtained.

[n] For female patients of childbearing potential only.

[o] For CD patients only. Hematocrit and albumin laboratory studies must be performed at each of these visits in order to calculate PCDAI.

[p] ESR is to be collected for CD patients only at each dosing visits for calculation of PCDAI.

[q] Infliximab concentration and ATI titers will be performed for both the Dose Escalation and Reference groups prior to each infusion and at the time of loss of response. Prior to crossing over to the Dose Escalation Group, patients in the Reference Group who lose clinical response must meet all inclusion criteria for the Dose Escalation Group, including Ctrough < 7 µg/mL and ATI titers ≤ 12,800 (see Section 4.1 inclusion criterion #10).

[r] The PCDAI or partial Mayo diaries will be completed by patients during the screening period. For calculation of PCDAI at Screening and/or Week 0 for CD patients in the Dose Escalation Group the hematocrit, ESR, and albumin values obtained during screening will be used. For calculation of PCDAI prior to the first 10 mg/kg dose for CD patients crossing over from the Reference Group to the Dose Escalation Group, the hematocrit, ESR, and albumin obtained within 2 weeks prior to the administration of the first 10 mg/kg dose will be used. The PCDAI or partial Mayo score should be calculated prior to infliximab administration at Week 0 for the Dose Escalation Group or prior to the administration of the first 10 mg/kg dose for patients crossing over from the Reference Group.

[s] For patients who discontinue treatment prior to Week 56 information needed for the PCDAI or partial Mayo scores with respect to questions such as stool frequency or quality, abdominal pain, and general well-being will be obtained from patient diary and/or recall.

[t] For cross over patients, the Wong-Baker FACES pain scale will be administered prior to the administration of the first and the third dose of 10 mg/kg of infliximab.

[u] For cross over patients stool frequency data will be collected prior to the administration of the first and the third dose of 10 mg/kg of infliximab.

[v] Required follow-up for adverse events after the Final Safety Visit is described in Section 12.3.

[w] The Week 0 PCDAI or partial Mayo score should be the highest of any values obtained during a period of up to 28 days prior to, or including, Week 0.

Note: (1) The maximum acceptable visit window for all visits after the Screening visit is ±7 days. Patients must meet all enrollment criteria for the Week 0 visit prior to the administration of infliximab.

(2) At an infusion visit, blood samples should be collected prior to infliximab administration. The same venipuncture can be used to collect serum samples for measuring infliximab concentration, ATI, blood draws for safety and efficacy, as well as the infusion of infliximab.

Key: 5-ASA = 5- aminosalicylic acid; ANA = antinuclear antibody; anti-dsDNA = anti-double stranded DNA antibody; ATI = antibody-to-infliximab; CD = Crohn's disease; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; TB = tuberculosis; TNF = tumor necrosis factor; PCDAI = pediatric Crohn's disease activity index; q8wk = every 8 weeks; QFT-TB = QuantiFERON-TB (test); UC = ulcerative colitis.

ABBREVIATIONS

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
6-TG	6-thioguanine
ACCENT	A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen
ACT 1	Active Ulcerative Colitis Trial 1
ACT 2	Active Ulcerative Colitis Trial 2
ADAPT	A Phase 4, Multicenter, Open-label Study of Serum Infliximab Concentrations and Efficacy and Safety of Dose Escalation in Pediatric Patients with Inflammatory Bowel Disease
ALT	alanine aminotransferase
ANA	antinuclear antibody
Anti-dsDNA	anti-double stranded DNA antibody
Anti-HBc	total hepatitis B core antibody
Anti-HBs	hepatitis B surface antibody
AST	aspartate aminotransferase
ATI	antibodies to infliximab
AZA	Azathioprine
BCG	Bacille Calmette-Guerin
BUN	blood urea nitrogen
CD	Crohn's disease
CI	confidence interval
CRF	case report form (paper or electronic as appropriate for this study)
CRP	C-reactive protein
DCF	data clarification form
DEVELOP	An Inflammatory Bowel DisEase Multicenter, ProspectiVE, LOng-term Registry of Pediatric Patients
DNA	deoxyribonucleic acid
ECLIA	electrochemiluminescence immunoassay
eDC	electronic data capture
EU	European Union
ESR	erythrocyte sedimentation rate
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HIV	human immunodeficiency virus
HSTCL	hepatosplenic T-cell lymphoma
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin
IRB	Institutional Review Board
ITT	intention-to-treat (population)
IUD	intrauterine device
IUS	intrauterine system
IV	Intravenous
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intention-to-treat (population)
MMF	mycophenolate mofetil
MTX	Methotrexate
PCDAI	Pediatric Crohn's Disease Activity Index
PGA	Physician's Global Assessment

PPD	purified protein derivative
PQC	product quality complaint
q8wk	every 8 weeks
QFT-TB	quantiFERON-TB
RBC	red blood cell
REACH	A Randomized, Multicenter, Open-label Study to Evaluate the Safety and Efficacy of Anti-TNFα Chimeric Monoclonal Antibody (Infliximab, REMICADE®) in Pediatric Patients with Moderate to Severe Crohn's Disease
SAP	Statistical Analysis Plan
SI	International System of Units
SUSAR	suspected unexpected serious adverse reaction
TB	Tuberculosis
TNF	tumor necrosis factor
UC	ulcerative colitis
US	United States
WBC	white blood cell

1. INTRODUCTION

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.

Remicade® (infliximab), a recombinant immunoglobulin G (IgG) 1-κ human-murine chimeric monoclonal antibody, is an antagonist of the cytokine tumor necrosis factor alpha (TNFα) that specifically binds and neutralizes both the soluble TNFα homotrimer and its membrane-bound precursor. Infliximab is indicated for treatment of several autoimmune diseases in which TNFα plays a major role, including adult patients with Crohn's disease (CD), ulcerative colitis (UC), rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, or plaque psoriasis as well as pediatric patients with CD or UC. Infliximab is administered via intravenous (IV) infusion. For the most comprehensive nonclinical and clinical information regarding infliximab refer to the most current local label.

Following the 23 Sep 2011 approval for infliximab for the treatment of pediatric patients with moderate to severe UC, the United States (US) Food and Drug Administration (FDA) requested that the sponsor obtain further data on the safety and efficacy of dose escalation in pediatric patients with inflammatory bowel disease (IBD) who have lost an initial response to infliximab.

Accordingly, the current study was designed with specific input from the FDA to evaluate whether trough concentrations at the time of loss of clinical response could be used to identify pediatric patients with CD or UC who have low infliximab exposures and would benefit from a dose increase above that currently approved without increasing the risk of serious adverse events. In addition, the correlation between trough serum infliximab concentrations and antibodies to infliximab (ATI) will be evaluated.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

Primary Objective

The primary objective of this study is to evaluate whether trough serum infliximab concentrations at the time of loss of clinical response will identify pediatric patients with IBD who would benefit (regain clinical response) from dose escalation above the currently approved dose (5 mg/kg every 8 weeks [q8wk]).

Overall safety will be assessed throughout the duration of the study.

Secondary Objectives

Secondary objectives of this study are to:

- Identify disease characteristics associated with maintenance of sustained clinical response in patients after dose escalation

- Evaluate the rate of serious adverse events in patients who receive an increased dose of infliximab due to loss of response (Dose Escalation Group) relative to the rate of serious adverse events in those patients in response who are maintained on infliximab 5 mg/kg q8wk (Reference Group)

2.2. Hypothesis

In pediatric IBD patients with loss of response, trough serum infliximab concentrations will be associated with regaining of response after dose escalation.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a multicenter, prospective, open-label study in pediatric patients with IBD who are receiving infliximab therapy (see Figure 1). The study will include 2 groups, enrolled based on entry criteria that include assessment of clinical response or loss of clinical response according to the criteria in Attachment 3 or 4, respectively, and as described below:

Dose Escalation Group (n=80): Pediatric patients with IBD who have received a) the recommended infliximab induction dosing regimen of 5 mg/kg at weeks 0, 2, and 6, have achieved clinical response and subsequently lost clinical response after at least 1 maintenance dose of 5 mg/kg q8wk (the last 2 doses occurring at least 48 days, but no more than 64 days, apart, with allowable dose range of 4.5 to 6 mg/kg); or,

b) an induction regimen with doses >6 mg/kg and have received at least 2 maintenance doses of 5 mg/kg q8wk (the last 2 doses at least 48, but no more than 64, days apart with allowable dose range of 4.5 to 6 mg/kg) and have demonstrated clinical response for at least 28 days after the most recent (second or later) 5 mg/kg maintenance dose; or,

c) maintenance doses >6 mg/kg within the past 6 months and at least 2 maintenance doses of 5 mg/kg q8wk (the last 2 doses occurring at least 48 days, but no more than 64 days, apart, with allowable dose range of 4.5 to 6 mg/kg) and have demonstrated a clinical response for at least 28 days after the most recent (second or later) 5 mg/kg maintenance dose.

These patients will dose escalate to 10 mg/kg q8wk at Week 0.

Reference Group (n=50): Pediatric patients with IBD who have received a) the recommended infliximab induction dosing regimen of 5 mg/kg at weeks 0, 2, and 6, and have achieved and maintained a stable clinical response* to infliximab after at least 1 maintenance dose of 5 mg/kg q8wk (the last 2 doses occurring at least 48 days, but no more than 64 days, apart, with allowable dose range of 4.5 to 6 mg/kg); or b) an

induction regimen with doses >6 mg/kg and have received at least 2 maintenance doses of 5 mg/kg q8wk (the last 2 doses at least 48, but no more than 64, days apart with allowable dose range of 4.5 to 6 mg/kg) and have demonstrated clinical response for at least 28 days after the most recent (second or later) 5 mg/kg maintenance dose; or,

c) maintenance doses >6 mg/kg within the past 6 months and at least 2 maintenance doses of 5 mg/kg q8wk (the last 2 doses occurring at least 48 days, but no more than 64 days, apart, with allowable dose range of 4.5 to 6 mg/kg) and have demonstrated a clinical response for at least 28 days after the most recent (second or later) 5 mg/kg maintenance dose.

* Patients with a stable clinical response to infliximab are defined as those patients who have achieved clinical response according to criteria in Attachment 3 for CD patients or Attachment 4 for UC patients and who did not initiate or receive increased doses of 5-aminosalicylic acid (5-ASA), corticosteroids, immunomodulators or antibiotics for the treatment of IBD for 4 weeks prior to screening.

Patients in the Reference Group who lose clinical response may cross over the Dose Escalation Group, provided they meet entry criteria including having $C_{trough} < 7$ µg/mL and ATI titers ≤ 12,800 (see Section 4.1, inclusion criterion #10 for the Dose Escalation Group).

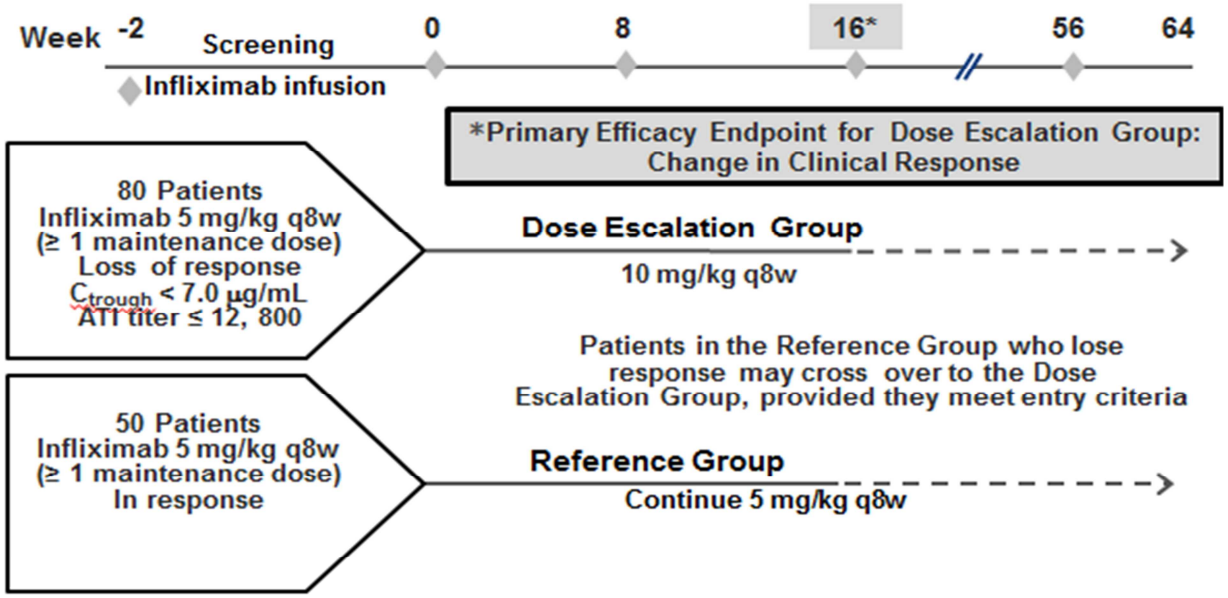
Although the Dose Escalation and Reference Groups will not be comparable in terms of disease activity, the Reference Group will provide safety information, serum infliximab concentration data, and ATI titer data in a contemporaneous IBD cohort undergoing infliximab therapy. Both the Dose Escalation and Reference Groups will include 60% CD patients and 40% UC patients at enrollment, to ensure a clinically meaningful number of patients by IBD diagnosis.

Patients in both groups will receive infliximab q8wk through Week 56, with the Final Safety Visit occurring 8 weeks after the last dose of infliximab. Investigators may discontinue patients who have not regained clinical response after receiving 2 doses of 10 mg/kg infliximab administered 8 weeks apart.

After obtaining informed consent/assent, detailed demographic and medical history, including qualitative and quantitative signs and symptoms present at initiation of infliximab therapy and the time of response, will be collected on all patients meeting inclusion and exclusion criteria at the time of enrollment. Review of concomitant medications as well as safety and efficacy assessments (Pediatric Crohn's Disease Activity Index [PCDAI] scores or partial Mayo scores) will be conducted at every study visit through Week 56. Samples will be collected for measurement of serum concentrations of infliximab and ATI titers at screening for patients in the Dose Escalation Group, prior to each infusion during the study for patients in each group, and at the time of loss of clinical response for patients in each group. If a UC patient in the Dose

Escalation Group undergoes optional ileocolonoscopy, Mayo scores will also be obtained. Refer to the Time and Events Schedule for all procedures to be performed over the course of the study. The end of the study will occur on the date of the last visit of the last patient participating in the study.

Figure 1: Dose escalation study diagram



3.2. Study Design Rationale

3.2.1. Trough Serum Infliximab Concentrations and Dose Escalation

Infliximab is highly effective for the treatment of pediatric IBD; however, 40% to 50% of patients may lose response to this agent within 1 year after the initiation of therapy, requiring dose escalation in order to regain response.[8,9] Loss of response may be explained by:

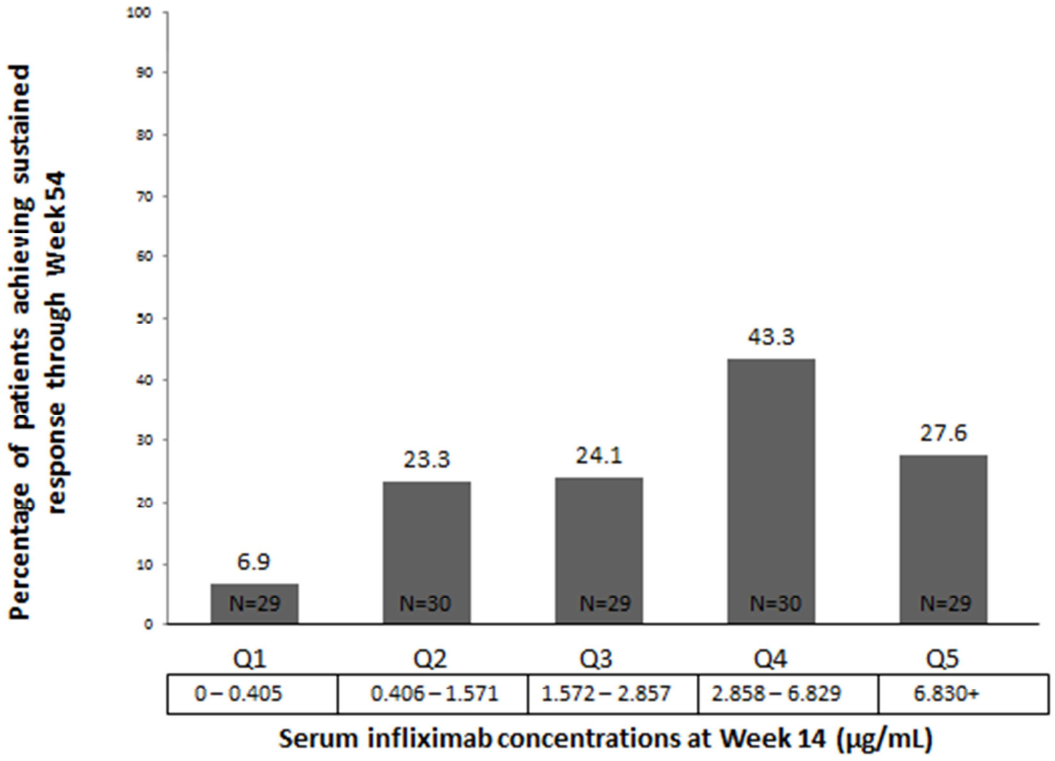
- Inadequate drug concentration (due to either inadequate dosing or rapid clearance), or
- Immunogenicity of infliximab (ie, the development of high-titer ATI), or
- Emergence of inflammatory processes independent of TNF.

Higher infliximab concentrations in the setting of low or undetectable levels of ATI have been associated with higher rates of clinical remission, lower serum C-reactive protein (CRP) concentrations, as well as endoscopic improvement in adult patients with both CD and UC.[4,11,15]

The Phase 3 infliximab program in adult patients with IBD provides exposure-response data that confirm a positive correlation between infliximab concentrations and clinical outcomes. Specifically, the Phase 3 clinical trial of infliximab in adult patients with CD, assessed the relationship between efficacy and exposure to infliximab, demonstrating a positive correlation between response status and median pre-infusion infliximab concentrations (ACCENT 1).[5]

Furthermore, examining the relationship between sustained clinical response rates at Week 54 in relation to trough levels at Week 14 stratified by quintiles demonstrates that response rates diminish above levels of 6.8 µg/mL (Figure 2).

Figure 2: Sustained response to 5 mg/kg infliximab maintenance treatment by quintile of Week 14 serum infliximab concentrations in adult Crohn's disease patients (ACCENT 1)

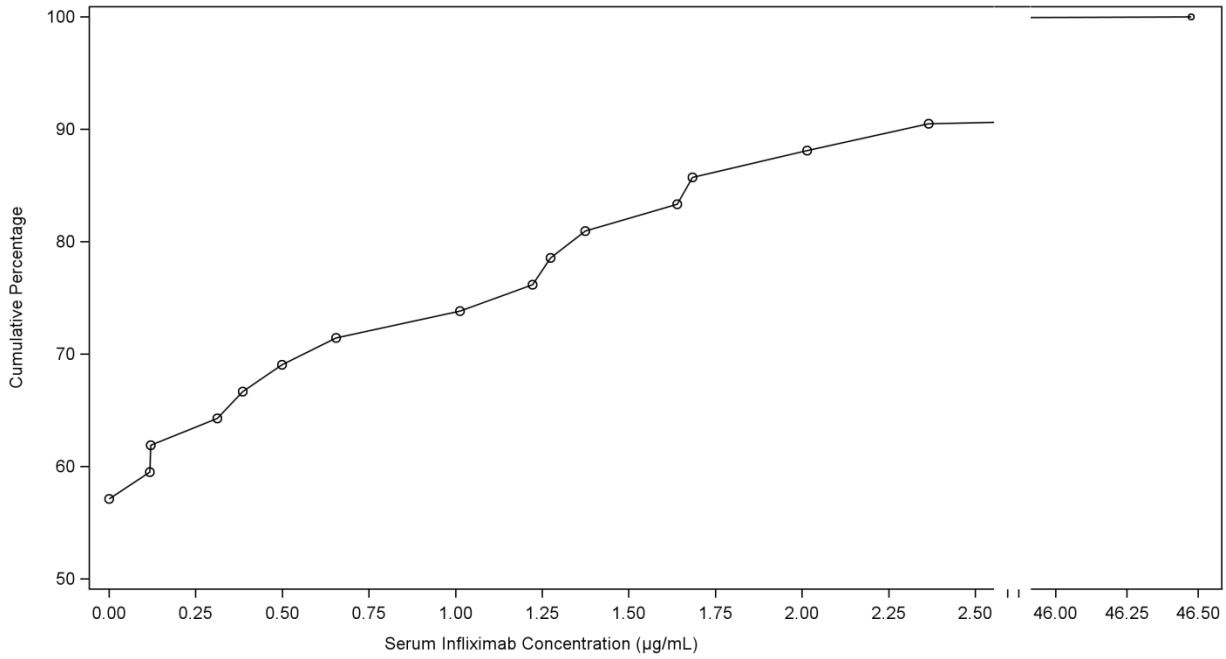


Similar analyses of data from the Phase 3 clinical trials of infliximab in adult patients with UC (ACT 1 and ACT 2),[1] demonstrate that infliximab concentrations above 6.8 µg/mL at Week 30 were associated with diminished proportions of patients achieving clinical response, mucosal healing, and clinical remission at Week 30.

The Phase 3 infliximab pediatric IBD program also demonstrated a positive relationship between infliximab concentrations and clinical response. In the Phase 3 pediatric CD study, REACH, patients with higher pre-infusion infliximab concentrations at Week 54 had greater improvements in change from baseline in PCDAI. The sponsor's Phase 3 study of pediatric patients with UC (Study C0168T72) demonstrated that at Week 8, higher serum infliximab concentrations were associated with greater proportions of patients achieving efficacy endpoints (clinical response, 92.9%; mucosal healing, 92.9%; clinical remission, 64.3%) versus those with lower serum concentrations (53.9%, 53.9%, 30.8%, respectively).[2] These studies, however, did not identify specific trough concentrations associated with sustained clinical response. Data from the Immunogenicity Substudy in DEVELOP demonstrated that among pediatric IBD patients receiving 5 mg/kg infliximab q8wk, > 50% had undetectable infliximab concentrations and

> 90% had infliximab concentrations < 7 µg/mL at the time of loss of response (data on file, Figure 3).

Figure 3: Infliximab concentration (ug/mL) at the time of loss of response in pediatric inflammatory bowel disease patients in the DEVELOP registry (n=39)



The similarity of infliximab pharmacokinetic properties between pediatric and adult patients with IBD has been well documented.[2,6] Based on the established exposure-response relationships demonstrated in adult patients with CD and UC, the documented pharmacokinetic comparability between adult and pediatric patients with IBD, and the data from the DEVELOP registry, pediatric IBD patients with loss of clinical response while on infliximab 5 mg/kg q8wk with serum infliximab concentrations < 7.0 µg/mL will most likely benefit from dose escalation.

3.2.2. Antibodies to Infliximab and Dose Escalation

The presence of ATI is associated with lower infliximab concentrations due to more rapid elimination of infliximab from serum secondary to the development of drug-anti-drug antibody complexes. Since serum infliximab concentration correlates with efficacy outcomes, the development of ATI in patients who initially respond to infliximab could potentially decrease the effectiveness of the drug. Indeed, Yanai et al (2014) reported that patients with subtherapeutic infliximab concentrations with high ATI titers had significantly higher rates of failure of early response to dose intensification as well as shorter duration of sustained response once it was regained, compared with patients with low ATI titers.[17] Finally, the association between the development of ATI and infusion reactions has also been documented.[3,12]

In the DEVELOP registry, 667 patients have participated to date in the Immunogenicity Substudy, in which ATI titers have been evaluated using the drug-tolerant

electrochemiluminescence immunoassay (ECLIA) method. A total of 24 patients in the Immunogenicity Substudy had infusion reactions, 6 of whom had serious infusion reactions. Of these 24 patients with infusion reactions, 29% (n=7) had ATI titers > 12,800 (data on file).

Also, within the Immunogenicity Substudy, 24 patients had ATI titers > 12,800, including the 7 patients with infusion reactions noted above. Of the 24 patients with ATI titers > 12,800, 71% did not have an infusion reaction, and 29% had infusion reactions. Based on data cited above, pediatric IBD patients with loss of clinical response while receiving infliximab 5 mg/kg q8wk with ATI titers ≤ 12,800 (using the ECLIA method) will most likely benefit from dose escalation, with consideration of the potential risk of infusion reactions.

3.2.3. Other Study Design Features

Infliximab will be administered open-label in order to meet the objectives of this study. The efficacy assessments chosen for this study, the PCDAI score and partial Mayo score, are validated, well-documented indices that measure clinical efficacy[10,11,16] Although the Dose Escalation and Reference Groups will not be comparable in terms of disease activity, the Reference Group will provide safety information, serum infliximab concentration data, and ATI titer data in a contemporaneous IBD cohort undergoing infliximab therapy.

4. PATIENT POPULATION

Screening for eligible patients will be performed within 28 days before the Week 0 administration of infliximab.

Pediatric patients with IBD undergoing infliximab therapy according to the local guidelines specified in the most current local label who meet the following inclusion and exclusion criteria are eligible to participate in the study.

If there is a question about the inclusion or exclusion criteria below, the investigator should consult with the appropriate sponsor representative before enrolling a patient in the study.

4.1. Inclusion Criteria

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

1. Must be male or female at least 6 years of age and less than 17 years of age at the time of enrollment

2. Must have a biopsy-confirmed diagnosis of CD or UC prior to study entry

3. Must meet concomitant medication stability criteria (see Section 8)

4. Is considered eligible according to the following tuberculosis (TB) screening criteria:
   a. Have no history of latent or active TB prior to screening
   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 prior to or simultaneously with the first on-study administration of infliximab at Week 0

d. Within 6 weeks prior to the first on-study administration of infliximab at Week 0, have a negative QuantiFERON-TB (QFT-TB) Gold test (see Attachment 1.1), or have a newly identified positive QFT-TB Gold test result in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated either prior to or simultaneously with the first on-study administration of infliximab at Week 0

e. If the QFT-TB Gold test is not approved/registered in that country or is not required per local guidelines, a negative tuberculin skin test or a newly identified positive tuberculin skin test result in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated either prior to or simultaneously with the first on-study administration of infliximab at Week 0 is additionally required (see Attachment 1.2)

f. Indeterminate QFT-TB Gold results should have the test repeated. In the event that the second QFT-TB Gold test result is also indeterminate, the patient should be excluded from the study.

g. Unless country or site guidelines do not recommend a chest radiograph as a necessary screening process prior to initiation of anti-TNF therapies, a chest radiograph (both posterior-anterior and lateral views) must have been performed within 3 months prior to infliximab initiation or during the pre-study infliximab treatment and read by a qualified radiologist; the results of which must show no evidence of current active TB or old inactive TB. Chest radiographs (both posterior-anterior and lateral views) must be performed as part of the screening process in all cases when either the tuberculin skin test and/or QFT-TB Gold test results for TB are positive or proof of previously performed negative chest radiograph cannot be obtained.

5. Must have negative stool results for enteric pathogens. Stool studies must include a stool culture and *Clostridium difficile* toxin assay. These must have been performed during screening or the current episode of disease exacerbation as long as the stool studies were performed within 4 months prior to the first on-study administration of infliximab at Week 0.

6. Must have screening laboratory test results as follows:

a. Hemoglobin: $\geq$ 7.5 g/dL

b. White blood cells (WBC): $\geq 2.5 \times 10^3$ cells/µL (SI: $\geq 2.5 \times 10^9$ cells/L)

c. Neutrophils: $\geq 1.5 \times 10^3$ cells/ µL (SI: $\geq 1.5 \times 10^9$ cells/L)

d. Platelets: $\geq 100 \times 10^3$ cells/ µL (SI: $\geq 100 \times 10^9$ cells/L)

e. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels not exceeding 2.0 times the upper limit of normal. If patients have ALT or AST levels between the ULN and 2x the ULN, clinically appropriate evaluations must be

performed (and documented in the record) prior to enrollment to rule out etiologies that would contraindicate treatment with infliximab.

f. Serum creatinine not to exceed:

- 6 to 10 years of age: 0.7 mg/dL (SI: 62 µmol/L)
- 11 to 12 years of age: 1.0 mg/dL (SI: 88 µmol/L)
- ≥ 13 years of age: 1.2 mg/dL (SI: 106 µmol/L)

7. Must be up to date with all immunizations in agreement with current local immunization guidelines for immunosuppressed patients prior to screening

8. Must have acceptable evidence of immunity to measles and varicella prior to the administration of infliximab at Week 0, including any of the following:

a. Documentation of age-appropriate vaccination for varicella and/or measles (that includes **two** doses of each vaccine), or
b. Verification of past varicella and/or measles infection by a healthcare provider (school or occupational clinic nurse, nurse practitioner, physician assistant, or physician), or
c. In the absence of (a) or (b) for varicella and/or measles, must have documentation of positive protective antibody titers (performed prior to or during screening) to varicella and/or measles.

9. If at increased risk for colon cancer, the patient must have either had a colonoscopy to assess the presence of dysplasia within 1 year prior to the first administration of infliximab at Week 0 or a colonoscopy to assess the presence of malignancy at the Screening Visit

Note: All patients who have had extensive colitis for ≥ 8 years, or disease limited to the left side of the colon for ≥ 10 years, are considered at increased risk. For patients with a pathology finding of "indefinite dysplasia with reactive atypia" on colonoscopy, the investigator should discuss the case with the medical monitor to determine eligibility.

10. Group-specific inclusion criteria are noted below:

Patients in the Dose Escalation Group:

a. Must have completed the recommended infliximab induction dosing regimen of 5 mg/kg at weeks 0, 2, and 6, and at least 1 maintenance dose of 5 mg/kg q8wk (the last 2 doses occurring at least 48 days, but no more than 64 days, apart, with allowable dose range of 4.5 to 6 mg/kg) and have demonstrated a clinical response according to the criteria in Attachment 3 for CD patients or Attachment 4 for UC patients

b. Patients who have received an induction regimen with doses greater than 6 mg/kg must have received at least 2 maintenance doses of 5 mg/kg q8wk (the last 2 doses occurring at least 48 days, but no more than 64 days, apart, with allowable dose range of 4.5 to 6 mg/kg) and have demonstrated a clinical response for at least 28

days after the most recent (second or later) 5 mg/kg maintenance dose according to the criteria in Attachment 3 for CD patients or Attachment 4 for UC patients

c. Patients who have received maintenance doses greater than 6 mg/kg within the past 6 months must have received at least 2 maintenance doses of 5 mg/kg q8wk (the last 2 doses occurring at least 48 days, but no more than 64 days, apart, with allowable dose range of 4.5 to 6 mg/kg) and have demonstrated a clinical response for at least 28 days after the most recent (second or later) 5 mg/kg maintenance dose according to the criteria in Attachment 3 for CD patients or Attachment 4 for UC patients

d. Must have lost clinical response, according to the criteria in Attachment 3 for CD patients or Attachment 4 for UC patients, after the first or subsequent q8wk maintenance dose of infliximab 5 mg/kg for patients who have completed the recommended infliximab induction dosing regimen (5 mg/kg at weeks 0, 2, and 6) or, after the most recent (second or later) q8wk maintenance dose of infliximab 5 mg/kg for patients with an induction regimen with doses >6 mg/kg or for patients with previous maintenance doses >6 mg/kg

e. Must not have discontinued infliximab therapy (discontinuation defined as period of ≥ 6 months without receiving a dose).

f. Must have received the last maintenance dose of infliximab at least 4 weeks but not more than 10 weeks prior to screening

g. Must have an infliximab C_{trough} < 7 µg/mL and ATI titers ≤ 12,800 at the time of loss of response*

h. Must have a PCDAI of > 30 points with both an abdominal pain and stool frequency sub-score of ≥ 5 (patients with CD)

i. Must have a partial Mayo score of ≥ 5 points with both stool frequency and rectal bleeding sub-scores of ≥ 1 (patients with UC)

j. Must meet **one** of the following criteria:*

- Have serum CRP > 0.287 mg/dL
- Have fecal calprotectin > 50 µg/g
- Have evidence of active disease (ulcerations) on ileocolonoscopy. The ileocolonoscopy must have occurred within 6 weeks prior to first 10 mg/kg dose.

* For patients undergoing screening for the Dose Escalation Group, those who do not meet entry criteria based on infliximab concentration and/or fecal calprotectin and/or CRP levels may have repeat infliximab concentration and/or fecal calprotectin and/or CRP levels performed during the screening process, provided that all entry criteria are met within 14 days prior to administration of the first 10 mg/kg dose of infliximab.

Patients in the Reference Group:

a. Must have completed the recommended infliximab induction dosing regimen of 5 mg/kg at weeks 0, 2, and 6, and have maintained a stable clinical response*

according to the criteria in Attachment 3 for CD patients or Attachment 4 for UC patients after at least 1 maintenance dose of 5 mg/kg q8wk (the last 2 doses occurring at least 48 days, but no more than 64 days, apart, with allowable dose range of 4.5 to 6 mg/kg)

* Patients with a stable clinical response to infliximab are defined as those patients who have achieved clinical response according to criteria in Attachment 3 for CD patients or Attachment 4 for UC patients and who did not initiate or receive increased doses of 5-aminosalicylic acid (5-ASA), corticosteroids, immunomodulators or antibiotics for the treatment of IBD for 4 weeks prior to screening.

b. Patients who have received an induction regimen with doses greater than 6 mg/kg must have received at least 2 maintenance doses of 5 mg/kg q8wk (the last 2 doses occurring at least 48 days, but no more than 64 days, apart, with allowable dose range of 4.5 to 6 mg/kg) and have demonstrated a clinical response for at least 28 days after the most recent (second or later) 5 mg/kg maintenance dose according to the criteria in Attachment 3 for CD patients or Attachment 4 for UC patients

c. Patients who have received maintenance doses greater than 6 mg/kg within the past 6 months must have received at least 2 maintenance doses of 5 mg/kg q8wk (the last 2 doses occurring at least 48 days, but no more than 64 days, apart, with allowable dose range of 4.5 to 6 mg/kg) and have demonstrated a clinical response for at least 28 days after the most recent (second or later) 5 mg/kg maintenance dose according to the criteria in Attachment 3 for CD patients or Attachment 4 for UC patients

d. Must not have discontinued infliximab therapy (discontinuation defined as period of ≥ 6 months without receiving a dose).

11. Prior to enrollment, a female must be either:

a. Not of childbearing potential: premenarchal; permanently sterilized (eg, bilateral tubal occlusion [which includes tubal ligation procedures as consistent with local regulations], hysterectomy, bilateral salpingectomy, bilateral oophorectomy); or otherwise be incapable of pregnancy, or

b. Of childbearing potential and practicing a highly effective method of birth control consistent with local regulations regarding the use of birth control methods for patients participating in clinical studies: eg, established use of oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device (IUD) or intrauterine system (IUS); barrier methods: condom with spermicidal foam/gel/film/cream/suppository or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository; male partner sterilization (the vasectomized partner should be the sole partner for that patient); true abstinence (when this is in line with the preferred and usual lifestyle of the patient)

c. Note: If the patient's childbearing potential changes after start the start of the study (eg, female who is not heterosexually active becomes active, premenarchal female experiences menarche) the patient must begin a highly effective method of birth control, as described above

12. A female patient of childbearing potential must have a negative urinary pregnancy test at both screening and Week 0

13. A female patient must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction for a period of 6 months after last dose of study medication

14. A male patient who is sexually active with a female of childbearing potential and has not had a vasectomy must agree to use a double barrier method of birth control eg, either condom with spermicidal foam/gel/film/cream/suppository or partner with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository, and all men must also not donate sperm during the study and for 6 months after receiving the last dose of infliximab

15. Each patient's legally acceptable representative must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study. Assent is also required of children capable of understanding the nature of the study as described in Section 16.2.3. If a patient turns 18 years of age after enrollment in the study, he/she must be re-consented.

16. Must be willing and able to adhere to the prohibitions and restrictions specified in this protocol

4.2. Exclusion Criteria

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

A patient is not eligible for enrollment if he/she has any of the following disease characteristics:

1. Must not require, or must not have required, within the 2 months prior to screening, surgery for active gastrointestinal bleeding, peritonitis, intestinal obstruction, or intra-abdominal or pancreatic abscess requiring surgical drainage, or other conditions possibly confounding the evaluation of benefit from infliximab treatment

2. Must not have presence or history of colonic or small bowel obstruction within 6 months prior to screening or radiographic or endoscopic evidence of a stricture with resulting obstruction (eg, dilation of the colon or small bowel proximal to the stricture on barium radiograph or an inability to traverse the stricture at endoscopy)

3. Must not have local manifestations of CD, such as fistulae, strictures, abscesses, or other disease complications for which surgery might be indicated. Enterocutaneous fistulae for which surgery is not indicated, are allowed.

4. Must not have presence of a stoma

5. Must not have documented short bowel syndrome (more than 100 cm in total of small bowel resected)

6. Must not have UC limited to the rectum only or to < 20 cm of the colon

7. Must not have severe extensive colitis as evidenced by:

   a. Investigator judgment that the patient is likely to require a colectomy within 12 weeks of baseline

      OR

   b. Symptom complex at screening or baseline visits that includes at least 4 of the following:

      1) Diarrhea with ≥ 6 bowel movements/day with macroscopic blood in stool

      2) Focal severe or rebound abdominal tenderness

      3) Persistent fever (≥ 37.5°C)

      4) Tachycardia (> 90 beats/minute)

      5) Anemia (hemoglobin < 8.5 g/dL)

8. Patients with UC must not have a history of extensive colonic resection (eg, less than 30 cm of colon remaining) that would prevent adequate evaluation of the effect of infliximab on clinical disease activity

9. Must not have a history of dysplasia or adenomatous colonic polyps that were not removed

A patient is not eligible for enrollment if he/she:

10. Is currently receiving any of the following concomitant medications:

    a. Immunomodulatory agents other than 6-mercaptopurine (6-MP), azathioprine (AZA), or methotrexate (MTX; including, but not limited to, 6-thioguanine [6-TG], cyclosporine, mycophenolate mofetil [MMF], tacrolimus, and sirolimus)

    b. Immunomodulatory biologic agents (including, but not limited to, anakinra, etanercept, certolizumab, adalimumab, rituximab, natalizumab, visilizumab, ustekinumab, and vedolizumab)

    c. Thalidomide or related agents

    d. Investigational (non-marketed) agents

    e. Oral corticosteroids at a dose > 50 mg of prednisone or its equivalent per day

    f. Require routine use (≥ 2 times per week) of antimotility agents for control of diarrhea (ie, diphenoxylate hydrochloride with atropine sulfate, loperamide, or other opioids)

    Note: While 5-ASAs and/or corticosteroids (≤ 50 mg of prednisone or its equivalent per day) are permitted:

    – A patient in the Dose Escalation Group must be on a stable dose of these medications for 2 weeks prior to screening, or he/she is ineligible for enrollment.

    – A patient in the Reference Group who is crossing over to the Dose Escalation Group must be on a stable dose of these medications for 2 weeks before dose escalation, or he/she is ineligible for dose escalation.

11. Has previously received:

    a. Natalizumab within 12 months of first infliximab administration

    b. Agents that deplete B or T cells (eg, rituximab, alemtuzumab, or visilizumab) within 12 months of first infliximab administration, or continue to manifest depletion of B or T cells more than 12 months after completion of therapy with lymphocyte depleting agents

    c. Cyclosporine, tacrolimus, sirolimus, or MMF within 8 weeks prior to first administration of infliximab at Week 0

    d. Any immunosuppressant biologic drug (approved or investigational) within 4 weeks prior to first administration of infliximab or within 5 half-lives of the investigational agent, whichever is longer, or is currently enrolled in an interventional study

    e. Apheresis (ie, Adacolumn apheresis) within 2 weeks prior to first administration of infliximab at Week 0

    f. Has used an invasive investigational medical device within 4 weeks prior to first administration of infliximab

A patient is not eligible for enrollment if he/she has any of the following infections or predisposition to infections:

12. Must not have a history of active granulomatous infection, histoplasmosis, or coccidioidomycosis, prior to screening

13. Must not have had a Bacille Calmette-Guerin (BCG) vaccination within 12 months of screening

14. Must not have a chest radiograph within 3 months prior to the first administration of study agent that shows an abnormality suggestive of a malignancy or current active infection, including TB

15. Must not have a nontuberculous mycobacterial or opportunistic infection (eg, cytomegalovirus, pneumocystosis, aspergillosis)

16. Must not have a persistently indeterminate (≥ 2) QFT-TB Gold test results; indeterminate results should be handled as outlined in Section 9.1

17. Must not have a history of, or ongoing, chronic or recurrent infectious disease, including but not limited to, chronic renal infection, chronic chest infection (eg, bronchiectasis), sinusitis, recurrent urinary tract infection (eg, recurrent pyelonephritis, chronic cystitis), an open, draining, or infected skin wound, or an ulcer

18. Must not have immune deficiency syndrome (eg, severe combined immunodeficiency syndrome, T-cell deficiency syndromes, B-cell deficiency syndromes, or chronic granulomatous disease)

19. Must not have a known history of infection with human immunodeficiency virus (HIV)

20. Must not be seropositive for antibodies to hepatitis C virus

21. Each patient must undergo screening for hepatitis B virus (HBV). At a minimum, this includes testing for HBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), and anti-HBc (total HBV core antibody); additional details are provided in Attachment 2.

    a. A patient who tests negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) ***is eligible*** for this study.

    b. A patient who tests positive for surface antigen (HBsAg+) ***is not eligible*** for this study, regardless of the results of other hepatitis B tests.

    c. A patient who tests negative for surface antigen (HBsAg-) and tests positive for total core antibody (anti-HBc+) and surface antibody (anti-HBs+) ***is eligible*** for this study.

    d. A patient who tests positive only for surface antibody (anti-HBs+) ***is eligible*** for this study.

    e. A patient who tests positive ***only*** for core antibody (anti-HBc+) must undergo further testing for hepatitis B deoxyribonucleic acid (HBV DNA test). If the HBV

DNA test is positive, the patient ***is not eligible*** for this study. If the HBV DNA test is negative, the patient ***is eligible*** for this study. If the HBV DNA test cannot be performed, the patient ***is not eligible*** for the study.

Note: For patients who are not eligible for this study due to HBV test results, consultation with a physician with expertise in the treatment of HBV infection is recommended.

22. Must not have received, or is expected to receive, any live virus or bacterial vaccination within 8 weeks (or longer as indicated in the package insert/summary of product characteristics of the relevant vaccine) prior to the first administration of infliximab

23. Must not have had a serious infection (eg, hepatitis, pneumonia, or pyelonephritis), have been hospitalized for an infection, or have been treated with parenteral antibiotics for an infection within 2 months prior to first administration of infliximab. Less serious infections (eg, acute upper respiratory tract infection, simple urinary tract infection) need not be considered exclusionary at the discretion of the investigator.

A patient is not eligible for enrollment if he/she has a history of malignancies or an increased potential for malignancy as described below:

24. Must not have presence of, or history of, any malignancy

25. Must not have a presence or history of lymphoproliferative disease including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy of unusual size or location (eg, nodes in the posterior triangle of the neck, infraclavicular, epitrochlear, or periaortic areas), or clinically significant hepatomegaly or splenomegaly

A patient is not eligible for enrollment if he/she has the following coexisting conditions or past medical history:

26. Must not have known allergies, a known hypersensitivity to human immunoglobulin proteins or other components of infliximab, or intolerance to infliximab or its excipients (refer to the most recent local label)

27. Must not have had a fever of unknown origin for longer than 3 weeks duration within 3 months prior to screening, unless thought likely to be associated with IBD

28. Must not have a concomitant diagnosis or history of congestive heart failure

29. Must not have a history of moderate or severe progressive, or uncontrolled liver or renal insufficiency; or significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, psychiatric, or metabolic disturbances

30. Must not have a concomitant diagnosis or history of systemic lupus erythematosus

31. Must not have a transplanted organ (with the exception of a corneal transplant performed > 3 months prior to the first administration of infliximab at Week 0)

32. Must not have a concomitant diagnosis or history of demyelinating disease, such as multiple sclerosis or optic neuritis

33. Must not have a current or prior history of substance abuse (drug or alcohol)

Other reasons for which a patient is not eligible for this study include the following:

34. Must not have poor tolerability of venipuncture or lack of adequate venous access for required blood sampling

35. Must not be pregnant, nursing, or planning pregnancy or fathering a child

36. Must not have any condition for which, in the opinion of the investigator, participation would not be in the best interest of the patient (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments

37. Must not be an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator

38. The patient and/or parent/guardian are not able to adhere to the protocol requirements

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a patient's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of infliximab is given such that he or she no longer meets all eligibility criteria, then the patient 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 patients 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. Must not receive a live virus or live bacterial vaccination during the study or within 6 months after the last administration of infliximab

2. Must not receive a BCG vaccination during the study or within 12 months after the last administration of infliximab

3. Must agree not to plan a pregnancy or father a child within 6 months following the last administration of infliximab

4. If sexually active, female patients must be practicing a highly effective method of birth control (eg, prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method [eg, condoms, diaphragm, or cervical cap, with spermicidal foam, cream, or gel], or male partner sterilization) as local regulations permit, during the study and for 6 months after receiving the last administration of infliximab

5. If sexually active, males must use a double barrier method of birth control and not donate sperm during the study and for 6 months after receiving the last administration of infliximab

6. Must not be enrolled in any of the following while participating in the study:

   a. Any interventional clinical trial with an investigational agent (ie, non-marketed agent)

   b. Any interventional clinical trial, observational study, and/or registry with inclusion/exclusion criteria that prohibit concurrent enrollment in other studies

5. TREATMENT ALLOCATION AND BLINDING

This is an open-label study. A patient will be allocated to the Dose Escalation Group or the Reference Group depending on response to his or her current treatment regimen as described in inclusion criterion #10.

6. DOSAGE AND ADMINISTRATION

Upon meeting enrollment criteria for the Dose Escalation Group (see inclusion criterion #10), patients will receive infliximab 10 mg/kg q8wk (Figure 1) at Week 0. Patients will be eligible to receive 56 weeks of therapy with infliximab at the escalated dose with a Final Safety Visit at Week 64. Investigators may discontinue patients in the Dose Escalation Group who have not regained clinical response after receiving 2 doses of 10 mg/kg infliximab, administered 8 weeks apart.

Upon meeting enrollment criteria for the Reference Group (see inclusion criterion #10), patients will receive 5 mg/kg q8wk. Those who lose clinical response during participation in the study will be eligible, if they meet the enrollment criteria for the Dose Escalation Group, to cross over to the Dose Escalation Group.

Patients in the Reference Group who lose response and cross over to the Dose Escalation Group must complete screening for the Dose Escalation Group and receive the first 10 mg/kg dose of infliximab within 40 weeks of enrollment into the study.

Patients who cross over from the Reference Group to the Dose Escalation Group will be eligible to receive a total of 56 weeks of therapy with infliximab, which includes duration of therapy while in the Reference Group prior to dose escalation.

7. TREATMENT COMPLIANCE

Infliximab will be administered as an IV infusion by qualified study-site personnel and the details of each administration will be recorded in the CRF (including date, start and stop times of the IV infusion, and volume infused).

8. PRESTUDY AND CONCOMITANT THERAPY

The name, dose, frequency, route of administration, the start and stop dates, and duration of any therapy taken by the patient for CD or UC at any time in the past (eg, 5-ASAs; corticosteroids; immunomodulators, including thiopurines; biologics; antibiotics) is to be recorded in the case report form (CRF). For biologics, brand (trade) names will be recorded.

In addition, any other prestudy therapies administered up to 30 days before the first administration of infliximab at Week 0 must be recorded at screening.

Concomitant therapies must be recorded throughout the study beginning at screening through the Final Safety Visit. Concomitant therapies should also be recorded beyond the Final Safety Visit only in conjunction with new or worsening adverse events or serious adverse events that meet the criteria outlined in Section 12.3.2.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens) different from infliximab must be recorded in the CRF. Recorded information will include the name of the therapy, treatment period, and its indication. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a patient into the study.

The following concomitant medications for IBD are allowed in this study: 5-ASAs, corticosteroids, immunomodulators (ie, 6-MP, AZA, MTX), and antibiotics.

For patients in the Dose Escalation Group:

- For patients receiving concomitant therapy with 5-ASAs, and/or corticosteroids, and/or immunomodulators, and/or antibiotics the dosage of these medications must be stable for 2 weeks before screening
- Between Week 0 and Week 16, concomitant IBD medications (ie, 5-ASAs, and/or corticosteroids, and/or immunomodulators, and/or antibiotics) should not be initiated or their dose increased
- For UC patients receiving 5-ASAs at baseline, the dose must remain stable for 16 weeks after dose escalation
- For patients receiving immunomodulators (ie, 6-MP, AZA, or MTX), corticosteroids or antibiotics at baseline, the immunomodulators and antibiotics may be tapered or may be discontinued at any time during the study, and corticosteroids may be tapered beginning at Week 0

For patients in the Reference Group who cross over to the Dose Escalation Group:

- Patients receiving concomitant therapy with 5-ASAs, and/or corticosteroids, and/or immunomodulators, and/or antibiotics, the dosage of these medications must be stable for 2 weeks before receiving the 10 mg/kg dose
- For 16 weeks after dose escalation, concomitant IBD medications (ie, 5-ASAs, and/or corticosteroids, and/or immunomodulators, and/or antibiotics) should not be initiated or their dose increased
- For UC patients receiving 5-ASAs at the time of dose escalation, the dose must remain stable for 16 weeks after dose escalation
- For patients receiving immunomodulators (ie, 6-MP, AZA, or MTX), corticosteroids, or antibiotics at the time of dose escalation, the immunomodulators and antibiotics may be tapered or may be discontinued at any time during the study, and corticosteroids may be tapered beginning at the time of dose escalation

Medications that are prohibited after enrollment are defined in Section 4.2, exclusion criteria #10 and #11.

For patients in ***both*** the Dose Escalation and the Reference Group:

Treatment with and tapering of corticosteroids (including budesonide) is at the discretion of the investigator. For those patients whom the investigator determines it is appropriate to taper the use of corticosteroids and budesonide, the following tapering schedule is recommended:

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 at 2.5 mg/week until 0 mg/day.
- Dose ≤ 10 mg/day prednisone or equivalent: taper daily dose by 2.5 mg/week until 0 mg/day.

Recommended tapering schedule for oral budesonide

Patients receiving budesonide should have their daily dose tapered by 3 mg every 3 weeks until 0 mg/day. Cases of hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients with CD and UC who were treated with AZA. Postmarketing cases of HSTCL have also been reported in adolescent and young adult patients with CD and UC who have received infliximab and other anti-TNF therapies with concomitant AZA or 6-MP therapy. Some of these patients had limited exposure to infliximab and other anti-TNF therapies. Investigators should carefully assess the potential risks and benefits of infliximab use in combination with the immunomodulators AZA or 6-MP in both the Dose Escalation and Reference Groups prior to initiating or continuing the use of these immunomodulators. Investigators are encouraged to individualize patient therapy and are permitted to discontinue immunomodulators during screening or at any time during the study.

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. Screening Procedures

Screening procedures will be performed as indicated in the Time and Events Schedule.

At the Screening Visit, written informed consent must be obtained from the patient's parent or legal guardian, and assent must be obtained from the patient. Informed consent and assent must be obtained for this study by the principal investigator or designee prior to conducting any protocol-specific procedure. Pre-screening stool sample consent may be obtained prior to the screening visit per local or site requirements.

Patients must undergo testing for TB (see Attachment 1.1 [QFT-TB test] or Attachment 1.2 [tuberculin skin test]) 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 (see Section 9.5.5). The patient should be asked about past testing for TB, including chest radiograph results and responses to tuberculin skin or other TB testing. Patient eligibility for enrollment based on TB test results is described in inclusion criterion #4.

Each patient must undergo screening for HBV. At a minimum, this includes testing for HBsAg, anti-HBs, and anti-HBc; additional details are provided in Attachment 2.

At screening and subsequent visits, PCDAI and Mayo diary cards will be distributed for patients to use over the course of the study. Patients (or their legally-acceptable representatives) will be instructed to complete the diary cards daily and will be reminded to bring the diary cards to each visit for data collection and review by the investigator/study coordinator. Information needed for the PCDAI or partial Mayo scores with respect to questions such as stool frequency or quality, abdominal pain, and general well-being will be obtained from the patient diary and/or recall at Week 0 and subsequent visits. CD patients (or their legally acceptable representatives) will be instructed to ensure that liquid stools reported on the PCDAI are indeed loose or watery.

Female patients of childbearing potential must have a negative urine pregnancy test at screening and a negative urine test at Week 0. Sexually active patients must consent to use a highly effective method of contraception and continue to use contraception for the duration of the study. The method(s) of contraception used by each patient must be documented.

An assessment of all screening laboratory test results, including serum infliximab concentration and ATI titers; clinical data; and concomitant medication data will be reviewed by the principal investigator or designee to confirm that the patient satisfies all inclusion criteria and does not violate any exclusion criteria. If a patient needs to be rescreened, this should be discussed with the sponsor and/or the sponsor's designee.

9.2. Study Procedures

The Time and Events Schedule summarizes the frequency and timing of assessments applicable to this study.

All visit-specific assessments should be completed before administration of infliximab. The maximum acceptable visit window for all visits after the screening visit is ± 7 days. Patients must meet all enrollment criteria prior to the first on-study administration of infliximab at Week 0.

The total blood volume to be collected from each patient will be approximately 124.5 mL over the course of the study; however, repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

While the Final Safety Visit is to occur at Week 64, investigators may recontact the patient's legal representative or the patient (if of age of consent) to obtain long-term follow-up information to determine the patient's safety or survival status (refer to Section 16.2.3).

Patients will be instructed that infliximab will not be made available to them by the sponsor after they have completed or discontinued from the study, and that they should return to their primary physicians to determine standard of care.

9.3. Clinical Assessments

9.3.1. Evaluations

The disease activity assessments listed below should be performed for both Reference and Dose Escalation Group patients.

9.3.1.1. Pediatric Crohn's Disease Activity Index (PCDAI)

The PCDAI is a validated clinical tool used to assess disease severity in pediatric patients with CD.[10] This assessment should be performed for all study visits at which infliximab is administered (Week 0 - Week 56/End of Treatment). The PCDAI collects information on the following disease-related variables:

- Total number of liquid stools, abdominal pain, and general well-being (scored by the patient or patient's legal representative);
- Extra-intestinal manifestations;
- Physical examinations of abdominal mass and, perirectal disease;
- Weight change and height change or, height velocity; and
- Hematocrit, erythrocyte sedimentation rate (ESR), and albumin.

The PCDAI score is calculated as the sum of the individual component scores and ranges from 0 to 100 points.

For calculation of PCDAI at Week 0 for CD patients in the Dose Escalation Group the hematocrit, ESR, and albumin values obtained during screening will be used. For calculation of PCDAI prior to the first 10 mg/kg dose for CD patients crossing over from the Reference Group to the Dose Escalation Group, the hematocrit, ESR, and albumin obtained within 2 weeks prior to the administration of the first 10 mg/kg dose will be used. The PCDAI should be calculated prior to infliximab administration at Week 0 for the Dose Escalation Group or prior to the administration of the first 10 mg/kg dose for patients crossing over from the Reference Group.

9.3.1.2. Mayo and Partial Mayo Score

The Mayo score is a validated clinical tool used to assess disease activity in patients with UC.[11] This assessment should be performed for all study visits at which infliximab is administered (Week 0 - Week 56/End of Treatment).

Mayo UC activity scores are as follows:

- Clinical remission: a score of ≤ 2 points, with no individual sub-score > 1
- Mildly active disease: a score of 3 to 5 points
- Moderately active disease: a score of 6 to 10 points
- Severe disease: a score of 11 to 12

Mayo scores are calculated using the following:

1) Stool frequency and rectal bleeding data from the most recent consecutive 3-day period prior to the visit excluding the day(s) that medications for constipation, diarrhea, or irregularity were taken, the day(s) of a procedure or preparation for a procedure that would affect bowel frequency and/or blood content of the stool, the 48 hours after the use of anti-motility agent(s), and the 72 hours after a colonoscopy;

2) The Physician's Global Assessment (PGA); and

3) The results of a sigmoidoscopy or colonoscopy.

Partial Mayo scores (which exclude endoscopic data[11]) range from 0 – 9 and are categorized as follows:

- Inactive disease: a score of 0 – 2
- Mild disease: a score of 3 – 4
- Severe disease: a score of 5 – 9

9.3.1.3. Wong-Baker FACES Pain Scale

The Wong-Baker FACES Pain Scale is a pain scale that combines pictures and numbers to allow pain to be rated by children over the age of 3.[4] The scale shows a series of faces ranging from a happy face at 0, "No hurt" to a crying face at 10 "Hurts worst". The patient must choose the face that best describes how they are feeling.

The Wong-Baker FACES Pain Scale should be completed prior to infliximab administration at Week 0, Week 16 and Week 56 visits for the Dose Escalation Group and Reference Group, or prior to the administration of the first and third 10 mg/kg dose for patients crossing over from the Reference Group. In addition, all patients who discontinue treatment will complete the Wong-Baker FACES pain scale at the time of treatment discontinuation visit.

9.3.1.4. Stool Frequency (Absolute Value)

Absolute stool frequency values will be recorded from patients' recall prior to infliximab administration at Week 0, Week 16 and Week 56 visits for the Dose Escalation Group and Reference group or prior to the administration of the first and third 10 mg/kg dose for patients crossing over from the Reference Group. In addition, stool frequency information should be obtained from all patients who discontinue treatment at the time of treatment discontinuation visit.

9.3.1.5. Optional Evaluations

For patients in the Dose Escalation Group, investigators may perform optional ileocolonoscopy during screening or as standard care within 6 weeks prior to the first infliximab 10 mg/kg dose, and again at Week 24 or later. For patients who cross over from the Reference Group to the Dose Escalation Group, investigators may perform optional ileocolonoscopy within 2 weeks prior to the first 10 mg/kg infliximab dose and at least 24 weeks after dose escalation.

9.3.2. Endpoints

Primary Endpoint

The primary efficacy endpoint is clinical response at Week 16 after dose escalation, defined as:

- CD patients: A decrease from baseline in PCDAI of ≥ 15 points with total score of ≤ 30 points
- UC patients: A decrease from baseline in partial Mayo score of ≥ 2 points and ≥ 30% and a decrease in the rectal bleeding sub-score by ≥ 1 point or achievement of an absolute sub-score of ≤ 1 point

Secondary Endpoints

Major secondary efficacy endpoint: Sustained clinical response through 56 weeks after dose escalation

Other pharmacokinetic and clinical remission secondary endpoint: The relationship between trough infliximab levels and clinical remission at Week 16 will be analyzed with the Reference Group and the Dose Escalation Group patients in a combined analysis

Other secondary efficacy endpoints:

1. For CD patients changes from baseline at Week 16 and at Week 56 in:
    - Abdominal pain and loose/watery stool frequency sub-scores of the PCDAI

- Abdominal pain using the Wong-Baker FACES scale
- Absolute stool frequency

2. For UC patients changes from baseline at Week 16 and at Week 56 in:
    - Stool frequency and rectal bleeding sub-scores of the partial Mayo score
    - Abdominal pain using the Wong- Baker FACES scale
    - Absolute stool frequency
3. Correlates of Wong-Baker FACES scale with clinical remission and response at Week 16
4. The association between abdominal pain PCDAI sub-score and the Wong-Baker FACES scale for CD patients

Secondary safety endpoint: The incidence of serious adverse events

9.4. Serum Infliximab Concentrations and Antibodies to Infliximab

Venous blood samples will be collected for measurement of serum concentrations of infliximab and ATI titers at the times shown in the Time and Events Schedule. Serum infliximab concentrations will be determined using a validated, enzyme-linked immunosorbent assay. Serum ATI titers will be determined using a validated, drug-tolerant ECLIA method. All samples will by assayed by the sponsor or its designee. All samples collected for detection of ATI titers will also be evaluated for serum infliximab concentration to enable interpretation of the antibody data.

Samples collected for analysis may additionally be used for additional evaluations, to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these samples. Patient confidentiality will be maintained.

9.5. Safety Evaluations

Details regarding an internal Safety Monitoring Committee are provided in Section 11.7.

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.

9.5.1. Adverse Events

Adverse events will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient'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.

9.5.2. Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected. The investigator must review the laboratory report, 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.

The following tests will be performed:

- Hematology Panel

  -hemoglobin
  -hematocrit
  -red blood cell (RBC) count
  -WBC count with differential
  -platelet count
  -percent reticulocytes

- Serum Chemistry Panel

  -sodium
  -potassium
  -chloride
  -bicarbonate
  -blood urea nitrogen (BUN)
  -creatinine
  -glucose
  -AST
  -ALT
  -gamma-glutamyltransferase (GGT)
  -total, direct, indirect bilirubin
  -alkaline phosphatase
  -uric acid
  -calcium
  -phosphate
  -albumin
  -total protein
  -magnesium

- Urine pregnancy testing for female patients of childbearing potential
- QFT-TB Gold test (or tuberculin skin test in countries where the QFT-TB Gold test is not approved/registered or is not required per local guidelines)
- Stool culture for enteric pathogens, including *Clostridium difficile* toxins. The following medications should be avoided for 48 hours prior to the sample collection: antacids, barium, bismuth, antidiarrheal medication, and oily laxatives.
- Stool fecal calprotectin
- Serology for Hepatitis B
- Serology for Hepatitis C
- Serology for varicella and measles antibody titers
- Determination of antinuclear antibody (ANA) and anti-double stranded DNA antibody (anti-dsDNA antibody) status
- ESR for CD patients only
- CRP
- Infliximab concentration and antibody to infliximab titers

- **Abnormal liver function tests.** If laboratory testing for a patient who is enrolled in the study and receiving study drug reveals an increase of serum aminotransferases (ALT or AST) to >3 x ULN and an increase of bilirubin to >2 x ULN, study agent administration should be suspended immediately. In addition, laboratory tests for ALT, AST, alkaline phosphatase, and total bilirubin should be confirmed by a retest within 24 hours if possible, but no later than 72 hours after notification of test results. See Attachment 5 (Liver Safety: Suggested Actions and Follow-up Assessments) for additional information on monitoring and assessment of abnormal liver function tests.

During the study, all abnormal laboratory values will require further explanation from the investigator. Clinically significant abnormal laboratory values should be repeated until they return to normal or are otherwise explained by the investigator.

Refer to the Time and Events Schedule for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

9.5.3. Physical Examination and Vital Signs

Complete physical examinations (including skin and genitourinary examination) are to be conducted.

Vital signs assessed in this study will include heart rate, blood pressure, temperature, height, and weight.

9.5.4. Screening Chest Radiograph

Unless country or site guidelines do not recommend a chest radiograph as a necessary screening process prior to initiation of anti-TNF therapies, a chest radiograph (both posterior-anterior and lateral views) must have been performed within 3 months prior to infliximab initiation or during the pre-study infliximab treatment and read by a qualified radiologist; the results of which must show no evidence of current active TB or old inactive TB.

Chest radiographs (both posterior-anterior and lateral views) must be performed as part of the screening process in all cases when either the tuberculin skin test and/or QFT-TB Gold test results for TB are positive or proof of negative chest radiograph performed prior to initiation of infliximab cannot be obtained.

9.5.5. Early Detection of Active Tuberculosis

To aid in the early detection of TB reactivation or new TB infection during study participation, patients must be evaluated for signs and symptoms of active TB at scheduled or unscheduled visits (refer to Time and Events Schedule) or by telephone contact approximately every 8 to 12 weeks. 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 patient may have TB reactivation or new TB infection, infliximab 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 patients may present as disseminated disease or with extrapulmonary features. Patients with evidence of active TB must immediately discontinue infliximab and should be referred for appropriate treatment.

Patients who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph, a repeat QFT-TB Gold test, a repeat tuberculin skin test in countries in which the QFT-TB Gold test is not approved/registered/required or the tuberculin skin test is mandated by local health authorities, and, if possible, referral to a physician specializing in TB to determine the patient's risk of developing active TB and whether treatment for latent TB is warranted. Infliximab administration should be interrupted during the investigation. A positive QFT-TB Gold test result should be considered detection of latent TB. If the result is indeterminate, the test should be repeated as outlined in Section 9.1. If recommended, treatment for latent TB must be initiated prior to or simultaneously with the administration of further infliximab. Patients who discontinue treatment for latent TB prematurely or who are noncompliant with therapy must immediately discontinue further administration of infliximab, and will be required to return to the study site 8 weeks after the last administration of infliximab, at which time the Week 64 procedures are to be performed.

Patients with recent exposure to TB, a history of a positive purified protein derivative (PPD) test, negative active TB evaluation and indeterminate QFT-TB TB Gold test should have an annual chest radiograph.

10. PATIENT COMPLETION/WITHDRAWAL

10.1. Completion

A patient will be considered to have completed the treatment and safety follow-up portions of the study if he/she has completed study assessments through Week 64.

10.2. Discontinuation of Study Treatment

If treatment with infliximab must be discontinued before the end of the treatment period, this will not result in automatic withdrawal of the patient from the study. Treatment with infliximab should be permanently discontinued if any of the following occur:

- The investigator believes that for safety reasons (eg, an adverse event) it is in the best interest of the patient to discontinue infliximab
- The patient becomes pregnant
- Reaction resulting in bronchospasm (both new onset infliximab-related and severe exacerbation of pre-existing asthma) with and without wheezing, and/or dyspnea requiring ventilatory support, and/or symptomatic hypotension with an absolute systolic blood pressure below the patient's gender and age- or height-specific normal value or a greater than 40 mmHg decrease in systolic blood pressure that occurs following an infliximab administration
- Reaction resulting in myalgia and/or arthralgia with fever and/or rash (suggestive of serum sickness and not representative of signs and symptoms of other recognized clinical syndromes) occurring 1 to 14 days after an infliximab infusion. These may be accompanied by other events including pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and/or headache.
- Opportunistic infection
- Malignancy
- Congestive heart failure
- Demyelinating disease
- The patient is deemed ineligible according to the following TB screening criteria:
  - A diagnosis of active TB is made
  - A patient 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 patient undergoing continued evaluation has a chest radiograph with evidence of current active TB and/or a positive QFT-TB Gold test result and/or a positive tuberculin skin test result in countries in which the QFT-TB Gold test is not approved/registered/required and/or an indeterminate QFT-TB Gold test result on repeat testing with an additional TB risk factor as determined by the medical monitor and investigator
  - A patient receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy
- Crohn's disease-related bowel surgery with the exception of abscess drainage and seton placement
- If, in the opinion of the patient and the investigator, a UC patient requires a colectomy (partial or total)

- The patient (or the patient's legal representative) withdraws consent for administration of infliximab
- The initiation of medications as specified in Section 4.2, exclusion criteria #10a-d and #11
- Severe hepatic function abnormalities, as described in Section 9.5 and Attachment 5

If a patient discontinues participation in the study, he/she will be required to return for a Final Safety Visit 8 weeks following the final administration of infliximab. At that time, the procedures and evaluations indicated in the Time and Events Schedule at Week 64 will be performed. All procedures and evaluations must be conducted prior to withdrawal of consent.

10.3. Withdrawal From the Study

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

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

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

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

11. STATISTICAL METHODS

Statistical analysis will be conducted 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 (SAP).

11.1. Patient Information

The modified intention-to-treat (mITT) population will be used as the primary analysis dataset for the primary endpoint. The mITT population includes all patients enrolled in the Dose Escalation Group who receive at least one 10 mg/kg dose of infliximab after enrollment, including those who cross over from the Reference Group to Dose Escalation Group.

The per-protocol population will include all patients who enrolled in the Dose Escalation Group including those who cross over from the Reference Group to the Dose Escalation Group, receive at least two 10 mg/kg doses of infliximab, and do not have major protocol deviations. Patients who met the following criteria will be excluded from the per-protocol analysis:

- Patients who meet loss of clinical response criteria who did not receive two 10 mg/kg doses, or
- Patients who did not meet loss of clinical response criteria but who did receive at least one 10 mg/kg dose.

The per-protocol population will be used as a sensitivity analysis for the primary endpoint. For patients who cross over from the Reference Group to the Dose Escalation Group, the data prior to and after crossover will be summarized for this subgroup, and these data will also be included in the corresponding Dose Escalation and Reference Groups.

The safety population will include all patients who received infliximab after enrollment. The treatment group is based on the treatment dose the patients actually received.

Patients' demographic and baseline disease characteristics will be summarized using descriptive statistics, for all patients, and by CD and UC subgroups. The baseline measurement is defined as the measurement collected at Week 0 prior to the infliximab dose or collected at the Screening Visit if not collected at Week 0.

11.2. Sample Size Determination

Both the Dose Escalation and Reference Groups will be composed of 60% CD patients and 40% UC patients. Accordingly, the proposed study will enroll 80 (48 CD and 32 UC) patients in the Dose Escalation Group and 50 (30 CD and 20 UC) patients in the Reference Group, with the conservative assumption that approximately 10 patients (20%) in the Reference Group may dose escalate.[8,9] Thus, the final sample size in the Dose Escalation Group is estimated to be 90 patients, with 54 CD patients and 36 UC patients (Figure 4).

The sample size estimation was calculated based on precision estimates for clinical response rates after dose escalation from 5 mg/kg q8w to 10 mg/kg q8w at Week 16, the primary efficacy endpoint.

It is anticipated the dropout rate due to loss of follow up and other non-efficacy related reasons by Week 16 will be about 5% of patients), based on the Phase 3 pediatric infliximab trials in CD and UC patients.[8,9] As indicated in Table 1, adjusting for dropout rate, a sample size of 76 - 85 patients (without or with cross over) will provide precision estimates between ± 8.5 – 11.2% for expected response rates between 20 - 50%, based on a 2-sided 95% confidence interval (CI). The anticipated range for clinical response is based on the response rates for adult patients undergoing infliximab dose escalation.[13,14]

There are currently no data available on pediatric patients with loss of response on 5 mg/kg q8w not receiving dose escalation. For the purposes of a conservative sample size calculation, a response rate of 5% was assumed for patients with loss of clinical response not receiving dose escalation, although it would be predicted that the actual response rate would be negligible (< 1%). At a significance level of 0.05 (2-sided), the statistical power is greater than 90% to detect at least a 15% increase in clinical response after dose escalation, for the overall Dose Escalation Group (N=76 – 85, without or with cross over). For the CD subgroup (N = 46 - 51, without or with cross over), the power is between 84% - 90%. For the UC subgroup (N = 30 - 34, without or with cross over), the power is between 70% - 74%.

When testing the association between infliximab concentration and regain of clinical response after dose escalation, using logistic regression to test the null hypothesis of no association between infliximab serum concentrations and clinical response, ie, $\beta = 0$ ($\alpha = 0.05$, 2-sided), a sample size of 76 - 85 patients (without or with cross over) will provide statistical power between 66% and 85% to detect β of 0.916, assuming the response rate is between 20 – 50%.

Figure 4: Sample size details by diagnosis with crossover assumptions

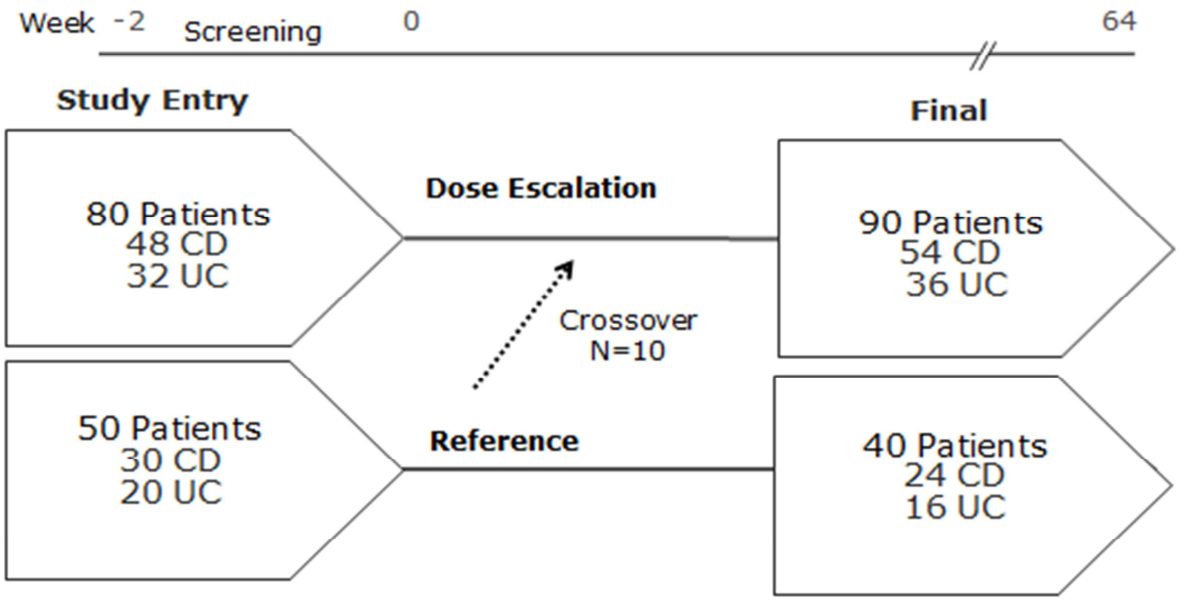


Table 1: Precision estimation for anticipated clinical response rates, adjusting for 5% non-efficacy related dropout rate prior to Week 16

Treatment group	Sample Size	Clinical Response Rate			
		20%	30%	40%	50%
Dose Escalation Group with Reference Group crossover	85	±8.5%	±9.7%	±10.4%	±10.6%
Dose Escalation Group without Reference Group crossover	76	±9.0%	±10.3%	±11.0%	±11.2%
CD patients (Dose Escalation Group with Reference Group crossover)	51	±11.0%	±12.6%	±13.4%	±13.7%
UC patients (Dose Escalation Group with Reference Group crossover)	34	±13.4%	±15.4%	±16.5%	±16.8%

Key: CD = Crohn's disease; UC = ulcerative colitis

In DEVELOP, the most common serious adverse event category has been gastrointestinal disorders, with an event rate of approximately 10.6 events per 100 patient-years among patients exposed to infliximab as the only biologic medication (data on file). The sample size of 80 - 90 dose escalation patients will provide a 95% CI of ± 6.4 - 6.7% around an event rate of 10.6% (ie, ± 6.4 - 6.7% estimated precision). The sample size of 40 - 50 patients in the Reference Group of the proposed study will provide a 95% CI of ± 8.5 - 9.5% around an event rate of 10.6% (ie, ± 8.5 - 9.5% estimated precision).

11.3. Efficacy Analyses

11.3.1. Analyses for the Primary Endpoint

11.3.1.1. Analyses

The primary endpoint is clinical response at Week 16, defined as:

- CD patients: A decrease from baseline in PCDAI of ≥ 15 points with total score of ≤ 30 points
- UC patients: A decrease from baseline in partial Mayo score of ≥ 2 points and ≥ 30% and a decrease in the rectal bleeding sub-score by ≥ 1 point or achievement of an absolute sub-score of ≤ 1 point

The following analyses are planned:

Analysis of clinical response rates at Week 16

For the primary analysis, the clinical response rate at 16 weeks after dose escalation and the surrounding 2-sided 95% CI will be estimated for the entire Dose Escalation Group. Assuming a response rate of 5% for patients with loss of clinical response not receiving dose escalation, the proposed study will demonstrate the efficacy of dose escalation if the lower limit of the 95% CI for the proportion of patients in clinical response at Week 16 is > 5%. For the patients who cross over from the Reference Group to the Dose Escalation Group, clinical response at 16 weeks after dose escalation will be included in the primary endpoint analysis. The clinical response rate at 16 weeks after dose escalation and the surrounding 95% CI (2-sided) will also be estimated for subgroups of CD and UC patients.

Analyses of the relationship between trough serum infliximab concentrations and clinical response at Week 16

Logistic regression will be performed to evaluate the relationship between serum infliximab concentration prior to dose escalation and clinical response at Week 16 after dose escalation in the Dose Escalation Group, including patients who cross over from the Reference Group.

The entire distribution of trough serum infliximab concentrations prior to the first 10 mg/kg infliximab dose will serve as the independent variable in these analyses, in which trough serum infliximab concentrations will be treated as a continuous variable. In additional analyses, trough serum infliximab concentrations prior to dose escalation will be treated as a categorical variable, where the association between the infliximab concentration cutoff value prior to dose escalation (eg, cutoffs of 3, 3.5, or 4 µg/mL or by quartiles) and clinical response will be evaluated. Inflammatory bowel disease diagnosis (CD or UC) will be included as a covariate in the logistic regression analysis.

The effect of potential confounding factors will be assessed, as appropriate, in the logistic regression analysis. The possible covariates may include age, sex, disease duration, duration of infliximab treatment prior to infliximab dose increase, antibodies to infliximab, and immunomodulator use.

Details of the analysis will be provided in the SAP.

11.3.1.2. Missing Data Handling for the Primary Endpoint Analyses

In the primary analysis of the primary endpoint, if a patient discontinues from the study prior to Week 16 due to 'loss of efficacy' or worsening of disease, the patient will be considered a non-responder. If a patient has missing data at Week 16 for other non-efficacy related reasons that are likely to be random (eg, loss of follow up), multiple imputations will be used to handle data missing at random. The details of multiple imputations will be provided in the SAP.

Sensitivity analyses will be conducted using 'worst case' non-responder imputation (ie, patients with missing data at Week 16 will be treated as non-responders). Completer analysis without imputation will also be performed as a sensitivity analysis. Logistic regression analysis will be performed using response data without imputation.

11.3.2. Analyses for the Secondary Endpoints

The major secondary efficacy endpoint is sustained clinical response at Week 56, defined as achieving clinical response per the primary endpoint definitions at Week 16 and maintaining clinical response at 1 year after dose escalation (Week 56). The proportions of patients achieving sustained clinical response will be summarized. Infliximab concentrations and ATI status over time will be summarized by sustained clinical response status at Week 56. Logistic regression methods will be used, as appropriate, to evaluate the association between sustained response and trough serum infliximab concentration and the impact of potential confounding factors may be assessed.

The other secondary efficacy endpoints include:

1. For CD patients changes from baseline at Week 16 and at Week 56 in:
    - Abdominal pain and loose/watery stool frequency sub-scores of the PCDAI
    - Abdominal pain using the Wong-Baker FACES scale
    - Absolute stool frequency
2. For UC patients changes from baseline at Week 16 and at Week 56 in:
    - Stool frequency and rectal bleeding sub-scores of the partial Mayo score
    - Abdominal pain using the Wong-Baker FACES scale
    - Absolute stool frequency

Descriptive statistics and 95% CIs will be provided for these endpoints. A Wilcoxon signed rank test or paired t-test will be used, when appropriate, to evaluate within patient change on these disease signs and symptoms measurements from baseline at Week 16 and at Week 56. Descriptive statistics will be used to summarize these measurements over time. The analysis will be performed for both the Dose Escalation and Reference groups.

The Sponsor will analyze how the Wong-Baker FACES scale correlates with clinical remission/response by performing a logistical regression to evaluate the association between Wong-Baker FACES scale and clinical response at Week 16.

In a secondary analysis, an ordinary regression model will be used to evaluate the association between abdominal pain PCDAI sub-score and the Wong-Baker FACES scale for CD patients.

Analyses for the secondary safety endpoint are described in Section 11.5.

11.3.3. Other Planned Efficacy Analyses

Descriptive summaries of clinical disease status (ie, PCDAI and partial Mayo scores) will include number of patients, mean, median, standard deviation, minimum and maximum values for continuous variables and frequency and percentage for categorical variables. PCDAI or partial Mayo scores over time and change from baseline will be summarized for the Dose Escalation and Reference groups, and by CD and UC subgroups.

For patients who cross over from the Reference Group to the Dose Escalation Group, the clinical disease status prior to and after crossover will be summarized. Graphic methods will be used, as appropriate, to display parameter estimates over time.

11.4. Serum Infliximab Concentrations and Antibodies to Infliximab

Serum infliximab concentrations and ATI titers will be listed for all patients with available data.

If the data do not allow for accurate assessment of serum infliximab concentrations (eg, incomplete administration of infliximab, missing information of dosing, and sampling times), they will be excluded from the analyses.

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All patients and samples excluded from the analyses will be clearly documented in the study report.

The proportion of ATI positive patients will be summarized for the Dose Escalation Group and the Reference Group. The partial PCDAI and partial Mayo scores will be summarized by ATI status. Infliximab concentrations will also be summarized for the Dose Escalation Group and the Reference Group.

The relationship between trough infliximab levels and clinical remission at Week 16 will be analyzed with the Reference Group and the Dose Escalation Group patients in a combined analysis.

For patients who cross over from the Reference Group to the Dose Escalation Group, the infliximab concentration and ATI status prior to and after cross over will be summarized.

11.5. Safety Analyses

Safety analysis will be performed on the safety population, where the treatment group is based on the dose the patients actually received.

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 treatment-emergent adverse events will be included in the analysis. Non-treatment-emergent adverse events will be presented in listings. For each adverse event, the percentage of patients who experience at least 1 occurrence of the given event will be summarized by treatment group.

As one of the secondary objectives of the study, adverse event and serious adverse event rates will be summarized for both the Dose Escalation and Reference and Groups, to evaluate the rate of serious adverse events in the Dose Escalation Group relative to the rate in the Reference Group. Adverse event and serious adverse event incidences per 100 patient-years of follow up will be summarized in a similar manner. For events of special interest, eg, serious infections, the 95% CI of event rates will be estimated for the Dose Escalation and the Reference Groups. Because the Dose Escalation and Reference Groups are not comparable in terms of disease activity, logistic regression or Cox proportional hazard models will be used to compare serious adverse events rates between these 2 groups, adjusting for potential confounding factors, such as disease severity, with the acknowledgment that these models will not be able to fully adjust for confounding by indication.

Averse events prior to and after crossover will be summarized for patients who cross over from the Reference Group to the Dose Escalation Group. The safety profile of these patients before and after dose escalation will provide additional data for the comparison of the incidence of serious adverse events between dosing regimens. Adverse events will also be summarized by CD and UC subgroups.

In addition, gastrointestinal and non-gastrointestinal adverse events will be summarized for the Dose Escalation and Reference Groups.

Summaries, listings, or patient narratives may be provided, as appropriate, for those patients who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the SAP) will be used in the summary of laboratory data. Descriptive statistics will be calculated for the Dose Escalation Group and the Reference Group for each laboratory measurement at baseline and at each scheduled time point as appropriate. Analyses for CD and UC subgroups will be performed. Frequency tabulations of the changes from baseline will be presented in pre- versus posttreatment cross-tabulations (with classes for below, within, and above normal ranges). A listing of patients with any laboratory results outside the reference ranges will be provided. A listing of patients with any markedly abnormal laboratory results will also be provided.

Vital Signs

Descriptive statistics will be used to summarize heart rate, blood pressure, temperature, height, and weight at baseline and changes from baseline over the course of the study as appropriate. The percentage of patients with values beyond clinically important limits will be summarized.

11.6. Interim Analysis

There will be no interim analyses performed.

11.7. Safety Monitoring Committee

An internal Safety Monitoring Committee will be established to monitor the safety data on an ongoing basis to ensure the continuing safety of the patients enrolled in this study. The committee will meet periodically to review the safety data (ie, adverse events and laboratory results). After the review, the Safety Monitoring Committee will make recommendations regarding the continuation of the study. The details will be provided in a separate charter. The Safety Monitoring Committee will consist of a clinician and a statistician, at a minimum. The Safety Monitoring Committee's responsibilities, authorities, and procedures will be documented in its charter.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of patients, 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 patient 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 European Union (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 patient 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 patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Adverse Events of Special Interest

- ***Serious Infections***: A serious infection is an infection diagnosed by a physician based on results of culture, microscopy, serology, biopsy, or imaging, or based on clinical judgment, that also meets the definition of a serious adverse event.
- ***Tuberculosis***: Any diagnosis of active or latent TB occurring in patients participating in the study must be reported by the investigator. 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.
- ***New Malignancy***: Any diagnosis of a malignancy in patients participating in the registry must be reported by the investigator. After the initial report of a malignancy (including during the screening visit), only new malignancies (defined as a malignancy that was not diagnosed prior to the time of the last visit/telephone contact in the study) are to be reported thereafter. These include lymphoproliferative disease including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy of unusual size or location (eg, nodes in the posterior triangle of the neck, intraclavicular, epitrochlear, or periaortic areas), or splenomegaly.

Although not considered an adverse event of special interest, investigators should report any occurrence of a premalignant condition.

- ***Dysplasia of the Colon***: The presence of dysplasia in the colon will be determined on the basis of biopsies obtained by colonoscopy and interpreted by a local pathologist. The determination of the need to conduct a colonoscopy or obtain biopsies will be made by the treating physician.
- ***New Autoimmune Disease***: Autoimmune diseases (including lupus-like syndrome, psoriasis, multiple sclerosis, or other demyelinating diseases) that are diagnosed during participation in the study should be reported. Following the recording of an autoimmune disease (including during the screening visit), only new autoimmune disease (defined as an autoimmune disease not diagnosed prior to the time of the last visit/telephone contact in the study) must be reported thereafter.
- ***Opportunistic Infection***: Opportunistic infections due to bacterial, mycobacterial, invasive fungal, viral, or parasitic organisms including, but not limited to aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, histoplasmosis, legionellosis, listeriosis, pneumocystosis, and tuberculosis must be reported.

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 infliximab, the expectedness of an adverse event will be determined by whether or not it is listed in the current local label. For a non-sponsor therapy with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the package insert/summary of product characteristics.

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.

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 patient (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest following administration of infliximab that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of infliximab
- Suspected abuse/misuse of infliximab
- Inadvertent or accidental exposure to infliximab
- Any failure of expected pharmacologic action (ie, lack of effect) of infliximab
- Unexpected therapeutic or clinical benefit from use of infliximab
- Medication error involving a sponsor product (with or without patient exposure to infliximab, eg, name confusion)

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 patient'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 8 weeks after the last dose of infliximab, 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.

All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

All adverse events, regardless of seriousness, severity, or presumed relationship to infliximab, 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.

Patients (or their designees) 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 patient 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
- Patient number

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 patient'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 infliximab or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (patient 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 patient'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 such as pending placement in long-term care facility)
- 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 patient in a study whether or not the event is expected or associated with infliximab, is considered a serious adverse event.

12.3.3. Adverse Events of Special Interest

Any newly identified adverse event of special interest occurring after the first administration of infliximab in patients participating in this clinical study must be reported by the investigator using the appropriate adverse event of special interest notification form within 24 hours of the event.

Note: These events are to be considered serious only if they meet the definition of a serious adverse event.

The sponsor is conducting a separate research study to learn more about HSTCL in patients with inflammatory bowel disease. Any patient who develops HSTCL during the course of this study

may be contacted to determine if he/she is interested in participating in the HSTCL research study.

12.3.4. Pregnancy

All initial reports of pregnancy in female patients or partners of male patients 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. If a patient becomes pregnant during the study, treatment with infliximab should be discontinued. The patient will be required to return for a follow-up safety visit 8 weeks after the last administration of infliximab.

Because the effect of infliximab on sperm is unknown, pregnancies in partners of male patients included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form.

Additional 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 on 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 patients, 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 on the Contact Information page(s), which will be provided as a separate document.

14. INFLIXIMAB INFORMATION

14.1. Physical Description of Infliximab

Infliximab will be supplied as a sterile, white, lyophilized powder in a single-use 20 mL vial. Each vial contains 100 mg infliximab. Infliximab will be reconstituted with 10 mL of Sterile Water for Injection, resulting in a concentration of 10 mg/mL infliximab for administration. Each mL of the solution contains 10 mg of infliximab, 50 mg of sucrose, 0.61 mg of dibasic sodium phosphate dihydrate, 0.22 mg of monobasic sodium phosphate monohydrate, and 0.05 mg of polysorbate 80.

The maximum dose of infliximab per infusion is 1 g.

14.2. Packaging

The investigational supplies will be uniquely packaged to assure that they are appropriately managed throughout the supply chain process.

14.3. Labeling

Infliximab labels will contain information to meet the applicable regulatory requirements.

14.4. Preparation, Handling, and Storage

The vials of infliximab must be stored in a secured refrigerator at 2°C to 8°C.

The physical stability of reconstituted infliximab has been demonstrated for at least 24 hours when stored at 25°C. However, because the infliximab formulation does not contain a preservative, it is recommended that the administration of the solution for infusion is started as soon as possible but within 3 hours of reconstitution and dilution.

Each vial must be reconstituted with Sterile Water for Injection using a syringe equipped with a 21-gauge or smaller needle (eg, 22-, 23-, or 25-gauge). The lyophilized powder should be completely dissolved within 5 minutes. Dissolution of the powder is accomplished by careful rotation of the vial. ***DO NOT SHAKE!*** Foaming of the solution on reconstitution is not unusual. Following reconstitution, the solution must be allowed to sit for 5 minutes to allow foaming to subside. The solution should be colorless to light yellow and opalescent. A few translucent particles may develop, as infliximab is a protein. ***DO NOT USE THE SOLUTION IF OPAQUE PARTICLES, DISCOLORATION, OR OTHER FOREIGN PARTICLES ARE PRESENT.*** The reconstituted solution must be combined from the appropriate number of vials and diluted in normal saline to a final volume of 250 mL. It is recommended that the infliximab infusion be started as soon as possible but within 3 hours after it has been reconstituted and diluted. Aseptic procedures must be used during the preparation and administration of the study material. The

infusion must be administered over a period of not less than 2 hours and must use an infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (pore size of 1.2 µm or less). The vials do not contain antibacterial preservatives. Therefore, any unused portion of the infusion solution should not be stored for reuse.

Additional details for the preparation and administration of infliximab are provided in the site investigational product manual.

14.5. Drug Accountability

The investigator is responsible for ensuring that all infliximab received at the site is inventoried and accounted for throughout the study.

All infliximab infusions administered to the patient must be documented on the drug accountability form. Infliximab will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of infliximab containers.

Infliximab 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 infliximab must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused infliximab will be documented on the drug return form. When the study site is an authorized destruction unit and infliximab 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.

Infliximab should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Infliximab will be supplied only to patients participating in the study. Infliximab may not be relabeled or reassigned for use by other patients. The investigator agrees neither to dispense infliximab 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:

- Site investigational product manual
- Laboratory manual
- PCDAI and partial Mayo diaries with user instructions
- CDC Growth Charts
- Wong-Baker FACES Pain Scale
- Stool frequency questionnaire

- Interactive web response system (IWRS) Manual
- Electronic Data Capture (eDC) Manual
- Sample ICF

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential patients will be fully informed of the risks and requirements of the study and, during the study, patients will be given any new information that may affect their decision to continue participation. They will be told that their consent/assent 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 patients who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent/assent voluntarily will be enrolled.

When referring to the signing of the ICF, the terms legal guardian and legally acceptable representative refer to the legally appointed guardian of the child with authority to authorize participation in research. For each patient, his or her parent(s) (preferably both parents, if available) or a legally acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. Assent must be obtained from children (minors) capable of understanding the nature of the study, depending on the institutional policies. For the purposes of this study, all references to patients who have provided consent (and assent as applicable) refers to the patient and his or her parent(s) or the patient's legal guardian(s) or legally acceptable representative(s) who have provided consent according to this process. Minors who assent to a study and later withdraw that assent should not be maintained in the study against their will, even if their parents still want them to participate.

The total blood volume to be collected is considered to be within the normal range allowed for this patient population over this time frame.[7]

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 patients. Compliance with this standard provides public assurance that the rights, safety, and well-being of study patients 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 patients)
- Local label (or equivalent information) and amendments/addenda
- Sponsor-approved patient recruiting materials
- Information on compensation for study-related injuries or payment to patients 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 patients
- 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 patients, data or study conduct), the ICF, applicable recruiting materials, and patient 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 patients, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to patients
- If applicable, new or revised patient recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to patients for participation in the study, if applicable
- New edition(s) of the local label
- 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 infliximab
- New information that may adversely affect the safety of the patients or the conduct of the study

- Deviations from or changes to the protocol to eliminate immediate hazards to the patients
- Report of deaths of patients 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 patients, 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. The reapproval should be documented in writing (excluding the ones that are purely administrative, with no consequences for patients, data, or study conduct).

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/Assent

Each patient (or a legally acceptable representative) must give written consent/assent 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) and assent forms that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the patient 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 patients or their legally acceptable representatives the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Patients 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 patient will receive for the treatment of his or her disease. Patients 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 patient 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 patient, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the patient or legally acceptable representative is authorizing such access, including permission to obtain information about his or her survival status, and agrees to allow his or her study physician to recontact the patient for the purpose of obtaining consent for additional safety evaluations, if needed, and subsequent disease-related treatments, or to obtain information about his or her survival status.

The patient 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 patient'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 patient.

If the patient 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 patient or legally acceptable representative is obtained.

Children (minors) or patients who are unable to comprehend the information provided can be enrolled only after obtaining consent of a legally acceptable representative. Assent must be obtained from children (minors) capable of understanding the nature of the study, depending on the institutional policies. Written assent should be obtained from patients who are able to write. A separate assent form written in language the patient can understand should be developed for adolescents. After having obtained the assent, a copy of the assent form must be given to the patient, and to the patient's parent and/or legally acceptable representative.

If a patient participating in this study turns 18 years of age after enrollment, the patient must be re-consented.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from patients 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 patients confidential.

The informed consent/assent obtained from the patient (or his or her legally acceptable representative) includes explicit consent/assent 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. Written informed consent must be obtained from the patient’s parent or legal guardian, and assent must be obtained from the patient. Informed consent and assent must be obtained for this study by the principal investigator or designee prior to conducting any protocol-specific procedure.

The patient 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.

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

No samples will be stored for additional 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, 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 patients, 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 IRB (and IEC 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 (see Contact Information page(s) provided separately). 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 infliximab 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, patient 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 patient:

- 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, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

17.3. Patient Identification, Enrollment, and Screening Logs

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

The patient identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure patient confidentiality, no copy will be made. All reports and communications relating to the study will identify patients by patient identification and date of birth. In cases where the patient is not randomized into the study, the date seen and date of birth will be used.

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

17.4. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the CRF: patient identification, eligibility, and study identification; study discussion and date of signed study and (if applicable) pre-screening stool sample collection informed consents; 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; infliximab administration information; and date of study completion and reason for early discontinuation of infliximab or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a patient should be consistent with that commonly recorded at the study site as a basis for standard medical care. Specific details required as source data for the study will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by patient interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

17.5. Case Report Form Completion

Case report forms are provided for each patient in printed or electronic format.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the patient's source documentation. All data relating to the study must be recorded in CRFs prepared by the sponsor. Data must be entered into CRFs in

English. Study site personnel must complete the CRF as soon as possible after a patient visit, and the forms should be available for review at the next scheduled monitoring visit.

All patient measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible. The investigator must verify that all data entries in the CRFs are accurate and correct.

All CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. The investigator or study-site personnel must adjust the CRF (if applicable) and complete the query.

Corrections to paper CRFs must be made in such a way that the original entry is not obscured. Correction fluid or tape must NOT be used. The correct data must be inserted, dated, and initialed by the investigator or an authorized member of the study-site personnel. If multi-part pressure-sensitive CRFs are used, the study-site personnel must not write on separated parts of the CRFs left at the study site once the original has been sent to the sponsor. Completed CRFs will be continuously submitted according to the sponsor's instructions and reviewed by the sponsor to determine their acceptability. If necessary, Data Correction/Clarification Forms (DCFs) will be generated and transmitted to the study site. The investigator or an authorized member of the study-site personnel must complete, sign, and date the DCFs.

If corrections to a paper CRF are needed after removal of the original CRF copy from the study site, a DCF will be used.

If corrections to an electronic CRF are needed after the initial entry into the CRF, this can be done in 3 different ways:

- 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).
- Study site manager can generate a query for resolution by the study-site personnel.
- Clinical data manager can generate a query for resolution by the 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 paper CRFs for accuracy and completeness during on-site monitoring visits and after their return to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. The data will be entered into the study database and verified for accuracy and consistency with the data sources.

The sponsor will review electronic CRFs 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 CRFs and all source documents that support the data collected from each patient, 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.

For CRFs completed on pressure-sensitive paper, a copy is to be retained in the archives of the sponsor. A second copy must be archived by the investigator.

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 use a combination of monitoring techniques to monitor this study, including central, remote, and/or on-site 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 CRFs with the hospital or clinic records (source documents). 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 documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. Findings from this review of CRFs and source documents 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 documentation 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.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

17.9. Study Completion/Termination

17.9.1. Study Completion

The study is considered completed with the last visit for the last patient participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final patient 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 patients 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 and comparison with the CRFs. Patient 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 infliximab 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, including research 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 infliximab, 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 CRF data from all study sites that participated in the study, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's database. 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 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 patient 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/or disclose the existence of and the results of clinical studies as required by law.

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ATTACHMENT 1: TUBERCULOSIS TESTING

Attachment 1.1: QuantiFERON®-TB Gold Testing

The QuantiFERON®-TB Gold test is one of the interferon-γ (IFN-γ) based blood assays for TB screening (Cellestis, 2009). 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 has been 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 central laboratory. The central laboratory will perform an ELISA to quantify the amount of IFN-γ present in the plasma using spectrophotometry and computer software analysis.

The central 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, US guidelines must be followed.

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

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Attachment 1.2: 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 Seruminstitut, 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 the US and many other 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.

In the US and Canada, 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.

In countries outside the US and Canada, 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, US 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, US guidelines must be followed.

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ATTACHMENT 2: HEPATITIS B VIRUS (HBV) SCREENING WITH HBV DNA TESTING

Patients must undergo screening for hepatitis B virus (HBV). At a minimum, this includes testing for HBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), and anti-HBc total (HBV core antibody total):

- Patients who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) ***are eligible*** for this study.
- Patients who test **negative** for surface antigen (HBsAg-) and test **positive** for core antibody (anti-HBc+) ***and*** surface antibody (anti-HBs+) ***are eligible*** for this study.
- Patients who test **positive only** for **surface antibody** (anti-HBs+) ***are eligible*** for this study.
- Patients who test **positive** for surface antigen (HBsAg+) ***are NOT eligible*** for this study, regardless of the results of other hepatitis B tests.
- Patients who test **positive only** for **core antibody** (anti-HBc+) must undergo further testing for the presence of hepatitis B virus deoxyribonucleic acid (HBV DNA test). If the HBV DNA test is **positive**, the patient ***is NOT eligible*** for this study. If the HBV DNA test is **negative**, the patient ***is eligible*** for this study. In the event the HBV DNA test cannot be performed, the patient ***is NOT eligible*** for this study.

For patients who **are not eligible for this study due to HBV test results**, consultation with a physician with expertise in the treatment of hepatitis B virus infection is recommended.

Eligibility based on hepatitis C and B virus test results	
Eligible	**Not Eligible**
HBsAg-, anti-HBc-, anti-HBs-	HBsAg+ (regardless of the results of other HB tests)
Anti-HBc+, Anti-HBs+	Seropositive for antibodies to hepatitis C virus
Anti-HBs+	
Patients only positive for core antibody (anti-HBc+) require further testing for HBV DNA	
HBV DNA-	HBV DNA+
	HBV DNA test cannot be performed
Legend: HBV (hepatitis B virus) anti-HBs (HBV surface antibody) HBsAg (HBV surface antigen) anti-HBc (HBV core antibody)	

ATTACHMENT 3: DEFINITION OF INITIAL RESPONSE AND LOSS OF RESPONSE TO INFLIXIMAB THERAPY FOR PATIENTS WITH CROHN'S DISEASE

The criteria for initial response and response followed by loss of response are described below.

Initial response to current therapy with infliximab

Based on available medical records or at screening **have or had at least 1 of the following evidences of response, as assessed by a treating physician:**

- Improvement in stool frequency
- Improvement in rectal bleeding
- Improvement in daily abdominal pain/discomfort
- Weight gain or voluntary weight stable/loss
- Improvement in perirectal disease
- Improvement in extra-intestinal manifestations

These signs and symptoms of Crohn's disease are offered only as a benchmark of the minimally acceptable criteria required to designate a patient as having had an adequate initial response to infliximab therapy. This benchmark acknowledges that the PCDAI is not routinely recorded in clinical practice.

Response followed by loss of response to current therapy with infliximab

Subjects must satisfy criteria A and B.

A. Initially responded to infliximab therapy (as per the criteria above)

AND

B. At screening have at least 1 of the following signs or symptoms related to recurrence of Crohn's disease, as assessed by a treating physician:

- Worsening in stool frequency
- Worsening in rectal bleeding
- Worsening in abdominal pain/discomfort
- Involuntary weight stable or weight loss
- Occurrence of or worsening in perirectal disease
- Occurrence of or worsening in extra-intestinal manifestations

These signs and symptoms of Crohn's disease are offered only as a benchmark of the minimally acceptable criteria required to designate a patient as having lost response to infliximab. This benchmark acknowledges that the PCDAI is not routinely recorded in clinical practice.

ATTACHMENT 4: DEFINITION OF INITIAL RESPONSE AND LOSS OF RESPONSE TO INFLIXIMAB THERAPY FOR PATIENTS WITH ULCERATIVE COLITIS

The criteria for initial response and response followed by loss of response are described below.

Initial response to current therapy with infliximab

Based on available records or at screening have or had at least 1 of the following evidences of response, as assessed by a treating physician:

- Improvement in stool frequency
- Improvement in rectal bleeding
- Improvement in daily abdominal discomfort

These signs and symptoms of ulcerative colitis are offered only as a benchmark of the minimally acceptable criteria required to designate a patient as having had an adequate initial response to infliximab therapy. This benchmark acknowledges that the Mayo Severity Index is not routinely recorded in clinical practice.

Response followed by loss of response to current therapy with infliximab

Subjects must satisfy criteria A and B.

C. Initially responded to infliximab therapy (as per the criteria above)

AND

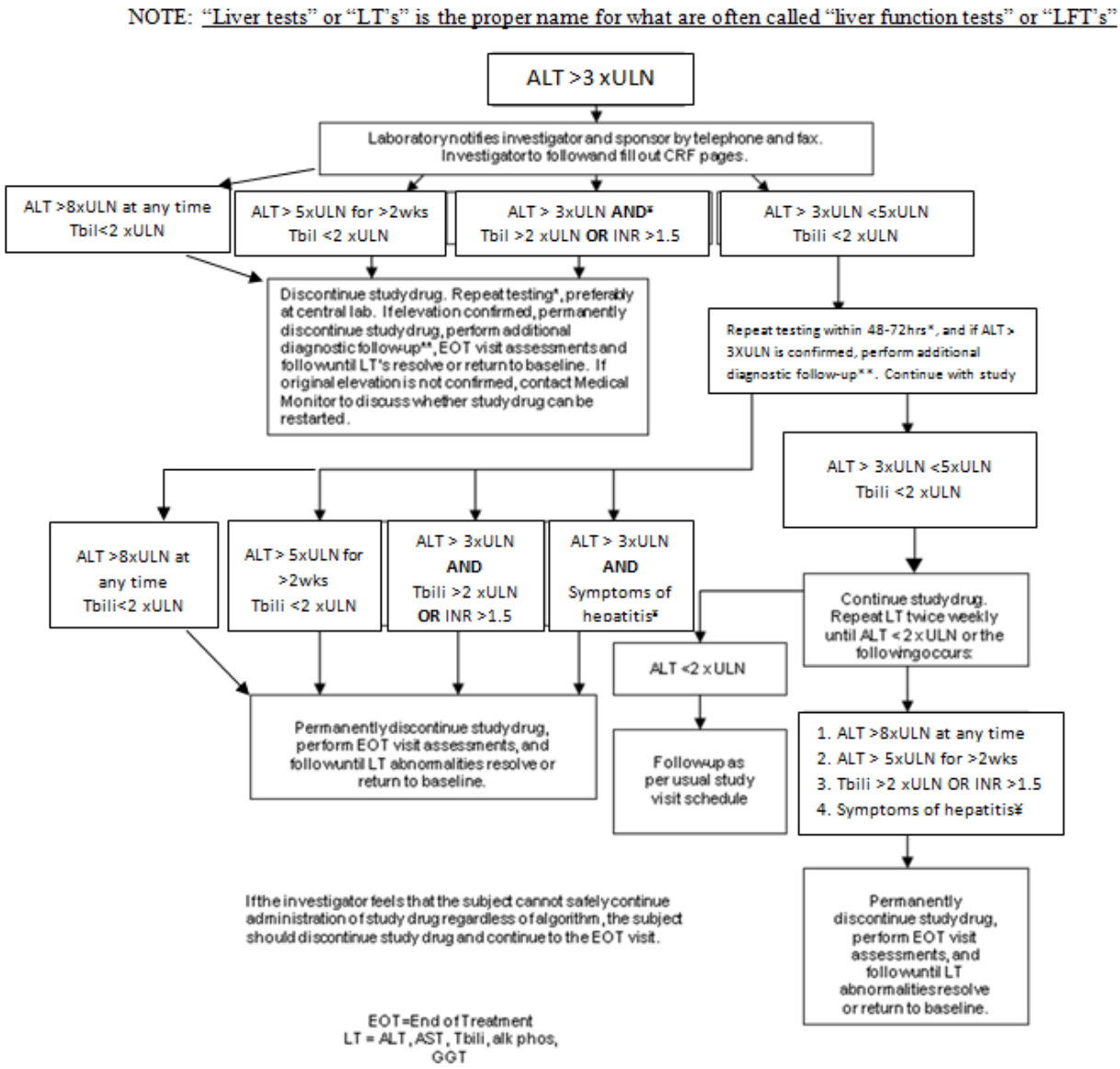
D. At screening have at least 1 of the following signs or symptoms related to recurrence of ulcerative colitis, as assessed by a treating physician:

- Worsening in stool frequency
- Worsening in rectal bleeding
- Worsening in daily abdominal discomfort

These signs and symptoms of ulcerative colitis are offered only as a benchmark of the minimally acceptable criteria required to designate a patient as having lost response to infliximab. This benchmark acknowledges that the Mayo Severity Index is not routinely recorded in clinical practice.

ATTACHMENT 5: LIVER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

Guideline Algorithm for Monitoring, Assessment, and Evaluation of Abnormal Liver Tests in Participants with No Underlying Liver Disease and Normal Baseline ALT, AST, Alkaline Phosphatase, and Bilirubin



*Repeat testing within 48-72 hours in patients with initial ALT elevations, particularly if these are not events reported previously with the drug. If ALT transient elevations have been already established as part of the safety profile, the required frequency of retesting can be decreased

¥ OR ALT >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

**SEE NEXT PAGE FOR TESTS AND EVALUATIONS TO BE OBTAINED

The complete work-up below (items 1-5) should be performed in every situation where "" appears above. Items 6-7 are optional, to be considered on case-by-case basis. All studies should be reported with appropriate source documentation.**

The study medical monitor should be notified when the abnormalities are detected and provided with an update of the results of the diagnostic work-up.

The following definition of patterns of Drug-Induced Liver Injury (DILI) is used when directing the work-up for potential DILI based on elevations of common liver tests (LT):

Histopathology	LT	Ratio (ALT/ULN)/(Alk Phos/ULN)
Hepatocellular	**ALT ≥3 × ULN**	**≥5**
Cholestatic	**ALT ≥3 × ULN**	**≤2**
Mixed	**ALT ≥3 × ULN and AP ≥2 × ULN**	**>2 to <5**

1. Obtain detailed history of present illness (abnormal LT's) including (if not already obtained at baseline) height, weight, body mass index (BMI). Assess for abdominal pain, nausea, vomiting, scleral icterus, jaundice, dark urine, pruritus, rash, fever, and lymphadenopathy. Assess for history of prior abnormal liver tests, liver disease including viral hepatitis, obesity, metabolic syndrome, congestive heart failure (CHF), occupational exposure to hepatotoxins, diabetes mellitus (DM), gallstone disease or family history of gallstone or liver disease. Specifically record history of alcohol use, other meds including acetaminophen, non-steroidal anti-inflammatory drugs (NSAID), over the counter (OTC) herbal supplements, vitamins, nutritional supplements, traditional Chinese medicines, and street drugs; and document whether or not there has been any recent change in any other prescription drugs and start-stop dates. Obtain travel history to endemic areas for hepatitis A, hepatitis E. Ask for history of any prior blood transfusions and when they were performed. Perform physical exam, obtain vital signs and BMI, and document presence or absence of scleral icterus, palpable liver including size, degree of firmness or tenderness, palpable spleen including size, ascites, and stigmata of chronic liver disease (spider angiomata, gynecomastia, palmar erythema, testicular atrophy). Allow free text in case report form for other relevant history and physical information.
2. Mandatory liver ultrasound with consideration of further imaging (eg, computerized tomography [CT], magnetic resonance imaging [MRI], magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), Doppler studies of hepatic vessels, etc., if indicated based on ultrasound findings or clinical situation).
3. If total bilirubin (Tbili) is >2xULN, request fractionation to document the fraction that is direct bilirubin and to rule out indirect hyperbilirubinemia indicative of Gilbert's syndrome, hemolysis or other causes of indirect hyperbilirubinemia. Complete blood count (CBC) with white blood count (WBC) and eosinophil count platelet count, international normalized ratio

(INR), and total protein and albumin (compute globulin fraction) should also be documented. If INR is abnormal, prothrombin time (PT), partial thromboplastin time (PTT) should be obtained and these values should be followed until normal, along with documentation of whether parenteral vitamin K was given along with the effect of such treatment on INR.

4. If initial LTs and ultrasound do not suggest Gilbert's syndrome, biliary tract disease or obstruction, viral hepatitis serology should be obtained including anti-hepatitis A virus immunoglobin M (anti-HAV IgM), anti-HAV total, hepatitis B surface antigen (HBsAg), anti-HBs, anti-HB core total, anti-HB core IgM, anti-hepatitis C virus (anti-HCV), anti-hepatitis E virus IgM (anti-HEV IgM) (even if has not traveled to an endemic area for hepatitis E), Epstein-Barr virus (EBV) and Cytomegalovirus (CMV) screen.
   - If patient is immunosuppressed, test for HCV RNA and HEV RNA.
   - If HBsAg or anti-HB core IgM or anti-HB core IgG positive, also get HBV DNA to detect active HepB, especially in patients who are immunosuppressed.
   - If all other hepatitis B serologic tests are negative and anti-HBc total is the only positive test, HBV DNA should be obtained to detect reactivation of hepatitis B.
5. Assuming that the history, physical, and initial imaging and laboratory has not revealed a cause of elevated LTs, screen for other causes of liver disease including: Total protein and albumin (estimate globulin fraction and obtain quantitative immunoglobulins if elevated), antinuclear antibody (ANA), anti-liver kidney microsomal antibody type 1 (anti-LKM1), anti-liver-kidney microsomal antibodies (anti-LKM antibodies), anti-smooth muscle antibodies (ASMA), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). If the pattern of laboratory abnormalities is not hepatocellular, but cholestatic or a mixed pattern (see definitions in table above), then gamma-glutamyl transferase (GGT), anti-mitochondrial antibody (AMA) and anti-neutrophil cytoplasmic antibody (pANCA) should also be tested. If there is an indication by history or elevated baseline LTs that there may be an underlying chronic liver disease possibly exacerbated by exposure to the study intervention in the clinical trial or making the participant more susceptible to DILI, test iron/Total iron binding capacity (TIBC) and ferritin (hemochromatosis), and alpha-1-antitrypsin level. If patient is <50 years of age, ceruloplasmin should also be tested to screen for Wilson's disease. If patient is sick enough to be hospitalized and is under age 50, a slit lamp examination to detect Kayser-Fleischer rings and a 24-hour urine collection for copper should be measured. Consider serum ethanol and/or acetaminophen level and urine drug screen as clinically appropriate.
6. A liver biopsy should be considered if autoimmune hepatitis remains a competing etiology and if immunosuppressive therapy is contemplated.

   A liver biopsy may be considered:

   - if there is unrelenting rise in liver biochemistries or signs of worsening liver function despite stopping the suspected offending agent.
   - if peak ALT level has not fallen by >50% at 30-60 days after onset in cases of hepatocellular DILI, or if peak Alk P has not fallen by >50% at 180 days in cases of cholestatic DILI despite stopping the suspected offending agent.
   - in cases of DILI where continued use or re-exposure to the implicated agent is expected.

- if liver biochemistry abnormalities persist beyond 180 days to evaluate for the presence of chronic liver diseases and chronic DILI.

7. If pertinent, copies of hospital discharge summary, radiology, pathology and autopsy reports should be obtained.

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): Andrew Greenspan, MD

Institution: Janssen Scientific Affairs, LLC

Signature: electronic signature appended at the end of the protocol 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.

SIGNATURES

Signed by	Date	Justification
Andrew Greenspan	20Feb2018, 18:36:37 PM, UTC	Document Approval