Janssen Research & Development

Statistical Analysis Plan

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 ADAPT; Phase 4

Remicade ® (infliximab)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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ABBREVIATIONS

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
6-TG	6-thioguanine
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
AE	adverse event
ALT	alanine aminotransferase
ANA	antinuclear antibody
Anti-dsDNA	anti-double stranded DNA antibody
AST	aspartate aminotransferase
ATI	antibodies to infliximab
ATC	Anatomical Therapeutic Chemical
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
DEVELOP	An Inflammatory Bowel DisEase Multicenter, ProspectiVE, LOng-term Registry of Pediatric Patients
DNA	deoxyribonucleic acid
ESR	erythrocyte sedimentation rate
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
IBD	inflammatory bowel disease
ICH	International Conference on Harmonisation
ITT	intention-to-treat (population)
IV	Intravenous
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
PT	Preferred Term
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
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SI	System of Units
SOC	System Organ Class
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TNF	tumor necrosis factor
UC	ulcerative colitis
US	United States
WBC	white blood cell
WHO-DD	World Health Organization-Drug Dictionary

TIME AND EVENTS SCHEDULE

Study Procedures [a, b]	Screening (Day -14)	Week								Week 64 (Final Safety Visit) [c] /Early Study Discontinuation
		0	8	16	24	32	40	48	56/ End of Treatment	
Informed consent/assent	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 [d]	X	X								
Concomitant medication review	X	X	X	X	X	X	X	X	X	X
Ileocolonoscopy [e]	X				X----------					
Physical examination (including skin examination) [f]	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[g]	X									
Fecal calprotectin [h, i]	X									
Tuberculosis evaluation [j]	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 [k]	X									
Hepatitis B testing	X									
Hepatitis C testing	X									
Varicella antibody titers [l]	X									
Measles antibody titers [l]	X									

Study Procedures [a, b]	Screening (Day -14)	Week 0	8	16	24	32	40	48	56/ End of Treatment	Week 64 (Final Safety Visit) [c] /Early Study Discontinuation
Urine pregnancy test [m]	X	X	X	X	X	X	X	X	X	X
Hematology and chemistry	X	X		X		X		X		X
Hematocrit			X [n]		X [n]		X [n]		X [n]	
Albumin			X [n]		X [n]		X [n]		X [n]	
ESR	X [i, n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	X [n]	
CRP	X [i]	X	X	X	X	X	X	X	X	
Infliximab concentration [o]	X [i]	X	X	X	X	X	X	X	X	X
Antibodies to infliximab [n]	X [i]	X	X	X	X	X	X	X	X	X
ANA and anti-dsDNA antibodies		X								X
PCDAI score or partial Mayo score [p]		X	X	X	X	X	X	X	X[q]	
FACES (Wong-Baker pain scale) [r]		X		X					X	
Stool Frequency [r]		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 [t]
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. 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 (e.g., 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.

e. 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 at least 24 weeks after dose escalation or later; refer to protocol Section 9.3.1.5 for further details.

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

g. Sample to be collected at screening visit, however, if not done, patient/caregiver may collect at home and return to the site within 24 hours of collection. Please refer to the Covance laboratory manual for further instructions.

h. For patients undergoing screening for the Dose Escalation Group, those who do not meet entry criteria based on fecal calprotectin and/or CRP levels may have repeat 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.

i. 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.

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

k. 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. 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.

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

m. For female patients of childbearing potential only.

n. For CD patients only. Note that at these visits, routine hematology and chemistry laboratory studies are not obtained; therefore, hematocrit and albumin laboratory studies must be performed in order to calculate PCDAI. In addition, ESR is to be collected for CD patients only at each of these visits for calculation of PCDAI.

o. 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 $C_{trough} < 7$ µg/mL and ATI titers ≤ 12,800 (see Protocol Section 4.1 inclusion criterion #10).

p. The PCDAI or partial Mayo diaries will be completed by patients during the screening period. 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 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.

q. 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.

r. 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.

s. 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.

t. Required follow-up for adverse events after the Final Safety Visit is described in Protocol Section 12.3.

Note: (1) The maximum acceptable visit window for all visits 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.

1. INTRODUCTION

This Statistical Analysis Plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for all planned analyses.

1.1. Study Objectives

Primary Objectives

- 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

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

1.2. 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). 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 antibodies to infliximab (ATI) titer data in a contemporaneous IBD cohort undergoing infliximab therapy.

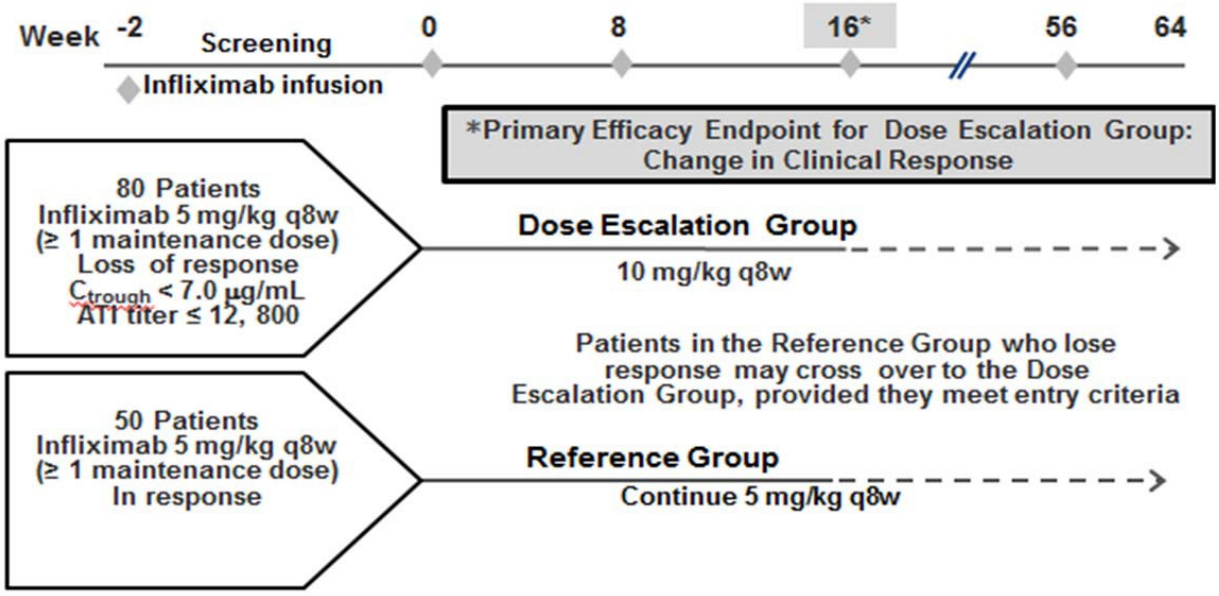
Both the Dose Escalation and Reference Groups will include 60% Crohn's disease (CD) patients and 40% ulcerative colitis (UC patients) at enrollment, to ensure a clinically meaningful number of patients by IBD diagnosis. Patients in both groups will receive infliximab q8wk through Week 56, with a Final 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.

At the time of enrollment in the trial, patients must be receiving infliximab at a dose of 5 mg/kg q8wk (range 4.5 mg/kg to 6 mg/kg with a ± 7 day window for all 3 induction doses and maintenance doses during the 6 months prior to infliximab administration at Week 0).

Upon meeting enrollment criteria for the Dose Escalation Group, 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.

Figure 1: Dose escalation study diagram



Upon meeting enrollment criteria for the Reference Group, patients will continue to 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. These patients 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.

After obtaining informed consent/assent, detailed demographic and medical history 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 at screening and at least 24 weeks after

dose escalation or later, 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. Refer to the Time and Events Schedule for all procedures to be performed over the course of the study.

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. Patients may discontinue before the end of treatment period per legitimate reasons but is required to return for a Final Safety Visit 8 weeks after the final administration of infliximab.

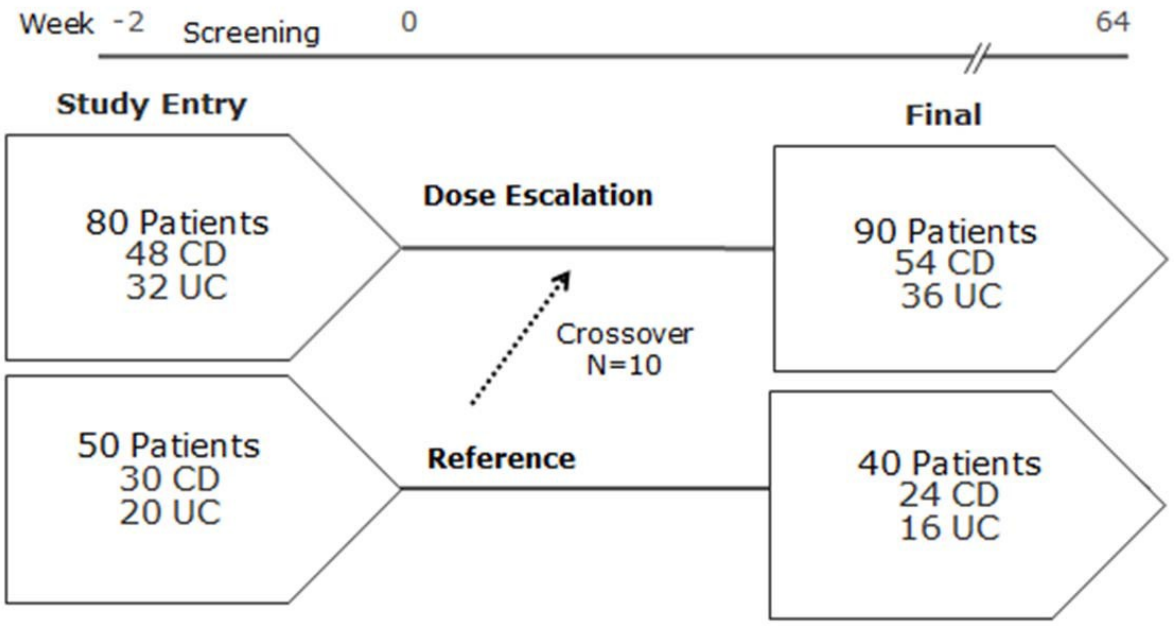
1.3. Statistical Hypotheses for the Primary Objectives

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

1.4. Sample Size Justification

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 (Figure 2).

Figure 2: Sample size details by diagnosis with crossover assumptions



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.[1,2] 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.[3,4]

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

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, i.e., $\beta = 0$ ($\alpha = 0.05$, 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%.

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% (i.e., ± 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% (i.e., ± 8.5 - 9.5% estimated precision).

1.5. Randomization and Blinding

Not applicable.

2. GENERAL ANALYSIS DEFINITIONS

2.1. Visit Windows

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

All visit-specific assessments (Table 2) should be completed before administration of infliximab. The maximum acceptable visit window for all visits is ± 7 days. Patients must meet all enrollment criteria for the Week 0 visit prior to the administration of infliximab.

Table 2: Visit windows

Scheduled Visit Number	Time Interval (label on output)	Time Interval (Day)[a]	Target Time Point
1	Screening	-14 to 0	-14 to 0
2	Week 0	1	1
3	Week 8	2-84	57
4	Week 16	85-140	113
5	Week 24	141-196	169
6	Week 32	197-252	225
7	Week 40	253-308	281
8	Week 48	309-364	337
9	Week 56	365-420	393
10	Week 64[b]		

[a] The first infliximab administration day in Week 0 is Study Day 1.

[b] : 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.

2.2. Pooling Algorithm for Analysis Centers

Not applicable.

2.3. Analysis Population

The analysis population includes all patients who received at least one infusion of infliximab after enrollment. The treatment group is based on the treatment dose the patients actually received. Patients who cross over from Reference Group to the Dose Escalation Group will be included in the Dose Escalation Group.

The analysis population will be used for: safety analysis, serum infliximab concentration and ATI listings, and planned efficacy Analysis.

2.4. Definition of Subgroups

2.4.1. CD and UC subgroups

Both the Dose Escalation and Reference Groups will be composed of 60% CD patients and 40% UC patients. Planned Efficacy and Safety Analyses will be performed by subgroups of CD and UC patients.

- Safety endpoint: Adverse Events (AEs) and SAEs.
- Other safety endpoints: clinical laboratory tests

2.5. Other General Definitions

2.5.1. Baseline Measurement

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.

2.5.2. Study Day and Study Duration

Study day 1 is defined as the first infliximab administration day in Week 0. For data recorded on/after the date of first infliximab administration, study day is computed as:

- Date of data collected – date of study day 1 + 1

For data recorded prior to the first infliximab administration, study day is computed as:

- Date of data collected – date of study day 1

Study end will be defined as the date of completion/discontinuation/withdrawal visit.

- Study duration (days) = date of study end – date of study day 1 +1

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

No interim analyses will be performed. 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.

4. SUBJECT INFORMATION

4.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics for the all enrolled subjects by treatment group. The continuous variables will be summarized descriptively by number of patients with non-missing values (n), mean, standard deviation (SD), median, minimum, maximum, 1st and 3rd quartiles. For the categorical variables, number of patients with non-missing values (n), number of patients and percentage within each category will be summarized.

The following demographics and baseline characteristics will be summarized:

- age at enrollment
- Years since IBD diagnosis at enrollment
- Gender
- Race
- Ethnicity
- Baseline body weight, height and BMI
- Type of IBD [CD, UC]

Duration of IBD/CD/UC Diagnosis (Years) at enrollment=
(Informed consent date –IBD/CD/UC Diagnosis Date + 1)/365.25

4.2. Disposition Information

The early discontinuation of study agent and early termination from the study will be listed. The number of patients who finished each scheduled visit will be summarized by treatment group.

4.3. Protocol Deviations

All protocol deviations will be presented in listings.

4.4. Prior and Concomitant Medications

Prior medications are those medications with a stop date earlier than the individual study start date (Study Day 1). Concomitant medications are those with a start date no later than the individual study end date (study completion/withdrawal date) and a stop date no earlier than the Study Day 1.

Medications, including 5-ASAs, corticosteroids, immunomodulators (including thiopurines), biologics and antibiotics) taken at baseline by the patient for CD or UC at any time in the past will be summarized by treatment groups for patients in the analysis population by number of patients and percentage.

5. EFFICACY

5.1. Analysis Specifications

5.1.1. Data Handling Rules

Calculation of the PCDAI score: The PCDAI is a validated clinical tool used to assess disease severity in pediatric patients with CD[5] and is calculated as the sum of the individual component scores and ranges from 0 to 100 points.

The PCDAI (see Attachment 1) collects information on the following disease-related variables:

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

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.

The PCDAI will only be calculated for a visit if ≥ 3 of the 5 components are available at that visit. When at least 3 of the 5 components are available, any missing components will be imputed by carrying forward the last non-missing component. If the PCDAI score cannot be calculated (i.e., <3 components available) at a visit, the PCDAI score will be considered missing.

Calculation of the Mayo and the partial Mayo score: The Mayo score is used to assess disease activity in patients with UC.[6] 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 3 components:

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)[6] range from 0 – 9

Mayo score/partial Mayo score will be missing if any component is missing.

5.2. Primary and Secondary Efficacy Endpoint(s)

5.2.1. Primary Efficacy Endpoint(s)

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: Response is defined as meeting both criteria.

  1) A decrease from baseline in partial Mayo score of ≥ 2 points and ≥ 30%

     and

  2) A decrease in the rectal bleeding sub-score by ≥ 1 point or the rectal bleeding sub-score is ≤ 1 point

5.2.2. Secondary Efficacy Variables

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

5.2.3. Data Presentation

Listings including primary, secondary efficacy endpoints, the Wong-Baker FACES Pain Scale , total scores of PCDAI and partial MAYO Scores and change from baseline over time for total PCDAI are provided for the dose escalation group in the analysis population.

5.3. 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 and ATI titers will be summarized for all patients in the analysis population with available data. A listing for ATI titers will be provided as well. If the data do not allow for accurate assessment of serum infliximab concentrations (e.g., 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.

6. SAFETY

Safety evaluations during the study include adverse events (AEs), clinical laboratory tests. Safety analyses will be performed on the safety population, where the treatment group is based on the dose the patient actually received. Safety analyses will be based on observed data.

6.1. Adverse Events

The incidence of AEs will be summarized by treatment group and MedDRA SOC and PT through Week 64. Treatment-emergent adverse events (TEAEs) 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 TEAEs will be included in the analysis. The proportion of subjects who experienced at least 1 occurrence of the following TEAEs will be summarized by treatment group:

- Any AEs
- SAEs
- AEs of special interest
- Reasonably related AEs (associated with the use of the drug)

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

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely on the AE eCRF page.

Adverse events will also be summarized by CD and UC subgroups.

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.

6.2. Clinical Laboratory Tests

Routine laboratory data for hematology and clinical chemistry will be collected according to the schedule in Time and Events Schedule. The laboratory data to be summarized are as follows:

- Hematology Panel
  - Hemoglobin
  - Hematocrit
  - WBC count with differential
- Serum Chemistry Panel
  - alkaline phosphatase
  - albumin
  - ALT
  - AST
  - total, direct, indirect bilirubin

Reference ranges and markedly abnormal results will be used in the summary of laboratory data. Frequency tabulations of subjects with any post-baseline markedly abnormal laboratory value will be presented by CD/UC subgroup and reference/dose escalation treatments. A listing of patients with any markedly abnormal laboratory results will be provided. Markedly abnormal laboratory criteria are defined in Table 3.

For a laboratory value to be considered markedly abnormal, all the criteria listed for a parameter in the following table must be met. For example, for a Hemoglobin value to be markedly abnormal, the Hemoglobin value must be < 100 and this value must be at least a 20 decrease from the baseline Hemoglobin value.

Summaries of laboratory data will be completed using all the available data at the time point of interest without imputing missing data.

Table 3: Markedly abnormal criteria for laboratory parameters	
Hematology Test	**Criteria for Markedly Abnormal Status**
Hemoglobin (g/L)	Decrease > 20.0 **AND** Value < 100.0
Hematocrit (%)	Value < 0.27
Total WBC ($x10^9$/L)	Value < 2.0 **OR** Value > 20.0
Neutrophils, absolute ($x10^9$/L)	Percent decrease ≥33 **AND** Value < 1.5
Lymphocytes, absolute ($x10^9$/L)	Percent decrease ≥ 33 **AND** Value < 1.5
Eosinophils, absolute ($x10^9$/L)	Percent increase ≥ 100 **AND** Value > 1.3
Platelet count ($x10^9$/L)	Percent decrease ≥50 **AND** Value < 75
Chemistry Test	**Criteria for Markedly Abnormal Status**
Alkaline phosphatase (U/L)	Percent increase ≥ 100 **AND** Value > 500
ALT (U/L)	Percent increase ≥100 **AND** Value > 150
AST (U/L)	Percent increase ≥ 100 **AND** Value > 150
Total bilirubin (umol/L)	Percent increase ≥ 100 **AND** Value > 51.3
Sodium (mmol/L)	(Increase ≥10 **AND** Value > 150) **OR** (Decrease ≥ 10 **AND** Value < 120)
Potassium (mmol/L)	(Increase ≥ 0.8 **AND** Value > 5.5) **OR** (Decrease ≥ 0.8 **AND** Value < 3.0)
Chloride (mmol/L)	Value < 85 **OR** Value > 120
BUN/Urea (mmol/L)	Percent increase ≥ 66 **AND** Value > 14.28
Creatinine (umol/L)	Percent increase ≥ 66 **AND** Value > 132.6
Albumin (g/L)	Decrease ≥ 10.0 **AND** Value < 30.0
Total protein (g/L)	Value < 45 **OR** Value > 100
Calcium (mmol/L)	(Increase ≥ 0.37 **AND** Value > 2.62) **OR** (Decrease ≥0.37 **AND** Value < 1.87)
Note: Increases and decreases above are relative to the baseline value. Baseline is defined as the closest measurement taken prior to or at Week 0.	

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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.
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ATTACHMENT

ATTACHMENT 1 PEDIATRIC CROHN'S DISEASE ACTIVITY INDEX

HISTORY SCORE (Recall, 1 week)

Abdominal Pain:

None _____ (0 points)

Mild - Brief, does not interfere with activities _____ (5)

Mod/Severe – daily, longer lasting, affects activities, nocturnal _____ (10)

Total _____

Stools (per day):

0 – 1 liquid stools, no blood _____ (0)

Up to 2 semi-formed with small blood or 2-5 liquid _____ (5)

Gross bleeding or ≥ 6 liquid or nocturnal diarrhea _____ (10)

Total _____

Subject Functioning- General well-being

No limitation of activities, well _____ (0)

Occasional difficulty in maintaining age appropriate activities, below par _____ (5)

Frequent limitation of activity, very poor _____ (10)

Total _____

History Score _____ (Max 30)

****

LABORATORY SCORE

HCT(%)	**≤ 10 yrs:**	≥ 33	____ (0)	**Males 11-14:**	≥ 35	____ (0)
		28-32	____ (2.5)		30-34	____ (2.5)
		< 28	____ (5)		< 30	____ (5)
	Females 11-19	≥ 34	____ (0)	**Males 15-19:**	≥ 37	____ (0)
		29-33	____ (2.5)		32-36	____ (2.5)
		< 29	____ (5)		< 32	____ (5)
ESR (mm/hr)		< 20	____ (0)			
		20-50	____ (2.5)			
		> 50	____ (5)			
Albumin (g/dL)		≥ 3.5	____ (0)			
		3.1-3.4	____ (5)			
		≤ 3.0	____ (10)			

Laboratory Score_____(Max 20)

GROWTH SCORE

Weight

Weight gain or voluntary weight stable/loss	_____ (0 points)
Involuntary weight stable, weight loss 1-9 %	_____ (5)
Weight Loss ≥ 10 %	_____ (10)

Total _____

Height

At diagnosis (Refer to percentile chart):

< 1 channel decrease	_____ (0)
≥ 1 and < 2 channel decrease	_____ (5)
≥ 2 channel decrease	_____ (10)

OR **Total _____**

Follow-up (Refer to growth velocity chart):

Height velocity	≥ -1 SD	_____ (0)
Height velocity	< -1 SD and > -2 SD	_____ (5)
Height velocity	≤ -2 SD	_____ (10)

Total _____

Growth Score _____ (Max 20)

****

PHYSICAL EXAMINATION SCORE

Abdomen

No tenderness, no mass	_____ (0)
Tenderness or mass without tenderness	_____ (5)
Tenderness, involuntary guarding, definite mass	_____ (10)

Total _____

Perirectal disease

None, asymptomatic tags	_____ (0)
1-2 indolent fistula, scant drainage, no tenderness	_____ (5)
Active fistula, drainage, tenderness or abscess	_____ (10)

Total _____

Physical Examination Score _____ (Max 20)

****

Extraintestinal Manifestation SCORE

(Fever ≥ 38.5°C for 3 days over past week, definite arthritis, uveitis, E. nodosum, P. gangrenosum)

None	_____ (0)
One	_____ (5)
≥ Two	_____ (10)
	Total _____

HISTORY SCORE	_____
LABORATORY SCORE	_____
GROWTH SCORE	_____
PHYSICAL EXAMINATION SCORE	_____
EXTRAINTESTINAL MANIFESTATION SCORE	_____
TOTAL PCDAI SCORE	_____