Janssen Research & Development*

DEVELOP™ Registry
REMICADEPIB4003

EU-specific Registry Protocol: Noninterventional

A Multicenter, Prospective, Long-term Registry of Pediatric Patients with Crohn's Disease or Ulcerative Colitis

Revised to incorporate Amendment 2: 11 Dec 2012

Original protocol: 26 Aug 2008

Amendment 1: 24 Jan 2011

Prepared by: Janssen Biotech, Inc.

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Infectious Diseases BVBA; Janssen R&D Ireland; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities.

Protocol Synopsis

Product: REMICADE® (infliximab)
Protocol Number: REMICADEPIB4003
EudraCT Number: N/A
Protocol Title: A Multicenter, Prospective, Long-term Registry of Pediatric Patients with Crohn's Disease or Ulcerative Colitis
Target Disease: Pediatric inflammatory bowel disease (IBD) defined as pediatric Crohn's disease (CD) or pediatric ulcerative colitis (UC).
Patients: Pediatric patients with a confirmed diagnosis of CD or UC for at least 2 months. Patients must be less than 17 years of age, but not younger than 6 years of age at the time of registry enrollment. Refer to the protocol for a complete description of inclusion/exclusion criteria. Note: The registry is also being conducted in North America under an interventional protocol (C0168Z02) and includes pediatric patients with a confirmed diagnosis of CD, UC, or IC who are less than 17 years of age at the time of enrollment. The registry will also be conducted in the EU under an interventional protocol (evaluating pediatric patients with CD and UC) and the current noninterventional protocol that is evaluating pediatric patients with CD or UC. A dose increase and immunogenicity substudies will be conducted under the interventional protocols. Data from all 3 of these registry protocols will be captured in 1 registry database and combined into 1 annual summary report for the Pediatric IBD registry.
Registry Objectives: The objective of this registry is to obtain long-term safety and clinical status information on pediatric patients with IBD (ie, CD or UC).
Registry Design: This is a multicenter, prospective, long-term registry of the safety and clinical status of pediatric patients with CD or UC who were treated with Remicade and/or other medical therapies for CD or UC. Information will be collected on patient demographics, disease characteristics, clinical status, quality of life, medications, and dosing information for Remicade, other biologics, and immune modulators as applicable. All adverse events, including those of special interest, such as dysplasias and malignancies of all types, infections, and new autoimmune disease, will be documented. Data will be collected every 6 months.
Treatment Regimen(s): Not applicable. There will be no randomized or nonrandomized assignments. Treatments and evaluations for IBD are as prescribed by the physician based on usual clinical practice.
Route of Administration: Not applicable
Interval Between First and Last Dose of Active IBD-Related Agent: Not applicable
Duration of Registry Participation: Patients will be followed for at least 20 years after enrollment in the registry.
Number of Patients: The 3 registry protocols will enroll approximately 4000 pediatric CD patients: approximately 2000 patients exposed to Remicade and an approximately equivalent number of patients treated with medical therapies other than Remicade. The protocols will also enroll approximately 2000 pediatric patients with UC or IC (UC/IC in North America; UC in the EU): approximately 1000 patients treated with Remicade and approximately 1000 patients treated with other IBD medications.
Number of Sites: Approximately 50 to 125 sites in the EU and North America.
Data Evaluations: Data analyses will include the following for all patients with IBD and by subgroups of CD and UC: Health status and outcome analyses: 1. Descriptive statistics for demographic data of pediatric patients with CD or UC, both with and without Remicade exposure 2. Summary of safety outcomes of pediatric patients with CD or UC, both with and without Remicade exposure

3. Summaries of medical therapies, clinical status, and quality of life for pediatric patients with CD or UC, both with and without Remicade exposure
Interim Analyses: Data will be summarized in annual reports for the duration of the registry. In addition, data may be summarized for targeted meetings and publications.

Table of Contents

Abbreviations

5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
ACCENT	A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen
AE	adverse event
AZA	azathioprine
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CRF	case report form
CRO	contract research organization
DEVELOP	An Inflammatory Bowel **D**is**E**ase Multicenter, Prospecti**VE**, **LO**ng-term Registry of **P**ediatric Patients
eCRF	electronic case report form
EC	Ethics Committee
EDC	Electronic Data Capture
EMEA	European Medicines Evaluation Agency
ESR	erythrocyte sedimentation rate
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GPPPA	Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment
HCT	hematocrit
HIPAA	Health Insurance Portability and Accountability Act
IBD	inflammatory bowel disease
IC	indeterminate colitis
ICH	International Conference on Harmonization
IgG	immunoglobulin G
MedDRA	Medical Dictionary for Regulatory Activities
PCDAI	Pediatric Crohn's Disease Activity Index
NDI	National Death Index
PIPEDA	Personal Information Protection and Electronic Documents Act
PQC	Product Quality Complaint
q8w	every 8 weeks
q12w	every 12 weeks
REACH	A Randomized, Multicenter, Open-label Study to Evaluate the Safety and Efficacy of Anti-TNFα Chimeric Monoclonal Antibody (Infliximab, REMICADE®) in Pediatric Subjects with Moderate to Severe Crohn's Disease
RESULTS	REMICADE Safety Under Long-term Study
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System™
SUA	serious unexpected associated (adverse reaction)
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TNF	tumor necrosis factor
UC	ulcerative colitis
US	United States
WHODRUG	World Health Organization Drug Dictionary

1 Introduction

1.1 Purpose of Registry

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. This high-affinity binding prevents the interaction of TNFα with its cellular receptors, thus attenuating inflammatory and other deleterious effects secondary to TNFα overproduction (Knight et al, 1993). Remicade is indicated for treatment of several autoimmune diseases in which TNFα plays a major role, and is typically administered via intravenous infusion in an outpatient setting with dosing intervals of 1 to 2 months.

The purpose of the establishment of a pediatric inflammatory bowel disease (IBD) registry is to provide additional information on patients with pediatric IBD (defined as Crohn's disease [CD] or ulcerative colitis [UC]) following initial approval of the Remicade indication for pediatric CD and UC. This registry fulfills a regulatory postmarketing commitment.

1.2 Background and Rationale

The safety and efficacy of Remicade were assessed in a randomized, open-label study in 112 pediatric patients who were aged 6 to 17 years and had moderately to severely active CD and an inadequate response to conventional therapies (REACH study). The median age was 13 years and the median Pediatric Crohn's Disease Activity Index (PCDAI) score was 40 (on a scale of 0 to 100). All patients were required to be on a stable dose of 6-mercaptopurine, azathioprine, or methotrexate; 35% of patients were also receiving corticosteroids at baseline.

All patients received induction dosing of Remicade 5 mg/kg at Weeks 0, 2, and 6. At Week 10, 103 patients were randomized to a maintenance regimen of Remicade 5 mg/kg given either every 8 or 12 weeks. At Week 10, 88% of patients were in clinical response (defined as a decrease from baseline in the PCDAI score of ≥ 15 points and total PCDAI score of ≤ 30 points), and 59% were in clinical remission (defined as PCDAI score of ≤ 10 points).

At both Weeks 30 and 54, the proportion of patients in clinical response was greater in the every 8 weeks (q8w) treatment group than in the every 12 weeks (q12w) treatment group (73% vs. 47% at Week 30, and 64% vs. 33% at Week 54). At both Weeks 30 and 54, the proportion of patients in clinical remission was also greater in the q8w treatment group than in the q12w treatment group (60% vs. 35% at Week 30, and 56% vs. 24% at Week 54).

For patients receiving corticosteroids at baseline, the proportion of patients able to discontinue corticosteroids while in remission at Week 30 was 46% for the q8w

maintenance group and 33% for the q12w maintenance group. At Week 54, the proportion of patients able to discontinue corticosteroids while in remission was 46% for the q8w maintenance group and 17% for the q12w maintenance group.

In terms of safety findings, the proportions of patients with 1 or more AEs or SAEs were similar between the maintenance groups. The proportion of patients with AEs that were considered to be infections was higher among patients receiving Remicade q8w compared with those receiving maintenance therapy q12w (Hyams et al, 2007).

The safety and efficacy of Remicade in pediatric UC were assessed in a randomized, open-label study in 60 pediatric patients who were aged 6 to 17 years (Study C0168T72; Hyams et al, 2012). Patients had moderately to severely active UC (defined as a Mayo score of 6 to 12, inclusive, at baseline, including an endoscopic subscore ≥ 2), despite current adequate treatment or had failed to respond to or tolerate treatment with 6-MP, AZA, corticosteroids, and/or 5-ASA compounds. All patients received an induction regimen of 5 mg/kg infliximab at Weeks 0, 2, and 6. Patients in clinical response at Week 8, as measured by the Mayo score, were randomized in a 1:1 ratio to receive 1 of 2 maintenance treatment regimens: infliximab 5 mg/kg administered q8w through Week 46 or q12w through Week 42. During the maintenance treatment phase, patients who lost response were eligible to increase their infliximab dose and/or dosing frequency 1 time.

At Week 8, Remicade induced a response in 44 of 60 (73.3%) patients (95% CI: 62.1% – 84.5%); a positive result was defined by 95% CI lower limit of 40%. Among responders, twice as many were in remission at Week 54 following the q8w regimen (8 of 21, 38.1%) when compared with the q12w regimen (4 of 22, 18.2%; p=0.146). Assuming the q8w remission rate for responders, the overall remission rate at Week 54 would be 28.6%. Serious adverse events and infusion reactions occurred in similar proportions of patients in the 2 groups. There were no deaths, malignancies, opportunistic infections, tuberculosis, or delayed hypersensitivity reactions. Overall, Remicade was safe and effective, inducing a response at Week 8 in 73.3% of pediatric patients with moderate to severely active UC who did not respond to conventional therapy.

To further assess the long-term outcomes of pediatric patients with CD or UC who have been treated with Remicade, the Sponsor has established this pediatric IBD-specific registry to monitor long-term safety and clinical status of pediatric patients with IBD. Particular attention will be directed to the occurrence of AEs and SAEs that may be reported in association with Remicade relative to other approved or commonly prescribed therapies, in addition to the disease clinical status and quality of life.

Physicians are advised to refer to the latest version of the REMICADE® (infliximab) package insert/summary of product characteristics for the most accurate and current information regarding the efficacy and safety of Remicade.

2 Registry Objectives

The objective of this registry is to obtain long-term safety and clinical status information on pediatric patients with IBD (ie, CD or UC).

3 Overview of Registry

3.1 Registry Design

Registry REMICADEPIB4003 is a multicenter, prospective, long-term registry of pediatric patients with a confirmed diagnosis of CD or UC for at least 2 months. Patients must be less than 17 years of age, but not younger than 6 years of age at the time of registry enrollment.

The registry is also being conducted in North America under an interventional protocol (C0168Z02) and includes pediatric patients with a confirmed diagnosis of CD, UC, or IC who are less than 17 years of age at the time of enrollment. The registry will also be conducted in the EU under an interventional protocol (evaluating pediatric patients with CD and UC) and the current noninterventional protocol that is evaluating pediatric patients with CD or UC. A dose increase and immunogenicity substudies will be conducted under the interventional protocols. Data from all 3 of these registry protocols will be captured in 1 registry database and combined into 1 annual summary report for the Pediatric IBD registry.

The 3 registry protocols will enroll approximately 4000 pediatric CD patients: approximately 2000 patients exposed to Remicade and an approximately equivalent number of patients treated with medical therapies other than Remicade. The protocols will also enroll approximately 2000 pediatric patients with UC or IC (UC/IC in North America; UC in the EU): approximately 1000 patients treated with Remicade and approximately 1000 patients treated with other IBD medications.

The patient enrollment period will be conducted over an approximate period of 12 years; the patient observation period is planned for approximately 20 years. The planned duration of the registry is approximately 32 years. The registry will be conducted at approximately 50 to 125 sites in the EU and North America.

There will be no randomized or nonrandomized treatment assignments. At each investigative site, participation in the registry should be offered to CD and UC patients based on the organization of the individual practice (eg, community-based office and/or hospital-based practice). Approximately equal numbers of patients who have been treated with Remicade (Remicade-exposed group), and patients exposed to other treatments-only (Remicade-nonexposed group), should be enrolled at each site. The Sponsor or its designee will monitor enrollment on an ongoing basis and reserves the right to limit enrollment to any patient group(s) in an individual site based on the enrollment of all participating sites. Additional details regarding patient enrollment are provided in the Registry Reference Manual.

Physicians will prescribe treatments based on usual clinical practice. There will be no restrictions on the use of commercially available medications. Pediatric patients who are participating in other registries or clinical trials (except as noted in Section 4.2) will not be excluded from participating in this registry. Other registry participation information will be documented on the data collection form.

After the enrollment visit, data will be obtained by the registry physician or designee every 6 months (see Attachment 1), via a review of the patient's medical records and/or direct contact (ie, preferably a medical encounter [eg, office visit/infusion]), and will include: disease characteristics; medications; dosing information for Remicade, other biologics, and immune modulators as applicable; clinical disease status; quality of life; and AEs (including dysplasias and malignancies of all types, infections, and autoimmune disease). If the patient is not available for a medical encounter, data may be collected from the patient's medical records and/or by direct contact (eg, a telephone call) during that specific data collection interval.

4 Patient Selection

4.1 Inclusion Criteria

To be eligible for participation in the registry, patients must meet all of the following criteria at enrollment:

1. Have a confirmed diagnosis of CD or UC for at least 2 months.

2. Are male or female at least 6 years of age, but less than 17 years of age.

3. The parent/legal guardian must be capable of providing written informed consent, and assent should be obtained from the child according to local regulations (age at which assent is given may vary by the EC).

4. The patient's physician expects the patient to be scheduled for a medical encounter (and/or other direct contact) at least every 6 months, as part of their usual care, at the time of enrollment.

4.2 Exclusion Criteria

Patients meeting any of the following criteria may not be enrolled in the registry:

1. Are less than 6 years of age or 17 years of age or older.

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

3. Have other Crohn's-like diseases that are associated with genetic diseases (eg, glycogen storage disease).

4. Are participating in any clinical trial for an investigational agent that is not commercially available.

5. Are currently participating in one of the Sponsor's trials for pediatric IBD.

5 Registry Plan

This registry will be conducted as appropriate in accordance with current FDA Regulations and guidelines, including Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, the European Clinical Trials Directive and associated guidelines, ICH guidelines on GCP, and the principles of the Declaration of Helsinki, as well as all other applicable national and local laws and regulations.

A designated CRO will be responsible for managing the operational aspects of the registry in partnership with the Sponsor.

Informed consent will be obtained by the registry physician, or designee, from all parents/legal guardians and the pediatric patients, according to applicable local regulations. Specifically, assent should be obtained from pediatric patients as appropriate (age at which assent is given may vary by EC) prior to collection of any information on safety and clinical status. During the registry, patients reaching the age of 18 years or their legal age of majority according to local regulations must provide written informed consent to continue participation in the registry.

Registry participants will be encouraged to remain in the registry. Registry physicians will be responsible for following up with patients who are not available for their registry-scheduled medical encounter/contact (see Section 7.4). Parents/legal guardians and patients who reach the age of 18 years or their legal age of majority according to local regulations during their participation in the registry have the right to voluntarily withdraw consent for registry participation at any time.

5.1 Data Collection Intervals

Data collection details are presented in Section 7.

5.1.1 Registry Entry

At registry enrollment (ie, baseline), the following information will be collected:

- Informed consent
- Demographics
- Medical history, family history, and baseline disease characteristics
- Physical examination
- Clinical disease status (ie, Physician Global Assessment, partial PCDAI (as applicable), partial Mayo score (as applicable)
- Medications (may include dose and frequency of CD/UC medications)
- Remicade dose, frequency, and dates of infusions, if applicable

- Quality of life assessment (ie, employment, disability, and school status questionnaire) by patients and/or parents/guardians

5.1.2 6-Month Follow-up

The following information will be collected approximately every 6 months after registry enrollment and through 20 years of follow-up as part of the registry-scheduled medical encounter/contact:

- Physical examination
- AEs (see Section 6.2 for SAE reporting)
- Clinical disease status (ie, Physician Global Assessment, partial PDCAI (as applicable), partial Mayo score (as applicable)
- Medications (may include dose and frequency of CD/UC medications)
- Remicade dose, frequency, and dates of infusions, if applicable
- Quality of life assessment (ie, employment, disability, and school status questionnaire) by patients and/or parents/guardians.

5.2 Quality of Life and Clinical Assessments

5.2.1 Quality of Life Assessment

Quality of life information (ie, employment, disability, and school status) will be collected using a questionnaire.

For all pediatric patients who are of school age, data on current grade level and school attendance will be collected. Employment status (full-time, part-time, or not employed), disability (receiving disability compensation or not), school (full- or part-time student, or not attending school) and lost work hours will be assessed by a questionnaire that was adapted from those used previously in the Sponsor's trials conducted in adult patients with CD and UC (Hanauer et al, 2002; Feagan et al, 2005; Rutgeerts et al, 2005).

5.2.2 Clinical Assessments

5.2.2.1 Physician Global Assessment

A physician global assessment, which is a subjective measure of the disease activity, will be recorded at enrollment and during the 6-month follow-up visits using a 4-point scale (quiescent normal, mild, moderate, and severe).

5.2.2.2 Pediatric Crohn's Disease Activity Index and Partial Pediatric Crohn's Disease Activity Index

The PCDAI is a validated multi-item measure of illness severity. In contrast to the adult-derived Crohn's Disease Activity Index (CDAI), the PCDAI includes linear growth and places less emphasis on subjectively-reported symptoms and more emphasis on laboratory parameters of intestinal inflammation (Hyams et al, 1991; Otley et al, 1999). The PCDAI includes the following measurements:

1. Subjective reporting of the degree of abdominal pain, stool pattern, and general well being (recall over the past week).

2. Presence of extraintestinal manifestations, such as fever, arthritis, rash, and uveitis.

3. Physical examination findings.

4. Weight change and either height change or height velocity.

5. Hematocrit (HCT), erythrocyte sedimentation rate (ESR), and serum albumin.

The PCDAI score is calculated as the sum of the individual component scores and ranges from 0 to 100. A partial PCDAI score will be used to evaluate patients at enrollment and at 6-month follow-up intervals. This will consist of the PCDAI score without the laboratory component (HCT, ESR, and albumin) of the assessment, which is 20% of the overall assessment. This partial PCDAI score is calculated as the sum of the 4 component scores, excluding the laboratory component score, and ranges from 0 to 80.

Note that once a patient turns 18 the partial PCDAI score will no longer be collected.

5.2.2.3 Mayo Score and Partial Mayo Score

The Mayo score is a validated clinical tool to assess disease activity in patients with UC. The Mayo score (Schroeder et al, 1987) was developed from the criteria of Truelove and Witts (1955) for mild, moderate, and severe UC; and from the criteria of Baron et al (1964) for grading the mucosal appearance. A Mayo UC activity score of ≤ 2 points, with no individual subscore > 1, indicates clinical remission; a score of 3 to 5 points indicates mildly active disease; a score of 6 to 10 points indicates moderately active disease; and a score of 11 to 12 points indicates severe disease. Partial Mayo scores (ie, Mayo scores using data from items 1 and 2 only [see below] without sigmoidoscopy or colonoscopy) will be determined from data obtained at enrollment and at 6-month follow-up intervals for patients with UC.

Mayo scores are calculated using:

1. The stool frequency and rectal bleeding data from the most recent consecutive 3-day period prior to the visit, excluding the following:

a. The day that medications for constipation, diarrhea, or irregularity were taken. (For patients maintained on a stable dose of bulking or stool softening agents throughout the trial, the days on which these agents are taken should not be excluded from consideration in calculating the Mayo score.)

b. The day(s) of a procedure or preparation for a procedure (eg, enemas, other laxatives, a clear liquid diet) that would affect bowel frequency and/or blood content of the stool.

c. The 48 hours after the use of antimotility agents (ie, diphenoxylate hydrochloride with atropine sulfate or loperamide).

d. The 72 hours immediately following a colonoscopy.

2. The Physician's Global Assessment.

3. The results of a sigmoidoscopy or colonoscopy.

6 Adverse Event Reporting and Follow-up

6.1 Definitions

For the purposes of this registry, and in accordance with ICH and the Sponsor's safety reporting guidelines, the following definitions will apply.

6.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product; such an occurrence does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Information on AEs will be collected by the study personnel on an ongoing basis in the medical chart and reported at 6-month intervals on the Electronic Data Capture (EDC) system to the Sponsor or designee during the registry.

6.1.2 Serious Adverse Event

An SAE is defined as any untoward medical occurrence that at any dose:

- results in death;
- is life threatening;

- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is 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 above; these should also usually be considered serious.

Suspected transmission of an infectious agent by a medicinal product should be reported as an SAE.

Hospitalization for underlying disease progression is considered an SAE. Hospitalization for an elective or planned procedure to treat a pre-existing condition is not considered an SAE unless it results in one of the other outcomes listed above.

6.1.3 Adverse Events of Special Interest

All AEs of special interest, irrespective of relationship to therapy, are to be reported to the Sponsor's designee by the site within 1 week (5 business days) of observation or notification of the event.

Events of special interest include the following:

- Serious infections
- TB
- New malignancy (including lymphomas)
- Dysplasia of the colon
- New autoimmune disease

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

6.1.3.1 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 an SAE as defined in Section 6.1.2.

6.1.3.2 Tuberculosis

Any diagnosis of active or latent TB occurring in patients participating in the registry 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 an SAE as defined in Section 6.1.2.

6.1.3.3 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 enrollment visit), only new malignancies (defined as a malignancy that was not diagnosed prior to the time of the last visit/telephone contact in the registry) should 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.

6.1.3.4 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.

6.1.3.5 New Autoimmune Disease

Autoimmune diseases (including lupus-like syndrome, psoriasis, multiple sclerosis, or other demyelinating diseases) that are diagnosed during the participation in the registry should be reported. Following the recording of an autoimmune disease (including during an enrollment visit), only new autoimmune disease (defined as an autoimmune disease not diagnosed prior to the time of the last visit/telephone contact in the registry) should be reported thereafter.

6.2 Reporting of Serious Adverse Events and Adverse Events of Special Interest

All deaths and malignancies must be reported to the Sponsor, or its designee, by the registry physician within 24 hours of observation or notification of the event.

All other SAEs (including all hospitalizations for underlying disease progression as well as other diagnoses) and AEs of special interest (see Section 6.1.3) occurring in patients treated with Remicade and/or other medical therapies must be reported to the Sponsor, or its designee, by the registry physician within 1 week (5 business days) of observation or notification of the event. Instructions for reporting an SAE and AEs of special interest are provided in the Registry Reference Manual. In addition, instructions for reporting SAEs in patients receiving non-Johnson & Johnson products are provided in the Registry Reference Manual. The name(s) and contact details of the individual(s) who should be contacted regarding safety issues or questions regarding the registry are also included in the Registry Reference Manual.

Serious unexpected associated (SUA) AEs and suspected unexpected serious adverse reactions (SUSARs) generated from the Sponsor's interventional trials will not be distributed to registry sites or their associated ECs. SUSAR line listings and Annual Safety Reports will be sent to Health Authorities where indicated, per local regulations.

The Sponsor assumes responsibility for appropriate reporting of SAEs that occur in patients exposed to Remicade to regulatory authorities. The registry physician must also report these events to the appropriate EC that approved the registry protocol unless otherwise required by local regulations and documented by the EC.

6.3 Follow-up of Serious Adverse Events and Adverse Events of Special Interest

All reported SAEs and AEs of special interest (see Section 6.1.3) will be followed until resolution unless the patient withdraws informed consent, or no additional information can be obtained despite due diligence in obtaining follow-up information (eg, patient or healthcare provider refuses to provide additional information; patient is lost to follow-up).

6.4 Pregnancy

Pregnancy is not an exclusion criterion in this registry. All pregnancies, including those in females and those in the partner of males participating in this registry, occurring during the registry must be reported to the Sponsor, or its designee, by the registry physician within 1 week (5 business days) of observation or notification of the occurrence. Instructions for reporting a pregnancy are provided in the Registry Reference Manual. The name(s) and contact details of the individual(s) who should be contacted regarding safety issues or questions regarding the registry are also included in the Registry Reference Manual. Although the occurrence of pregnancy is not an SAE, all efforts will be made to obtain follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant by the registry physician, Sponsor, or designee, as long as the parent continues participation in the registry.

6.5 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.

6.5.1 Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel as soon as possible 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 6.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

6.5.2 Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are located in the Registry Reference Manual.

7 Data Collection

Information needed during the data collection periods should be obtained by the registry physician or designee via review of the patient's medical records and/or direct contact, ie, preferably a medical encounter (office visit/infusion). If the patient is not available for an office visit, then data collection may include information from the patient's medical records during the specified period of the data collection interval and direct communication (eg, telephone call).

The registry physician, or designee, at each participating registry site will complete the eCRF and provide information at specified intervals as described in Section 5.1 unless it is an AE of special interest or an SAE, which should be reported as detailed in Sections 6.1.3 and 6.2, respectively. Detailed instructions for completion of the eCRF pages are provided in the EDC system. Data from patient questionnaires (quality of life assessment) will also be collected every 6 months and entered into the EDC system.

All eCRFs will be tracked and archived following GCP/ICH guidelines.

7.1 Data Handling

The CRO will develop a clinical database from eCRFs provided by the Sponsor. The clinical database will use the most current version of MedDRA for coding medical history, concomitant medications, and AEs.

Data from all 3 registry protocols as described in Section 3.1 will be captured in 1 registry database and combined into 1 annual summary report for the Pediatric IBD Registry.

The database will be transferred electronically to the Sponsor in the form of SAS transport files, consisting of SAS data sets and SAS format catalogs according to the Sponsor's specifications and timelines.

7.2 Site Training

All sites will be trained on the protocol, registry logistics, and the EDC system. Retraining will be conducted every 2 years or more frequently if needed. As part of the educational sessions, investigators will be reminded of the processes and importance of reporting AEs, SAEs, and other AEs of special interest. Additionally, updated diagnostic criteria (eg, TB diagnosis) for the detection of AEs of special interest and other registry-specific information will be communicated to the sites.

7.3 Site Monitoring

The Sponsor or its designee will perform onsite monitoring/remote monitoring contacts (eg, via phone follow-up) consistent with the Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (GPPPA). In the event that site monitoring identifies under-reporting of SAEs or AEs of special interest, additional monitoring and site education will be performed.

7.4 Patient Follow-up and Retention

The registry physician is responsible for the follow-up and retention of patients enrolled at their investigative site using the Patient Follow-up and Retention Plan provided in Appendix A.

The Sponsor or its designee (if allowed by local regulation) is responsible for follow-up on patients who move away from the investigative site or leave the registry for other reasons but agree to continue their participation in the registry. Every effort will be made to identify a registry investigative site in the geographic area that the patient is moving to. For further details on patient follow-up, please refer to the Patient Transition Plan in the Registry Reference Manual.

7.5 Transitional Follow-up

It is expected that pediatric patients will eventually transition their care to an adult gastroenterologist in late adolescence or young adulthood. A patient will be considered a transition patient when the patient is no longer being followed by the pediatric gastroenterologist who is a member of the registry. If a patient transfers their gastroenterologic care from a registry physician to an internist gastroenterologist, or other physician not participating in the registry, they or their parents/legal guardians will be asked to continue their participation in the registry (see Section 7.4). For further details on follow-up of patients who elect to continue participation, please refer to the Patient Transition Plan in the Registry Reference Manual.

8 Analytical Methods

Analyses will be conducted based on the SAP and this Registry Protocol. All SAS programs and statistical output will be developed, validated, and documented according to standard operating procedures as well as GCP guidelines.

Descriptive statistics will be computed overall and by disease (CD or UC) for the prescribed treatment categories (ie, Remicade-exposed and Remicade non-exposed groups). Analysis cohorts may be defined based on biologic medication exposure, include Remicade only, anti-TNF biologics only, non anti-TNF biologics only, non-biologics only, and anti-TNF and non-anti-TNF biologics. The detailed cohort definitions will be specified in the SAP. Appropriate descriptive statistics, including number and percent of patients, mean, median, standard deviation, minimum and maximum values will be used to summarize the demographic characteristics.

Data for dose and administration frequency will be collected for Remicade, other biologic agents, and immunomodulators prescribed during participation in the registry. The duration of therapies administered during participation in the registry will be recorded. The use of medications will be summarized. The incidences of AEs and SAEs will be reported, and adverse event rate per 100 patient years will be calculated.

Summaries of clinical disease status (PGA, partial PCDAI, partial Mayo Score) for patients who were prescribed Remicade and non-Remicade treatments will include number, mean, median, standard deviation, minimum and maximum values for continuous variables and frequency and percentage for categorical variables. The results of quality of life assessments (ie, employment, disability, and school status questionnaire) will be summarized as percentages and other descriptive statistics.

9 Registry Reports

9.1 Annual Registry Report

The Sponsor and/or its designee will prepare and provide an annual summary report for the registry to the FDA and EMA. Annual reports will include accrual rates as well as summary demographic data, total numbers of AEs, and total person-years of follow-up. In addition, the data may be summarized periodically for presentation at professional conferences and sessions, as appropriate.

9.2 Final Registry Report and Publications

The Sponsor and/or its designee will submit a final registry report to the FDA and EMA upon completion of approximately 20 years of observation after the last CD and/or UC patient is enrolled. Any publications based on these data will be patient to the usual Sponsor publication policies.

10 Registry Physician's Statement of Agreement

All responsible parties have provided a written statement agreeing to the content of the proposal and the confidential nature of the documentation made as part of this registry, and acknowledging that the Sponsor has the right to discontinue this registry at any time and/or amend this registry as appropriate.

11 Ethical Considerations and Privacy of Personal Data

The informed consent and assent forms as applicable will be prepared according to the institutional requirements for informed consent and the applicable regulations. The appropriate EC must approve the protocol, informed consent documents, and any other documents as appropriate.

Patient information collected in this registry will comply with the standards for protection of privacy of individually identifiable health information according to local privacy laws.

12 References

Feagan BG, Bala M, Yan S, Olson A, Hanauer S. Unemployment and disability in patients with moderately to severely active Crohn's disease. *J Clin Gastroenterol.* 2005;39:390-5.

Baron JH, Connell AM, Lennard-Jones JE. Variation between observers in describing mucosal appearances in proctocolitis. *Br Med J.* 1964;1:89-92.

Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT 1 randomised trial. *Lancet* 2002;359:1541-1549.

Hyams JS, Ferry GD, Mandel FS, et al. Development and validation of a pediatric Crohn's disease activity index. *J Pediatr Gastroenterol Nutr.* 1991;12:439-47.

Hyams J, Crandall W, Kugathasan S, et al; for the REACH Study Group. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology*. 2007;132:863-73.

Hyams J, Damaraju L, Blank M, et al. Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis. *Clin Gastro and Hepat*. 2012;10:391-399.

Knight DM, Trinh H, Le J, et al. Construction and initial characterization of a mouse-human chimeric anti-TNF antibody. *Mol Immunol.* 1993;30:1443-53.

Otley A, Loonen H, Parekh N, Corey M, Sherman PM, Griffiths AM. Assessing activity of pediatric Crohn's disease: which index to use? *Gastroenterology.* 1999;116:527-31.

REMICADE® (infliximab) for IV Injection prescribing information. Janssen Biotech, Inc. Horsham, PA 19044.

Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2005;353:2462-76.

Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med.* 1987;317:1625-9.

Truelove SC, Witts LJ. Cortisone in ulcerative colitis: final report on a therapeutic trial. *Br Med J.* 1955;2:1041-8.

Attachment 1 Schedule of Events

Procedure	At Enrollment	Every 6 Months After Enrollment[b]
Informed consent	X[a]	
Demographics	X	
Medical history	X	
Physical exam	X	X
Clinical disease status[c]	X	X
Quality of life assessment (ie, employment, disability, and school status questionnaire)	X	X
Medications (may include dose and frequency of CD or UC medications)	X	X
Adverse events		X

a. At entry, informed consent/assent will be obtained from parent/legal guardian of patient prior to collection of long-term follow-up data. During the registry, informed consent will be obtained from patients reaching 18 years of age during their participation in the registry.

b. For a period of 20 years from registry enrollment. For additional information pertaining to patient follow-up, refer to Sections 7.4 and 7.5.

c. Includes clinical assessments of Physician Global Assessment, partial PCDAI, and partial Mayo score as appropriate. Note that once a patient turns 18 the partial PCDAI will no longer be collected.

Attachment 2 Protocol History

Original Protocol: 26 Aug 2008

Amendment 1: 24 Jan 2011

Amendment 2: 11 Dec 2012

Amendment 1 24 Jan 2011

The protocol has been revised to incorporate this amendment, which applies to all study centers. The rationale and description of the changes to the protocol are provided below. Minor formatting and typographical errors have also been corrected to improve the clarity and accuracy of the protocol text; these changes do not affect the overall conduct of the study.

1. Centocor Ortho Biotech Services, LLC was changed to Centocor Ortho Biotech Inc as a correction. Centocor, B.V. was changed to Janssen Biologics, BV due to the company name change. In addition, the title page and list of abbreviations were modified and all references to Centocor were removed from the protocol and replaced with the term Sponsor. The address of Centocor Ortho Biotech Inc was updated as a correction.

Sections Affected	Original Content	Amended/New Content
Title page	Centocor Ortho Biotech Services, LLC Medical Affairs 800 Ridgeview Drive Centocor B.V. Einsteinweg 92 2333 CD Leiden The Netherlands	Centocor Ortho Biotech **Inc.*** **850** Ridgeview Drive ***Centocor Ortho Biotech Inc. (COBI) is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the Sponsor for COBI studies may vary, such as, but not limited to Janssen Biologics BV; Centocor Ortho Biotech Products, L. P.; Janssen-Cilag International NV; or Janssen-Ortho, Inc. The term "Sponsor" is used throughout the document to represent these various legal entities.*** **Janssen Biologics BV** Einsteinweg 92 2333 CD Leiden The Netherlands
List of Abbreviations		**COBI Centocor Ortho Biotech Inc.**
This change has been made throughout the protocol as appropriate.	Centocor	*In general terms:* **Sponsor** or **Sponsor's**

2. Enrollment is subject to market uptake and the original enrollment period of 24 months was extended to 96 months based on the ability of sites to enroll eligible patients into the study across centers in North America and Europe, while maintaining a balance of patients in each study cohort. In approximately the first 36 months of the study, 1572 patients have been enrolled. As clarification and to avoid redundancy, the sentence stating the planned duration of the registry to be 22 years has been deleted as the total duration of the registry has already been described (approximately 96 months enrollment and 20 years observation).

Sections Affected	Original Content	Amended/New Content
3.1 Registry Design (paragraph 3)	The total number of patients from the 3 registry protocols will be approximately 2,000 pediatric patients with CD who have been treated with Remicade as prescribed by their physicians. The control group for these Remicade-treated CD patients will include approximately 2,000 pediatric patients with CD who were prescribed therapies other than Remicade, likewise by their physicians. In North America, approximately 1,000 pediatric patients with UC or IC will also be enrolled independent of the UC or IC medical therapies prescribed by the treating physician. The patient enrollment period will be conducted over 24 months; the patient observation period is planned for approximately 20 years. The planned duration of the registry is approximately 22 years. The registry will be conducted at approximately 50 to 100 sites in the EU and North America.	The total number of patients from the 3 registry protocols will be approximately 2,000 pediatric patients with CD who have been treated with Remicade as prescribed by their physicians. The control group for these Remicade-treated CD patients will include approximately 2,000 pediatric patients with CD who were prescribed therapies other than Remicade, likewise by their physicians. In North America, approximately 1,000 pediatric patients with UC or IC will also be enrolled independent of the UC or IC medical therapies prescribed by the treating physician. The patient enrollment period will be conducted over **approximately 96** months; the patient observation period is planned for approximately 20 years. The registry will be conducted at approximately 50 to 100 sites in the EU and North America.

3. The protocol has text that requires that a patient who reaches 18 years of age while in the study must provide written informed consent to continue in the study. This was clarified such that patients are to provide written consent at 18 years of age or at the time of their legal age of majority according to local regulations.

Sections Affected	Original Content	Amended/New Content
5 Registry Plan (paragraph 3, sentence 3)	During the registry, patients reaching the age of 18 years must provide written informed consent to continue participation in the registry.	During the registry, patients reaching the age of 18 years **or their legal age of majority according to local regulations** must provide written informed consent to continue participation in the registry.
(paragraph 4, sentence 3)	Parents/legal guardians and patients who reach the age of 18 years during their participation in the registry have the right to voluntarily withdraw consent for registry participation at any time.	Parents/legal guardians and patients who reach the age of 18 years **or their legal age of majority according to local regulations** during their participation in the registry have the right to voluntarily withdraw consent for registry participation at any time.

4. The definition of an SAE was updated to reflect the current definition per Volume 9A of The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use (September 2008).

Sections Affected	Original Content	Amended/New Content
6.1.2 Serious Adverse Event (new paragraph 3 added)		**Suspected transmission of an infectious agent by a medicinal product should be reported as an SAE.**

5. The anticipated date of submitting a final registry report was extended from June 30, 2027 to after 20 years of observation after the last patient is enrolled. The anticipated date for the last patient to be enrolled is December 2015. Specific dates were removed and clarification was added that the report will also be submitted to the European Medicines Evaluation Agency (EMEA).

Sections Affected	Original Content	Amended/New Content
9.2 Final Registry Report and Publications (paragraph 1, sentence 1)	Centocor and/or its designee will submit a final registry report to the FDA by June 30, 2027.	**The Sponsor** and/or its designee will submit a final registry report to the FDA **and EMEA upon completion of approximately 20 years of observation after the last patient is enrolled.**

6. Text describing the use of a secure technology for collection of and dissemination of data during the life of the registry was removed, as direct contact between the CRO and patient is not possible in Europe. Instead, the registry physician will continue following the patient and will contact the patient every 6 months to ask the questions on the questionnaire. Details on the follow-up are contained in the EU Patient Transition Plan.

Sections Affected	Original Content	Amended/New Content
7.4 Patient Follow-up and Retention (paragraph 2)	Centocor or its designee is responsible for follow-up on patients who move away from the investigative site or leave the registry for other reasons but agree to continue their participation in the registry. Every effort will be made to identify a registry investigative site in the geographic area that the patient is moving to. If a suitable investigative site is not available in the new geographic area, the patient will be informed that Centocor's designee will follow-up with him/her directly to obtain subsequent interval registry data for the duration of their participation in the registry.	**The Sponsor** or its designee **(if allowed by local regulation)** is responsible for follow-up on patients who move away from the investigative site or leave the registry for other reasons but agree to continue their participation in the registry. Every effort will be made to identify a registry investigative site in the geographic area that the patient is moving to. **For further details on patient follow-up, please refer to the Patient Transition Plan in the Registry Reference Manual.**
7.5 Transitional Follow-up	It is expected that pediatric patients will eventually transition their care to an adult gastroenterologist in late adolescence or young adulthood. When patients transfer their gastroenterologic care from a registry physician to an internist gastroenterologist, or other physician not participating in the registry, they or their parents/legal guardians will be asked to continue their participation in the registry (see Section 7.4). If the patient elects to continue participation, Centocor or its designee will establish a secure technology (eg, website or telephone) for collection and dissemination of data during the life of the registry. The technology will allow access to those patients who have transferred their care from a registry physician to another physician to allow continued follow-up for the 20-year period. The technology will allow collection of predefined data points (including AEs, clinical status, and quality of life) every 6 months. If an AE or SAE is reported, the patient will be contacted for follow-up information and to provide consent to obtain additional information from the treating physician.	It is expected that pediatric patients will eventually transition their care to an adult gastroenterologist in late adolescence or young adulthood. When patients transfer their gastroenterologic care from a registry physician to an internist gastroenterologist, or other physician not participating in the registry, they or their parents/legal guardians will be asked to continue their participation in the registry (see Section 7.4). **For further details on follow-up of patients who elect to continue participation, please refer to the Patient Transition Plan in the Registry Reference Manual.**

7. Other general changes or clarifications were made to the text of the protocol as shown below.

Sections Affected	Original Content	Amended/New Content
5.2.2.2 Pediatric Crohn's Disease Activity Index (paragraph 1, sentence 1)	The PCDAI, a validated multi-item measure of illness severity, in contrast to the adult-derived Crohn's Disease Activity Index (CDAI) includes linear growth and places less emphasis on subjectively-reported symptoms rather than on laboratory parameters of intestinal inflammation…	The PCDAI **is** a validated multi-item measure of illness severity**. I**n contrast to the adult-derived Crohn's Disease Activity Index (CDAI)**, the PCDAI** includes linear growth and places less emphasis on subjectively-reported symptoms **and more emphasis** on laboratory parameters of intestinal inflammation…
6.4 Pregnancy (paragraph 1, sentence 2) (paragraph 1, sentence 5)	All pregnancies occurring during the registry…. Although the occurrence of pregnancy is not an SAE, all efforts will be made to obtain follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant by the Sponsor or designee.	All pregnancies**, including those in females and those in the partners of males participating in this registry,** occurring during the registry… Although the occurrence of pregnancy is not an SAE, all efforts will be made to obtain follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant by **the registry physician,** Sponsor, or designee**, as long as the parent continues participation in the registry.**
7.1 Data Handling (paragraph 1, sentences 2 and 3)	The clinical database will use version 10.0 of the MedDRA or the latest version, for coding medical history, concomitant medications, and AEs. Medications will be coded using the 2007 version of the World Health Organization Drug Dictionary (WHODRUG) or the latest version.	The clinical database will use **the most recent** version of MedDRA for coding medical history, concomitant medications, and AEs. Medications will be coded using the **latest** version of the World Health Organization Drug Dictionary (WHODRUG).
11 Ethical Considerations and Privacy of Personal Data	The informed consent and assent forms as applicable will be prepared according to the institutional requirements for informed consent and the applicable regulations. The appropriate IBR/EC must approve the protocol, informed consent documents, and any other documents as appropriate. Patient information collected in this registry will comply with the standards for protection of privacy of individually identifiable health information as promulgated in the Health Insurance Portability and Accountability Act (HIPAA) and as mandated in Title 45 Code of Federal Regulations, Part 160 (Subparts A and E) and Part 164. All efforts will be made to ensure that this registry will be	The informed consent and assent forms as applicable will be prepared according to the institutional requirements for informed consent and the applicable regulations. The appropriate **EC** must approve the protocol, informed consent documents, and any other documents as appropriate. Patient information collected in this registry will comply with the standards for protection of privacy of individually identifiable health information **according to local privacy laws.**

Sections Affected	Original Content	Amended/New Content
	HIPAA-compliant; participating registries will receive detailed instruction on compliance with patient privacy.	

8. The definition of an active patient is now clarified as one who has had a medical or non-medical encounter visit. Additional clarification is also now provided if attempts to contact an active patient are unsuccessful, including performing a periodic search of the National Death Index (NDI) or equivalent data source based on local or region-specific guidelines subject to local access requirements (eg, a publicly accessible death registry, a public obituary database) for evidence of the patient's status.

Sections Affected	Original Content	Amended/New Content
Appendix A (paragraphs 1 and 2 and last paragraph)	1. An active patient is defined as a patient who has made contact with their designated registry site personnel within 60 days of a registry-scheduled medical encounter. 2. A patient lost to follow-up is defined as one who has not made contact with their designated registry site within 60 days of a registry-scheduled medical encounter and has not formally withdrawn consent for participation in the registry. b) Upon completion of the algorithm, if site personnel are not successful in contacting the patient, the site personnel will inform Centocor's designee Centocor's designee will be required to perform a periodic search of the National Death Index (NDI) for evidence of the patient's status**.**	1. An active patient is defined as a patient who has **had a medical or non-medical encounter visit** with their designated registry site personnel within 60 days of a registry-scheduled encounter **visit**. 2. **If no encounter visit is confirmed and the patient** has not formally withdrawn consent for participation in the registry **the patient should be contacted as outlined below.** b) Upon completion of the algorithm, if site personnel are not successful in contacting the patient, the site personnel will inform **and work with the Sponsor**'s designee to perform a periodic search of the National Death Index (NDI) **or equivalent data source (please refer to local or region-specific guidelines) subject to local access requirements (eg, a publicly accessible death registry, a public obituary database**) for evidence of the patient's status**.**

Amendment 2 11 Dec 2012

The protocol has been revised to incorporate this amendment, which applies to all study centers. The rationale and description of the changes to the protocol are provided below. Minor formatting and typographical errors have also been corrected to improve the clarity and accuracy of the protocol text; these changes do not affect the overall conduct of the study.

.

1. Description/Rationale: The Sponsor name has been updated to reflect the change in names to Janssen Biologics, BV and Janssen Biotech, Inc; accordingly the cover page was updated, and throughout the document reference to Centocor was changed to the Sponsor.

Sections Affected	Original Content	Amended/New Content
Cover Page	None Centocor Ortho Biotech, Inc. Medical Affairs 850 Ridgeview Drive Horsham, PA 19044 USA Centocor Einsteinweg 92 2333 CD Leiden The Netherlands No text	**Janssen Research & Development*** ***Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Infectious Diseases BVBA; Janssen R&D Ireland; or Janssen Research & Development, LLC.** **Prepared by: Janssen Biotech, Inc.** **Confidentiality Statement**
Throughout the document as necessary	Centocor Ortho Biotech, Inc. (COBI) Centocor, B.V. Schering-Plough	**Sponsor**

2. Description/Rationale: The cover page was updated to include the name Registry.		
Sections Affected	Original Content	**Amended/New Content**
Cover page	Registry REMICADEPIB4003	**DEVELOP™** Registry REMICADEPIB4003

3. Description/Rationale: The protocol was updated to allow enrollment of ulcerative colitis (UC) patients. Text has been updated and/or clarified.		
Sections Affected	Original Content	**Amended/New Content**
Throughout the document as necessary, where Crohn's disease (CD) was mentioned this was updated to include ulcerative colitis (UC) or inflammatory bowel disease (IBD) defined as CD or UC	CD	CD **or UC** **IBD**
Synopsis, Number of Patients 3.1 Registry Design, paragraph 3	The total number of patients from the 3 registry protocols will be approximately 2,000 pediatric patients with CD who have been exposed to Remicade. The control group for the Remicade-treated CD patients will include approximately 2,000 pediatric patients with CD who were treated with medical therapies other than Remicade. In North America, approximately 1,000 pediatric patients with UC or IC will also be enrolled independent of the UC or IC medical therapies received.	**The 3 registry protocols will enroll approximately 4000 pediatric CD patients: approximately 2000 patients exposed to Remicade and an approximately equivalent number of patients treated with medical therapies other than Remicade. The protocols will also enroll approximately 2000 pediatric patients with UC or IC (UC/IC in North America; UC in the EU): approximately 1000 patients treated with Remicade and approximately 1000 patients treated with other IBD medications.**
Synopsis, Number of Sites 3.1 Registry Design, paragraph 4, last sentence	Approximately 50 to 100 sites in the EU and North America.	Approximately 50 to **125** sites in the EU and North America.
Synopsis, Data Evaluations	CD outcome analyses: 1. Descriptive statistics for demographic data of pediatric patients with CD, both with and without Remicade exposure 2. Summary of safety outcomes of pediatric patients with CD, both with and without Remicade exposure 3. Summaries of medical therapies, clinical status, and quality of life for pediatric patients with CD, both with and without Remicade exposure	Data analyses will include the following **for all patients with IBD and by subgroups of CD and UC:** **Health status and** outcome analyses: 1. Descriptive statistics for demographic data of pediatric patients with CD or UC, both with and without Remicade exposure 2. Summary of safety outcomes of pediatric patients with CD or UC, both with and without Remicade exposure 3. Summaries of medical therapies, clinical status, and quality of life for pediatric patients with CD or UC, both with and without Remicade exposure
3.1 Registry Design, paragraph 4	The patient enrollment period will be conducted over approximately 96 months; the patient observation	The patient enrollment period will be conducted over an approximate **period of 12 years**; the patient observation

	period is planned for approximately 20 years. The registry will be conducted at approximately 50 to 100 sites in the EU and North America.	period is planned for approximately 20 years. **The planned duration of the registry is approximately 32 years.** The registry will be conducted at approximately 50 **to 125** sites in the EU and North America.
5.1.1 Registry Entry, bullet 5	• Clinical disease status	• Clinical disease status **(ie, Physician Global Assessment, partial PCDAI (as applicable), partial Mayo score (as applicable)**
5.1.2 6-Month Follow-up, bullet 3	• Physician global assessment	• Clinical disease status **(ie, Physician Global Assessment, partial PCDAI (as applicable), partial Mayo score (as applicable)**
5.2.2.3 New Section	None	**5.2.2.3 Mayo Score and Partial Mayo Score** **The Mayo score is a validated clinical tool to assess disease activity in patients with UC. The Mayo score (Schroeder et al, 1987) was developed from the criteria of Truelove and Witts (1955) for mild, moderate, and severe UC; and from the criteria of Baron et al (1964) for grading the mucosal appearance. A Mayo UC activity score of ≤ 2 points, with no individual subscore > 1, indicates clinical remission; a score of 3 to 5 points indicates mildly active disease; a score of 6 to 10 points indicates moderately active disease; and a score of 11 to 12 points indicates severe disease. Partial Mayo scores (ie, Mayo scores using data from items 1 and 2 only [see below] without sigmoidoscopy or colonoscopy) will be determined from data obtained at enrollment and at 6-month follow-up intervals for patients with UC.** **Mayo scores are calculated using:** **1. The stool frequency and rectal bleeding data from the most recent consecutive 3-day period prior to the visit, excluding the following:** **a. The day that medications for constipation,**

		diarrhea, or irregularity were taken. (For patients maintained on a stable dose of bulking or stool softening agents throughout the trial, the days on which these agents are taken should not be excluded from consideration in calculating the Mayo score.) **b. The day(s) of a procedure or preparation for a procedure (eg, enemas, other laxatives, a clear liquid diet) that would affect bowel frequency and/or blood content of the stool.** **c. The 48 hours after the use of antimotility agents (ie, diphenoxylate hydrochloride with atropine sulfate or loperamide).** **d. The 72 hours immediately following a colonoscopy.** **2. The Physician's Global Assessment.** **3. The results of a sigmoidoscopy or colonoscopy.**
8 Analytical Methods, section revised to include UC patients	**8 Analytical Methods** The CRO SAS programmers and statistician will provide for the generation and quality control of the final tables and listings. All of the programming will be completed based on the SAP and this Registry Protocol. All SAS programs and statistical output will be developed, validated and documented according to standard operating procedures as well as GCP guidelines. The CRO statistician will be responsible for providing the statistical appendices to the clinical	**8 Analytical Methods** **Analyses will be conducted based on the SAP and this Registry Protocol. All SAS programs and statistical output will be developed, validated, and documented according to standard operating procedures as well as GCP guidelines.** **Descriptive statistics will be computed overall and by disease (CD or UC) for the prescribed treatment categories (ie, Remicade-exposed and Remicade non-exposed groups). Analysis cohorts may be defined based**

	registry report. The Sponsor will approve the final SAP. **8.1 Patients with CD** Descriptive statistics will be computed overall and for the prescribed treatment categories (ie, Remicade-exposed and Remicade non-exposed groups). Data from patients who will be prescribed treatments other than Remicade will be summarized by treatment regimens. Appropriate descriptive statistics, including number and percent of patients, mean, median, standard deviation, minimum and maximum values will be used to summarize the demographic characteristics. Data for dose and administration frequency will be collected for Remicade, other biologic agents, and immunomodulators prescribed during participation in the registry. The duration of all therapies administered during participation in the registry will be recorded. The incidences of AEs and SAEs will be reported, and the corresponding 95% confidence intervals will be provided for clinically important AEs and SAEs. The use of medications will be summarized. Summaries of clinical status for patients with CD who were prescribed Remicade and non-Remicade treatments will include number, mean, median, standard deviation, minimum and maximum values. The results of quality-of-life assessments (ie, employment, disability, and school status questionnaire) will be summarized as percentages.	**on biologic medication exposure, include Remicade only, anti-TNF biologics only, non anti-TNF biologics only, non-biologics only, and anti-TNF and non-anti-TNF biologics. The detailed cohort definitions will be specified in the SAP. Appropriate descriptive statistics, including number and percent of patients, mean, median, standard deviation, minimum and maximum values will be used to summarize the demographic characteristics.** **Data for dose and administration frequency will be collected for Remicade, other biologic agents, and immunomodulators prescribed during participation in the registry. The duration of therapies administered during participation in the registry will be recorded. The use of medications will be summarized. The incidences of AEs and SAEs will be reported, and adverse event rate per 100 patient years will be calculated.** **Summaries of clinical disease status (PGA, partial PCDAI, partial Mayo Score) for patients who were prescribed Remicade and non-Remicade treatments will include number, mean, median, standard deviation, minimum and maximum values for continuous variables and frequency and percentage for categorical variables. The results of quality of life assessments (ie, employment, disability, and school status questionnaire) will be summarized as percentages and other descriptive statistics.**
Attachment 1, footnote c, sentence 1	Includes clinical assessment of physician global assessment.	Includes clinical assessments of Physician Global Assessment, partial PCDAI, and partial Mayo score as appropriate.

4. Description/Rationale: Text was deleted regarding what Remicade has been approved for in the US as this is not applicable to this study.		
Sections Affected	Original Content	**Amended/New Content**
1.1 Purpose of the Registry, paragraph 1, last sentence removed	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. This high-affinity binding prevents the interaction of TNFα with its cellular receptors, thus attenuating inflammatory and other deleterious effects secondary to TNFα overproduction (Knight et al, 1993). Remicade is indicated for treatment of several autoimmune diseases in which TNFα plays a major role, and is typically administered via intravenous infusion in an outpatient setting with dosing intervals of 1 to 2 months. Remicade has been approved in the US for the treatment of adults and children with Crohn's disease (CD) and adults with ulcerative colitis (UC), rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA).	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. This high-affinity binding prevents the interaction of TNFα with its cellular receptors, thus attenuating inflammatory and other deleterious effects secondary to TNFα overproduction (Knight et al, 1993). Remicade is indicated for treatment of several autoimmune diseases in which TNFα plays a major role, and is typically administered via intravenous infusion in an outpatient setting with dosing intervals of 1 to 2 months.

5. Description/Rationale: A paragraph was modified because the text was not applicable in the context of this protocol.		
Sections Affected	Original Content	**Amended/New Content**
1.2 Background and Rationale, paragraph 2, last sentence removed	All patients received induction dosing of Remicade 5 mg/kg at Weeks 0, 2, and 6. At Week 10, 103 patients were randomized to a maintenance regimen of Remicade 5 mg/kg given either every 8 or 12 weeks. At Week 10, 88% of patients were in clinical response (defined as a decrease from baseline in the PCDAI score of ≥ 15 points and total PCDAI score of ≤ 30 points), and 59% were in clinical remission (defined as PCDAI score of ≤ 10 points). The proportion of	All patients received induction dosing of Remicade 5 mg/kg at Weeks 0, 2, and 6. At Week 10, 103 patients were randomized to a maintenance regimen of Remicade 5 mg/kg given either every 8 or 12 weeks. At Week 10, 88% of patients were in clinical response (defined as a decrease from baseline in the PCDAI score of ≥ 15 points and total PCDAI score of ≤ 30 points), and 59% were in clinical remission (defined as PCDAI score of ≤ 10 points).

	pediatric patients achieving clinical response at Week 10 compared favorably with the proportion of adults achieving a clinical response in an adult study of CD (ACCENT I study; Feagan et al, 2005).	

6. Description/Rationale: Efficacy and safety information was added for Study C0168T72, which enrolled pediatric patients with UC.		
Sections Affected	Original Content	**Amended/New Content**
1.2 Background and Rationale, new paragraphs 6 and 7	None	**The safety and efficacy of Remicade in pediatric UC were assessed in a randomized, open-label study in 60 pediatric patients who were aged 6 to 17 years (Study C0168T72; Hyams et al, 2012). Patients had moderately to severely active UC (defined as a Mayo score of 6 to 12, inclusive, at baseline, including an endoscopic subscore ≥ 2), despite current adequate treatment or had failed to respond to or tolerate treatment with 6-MP, AZA, corticosteroids, and/or 5-ASA compounds. All patients received an induction regimen of 5 mg/kg infliximab at Weeks 0, 2, and 6. Patients in clinical response at Week 8, as measured by the Mayo score, were randomized in a 1:1 ratio to receive 1 of 2 maintenance treatment regimens: infliximab 5 mg/kg administered q8w through Week 46 or q12w through Week 42. During the maintenance treatment phase, patients who lost response were eligible to increase their infliximab dose and/or dosing frequency 1 time.** **At Week 8, Remicade induced a response in 44 of 60 (73.3%) patients (95% CI: 62.1% –84.5%); a positive result was defined by 95% CI lower limit of 40%. Among responders, twice as many were in remission at Week 54 following the q8w regimen (8 of 21, 38.1%) when compared with the q12w regimen (4 of 22, 18.2%; p=0.146). Assuming the q8w remission rate for responders, the overall remission rate at Week 54 would be 28.6%. Serious adverse events and infusion reactions occurred in similar proportions of patients in the 2 groups. There were no deaths, malignancies, opportunistic**

		infections, tuberculosis, or delayed hypersensitivity reactions. Overall, Remicade was safe and effective, inducing a response at Week 8 in 73.3% of pediatric patients with moderate to severely active UC who did not respond to conventional therapy.

7. Description/Rationale: Text was clarified in the synopsis such that all adverse events were being collected in addition to those of special interest.		
Sections Affected	Original Content	**Amended/New Content**
Synopsis, Registry Design	This is a multicenter, prospective registry of long-term safety and clinical status of pediatric patients with CD who were treated with Remicade and/or other medical therapies for CD. Information will be collected on patient demographics, disease characteristics, clinical status, quality of life, medications, and dose and frequency of administration of Remicade, other biologics, and immune modulators. Adverse events, including dysplasias and malignancies of all types, infections, and autoimmune disease, will be documented. Data will be collected every 6 months.	This is a multicenter, prospective, **long-term** registry of **the** safety and clinical status of pediatric patients with CD or UC who were treated with Remicade and/or other medical therapies for CD **or UC**. Information will be collected on patient demographics, disease characteristics, clinical status, quality of life, medications, and **dosing information** for Remicade, other biologics, and immune modulators **as applicable**. **All** adverse events, **including those of special interest, such as** dysplasias and malignancies of all types, infections, and **new** autoimmune disease, will be documented. Data will be collected every 6 months.

8. Description/Rationale: Exclusion criterion number 5 was modified for clarity.		
Sections Affected	Original Content	**Amended/New Content**
4.2 Exclusion Criteria, number 5	6. Are currently participating in one of the Sponsor's trials for pediatric CD (eg, RESULTS [C0168T45]).	1. Are currently participating in one of the Sponsor's trials for pediatric **IBD.**

9. Description/Rationale: A clarification was made that once a patient turns 18 the partial PCDAI score will no longer be collected.		
Sections Affected	Original Content	**Amended/New Content**
5.2.2.2 Pediatric Crohn's Disease Activity Index and Partial Pediatric Crohn's Disease Activity Index, new sentence at end of section	None	Note that once a patient turns 18 the partial PCDAI score will no longer be collected.

Attachment 1, Schedule of Events, footnote c, last sentence		

10. Description/Rationale: Text was modified such that investigators should be aware that premalignant conditions should be reported.		
Sections Affected	Original Content	**Amended/New Content**
6.1.3 Adverse Events of Special Interest, new last sentence	None	**Although not considered an AE of special interest, investigators should report any occurrence of a premalignant condition.**

11. Description/Rationale: Text was added to provide direction in the event of a product quality complaint.		
Sections Affected	Original Content	**Amended/New Content**
New Section 6.5 Product Quality Complaint Handling	None	**6.5 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.** **6.5.1 Procedures** **All initial PQCs must be reported to the sponsor by**

		the study-site personnel as soon as possible 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 6.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.** **6.5.2 Contacting Sponsor Regarding Product Quality** **The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are located in the Registry Reference Manual.**

12. Description/Rationale: A correction was made in data collection.		
Sections Affected	Original Content	**Amended/New Content**
7 Data Collection, paragraph 2, last 2 sentences	Detailed instructions for completion of the eCRF pages are provided in the CRF Binder. Data from patient questionnaires (quality of life assessment) will also be collected every 6 months via hard copy, fax/scan, or a secure technology.	Detailed instructions for completion of the eCRF pages are provided in the **EDC system**. Data from patient questionnaires (quality of life assessment) will also be collected every 6 months **and entered into the EDC system**.

13. Description/Rationale: Corrections were made in data handling, and repeat information was deleted.		
Sections Affected	Original Content	**Amended/New Content**
7.1 Data Handling, paragraph 1, last sentence deleted and paragraph 2, revised	The CRO will develop a clinical database from eCRFs provided by the Sponsor. The clinical database will use the most recent version of MedDRA for coding medical history, concomitant medications, and AEs. Medications will be coded using the latest version of the World Health Organization Drug Dictionary (WHODRUG).	The CRO will develop a clinical database from eCRFs provided by the Sponsor. The clinical database will use the most current version of MedDRA for coding medical history, concomitant medications, and AEs. **Data from all 3 registry protocols as described in Section 3.1 will be captured in 1 registry database and combined into 1 annual summary report for the Pediatric IBD**

	The registry is conducted in North America (Protocol C0168Z02) and includes pediatric patients with a confirmed diagnosis of IBD (ie, CD, UC, or IC) who are less than 17 years of age at the time of enrollment and includes an immunogenicity substudy. The registry will also be conducted in the EU under an interventional and a noninterventional protocol. Specifically, protocol REMICADEPIB4003 will enroll pediatric patients with a confirmed diagnosis of CD only and are aged 6 years to less than 17 years of age at the time of enrollment. There will not be an immunogenicity substudy in this noninterventional protocol. Protocol REMICADEPIB4002 will also enroll only pediatric patients with a confirmed diagnosis of CD who are aged 6 years to less than 17 years of age at the time of enrollment. However, the immunogenicity substudy will be part of this interventional protocol. Data from all 3 of these registry protocols will be captured in 1 registry database and combined into 1 annual summary report for the Pediatric IBD Registry.	**Registry.**

14. Description/Rationale: Text for site monitoring was updated to include remote monitoring contacts and text was removed.		
Sections Affected	Original Content	**Amended/New Content**
7.3 Site Monitoring, paragraph 1, sentence 1	The Sponsor or its designee will perform onsite monitoring consistent with the Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (GPPPA).	The Sponsor or its designee will perform onsite monitoring/**remote monitoring contacts (eg, via phone follow-up)** consistent with the Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (GPPPA).
Last paragraph removed	For cause monitoring may also occur (see Registry Reference Manual for details).	

15. Description/Rationale: The definition of when a patient is considered to have entered Transitional Follow-up was added for clarity.		
Sections Affected	Original Content	**Amended/New Content**

7.5 Transitional Follow-up, new sentence 2	None	**A patient will be considered a transition patient when the patient is no longer being followed by the pediatric gastroenterologist who is a member of the registry.**

Appendix A Patient Follow-up and Retention Plan

1. An active patient is defined as a patient who has had a medical or non-medical encounter visit with their designated registry site personnel within 60 days of a registry-scheduled encounter visit.

2. If no encounter visit is confirmed and the patient has not formally withdrawn consent for participation in the registry the patient should be contacted as outlined below.

3. Procedure for tracking a patient lost to follow-up:

    a) The site personnel will follow the algorithm below for contacting those patients lost to follow-up:

        i. Three contact attempts will be made utilizing the patient participant's given address or phone number either via phone or by regular mail. Contact attempts will be made once every week for 3 consecutive weeks, after 60 days of a registry scheduled medical encounter have passed.

        ii. As appropriate, additional contact attempts will be made by e-mail.

        iii. The final contact attempt, using the patient's contact information, will be made using Registered/certified letter.

        iv. Three contact attempts will be made to an extended family member in order to secure forwarding/contact information for the patient participant, within 1 week after final contact attempt has been made to the patient participant.

        v. If forwarding information is obtained, additional contact attempts will be made to reach the patient participant utilizing the forwarding information.

    b) Upon completion of the algorithm, if site personnel are not successful in contacting the patient, the site personnel will inform and work with the Sponsor's designee to perform a periodic search of the National Death Index (NDI) or equivalent data source (please refer to local or region-specific guidelines) subject to local access requirements (eg, a publicly accessible death registry, a public obituary database) for evidence of the patient's status.

LAST PAGE