Study C87075

Protocol Amendment 5

SECURE

A Non-Interventional Long-term Post-Marketing Registry of Patients Treated with Certolizumab Pegol (Cimzia®) for Crohn's Disease

IND Number: 011197

UCB Biosciences, Inc.
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Hereafter "UCB"

| Protocol/Amendment Number | Date | Type of amendment |
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# STUDY CONTACT INFORMATION

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# SERIOUS ADVERSE EVENT REPORTING

| **SAEs, Pregnancy, and Breastfeeding Reporting (24h/7d)** | | |
|---|---|---|
| **Primary** | **Internet** | *www. secure-cimziadata.com* |
| | **Fax**: | +1 (888) 772 6919 (PRA number to be used if site is unable to access the electronic data capture [EDC] system) |
| | **Phone:** | +1 (800) 772 3125 Study code 707501 (PRA number for EDC questions) |
| | **Phone:** | +1 (866) 822 0068 (UCB number for questions related to adverse event reporting) |
| | **Email:** | chosafety@praintl.com (PRA contact) |
| **Site Support** | | |
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| **Patient Interview Service** | | |
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| | |
|---|---|
| AE | adverse event |
| anti-TNFα | anti-tumor necrosis factor alpha |
| CD | Crohn's disease |
| CI | confidence interval |
| CPM | Clinical Project Manager |
| CRO | Contract Research Organization |
| CSE | cross-section echocardiography |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| EEG | Electroencephalogram |
| EMG | Electromyogram |
| FDA | Food and Drug Administration |
| HBI | Harvey-Bradshaw Index |
| IRB | Institutional Review Board |
| MedDRA® | Medical Dictionary for Regulatory Activities |
| MRI | Magnetic Resonance Imaging |
| p-y | patient years |
| RR | Rate ratio |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| TNF | tumor necrosis factor |

| | |
|---|---|
| USA | United States of America |
| WHO Drug | World Health Organization Drug |

# 1 INTRODUCTION

Following the Food and Drug Administration (FDA) approval of certolizumab pegol (Cimzia®) for Crohn's disease (CD), UCB has committed to collect additional long-term, post-marketing safety data on patients exposed to the product in a real-life setting. To achieve this goal, a pharmacoepidemiologic study entitled SECURE was designed. The study began in January 2009 with the goal of collecting prospective data on 2000 patients prescribed Cimzia and a 2000 patient comparator group prescribed other treatments (including biologics) for CD.

The protocol has been amended (Amendment 5) to cease enrolling patients into the SECURE registry (protocol C87075). The decision was based on the results of a current interim analysis that indicated that no new safety issues had emerged from the currently known safety profile of Cimzia. Patients who already enrolled in C87075 at the time of discontinuation will continue to be followed.

The SECURE registry represents a significant addition to post-marketing safety assessments based on spontaneous reports. The study is anticipated to continue monitoring all enrolled patients for approximately 8 years after enrollment. Section 14 provides detailed information on protocol history since Final Version.

# 2 REGISTRY RATIONALE

This study is a post-approval commitment study designed to monitor the long-term safety of Cimzia compared to other CD treatments when used in customary clinical practice in patients with CD. Enrolled patients will be followed for approximately 8 years during normal Investigator visits and through direct patient follow-up in the form of web, mail surveys and/or phone follow-up calls. All patients will receive and use their medications according to their normal course of medical treatment per Investigator clinical judgment.

The treating Investigator is requested to report all serious adverse events (SAEs) and nonserious adverse events (AEs) of interest to the registry. These events will be collected and summarized in aggregate.

# 3 REGISTRY OBJECTIVE

The objective of this registry is to measure the safety outcomes among Cimzia patients compared to those that occur while on a different CD treatment regimen.

All SAEs and AEs of interest will be collected and summarized (see Section 5). The AEs of interest are: selected autoimmune disorders and demyelinating disorders, serious infections including opportunistic infections, hypersensitivity reactions, lymphoma and other malignancies. In addition, UCB plans to evaluate aplastic anemia and serious cardiac events (specifically, CHF). All these events represent serious risks known to the class of tumor necrosis factor (TNF) blocking agents. During the development program for CD and rheumatoid arthritis consisting of over 6,000 subjects, reported events were consistent with the class.

# 4 REGISTRY STUDY PLAN

## 4.1 Investigator Selection Criteria

Selected gastroenterologists and internal medicine Investigators from both community-based and academic practice settings (75% and 25% respectively) will be approached to participate in this registry. Investigators will be asked to provide a confidentiality agreement, recruitment questionnaire, signed protocol signature page, signed study contract, Form FDA 1572, Financial Disclosure Form, current CV, and receive Institutional Review Board (IRB) approval prior to study activation. Once activated, Investigators will be able to consent patients using their IRB approved template and enroll patients into the study. Each Investigator should be able to recruit a minimum of 5 patients prescribed Cimzia and/or 5 patients prescribed other treatments.

## 4.2 Selection of Study Population

This is a long-term observational study in the USA that includes a total of 3045 CD patients (1371 in the Cimzia Cohort and 1674 in the Comparison Cohort) as of Mar 2017. To ensure a sufficient number of Cimzia-treated patients in the registry, approximately half of enrolled patients will be receiving Cimzia for ≤12 months or about to receive Cimzia at the time of enrollment. The study will be conducted in all regions in the USA at approximately 280 enrolling investigative sites.

Recruitment of Cimzia-treated and comparator patients will be monitored and controlled as needed in order to ensure balanced enrollment over time.

Quarterly progress reports will be sent to the FDA during the patient recruitment period.

## 4.3 Subject Inclusion/Exclusion Criteria

Patients who meet all of the following criteria will be eligible for inclusion into the SECURE Registry:

- Patient (or his/her legally acceptable representative) is able to provide written informed consent to permit collection of data.
- Patient must be 18 years of age or older.
- Patient must have medically documented CD.
- The decision to prescribe Cimzia or other medications has been made by the Investigator independently of the decision to include the patient in the study.
- Patients participating in randomized, blinded clinical trials for CD or other conditions are not eligible for inclusion into the SECURE registry. Involvement in other registries, where patients follow routine clinical practice, is permitted, however.

**Cimzia-treated patients**

For a patient to qualify as being treated with Cimzia, they must meet one of the following criteria:

- Patient is receiving treatment with Cimzia for the first time. Patient must receive Cimzia treatment within 2 months of enrollment into the registry.
- Patient is currently receiving treatment with Cimzia for ≤12 months. Patients must also receive a Cimzia dose within 2 months following enrollment into the registry.

**Comparator patients**

Patients enrolled in the comparator group are eligible to participate in the registry if one of the following criteria is fulfilled:

- Patient is switching CD treatments or beginning CD treatment for the first time. Previous Cimzia treatment is prohibited in the comparator group.
- Patient must receive new CD treatment within 2 months of enrollment into the registry.

Patients must fit into at least ONE of the following 3 criteria:

- Patient is currently receiving for CD anti-TNF treatment (or other approved biologics) for ≤12 months. Patient must receive anti-TNF treatment (or other biologics) within 2 months following enrollment into the registry.
- Patient is currently receiving immunosuppressant therapy for ≤12 months. Patient must receive immunosuppressant therapy within 2 months following enrollment into the registry.
- Patient is currently receiving systemic steroid therapy for ≤12 months. Patient must receive systemic steroid therapy within 2 months following enrollment into the registry.

## 4.4 Study Procedures

Patient care will follow current clinical practice for CD at the respective site. No additional diagnostic or monitoring procedures will be applied. The choice of medical treatment will be made independently by the Investigator in the regular course of practice and will not be influenced by participation in the study protocol.

The Investigator will treat the patient according to standard medical practice for CD at the respective site. Investigators are free to add or withdraw any medication, or to withdraw the patient from the study at their own discretion. Patients are likely to receive other treatments for CD as part of their treatment plan in the regular course of practice.

Cimzia or other medications will not be provided nor paid for by the Sponsor.

## 4.5 Schedule of Assessments

No mandatory visits are required as part of this protocol. All visits will be scheduled and conducted per sites standard of care. Standard of care is defined as: A diagnostic and

customary clinical treatment/practice process that a clinician should follow for a Crohn's disease patient, a certain type of illness, or clinical circumstance.

Investigators will complete the baseline data for each patient after enrollment into the study and includes the signing of the Informed Consent Form (ICF). Follow-up data for patient visits will be reported in accordance to sites standard of care or clinical judgment appointments. Telephone contacts are permitted. All data, as described in Section 4.8.2, are to be collected as available during the telephone contacts.

In an effort to minimize missing data and unreported events over the 8-year Follow-Up Period, patients will directly report data in parallel to the Investigator reported data. Direct patient follow-up will occur every 3 months after enrollment (months 3, 6, 9, 12, etc) via a web-based system, by mail or by phone - as preferred by the patient. If a patient does not provide the information via the web, mail or by phone within approximately 1 week after the 3 month due date, the study patient interview service will call the patient to obtain the required information over the phone. Safety information collected directly from the patient will be available for the study investigative site to review. If 8 consecutive quarterly patient surveys have not been at least partially completed, further attempts at patient contact are not required. The Investigator will be requested to confirm whether the patient status should be changed to 'Lost to Follow-up'.

| | **Study Entry (Baseline)** | **Investigator-Reported Follow-up[b]** | **Direct Patient Follow-up Year 1-8** |
|---|---|---|---|
| | **ENROLLMENT** | **PER STANDARD OF CARE** | **EVERY 3 MONTHS** |
| Written informed consent | X | | |
| Assessment of inclusion/exclusion criteria | X | | |
| Demography | X | | |
| Crohn's disease history | X | | |
| Medical and surgical history | X | | |
| Family history | X | | |
| Reason for initiating Cimzia or other medication | X | | |
| Planned Cimzia or other medication treatment period | X | X | |
| CD treatment medication changes and reason | | X | X |
| Concomitant medications | X | X | X |
| All SAEs and AEs of interest since time of last completed follow-up[a] | | X | |

| | Study Entry (Baseline) | Investigator-Reported Follow-up[b] | Direct Patient Follow-up Year 1-8 |
|---|---|---|---|
| | **ENROLLMENT** | **PER STANDARD OF CARE** | **EVERY 3 MONTHS** |
| Major changes in health status since last completed follow-up | | | X |
| Investigator's assessment of disease severity | X | X | |
| Investigator's HBI[c] (see APPENDIX A) | X | X[e] | |
| Patient's Modified HBI[d] | X | | X |
| Patient's assessment of disease severity | X | | X |
| Reasons for discontinuation from registry (early termination or end of Year 8) | | X | |

AE=adverse event; CD=Crohn's disease; HBI=Harvey-Bradshaw Index; SAE=serious adverse event

[a] All SAEs and AEs of interest are to be reported through the registry.

[b] Telephone contacts are permitted.

[c] This may also be completed by qualified site personnel as designated by the Investigator.

[d] The Modified HBI does not include the abdominal mass question.

[e] The Modified HBI is completed during the Investigator telephone contact instead of the full HBI.

## 4.6 Informed Consent

The patient (or his/her legally acceptable representative) must be able to provide written informed consent for participation in this registry and release of their data to UCB (sponsor) and the Contract Research Organization (CRO) for analysis. Prior to obtaining informed consent, the Investigator or designee will explain to the patient the nature and purpose of the study. After informed consent is obtained, the patient will complete a "Patient Contact Form", which will request contact information (phone number, email address, and physical address). This form will be submitted to an independent patient interview service by the Investigator. Information and instructions informing patients about the Follow-Up Period and how to report AEs is included in the Informed Consent Form. The original document will be placed in the patient's medical record and a signed copy given to the patient.

Medication guides will be provided per standard of care.

Upon enrollment, patients will receive an enrollment kit that includes general registry information, including a patient card that identifies them as a participant in the SECURE Registry. The card informs the treating Investigator that the patient is participating in a registry study, and provides instructions for the treating Investigator on how to report AE or other treatment information to the Investigator.

## 4.7 Participation and Retention Strategies

Individual patient follow-up is approximately 8 years after enrollment, regardless of discontinuation of Cimzia or other medications.

As a means to retain patient participation, patients are followed up directly via a web-based system or if preferred, by mail (including a prepaid self-addressed return envelope) or by the phone every 3 months throughout the study (unless the patient withdraws consent or is deemed lost to follow-up) to complete a patient survey. "Lost to follow-up" is defined as a patient who goes 2 years with no data being collected/reported (2 years without Investigator visit/telephone contact or failure to at least partially complete 8 consecutive quarterly patient surveys; further attempts at patient contact are not required). The patients will receive emails or postal mail reminding them to complete the survey. If they have not completed the survey one week after the due date, they will be called by the independent patient interview service to complete the survey via phone. Patients completing the quarterly surveys will receive a nominal appreciation gift (if approved by the site's IRB).

In the event an Investigator retires, or discontinues participation from the registry, the following transition plan is in place to enable continuing participation of their patients. The Informed Consent Form include wording explaining that if the patient's Investigator discontinues participation in the registry, or retires, the independent patient interview service will be notified and the name and contact information of the closest participating study Investigator that they can contact during the remainder of their participation in the registry. The new Investigator and the patient should document re-consent of the transition. The registry can continue to collect the direct patient-reported data without the need for re-consent. If the patient is unable or unwilling to be followed by a new Investigator, the patient must be discontinued from the study.

In the event a patient moves to a new location or chooses to leave their current Investigator, patients are provided with information upon enrollment as to how to locate a participating Investigator in their area or how to provide the registry information to a new Investigator that may not yet be participating. Participating patients will have access to all of this information on the study specific web portal.

The goal of these strategies is to enhance patient retention activity, potentially resulting in a lower drop-out rate and improved quality of data.

Over the course of a long-term study, patient death may occur. Additionally, patients may develop serious co-morbidities that cause them to become "lost to follow-up" in the Registry. Periodically throughout the study, and in case of "lost to follow-up", searches of appropriate databases, such as the national death index and state cancer registries, death or cancer registries will be performed for any matches. In addition, the sponsor may utilize patient-centric data warehouse organization(s), to extract de-identified data from healthcare channels in the US. Data sources include, but are not limited to, medical claims, pharmacy claims, hospital charge master records, behavioral and demographic information, oncology electronic

medical records (EMR), long-term care pharmacy, and laboratory data. The output from this activity will not be used to solicit additional events from Investigators.

## 4.8 Data Collection Strategies

All investigator-reported data must be retained as source data in the patient's medical record. Data will be collected for this registry study from both the Investigators and patients using electronic data capture (EDC) system. Participating Investigators and enrolled patients (web-based participants) will enter the applicable data for each collection interval into a specific electronic case report form (eCRF). Enrolled patients requesting mail surveys will return the completed paper survey in the prepaid self-addressed return envelope and the applicable data will be entered in the specific eCRF by the independent patient interview service. Data collected from enrolled patients by phone will be entered in the eCRF by the independent patient interview service.

A study-specific web portal will be created and used as a centralized location for prospective Investigators and patients to find basic registry study information. For participating Investigators, a restricted area of the web portal may be accessed via SECURE username and password. The restricted area of the web portal will contain study-related material such as the protocol, trainings, study communications, as well as the link for the eCRF for data entry.

As this is an 8-year follow up registry study, the technologies used for this registry such as EDC will be 21 CFR Part 11 compliant and evaluated on an on-going basis throughout the registry study to ensure upgrades are made when necessary.

### 4.8.1 Enrollment Visit

For each patient enrolled in this registry, the Investigator will document the following information into the corresponding eCRFs within the registry study EDC system:

- Demographic information such as gender, age, race, ethnicity, household income, occupation and smoking status
- Crohn's disease history, including length of time since initial presentation of symptoms, date of diagnosis, all past treatment and surgeries for CD (with special focus on anti-TNFα and other biologics), and reason for switch to Cimzia or other medications since diagnosis and within the past 3 months
- Investigator's assessment of CD severity
- Investigator's completion of the Harvey-Bradshaw Index (HBI) – See Section 12.1 APPENDIX A. This may also be completed by qualified site personnel as designated by the Investigator
- Patient's assessment of CD severity
- Patient's completion of the modified HBI. The modified HBI does not include the abdominal mass question contained in the full HBI

- Other medical history including current medical status, concomitant medications, and planned treatment period (if known) with special focus on previous occurrence of each AE of interest and related risk factors (eg, history of serious infections, conditions that might place a patient at higher risk of serious infection)

### 4.8.2 Follow-Up Period

Each study Investigator or patient will be contacted by the CRO at regular intervals throughout the study to ensure they are entering data in the eCRF at the following frequencies:

- Every six months for Investigator-reported information. Telephone contacts are permitted.
- Every three months for patient-reported information (web, mail survey or phone)

The following data will be collected as available by the Investigator in EDC at each follow-up interval:

- All SAEs and AEs of interest that have been reported since last follow-up
- Investigator's HBI completed at clinic visits or modified HBI completed during telephone contacts. This may also be completed by qualified site personnel as designated by the Investigator
- Investigator's assessment of disease severity
- Full details on exposure (eg, dose, frequency) to Cimzia or other medication
- Any changes in medication
- Reasons for discontinuation of Cimzia and/or other medication for CD

The following data will be collected from the patient at each quarterly interval:

- Any major changes in health status that may have occurred since last follow-up
- Patient's Modified HBI
- Patient's assessment of disease severity
- Full details on exposure to Cimzia or other medications
- Any changes in medication
- Any administrative changes such as change in contact information

# 5 ADVERSE EVENTS OF INTEREST, SERIOUS ADVERSE EVENTS, CASE AND EXPOSURE DEFINITIONS

Serious adverse events and AEs of interest are the focus of this registry; Investigators are not expected to enter nonserious AEs in the eCRF except for AEs of interest regardless of seriousness.

## 5.1 Definitions

**Adverse Event (AE):** Any untoward medical occurrence in a patient administered a pharmaceutical product or device and that does not necessarily have a causal relationship between the product and event. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom temporally associated with a medicinal product, whether or not related to the medicinal product.

**Serious Adverse Event (SAE):** Any untoward medical occurrence which results in:

- Death
- Is life-threatening
- Requires inpatient hospitalization, or prolongs hospitalization
- Results in persistent or permanent disability or incapacitation
- Results in a congenital anomaly, or birth defect
- Any important medical event that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above should also be reported as an SAE. These events include but are not limited to peripheral or pulmonary edema which requires diuresis in an emergency room or out-patient setting, aplastic anemia/pancytopenia, serious cardiac event or an infection requiring treatment with parenteral antibiotics, etc.

All SAEs must be reported within 24 hours of being acknowledged by the Investigator.

## 5.2 Adverse Events of Interest

- Autoimmune disorders, such as:
  - systemic lupus erythematous
  - rheumatoid arthritis
- Demyelinating disorders, such as:
  - multiple sclerosis
  - Guillain-Barre syndrome
  - chronic inflammatory demyelinating polyneuropathy
- Serious infections including opportunistic infections, such as:
  - tuberculosis
  - pneumonia
- Lymphoma and other malignancies, such as:

  - hepatosplenic T-cell lymphoma
  - non-Hodgkin's lymphoma
  - solid malignancies
- Acute hypersensitivity reactions occurring within 2 hours of drug administration, such as:
  - urticaria, rash, pruritus, flushing, swollen lips/tongue/pharynx, wheezing, dyspnea, hypotonia, cramping, abdominal pain, and vomiting
- Other events:
  - congestive heart failure
  - aplastic anemia, pancytopenia, thrombocytopenia, neutropenia and leucopenia
  - serious bleeding events
  - serious skin reactions (eg, Stevens Johnson Syndrome, toxic epidermal necrosis, and erythema multiforme)

When available, narrow scope SMQs (Standardized MedDRA Queries) from the Medical Dictionary for Regulatory Activities (MedDRA®) version 17.0 will be used to define the AEs of interest (Section 5.2). Adverse events of interest that are the clinical endpoints for the SECURE registry will be confirmed by review of the results of diagnostic tests and diagnostic criteria used by the Investigator which are further explained within each section below.



**Table 5–1: Standardized MedDRA Queries for select adverse events of interest**

| Event | SMQ Title | SMQ Code | SMQ Scope |
|---|---|---|---|
| Malignancy | Malignant tumours | 20000194 | Narrow PTs |
| Congestive Heart Failure | Cardiac failure | 20000004 | Narrow PTs |
| Serious skin reactions | Severe cutaneous adverse reactions | 20000020 | Selected Narrow PTs |
| Hypersensitivity reactions | Anaphylactic reaction | 20000021 | Narrow/Broad PTs |
| Serious bleeding events | Haemorrhage | 20000038 | Narrow PTs |
| Aplastic anemia | Haematopoietic cytopenias affecting more than one type of blood cell | 20000028 | Narrow PTs |
| Aplastic anemia | Haematopoietic erythropenia | 20000029 | Narrow PTs |

**Table 5–1: Standardized MedDRA Queries for select adverse events of interest**

| Event | SMQ Title | SMQ Code | SMQ Scope |
|---|---|---|---|
| Aplastic anemia | Haematopoietic leukopenia | 20000030 | Narrow PTs |
| Aplastic anemia | Haematopoietic thrombocytopenia | 20000031 | Narrow PTs |

For events in which SMQs are not available, MedDRA v 17.0 Preferred Terms (PT) for the System Organ Class (SOC) and High-Level Group Term (HLGT) categories will be used as appropriate. For AEs of interest, where no SMQ is available, medical review will occur to select AEs (eg demyelinating disorders, autoimmune disorders and serious infections). Additional detail on the clinical validation of the primary endpoints is presented below although all safety events that meet the definition of AEs of interest will be collected and summarized as part of the study.

### 5.2.1 Autoimmune disorders

For this category, the primary events are Systemic Lupus Erythematous and Rheumatoid Arthritis.

The diagnosis has to be supported with medical history and physical findings, serologic evidence and other evidence from biopsy, laboratory results, imaging results, or other specialized testing, where appropriate, and the exclusion of other disorders which might cause a similar pattern of findings.

### 5.2.2 Demyelinating disorders

For this category, the primary event is Multiple Sclerosis. Guillain-Barre syndrome and chronic inflammatory demyelinating polyneuropathy will be analyzed as autoimmune disorders.

Medical history and physical findings, laboratory results, imaging results (eg, MRI) and any other specialized test (EEG, EMG, CSF analysis) results have to be considered in determining the final diagnosis.

### 5.2.3 Serious and Opportunistic Infections

Serious infections are defined as all infections meeting the definition of an SAE, and/or an infection requiring parenteral administration of antibiotics.

For the opportunistic infection category, the primary events are tuberculosis and pneumonia. The definitive diagnosis of pneumonia and tuberculosis may be confirmed by obtaining sputum smears or relevant biopsies and verifying by cultures. Infections not usually seen in immunocompetent patients or infections that have an accelerated pathogenesis or a more severe outcome in a given setting will also be considered opportunistic infections.

### 5.2.4 Lymphoma and Other Malignancies

For this category, the primary events are lymphoma, including hepatosplenic T cell lymphoma and non-Hodgkin lymphoma, and solid malignant tumors which are captured on malignancy forms.

Diagnosis has to be confirmed by tissue biopsy for histopathology (sources of tissue samples for review may include those obtained from an excisional biopsy) -a tissue sample from the affected nodes or organ, a needle aspiration, or a bone marrow biopsy. Pathohistological results have to correlate clinically with imaging results and/or any other pertinent information prior to determining the final diagnosis.

### 5.2.5 Hypersensitivity Reaction

Primary endpoints for hypersensitivity reaction are events meeting the criteria of an anaphylactic reaction and acute hypersensitivity reaction occurring within 2 hours of drug administration. As described in the case definition below, anaphylactic events include all terms listed in Category A, which consists of the narrow terms Type I hypersensitivity, anaphylactic shock and anaphylactoid reaction. In addition, combinations of the AE terms listed in Categories B, C and D will also be defined as anaphylactic events.

Category A: anaphylactic reaction, Type I hypersensitivity, anaphylactic shock, anaphylactoid reaction

Category B: dyspnoea, chest discomfort, cough, swollen tongue, oedema mouth, throat tightness, wheezing, laryngeal oedema, respiratory distress, sensation of foreign body, asthma, sneezing

Category C: swelling face, urticaria, pruritus, rash, eye swelling, pruritus generalized, rash, generalized, flushing, erythema, swelling, eye pruritus, lip swelling, rash pruritic, rash, erythematous, eyelid oedema, ocular hyperaemia, injection site urticaria, angioedema

Category D: hypotension, blood pressure decreased

To meet the definition of an anaphylactic event, a case has to meet one of the following criteria:

1. A narrow term or a term from Category A;
2. A term from Category B (Upper Airway/Respiratory) AND a term from Category C (Angioedema/Urticaria/Pruritus/Flush);
3. A term from Category D (Cardiovascular/Hypotension) AND either a term from Category B (Upper Airway/Respiratory) or a term from Category C (Angioedema/Urticaria/Pruritus/Flush)

### 5.2.6 Congestive heart failure

Congestive heart failure (CHF) is the primary endpoint for cardiac events of interest. CHF will be defined by Framingham criteria. The diagnostic criteria include physical findings of low cardiac output or increased cardiac workload and radiographic evidence (chest X-ray,

ECG, Echocardiogram, CT, MRI, angiogram) and laboratory findings, ECG and imaging results and any other specialized test results have to be considered for final diagnosis. CHF present at baseline and worsening during the study (worsening of New York Heart Association (NYHA) functional classification) will be captured, as well as new onset CHF.

### 5.2.7 Aplastic anemia

Aplastic anemia is a primary endpoint. Diagnosis must be confirmed by complete blood count (CBC) with peripheral smear, and bone marrow biopsy. Findings of pancytopenia (neutropenia, thrombocytopenia, and anemia), a reduction in the absolute number of reticulocytes, and a hypocellular bone marrow could be used to confirm the diagnosis.

### 5.2.8 Serious bleeding events

For this category, bleeding events meeting the criteria of an SAE are primary endpoints.

### 5.2.9 Serious skin reactions

For this category, primary endpoints are Erythema multiforme, Stevens Johnson's syndrome, and Toxic epidermal necrolysis.

## 5.3 Anticipated Serious Adverse Events

The following list of Anticipated SAEs has been identified as these events are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure. This original list will remain in effect for the duration of the protocol.

This list does not change the Investigator's obligation to report all serious AEs (including Anticipated SAEs) as detailed in Section 5.4.

**Crohn's disease**
**perianal abscess**
**abdominal pain**

## 5.4 Adverse Event Reporting to the Registry

Serious adverse events and AEs of interest are the focus of this registry; Investigators are expected to enter all SAEs and AEs of interest in the eCRF.

All SAEs and all AEs of interest will be entered in the EDC system within 24 hours of site notification and will be automatically forwarded to PRA, International for assessment and further processing as per regulatory requirements and UCB procedures (see Figure 5–1, Event Reporting Process for flow of activity).

Any major changes in health status reported by the patient during the every 3 month patient follow-up will be sent to the Investigator for medical confirmation. Once medical confirmation is obtained, the Investigator will report the event through the EDC system.

To ensure the capture of any events that might occur between patient or Investigator data entry intervals, each patient will be provided a safety reporting process patient card that they

can present to an Investigator if they have an event. The card will contain instructions for the Investigator on how to report event information.

Information and instructions informing patients about the Follow-Up Period and how to report AEs is included in the Informed Consent Form. More detailed instructions to sites regarding reporting of SAEs and AEs of interest are provided in the UCB safety Guidance booklet.

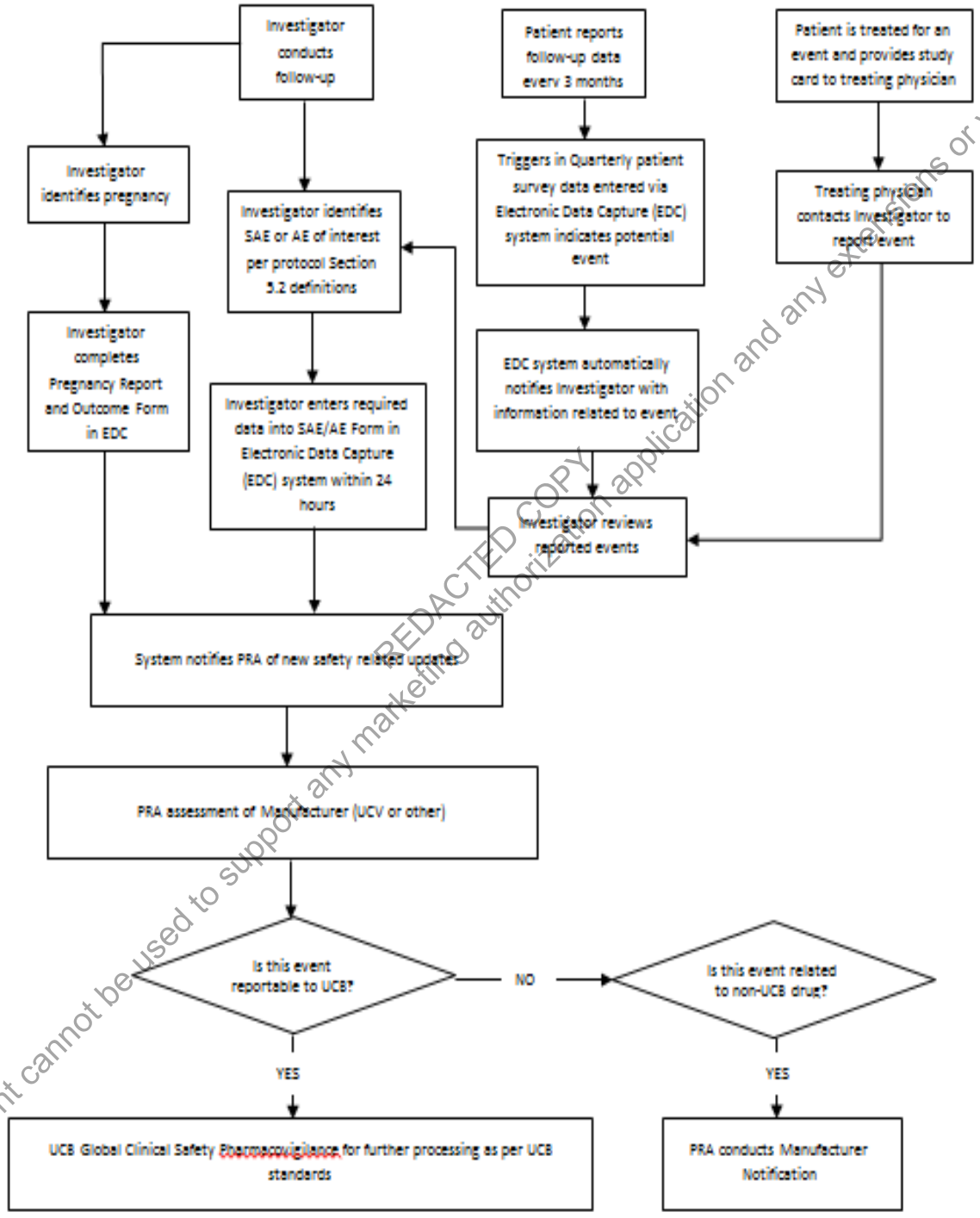
## 5.5 Pregnancy and Breastfeeding

Investigators are required to report pregnancy and breastfeeding of study participants; and pregnancy of study participant partners. An informed consent form will be provided to a study participant's partner who becomes pregnant during the study; and who will be willing to provide information on pregnancy course and outcome. More detailed instructions to sites regarding reporting of pregnancy and breastfeeding are provided in the UCB safety Guidance booklet.

## 5.6 UCB Pharmacovigilance Reporting

Adverse events collected from the registry that occur within 70 days of last Cimzia dose will be included in UCB's safety database and reported to the FDA as per regulatory reporting guidelines. Registry cases of malignancy, death, and pregnancy will be included in UCB's safety database and reviewed and evaluated for FDA reporting even if the event occurs after 70 days of last Cimzia dose. Any reports received prior to start of the registry and after completion of the study will be evaluated and reported as per standard UCB pharmacovigilance plans for spontaneous reporting.

## Figure 5–1: Event reporting process






AE=adverse event; EDC=electronic data capture; SAE=serious adverse event

# 6 STATISTICAL CONSIDERATIONS

## 6.1 Endpoints

The objective of this registry is to measure the safety outcomes among Cimzia patients compared to those that occur while on a different CD treatment.

### 6.1.1 Primary Endpoints

The primary outcome of this observational study is malignancy. Additionally, the following safety events will be investigated:

- Autoimmune disorders
- Demyelinating disorders
- Serious infections or opportunistic infections
- Hypersensitivity reactions
- Other events:
  - congestive heart failure
  - aplastic anemia
  - serious bleeding events
  - serious skin reactions

MedDRA coding version 17.0 will be used to identify and define AEs of interest. The specific MedDRA codes used to determine AEs of interest will be provided in the SAP. Narrow scope SMQs and clinical validation of primary endpoints are provided in Section 5.2 of the protocol.

### 6.1.2 Secondary Endpoints

Secondary endpoints include the following:

- Changes in HBI rating scale from baseline to each post-baseline assessment
- Changes in Investigator's assessment of disease from baseline to each post-Baseline assessment
- Changes in the patient's disease assessment of disease from Baseline to each post-Baseline assessment

## 6.2 Comparator Group

Given that patients will be followed for 8 years, it is anticipated that patients will switch CD medications while enrolled in the registry. Therefore, an individual's treatment at baseline will most likely not reflect their exposure throughout the study. Two comparisons may be

used to reflect these treatment changes over time and provide context for events reported to the registry: (1) a comparison of Cimzia event rates compared to all other CD treatment event rates across patients, and (2) case-crossover comparison or a within patient comparison.

- Cimzia event rates versus all other CD treatment event rates

Incidence and recurrence rates may be calculated for Cimzia and compared to all other CD treatment event rates across patients. Class-specific and product-specific event rates may also be calculated, if appropriate.

- Case-crossover comparisons

Case-crossover studies are useful for investigating the effect of transitory exposures on acute events. By having patients act as their own controls, this design eliminates between-person confounding on non-time varying characteristics, such as baseline disease and treatment characteristics and gender. However, there is still the potential for within-person confounding due to changes in the patient's profile over time (eg, changes in prescribing or in disease severity).

The incidence of safety events with short-term latency may also be compared within patients for patients that switch treatments at the time of enrollment into the registry and/or while participating in the registry. For this type of comparison, if applicable, the incidence of events of short-term latency within the first 6 months of receiving a new treatment may be compared to the incidence of the same events when beginning another new treatment.

## 6.3 Determination of Sample Size

Prior to Amendment 5, the study planned for a total of 4000 patients (2000 patients per arm). A total of 3045 patients (1371 in the Cimzia Cohort and 1674 in the Comparison Cohort) were enrolled as of Mar 2017. The total duration of participation (treatment and follow-up) of 8 years is planned for each patient. Assuming an 8% annual drop-out rate (1) (withdrawal, lost-to-follow-up or death), approximately 25,000 (12,500 per arm) total patient years (p-y) post-enrollment is expected in this registry. With a two-sided significance level of 0.05, the study is designed to have at least 80% power to detect incidence rate ratios (calculated based on observed rates in the control group) of 1.5 for serious infections, 3.3 for lymphoma, and 1.56 for solid malignancies after 8 years. Event rate estimates for this study were calculated using corresponding event rates observed in a CD anti-TNFα registry study control group (1, 2).

## 6.4 Statistical Analyses

All analyses will be performed on the eligible population, defined as all patients enrolled in this non-interventional study that meet eligibility requirements. All data captured from enrollment to last completed follow-up (Investigator or direct-to-patient) will be included.

Specifics to the primary and secondary analyses are outlined below and described in more detail in the SAP. All statistical analyses will be conducted using SAS version 9.1.3 or higher.

### 6.4.1 Primary Analyses

Safety events will be categorized based on event types (eg, malignancies, infections, demyelinating disorders, hypersensitivity reactions, and autoimmune disorders) with analyses conducted for each category. Analysis of specific outcomes may be conducted if appropriate.

Event rates will be calculated by dividing the number of reported safety events by the person-years at risk. Cimzia-specific rates will be calculated and compared to all other CD treatment rates. Incidence rates will be calculated by dividing the number of subjects who had reported safety events by the appropriate person-years at risk.

For incidence rate and event rate calculations, the number of events will be determined for Cimzia and for all other CD treatments based on the date of the last dose received before event onset and treatment class-specific half-life exposure of the medication. The exposure half-lives used for rate calculations for each treatment class are as follows:

- Corticosteroids: 7 days
- Immunosuppressants: 28 days
- Biologic agents (including Cimzia): 70 days

Propensity scores will be used to assess the comparability of patients who are receiving Cimzia at baseline and those who are receiving another CD medication and will be incorporated into the primary analysis. Two-sided 95% confidence intervals (CIs) will be calculated for all rates.

Appropriate analytical methodologies will be used to investigate the effect of time varying confounders.

Cancer progresses in several stages before reaching a detectable, malignant state. While this latency period may differ by cancer type, it is generally believed to occur over a long time period (Ecsedy and Hunter, 2002). Thus, a treatment-related event may not be seen until years after the initial exposure. In contrast, acute events typically have very short latency periods; therefore, it is unlikely that a treatment-related event will occur after exposure to the product has ended. For this reason, 2 different methods of person-time at risk calculations will be used, one for malignancy events (Section 6.4.1.1) and one for acute events (Section 6.4.1.2).

#### 6.4.1.1 Malignancy Events

The following analyses will be conducted to better elucidate treatment patterns and treatment attribution in malignancy events:

- The number of malignancy events and number of patients experiencing malignancy events will be tabulated by the number of CD treatments received during the study. Also, the mean number of treatments received per patient in the Cimzia and comparator groups (based on baseline assignment) will be calculated, as well as for both groups combined.
- The number of malignancy events and number of patients experiencing malignancy events will be tabulated by treatment patterns for biologics observed in the study. The

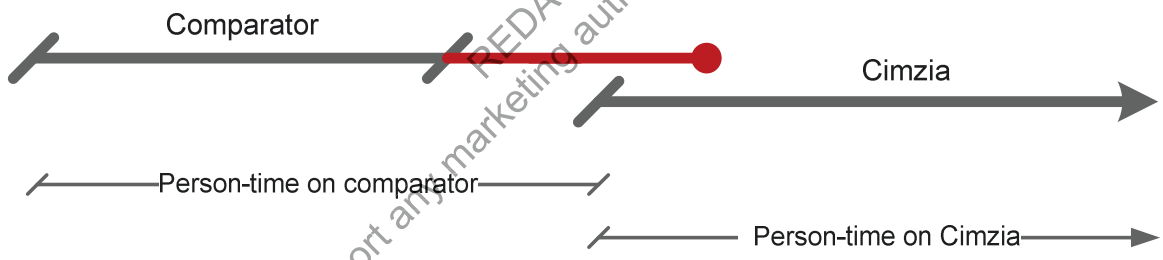
name and order of the biologic treatment will be specified in the summary table (eg, "A-B" implies that patients received two different biologics, "A" followed by "B"; "C" implies that patients received one biologic "C" throughout the study; "A-C-D" implies that patients received three different biologics, in the order of "A", "C", then "D", etc.).

- The number of malignancy events and the number of patients experiencing malignancy events will be tabulated by the type of CD therapy received (monotherapy versus combination therapy). If a patient received combination therapy (TNF-α antagonist plus immunosuppressant) at least once during the study, then this patient will be included in the combination therapy category.

Due to the long latency of malignancy, gaps in exposure will not be factored into person-time calculations for malignancies. Any patient exposed to Cimzia during the study will only contribute person time to the Cimzia cohort from that point onward Figure 6–1.

As an example, if a malignancy should occur any time after Cimzia exposure, it will be attributed to Cimzia. If a malignancy occurred in a patient prior to Cimzia exposure or in a patient with no Cimzia exposure, then it would be attributed to comparator. Thus, a patient may have exposure to multiple biologics, but any malignancies diagnosed after treatment with Cimzia would be systematically attributed to Cimzia.

**Figure 6–1: Example person-time at risk for malignancy events**




#### 6.4.1.2 Acute Events

The primary analysis for acute events will be time-to-event analyses using Cox proportional hazard modeling. A Kaplan-Meier analysis will be performed censoring patients at the time of their first treatment switch during the study period, including patients who switch from one non-Cimzia treatment to another non-Cimzia treatment, as a secondary analysis.

Exposure person-time at risk will be calculated for each CD treatment using the following equation:

$$Last\ Date - First\ Date + 1$$

First date is defined as the latest enrollment date or first dose date. Last date is defined as the earliest of the following:

- Date of safety event of interest (for incidence rate calculations only)
- Last dose date + treatment class-specific half-life exposure for product

- Date of discontinuation, withdrawal, or data cut-off

Any gaps in exposure, as illustrated in the figure below, will be excluded from person-time at risk calculations for acute events. Class-specific and product-specific person-time at risk may also be calculated if appropriate.

**Figure 6–2: Example person-time at risk for acute events**

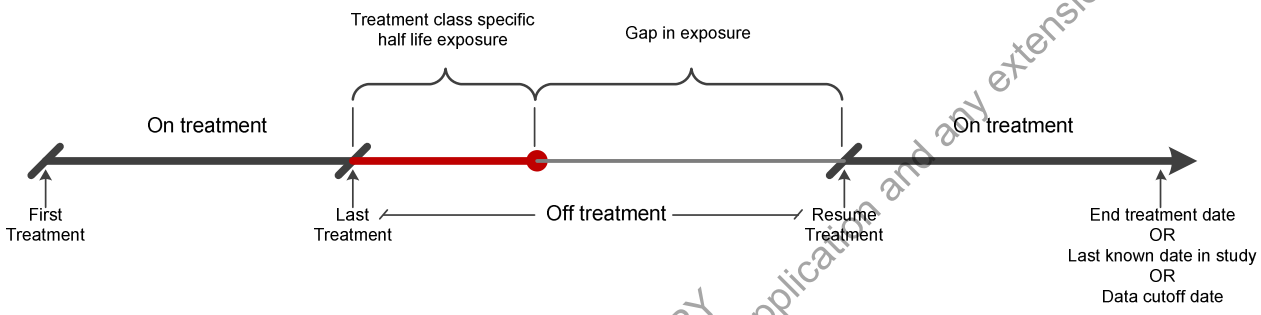



Figure 6–2 presents an example of a patient's exposure history. For this example, exposure person-time at risk would be calculated as follows:

Exposure person-time = (Last treatment date + Treatment class-specific half-life) – First treatment date + 1) + (earliest of End treatment date + treatment class-specific half-life exposure, last date in study, data cutoff date) – Resume treatment date + 1).

Further details on all person-time calculations will be provided in the SAP.

#### 6.4.1.3 Propensity Scores

Treatment selection in an observational study is not random; instead, the decision to start, stop, or remain on treatment is complex, factoring disease severity, past response to treatment, socio-economic status, and Investigator/patient preference. Therefore, patients in an observational study may vary substantially by demographics and disease characteristics based on treatment selection. These differences in baseline characteristics may influence the number, type, and severity of outcomes reported. Propensity score analysis assesses the impact of differences in baseline characteristic on treatment selection, so that comparability between treatment populations may be evaluated and quantified.

##### 6.4.1.3.1 Propensity score variables

Propensity scores will be calculated for each patient using all collected, potential confounding variables. These variables include (but are not limited to) the following Baseline characteristics:

- Age
- Gender
- Race

- Smoking status
- Other biologic treatment use in the year prior to Baseline
- Immunosuppressant use in the year prior to Baseline
- Corticosteroid use in the year prior to Baseline
- Disease location
- Diagnosed with fistulas
- Duration of disease
- Investigator assessment of disease severity
- Number of Crohn's related hospitalizations in the year prior to Baseline
- Number of surgical resections in the year prior to Baseline
- Disease extent

#### 6.4.1.3.2 Propensity score estimation and analysis

The propensity score represents the probability that a specific patient receives Cimzia conditional on the included confounding factors. Patients will be classified based on propensity score quintiles. The distribution of the propensity scores will be summarized by treatment selection and by quintiles. The variables to be included in the propensity score analysis were selected a priori using a directed acyclic graph (DAG). This approach has the advantage of improving the statistical efficiency of a model. It also minimizes the introduction of bias which may result from more traditional confounder identification and adjustment approaches (Shrier and Platt, 2008).

It is possible that some of the strata may contain only patients from either the Cimzia cohort or from the comparator cohort, which could lead to invalid comparisons. To ensure adequate performance of the propensity score stratification, a common support region or a sufficient overlap of the distribution of the variables in Cimzia and comparator cohorts are needed prior to creating the quintiles. The common support ensures that any combination of Baseline prognostic factors in the Cimzia cohort would also be observed in the comparator cohort. To evaluate adequate overlap of the propensity scores, 2 methods will be used:

- *Graphical method*. A visual inspection of the density distribution of the propensity scores in both Cimzia and comparator cohorts will be performed (Lechner, 2000). The extent of overlap should be evident from simple histograms or density distribution plots of the propensity scores from Cimzia and comparator cohorts. A more formal analysis using the Kolmogorov-Smirnov test for the equality of the propensity score distributions in the 2 groups will also be conducted to confirm the results of the visual assessment (Massey, 1951).
- *Minima-Maxima Rule*. The lower bound of the propensity scores will be determined as the larger of the minima of the scores in the 2 treatment groups while the upper

bound will be computed as the smaller of the maxima. As an example, if Cimzia and the comparator propensity scores range from 0.01 to 0.8 and from 0.03 to 0.8, respectively, then the common region will be defined as [0.03, 0.8].

Given that the determination of a common region/overlap may result in the exclusion of patients outside the distribution common to both groups, the number of patients kept in the analysis will be maximized by not discarding observations that are close to the upper and lower bounds. To evaluate the effect of patients treated contrary to prediction, propensity score quintiles will be determined using 2 different criteria for inclusion in the score:

- Unrestricted, where only patients inside the distribution common to both groups are included
- Restricted using a 0.01 caliper, where only patients within the 1 to 99 percentiles are included

The calculation of the quintiles using 2 different methods provides a natural way of evaluating the robustness of study findings. Once a common support region is found, only non-discarded patients will be used in further propensity score analyses aimed at estimating treatment effects.

Sensitivity analyses will be conducted to evaluate the potential effect of different levels of hypothetical confounding on registry findings (Lash et al, 2009). Appropriate analytical methodologies will also be used to investigate the effect of time varying confounders.

#### 6.4.1.4 Event Rate Comparisons

In addition to the propensity score analysis, comparisons between Cimzia event rates and all other CD treatment rates for comparator products will be examined using RRs and corresponding 95% CIs from conventional multivariate regression analyses. The same vector of covariates that are included in the propensity score analysis will be also used as confounders in the conventional multivariate regression analyses. This will allow for an assessment of the robustness of study findings. It is important to note, however, that the interpretation of any rate ratios using conventional modeling may be hindered if there are substantial differences in the characteristics of patients in the Cimzia and comparator cohorts.

Rate ratios comparing Cimzia event rates to other frequently used CD treatments or treatment classes will also be calculated as appropriate.

### 6.4.2 Secondary Analyses

Descriptive statistics on the Investigator's assessment of disease at study entry will be presented. Disease severity, measured by Investigator's and patient's assessment, will be used to quantify the potential influence of disease severity on the safety profile. Demographics and baseline patient characteristics, including medical history, CD history, physical examination findings (if available), vital signs (if available), the HBI score, patient's assessment, and reasons for treatment and study discontinuation will be summarized. Concomitant medications will be presented following the World Health Organisation Drug (WHO Drug)

classification. Characteristics of treatment with Cimzia or other medication such as planned treatment duration and actual duration of therapy will be tabulated. A stratified analysis by cumulative Cimzia exposure may also be performed for malignancy events to identify potential patterns in long-term use of Cimzia.

All AEs will be summarized descriptively by MedDRA Primary System Organ Class and Preferred Term (latest version at each interim analysis). Each interim analysis will indicate the MedDRA version that was utilized. Additional tables will summarize those AEs by severity and relationship to study drug as well as separate tables for AEs leading to withdrawal from the study, SAEs and deaths.

Further details on all analyses will be provided in the SAP.

### 6.5 Interim Analyses

Data captured for the study will be analyzed periodically, and at the end of the study. Supplemental data analyses may be performed throughout the study in addition to the periodic and final analyses.

## 7 ETHICS REQUIREMENTS

### 7.1 Institutional Review Board

Institution requirements of an institutional review board approval or notification of this protocol, related informed consent and/or participant materials shall be the Investigator's responsibility to secure such approval prior to initiating study procedures.

## 8 COMPLETION OF THE STUDY

The Investigator will conduct this study in compliance with the protocol and all applicable regulatory and legal requirements. UCB reserves the right to terminate this study at any time, either in its entirety or at an individual Investigator's site, for reasonable cause provided that notification in writing is provided at a reasonable time in advance of the intended termination. The Investigator may terminate the study at their site for reasonable cause, after providing written notification to UCB within a reasonable time in advance of the intended termination.

## 9 USE OF INFORMATION AND PUBLICATION

Authorship of planned manuscripts for submission to medical journals shall be determined in accordance with the International Committee of Medical Journal Editors (ICMJE) Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

The Investigator agrees that if the Investigator is part of a multi-center study, the Investigator shall coordinate in advance any intended disclosure of the results of the trial with UCB to ensure that the results of individual Investigators are not published or presented before those of the multi-center study, unless otherwise agreed by in writing by UCB.

Subject to the following paragraph, the authors have the final responsibility for the content of their own publication(s) and the decision to submit it/them for publication.

Any planned manuscript, presentation, abstract, or other intended disclosure of the results of the trial or otherwise originating from the study shall be made available for review to UCB at least thirty (30) days before submission for publication or any other means of disclosure in order to allow UCB to protect its intellectual property.

In the rare event that such disclosure would affect the patentability of any invention to which UCB has rights, UCB shall have the right to request an additional delay to the proposed disclosure of no more than ninety (90) days so as to allow UCB to preserve its intellectual property.

# 10 DISCLOSURE OF TRIAL INFORMATION

UCB alone shall be responsible for the registration of clinical trials in a public trials registry and for the disclosure of trials results on a publicly accessible web site.

# 11 REFERENCES

Ecsedy J, Hunter D. Textbook of Cancer Epidemiology. Eds, Hans-Olov Adami, David Hunger, and Dimitrios Trichopoulos. New York, NY: Oxford University Press, Inc; 2002.

Lash TL, Fox MP, Fink AK. Applying Quantitative Bias Analysis to Epidemiologic Data. Springer. 2009.

Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Chen DM, et al. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. Clin Gastroenterol Hepatol 2006;4:621-30.

Lichtenstein GR, Cohen RD, Feagan BGG, Sandborn WJ, Salzberg BA, Chen DM, et al. Safety of infliximab and other Crohn's disease therapies – TREAT Registry data with nearly 15,000 patient-years of follow-up. Gastroenterology 2006;130 (4 Suppl 2):A71.

Massey, FJ. The Kolmogorov-Smirnov Test for Goodness of Fit. Journal of the American Statistical Association. Vol. 46, No. 253, 1951, pp. 68–78.

Shrier I, Platt RW. Reducing bias through directed acyclic graphs. BMC Med Res Methodol. 2008 Oct 30;8:70

# 12 APPENDICES

## 12.1 Appendix A: Harvey-Bradshaw Index (HBI)

| Assessments | | | | | |
|---|---|---|---|---|---|
| Assessment | | | Questions | | |
| Template | Name | Version | Table | Prompt | Format |
| None | Harvey-Bradshaw Index (HBI) | 1 | | General Well-being: | ▫ 0 = Very well<br>▫ 1 = Slightly below par<br>▫ 2 = Poor<br>▫ 3 = Very poor<br>▫ 4 = Terrible |
| | | | | Abdominal pain: | ▫ 0 = None<br>▫ 1 = Mild<br>▫ 2 = Moderate<br>▫ 3 = Severe |
| | | | | Number of liquid stools per day: | _ _ |
| | | | | Abdominal mass: | ▫ 0 = None<br>▫ 1 = Dubious<br>▫ 2 = Definite<br>▫ 3 = definite and tender |
| | | | | **Complications:** | |
| | | | | arthralgia | ▫ 0 = No<br>▫ 1 = Yes |
| | | | | uveitis | ▫ 0 = No<br>▫ 1 = Yes |
| | | | | erythema nodosum | ▫ 0 = No<br>▫ 1 = Yes |
| | | | | aphthous ulcers | ▫ 0 = No<br>▫ 1 = Yes |
| | | | | pyoderma gangrenosum | ▫ 0 = No<br>▫ 1 = Yes |
| | | | | anal fissure | ▫ 0 = No<br>▫ 1 = Yes |
| | | | | new fistula | ▫ 0 = No<br>▫ 1 = Yes |
| | | | | abscess | ▫ 0 = No<br>▫ 1 = Yes |

# 13 DECLARATION AND SIGNATURE OF INVESTIGATOR

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.

I will ensure that all subInvestigators and other staff members read and understand all aspects of this protocol.

I have received and read all study-related information provided to me.

The objectives and content of this protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by UCB.

All rights of publication of the results reside with UCB, unless other agreements were made in a separate contract.

Investigator:

| | |
|---|---|
| Printed Name | Date/Signature |

# 14 AMENDMENTS

## 14.1 Protocol amendment 1

Rationale for the amendment

The protocol has been amended to address feedback from the FDA, update administrative changes, and correct minor typographical and wording errors. In addition, the eligibility criteria for the Cimzia cohort has been broadened to permit start of anti-TNF treatment based entirely on the Investigator's discretion and text to ensure balanced enrollment in the non-Cimzia and the Cimzia cohorts has been included. Furthermore, reporting of partner pregnancy and breastfeeding has been added as per current UCB procedures and AE reporting information has been updated.

Modifications and changes

Global changes

The following changes were made throughout the protocol:

- Internet address for SAE, pregnancy, and breastfeeding reporting has been added.
- Toll-free numbers for site support and patient interview service have been included.
- Contact information for the Clinical Program Director has been updated.
- Text regarding balanced enrollment of subjects in the non-Cimzia and Cimzia cohorts was added.
- Restriction of eligibility criteria for the Cimzia cohort to medical documentation of >3 months duration has been removed.
- An eligibility criterion for the non-Cimzia cohort was added.
- As an alternative to the web-based survey and if requested by the patient, the patient survey will also be sent by mail (including a postage prepaid self-addressed return envelope).
- Acute hypersensitivity reactions and solid malignancies have been added to the list of AEs of special interest to be evaluated.
- Text on SAE and AE of interest reporting has been updated.
- Partner pregnancy and breastfeeding reporting requirements have been included.
- Hypersensitivity reactions have been added as a primary endpoint.

**Specific changes**

Change #1

The following was added to the title page:

| Protocol/Amendment Number | Date |
|---|---|
| Protocol | 06-Jan-2009 |
| Protocol Amendment 1 | 24-Jun-2009 |

**Change #2**

2 CONTACT INFORMATION

**UCB Contributors:**

**Clinical Program Director (Study related questions)**

Name: [redacted] Phone: [redacted]

Fax: [redacted]

**Has been changed to:**

**UCB Contributors:**

**Clinical Program Director (Study related questions)**

Name: [redacted] Phone: [redacted]

Fax: [redacted]

**Change #3**

2 CONTACT INFORMATION

| | | | |
|---|---|---|---|
| **SAEs Reporting (24h/7d)** | | | |
| | | | |
| | **Fax**: | +1 800 880-6949 | |
| | | | |
| | | | |
| | **Phone**: | +1 (678) 799-4007 | |
| | | | |

**Has been changed to:**

| | | | |
|---|---|---|---|
| **SAEs, Pregnancy, and Breastfeeding Reporting (24h/7d)** | | | |
| **Primary** | **Internet** | ***www.secure-cimziadata.com*** | |
| Alternative | **Fax**: | +1 (800) 880 6949 | |
| | | | |
| **Site Support** | | | |
| | | | |
| | **Phone:** | **+1 (800) 772 3125 (reference number: 707501)** | |

| | | | |
|---|---|---|---|
| **SAEs, Pregnancy, and Breastfeeding Reporting (24h/7d)** | | | |
| | | | |
| **Patient Interview Service** | | | |
| | | | |
| | **Phone:** | **+1 (877) 580 7246** | |
| | | | |

**Change #4**

6. REGISTRY RATIONALE

Patients will be followed for approximately 10 years during normal Investigator visits and through direct patient follow-up in the form of web surveys and follow-up calls, during which the counts and frequency of serious adverse events (SAEs) and adverse events (AEs) will be collected. All patients will receive and use their medications according to their normal course of medical treatment per Investigator clinical judgment.

**Has been changed to:**

Patients will be followed for approximately 10 years during normal Investigator visits and through direct patient follow-up in the form of web, mail surveys and/or phone follow-up calls, during which the counts and frequency of all serious adverse events (SAEs) and nonserious adverse events (AEs) of interest will be collected. All patients will receive and use their medications according to their normal course of medical treatment per Investigator clinical judgment.

**Change #5**

7. REGISTRY OBJECTIVE

All SAEs and AEs will be collected and summarized (see Section 9). The AEs of primary interest are: autoimmune disorders, demyelinating disorders, serious and opportunistic infections, lymphoma and other malignancies.

**Has been changed to:**

All SAEs and nonserious AEs of interest will be collected and summarized (see Section 9). The AEs of primary interest are: autoimmune disorders, demyelinating disorders, serious infections including opportunistic infections, hypersensitivity reactions, lymphoma and other malignancies.

**Change #6**

8.1 Investigator Selection Criteria

**The following last sentence in the paragraph has been deleted:**

Normal distribution of Crohn severity disease needs to be reflected in the patients recruited.

**Change #7**

8.2 Selection of Study Population

This is a long-term observational study in the USA that will include 2000 Cimzia-treated Crohn's disease patients and 2000 patients treated with other Crohn's disease medications. The study will be conducted in all regions in the USA at approximately 300 enrolling investigative sites. In order to allow appropriate matching, recruitment will be stratified by disease severity (mild/moderate/severe), use of other anti-TNFα, age and gender. . Stratification strategy will be outlined in the SAP.

**Has been changed to:**

This is a long-term observational study in the USA that will include 2000 Cimzia-treated Crohn's disease patients and 2000 patients treated with other Crohn's disease medications. The study will be conducted in all regions in the USA at approximately 300 enrolling investigative sites.

Recruitment into both cohorts will be monitored and controlled as needed in order to ensure balanced enrollment over time. In order to ensure reasonable balance between both cohorts, recruitment will be frequency matched for disease severity (mild/moderate/severe), age categories and gender.

**Change #8**

8.3 Subject Inclusion/Exclusion Criteria

Patients who meet all of the following criteria will be eligible for inclusion into the SECURE Registry:

- Patient (or his/her legally acceptable representative) is able to provide written informed consent (patients under the age of consent must provide assent) to permit collection of data. Patients who join the registry prior to legal age of consent will provide written informed consent as an adult upon reaching the legal age of consent.
- Patient must have medically documented Crohn's disease > 3 months duration prior to study entry.
- The decision to prescribe Cimzia or other medications has been made by the Investigator independently of the decision to include the patient in the study.
- **Cimzia cohort** - Patient must be about to receive treatment with Cimzia as part of a pre-existing management plan for Crohn's disease or has already been receiving treatment with Cimzia for < 6 months.
- **Comparison cohort** – Patient must be about to receive treatment with any other medication as part of a pre-existing management plan for Crohn's disease or has already been receiving treatment. Previous Cimzia treatment is prohibited for the control arm.

**Has been changed to:**

Patients who meet all of the following criteria will be eligible for inclusion into the SECURE Registry:

- Patient (or his/her legally acceptable representative) is able to provide written informed consent (patients under the age of consent must provide assent) to permit collection of data. Patients who join the registry prior to legal age of consent will provide written informed consent as an adult upon reaching the legal age of consent.
- Patient must have medically documented Crohn's disease.
- The decision to prescribe Cimzia or other medications has been made by the Investigator independently of the decision to include the patient in the study.

**Cimzia cohort**

- Patient must be about to receive treatment with Cimzia as part of a pre-existing management plan for Crohn's disease or has already been receiving treatment with Cimzia for < 6 months.

**Comparison cohort**

- Patient must be about to receive treatment with any other medication as part of a pre-existing management plan for Crohn's disease or has already been receiving treatment. Previous Cimzia treatment is prohibited for the control arm.
- Patients are eligible for the comparison cohort if one of the following criteria is fulfilled:
  - currently receiving or history of anti-TNF treatment
  - currently receiving or history of immunosuppressant therapy within 6 months
  - currently receiving or history of systemic steroid therapy within 6 months

**Change #9**

8.5 Schedule of Assessments

Direct patient follow-up will occur every 3 months after enrollment (months 3, 6, 9, 12,...) via a web-based system. If a patient does not enter the information via the web within approximately 1 week after the 3 month due date, the study patient interview service will call the patient to obtain the required information over the phone.

**Has been changed to:**

Direct patient follow-up will occur every 3 months after enrollment (months 3, 6, 9, 12,...) via a web-based system, by mail or phone as requested by the patient. If a patient does not provide the information via the web, mail or phone within approximately 1 week after the 3 month due date, the study patient interview service will call the patient to obtain the required information over the phone.

**Change #10**

8.5 Schedule of Assessments

| | Study Entry (Baseline) | Investigator-Reported Follow-up Year 1-10 | Direct Patient Follow-up Year 1-10 |
|---|---|---|---|
| | **ENROLLMENT** | **EVERY 6 MONTHS** | **EVERY 3 MONTHS** |
| **Written informed consent/assent** | **X** | | |
| **Assessment of inclusion/exclusion criteria** | **X** | | |
| **Demography** | **X** | | |
| **Crohn's disease history** | **X** | | |
| **Medical and surgical history** | **X** | | |
| **Family history** | **X** | | |
| **Reason for initiating Cimzia® or other medication** | **X** | | |
| **Planned Cimzia® or other medication treatment period** | **X** | **X** | |
| **CD treatment medication changes and reason** | | **X** | **X** |
| **Concomitant medications** | **X** | **X** | **X** |
| **SAEs and AEs of interest since time of last completed follow-up** | | **X** | |
| **Major changes in health status since last completed follow-up** | | | **X** |
| **Investigator's assessment of disease** | **X** | **X** | |
| **HBI (see APPENDIX A)** | **X** | **X** | |
| **Patient's disease assessment** | **X** | | **X** |
| **Reasons for discontinuation from registry (early termination or end of Year 10)** | | **X** | |

**Has been changed to:**

| | Study Entry (Baseline) | Investigator-Reported Follow-up Year 1-10 | Direct Patient Follow-up Year 1-10 |
|---|---|---|---|
| | **ENROLLMENT** | **EVERY 6 MONTHS** | **EVERY 3 MONTHS** |
| Written informed consent/assent | X | | |
| Assessment of inclusion/exclusion criteria | X | | |
| Demography | X | | |
| Crohn's disease history | X | | |
| Medical and surgical history | X | | |
| Family history | X | | |
| Reason for initiating Cimzia or other medication | X | | |
| Planned Cimzia or other medication treatment period | X | X | |
| CD treatment medication changes and reason | | X | X |
| Concomitant medications | X | X | X |
| All SAEs and nonserious AEs of interest since time of last completed follow-up* | | X | |
| Major changes in health status since last completed follow-up | | | X |
| Investigator's assessment of disease | X | X | |
| HBI (see APPENDIX A) | X | X | |
| Patient's disease assessment | X | | X |
| Reasons for discontinuation from registry (early termination or end of Year 10) | | X | |

*All serious adverse events; and nonserious adverse events of interest from both study arms are to be reported through the registry.

**Change #11**

8.7 Participation and Retention Strategies

As a means to retain patient participation, patients are followed up directly via web-based system every 3 months throughout the study (unless the patient withdraws consent or is deemed lost to follow-up) to complete an on-line patient survey. "Lost to follow-up" is defined as a patient who goes one year with no data being collected/reported (1 year without Investigator visit and 4 consecutive quarterly patient surveys not completed). After informed consent/assent is obtained, the patient will complete a "Patient Contact Form", which will request contact information (phone number, email address, and physical address). This form will be submitted to an independent patient interview service by the enrolling physician. The patients will receive emails reminding them to complete the survey. If they have not completed the survey after one week, or they do not have internet access, they will be called by the independent patient interview service to complete the survey via telephone. For each survey the patient completes, they will receive a nominal appreciation gift.

**Has been changed to:**

As a means to retain patient participation, patients are followed up directly via a web-based system or if requested, by mail (including a prepaid self-addressed return envelope) or by phone every 3 months throughout the study (unless the patient withdraws consent or is deemed lost to follow-up) to complete a patient survey. "Lost to follow-up" is defined as a patient who goes one year with no data being collected/reported (1 year without Investigator visit and 4 consecutive quarterly patient surveys not completed). After informed consent/assent is obtained, the patient will complete a "Patient Contact Form", which will request contact information (phone number, email address, and physical address). This form will be submitted to an independent patient interview service by the enrolling physician. The patients will receive emails or mail reminding them to complete the survey. If they have not completed the survey one week after the due date, they will be called by the independent patient interview service to complete the survey via phone. For each survey the patient completes, they will receive a nominal appreciation gift.

**Change #12**

8.8 Data Collection Strategies

All Investigator-reported data must be retained as source data in the patient's medical record. Data will be collected for this registry study from both the enrolling physicians and patients using electronic data capture (EDC). Participating enrolling physicians and enrolled patients will enter the applicable data for each collection interval into a specific electronic case report form (eCRF).

**Has been changed to:**

All Investigator-reported data must be retained as source data in the patient's medical record. Data will be collected for this registry study from both the enrolling physicians and patients using electronic data capture (EDC). Participating enrolling physicians and enrolled patients (web-based participants) will enter the applicable data for each collection interval into a specific electronic case report form (eCRF). Enrolled patients requesting mail surveys will return the completed paper survey in the prepaid self-addressed return envelope and the applicable data will be entered in the specific eCRF by the independent patient interview service. Data collected from enrolled patients by phone will be entered in the eCRF by the independent patient interview service.

**Change #13**

8.8.1 Enrollment Visit

**Bullet point #2**

- Crohn's disease history, including length of time since initial presentation of symptoms, date of diagnosis, all past treatment and surgeries for Crohn's disease (with special focus on anti-TNFα biologics), and reason for switch to Cimzia or other medications since diagnosis and within the past 3 months

**Has been changed to:**

- Crohn's disease history, including length of time since initial presentation of symptoms, date of diagnosis, all past treatment and surgeries for Crohn's disease (with special focus on anti-TNFα and other biologics), and reason for switch to Cimzia or other medications since diagnosis and within the past 3 months

**Change #14**

8.8.2 Follow-up Period

Each study enrolling physician or patient will be contacted at regular intervals throughout the study to ensure they are entering required data at the following frequencies:

- every six months for Investigator-reported information
- every three months for patient-reported information (web survey or telephone)

The following data will be collected by the enrolling physician in EDC at each follow-up interval:

- Any SAEs/AEs of interest that may have occurred since last follow-up
- HBI
- Investigator's disease severity assessment (including HBI)
- Full details on exposure (e.g., dose, frequency) to Cimzia or other medication
- Any changes in medication
- Reasons for discontinuation of Cimzia and/or other medication for Crohn's disease

**Has been changed to:**

Each study enrolling physician or patient will be contacted at regular intervals throughout the study to ensure they are entering required data at the following frequencies:

- every six months for Investigator-reported information
- every three months for patient-reported information (web, mail survey or phone)

The following data will be collected by the enrolling physician in EDC at each follow-up interval:

- All SAEs and nonserious AEs of interest that have been reported since last follow-up
- HBI
- Investigator's disease severity assessment (including HBI)
- Full details on exposure (e.g., dose, frequency) to Cimzia or other medication
- Any changes in medication
- Reasons for discontinuation of Cimzia and/or other medication for Crohn's disease

**Change #15**

9.1 Definitions

**Serious Adverse Event (SAE):** Any adverse drug reaction which results in:

**Has been changed to:**

**Serious Adverse Event (SAE):** Any untoward medical occurrence which results in:

**And the following has been added:**

All Serious Adverse Events (of interest or other) must be reported within 24 hours of being acknowledged by the Investigator.

**Change #16**

9.2 Adverse Events of Interest

- Lymphoma and other malignancies, such as:
  - hepatosplenic T-cell lymphoma
  - non-Hodgkin's lymphoma

**Has been changed to:**

- Lymphoma and other malignancies, such as:
  - hepatosplenic T-cell lymphoma
  - non-Hodgkin's lymphoma
  - solid malignancies

**And the following was added:**

- Acute hypersensitivity reactions occurring within 2 hours of drug administration, such as:
  - urticaria, rash, pruritus, flushing, swollen lips/tongue/pharynx, wheezing, dyspnea, hypotonia, cramping, abdominal pain, and vomiting

**Change #17**

**The following has been deleted:**

9.3 Other Adverse Events

Other adverse event for both Cimzia and Control arms will be collect through the registry according to the judgment of the Investigator.

**Change #18**

9.4 Case Definition:

Cimzia Case:

Cases will be attributable to Cimzia identified by two methods. The first method will assume a case will be attributable to Cimzia after the first dose of the medication regardless of medication discontinuation and time to onset of disease. The second method will be a series of sensitivity analyses and stratifications to evaluate different clinically driven definition of cases attributable to drug. Specifics on data handling guidelines for managing missing or partial data will be documented in the SAP.

Control Case:

Cases will be attributable to non-Cimzia medications identified by two methods. The first method will assume a case will be attributable to the non-Cimzia medication after the first dose of the medication regardless of medication discontinuation and time to onset of disease. The second method will be a series of sensitivity analyses and stratifications to evaluate different clinically driven definition of cases attributable to drug. Specifics on data handling guidelines for managing missing or partial data will be documented in the SAP.

Has been changed to:

9.3 Case Definition:

Cimzia Case:

Cases will be attributable to Cimzia identified by two methods. The first method will assume a case will be attributable to Cimzia after the first dose of the medication regardless of medication discontinuation and time to onset of the event. The second method will be a series of sensitivity analyses and stratifications to evaluate different clinically driven definition of cases attributable to drug. Specifics on data handling guidelines for managing missing or partial data will be documented in the Statistical Analysis Plan (SAP).

Control Case:

Cases will be attributable to non-Cimzia medications identified by two methods. The first method will assume a case will be attributable to the non-Cimzia medication after the first dose of the medication regardless of medication discontinuation and time to onset of the event. The second method will be a series of sensitivity analyses and stratifications to evaluate different clinically driven definition of cases attributable to drug. Specifics on data handling guidelines for managing missing or partial data will be documented in the SAP.

**Change #19**

9.7 Adverse Event Reporting

All adverse events will be forwarded to UCB Global Clinical Safety and Pharmacovigilance for assessment of reportability (expedited 15-day or periodic report) as per UCB standard pharmacovigilance plan in compliance with 21 CFR 600 (see Figure 9.1– Event Reporting Process for flow of activity).

Any major changes in health status reported by the patient during the every 3 month patient follow-up will be sent to the enrolling physician for medical confirmation. Once medical confirmation is obtained, the enrolling physician will enter the event into the study EDC system and will be forwarded to UCB Global Clinical Safety and Pharmacovigilance for assessment of reportability (expedited 15-day or periodic report) as per UCB standard pharmacovigilance plan in compliance with 21 CFR 600 as described above.

**Has been changed to:**

Serious adverse events and nonserious adverse events of interest from both study arms are to be reported through the registry.

All adverse events reported through registry will be forwarded to UCB Global Clinical Safety and Pharmacovigilance for assessment and further processing as per regulatory requirements and UCB procedures (see Figure 5–1– Event Reporting Process for flow of activity).

Any major changes in health status reported by the patient during the every 3 month patient follow-up will be sent to the enrolling physician for medical confirmation. Once medical confirmation is obtained, the enrolling physician will report the event through the study EDC system.

Information and instructions informing patients about the follow-up period and how to report adverse events is included in the Informed Consent Form.

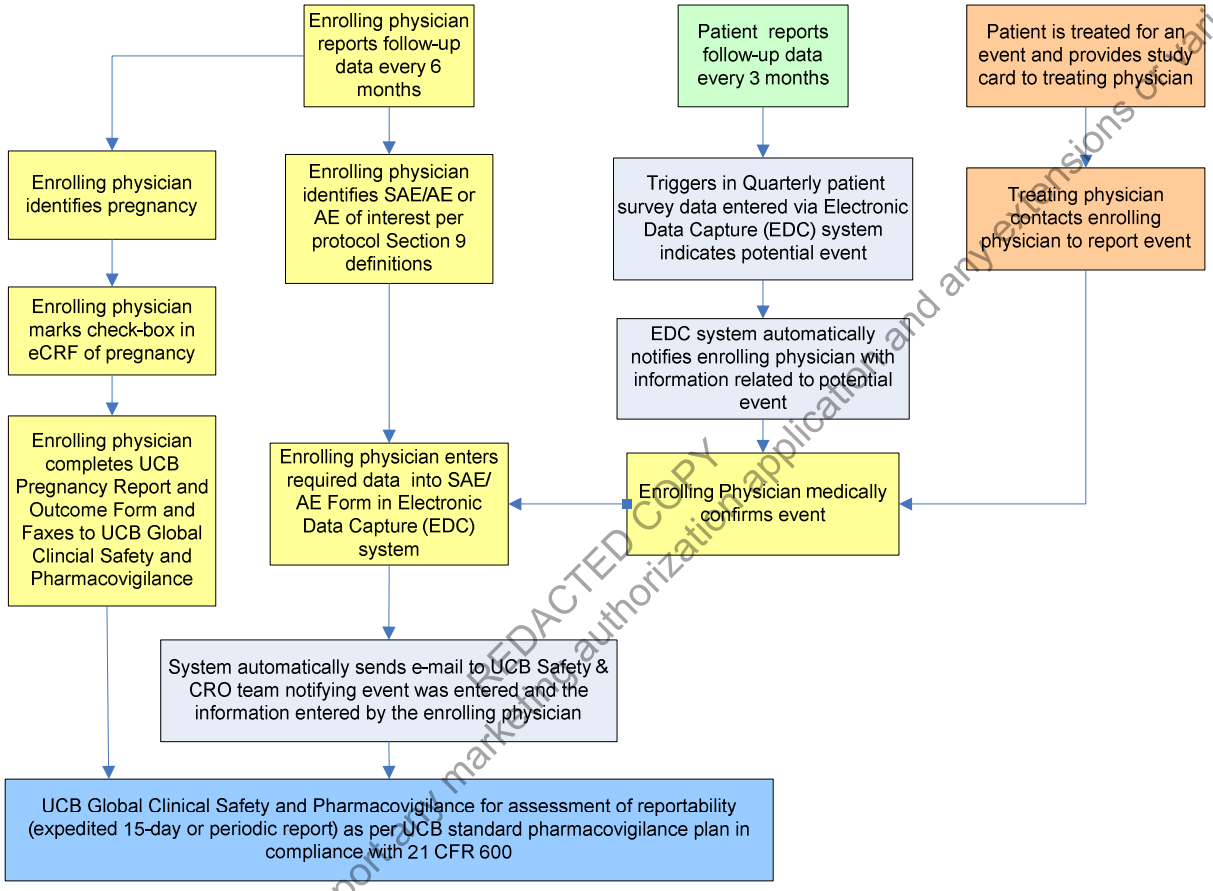
**Change #20**

**9.8 Pregnancy**

All reports of pregnancy (fetal-exposure) for an enrolled patient during the registry will be evaluated and processed as an SAE per UCB standard pharmacovigilance plans. Enrolling physician will be instructed to report a pregnancy in the study EDC system via a check-box. Completion of the pregnancy check-box in the study EDC will trigger a notification to UCB Global Clinical Safety and Pharmacovigilance. The enrolling physician will be prompted to manually complete the UCB Pregnancy Report and Outcome Form and fax to UCB Global Clinical Safety and Pharmacovigilance. All cases will be followed to outcome of the

pregnancy. All newborns will be monitored and evaluated for any adverse events due to in-utero exposure.

**Figure 9-1 Event Reporting Process**

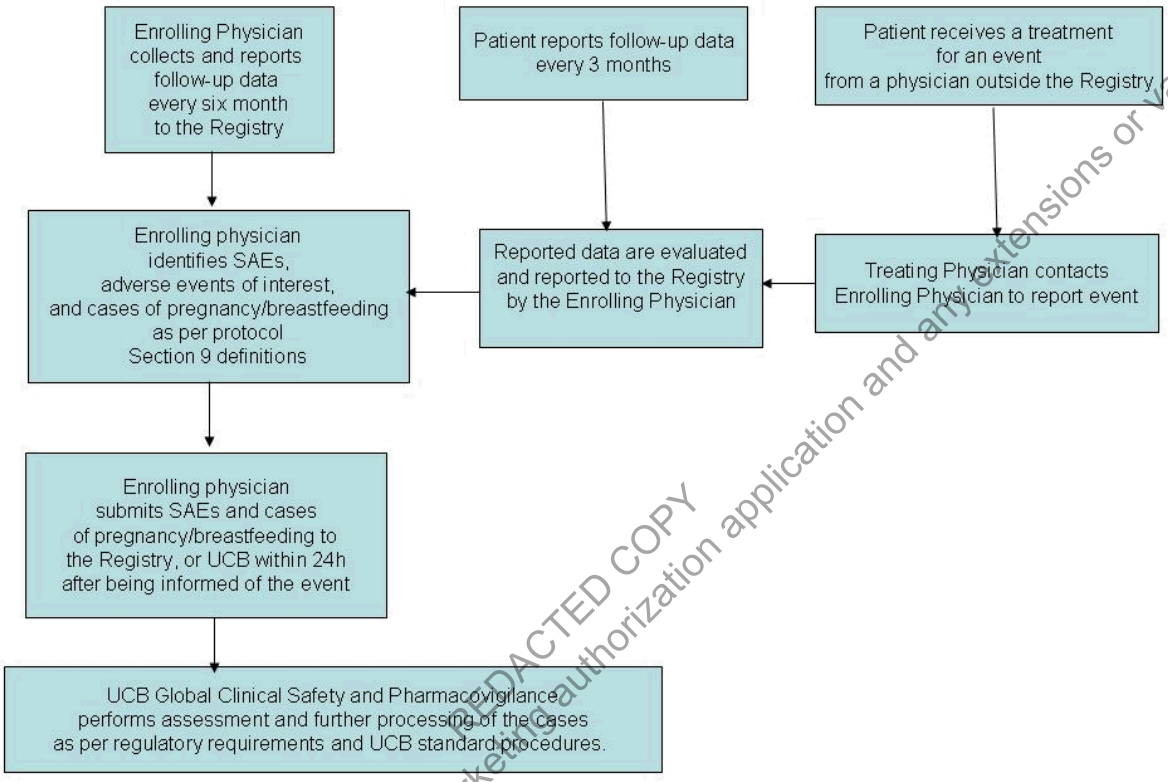



**Has been changed to:**

## 9.8 Pregnancy and breastfeeding

Physicians will be instructed to report pregnancy and breastfeeding of study participants; and pregnancy of study participant partners. An informed consent form will be provided to a study participant's partner who becomes pregnant during the study; and who will be willing to provide information on pregnancy course and outcome.

**Figure 9-1 Event Reporting Process**






**Change #21**

10.2 Endpoints

Primary Endpoints

The objective of this registry study is to track safety outcomes of patients who have taken Cimzia for treatment of Crohn's disease compared to a non-Cimzia control population. All AEs and SAEs will be collected and summarized. The AEs of primary interest are:

- Autoimmune disorders
- Demyelinating disorders
- Serious and opportunistic infections
- Lymphoma and other malignancies

**Has been changed to:**

Primary Endpoints

The objective of this registry study is to track safety outcomes of patients who have taken Cimzia for treatment of Crohn's disease compared to a non-Cimzia control population. All SAEs and nonserious AEs of interest will be collected and summarized.

The AEs of primary interest are:

- Autoimmune disorders
- Demyelinating disorders
- Serious infections including opportunistic infections
- Lymphoma and other malignancies
- Hypersensitivity reactions

**Change #22**

10.2 Endpoints

Secondary Endpoints

Characteristics and potential confounders of the population will be assessed on the basis of data collecting regarding:

- Demographics (gender, age, race, ethnicity, socioeconomic status, occupation and smoking status ) including special populations such as pregnant women, children and the elderly
- Crohn's disease history (including all past treatment for Crohn's disease with special focus on all previous treatment with anti-TNFα biologics, and reason for switch to Cimzia or other medication, if applicable)
- Other medical history including medical status at study entry
- Concomitant medications
- SAE/other AEs

**Has been changed to:**

Characteristics and potential confounders of the population will be assessed on the basis of data collecting regarding:

- Demographics (gender, age, race, ethnicity, socioeconomic status, occupation and smoking status ) including special populations such as pregnant women, children and the elderly
- Crohn's disease history (including all past treatment for Crohn's disease with special focus on all previous treatment with anti-TNFα or other biological therapies, and reason for switch to Cimzia or other medication, if applicable)
- Other medical history including medical status at study entry
- Concomitant medications
- SAE/other AEs

**Change #23**

### 10.4 Statistical Analyses

**Primary Analyses:**

Frequency and counts will be calculated for the occurrence of serious infections, including opportunistic infections, and malignancies including lymphoma, demyelinating disorders and autoimmune disorders. Calculations will be performed using both the cumulative incidence (proportion) and the incidence rate of events (events per person-time).

**And the last sentence**

Further details on all analyses will be provided in the Statistical Analysis Plan (SAP).

**Have been changed to:**

**Primary Analyses:**

Frequency and counts will be calculated for the occurrence of serious infections including opportunistic infections, and malignancies including lymphoma, demyelinating disorders, hypersensitivity reactions, and autoimmune disorders. Calculations will be performed using both the cumulative incidence (proportion) and the incidence rate of events (events per person-time).

**And the last sentence**

Further details on all analyses will be provided in the SAP.

**Change #24**

17. PROTOCOL SIGNATURE PAGE

**Authorized signature on behalf of UCB:**

**UCB Clinical Program Director (or designee)**

_____ _____

Signature Date

Name: [redacted]

Clinical Program Director

**Has been changed to:**

18. PROTOCOL SIGNATURE PAGE

**Authorized signature on behalf of UCB:**

**UCB Clinical Program Director (or designee)**

_____ _____

Signature Date

Name: [redacted]

Clinical Program Director

## 14.2 Protocol amendment 2

Rationale for the amendment:

The protocol has been amended to comply with FDA guidance for anticipated SAEs, revise the AE, SAE, and AE of interest reporting process, and to allow telephone contacts. Assessment of disease severity and HBI were clarified at Enrollment and Follow-Up visits. Selection of the study population was changed from frequency-matched recruitment to retrospective frequency matching. UCB contact information was updated. Other changes to correct inconsistencies and to adhere to current UCB style and formatting were made.

Specific changes

Change #1 Title page, Company address

Old text –

UCB Inc
1950 Lake Park Drive
USA - GA 30080 Smyrna
UNITED STATES

Has been changed to –

**UCB Biosciences, Inc.**
**A Member of the UCB Group of Companies**
**8010 Arco Corporate Drive**
Raleigh, NC 27617
**UNITED STATES**

Change #2 Section 2; Contact information

Old text –

**UCB Contributors:**

**Clinical Program Director (Study related questions)**

Name: [redacted] Phone: [redacted]

Fax: [redacted]

**Clinical Project Manager (CPM)**

Name: [redacted] Phone: [redacted]

Fax: [redacted]

| **SAEs, Pregnancy, and Breastfeeding Reporting (24h/7d)** | | |
|---|---|---|
| Primary | Internet | *www. secure-cimziadata.com* |
| Alternative | Fax: | +1 (800) 880 6949 |
| | | |

Has been changed to –

**UCB Contributors:**

**Sponsor Clinical Program Director (Study related questions)**

**Name:** [redacted]**, DVM** **Phone:** [redacted]

**Fax:** [redacted]

**Clinical Project Manager**

**Name:** [redacted] **Phone:** [redacted]

**Fax:** [redacted]

**Clinical Trial Biostatistician**

**Name:** [redacted] **Phone:** [redacted]

**Fax:** [redacted]

**Study Investigator**

**Name:** [redacted], **MD** **Phone:** [redacted]

**Fax:** [redacted]

| **SAEs, Pregnancy, and Breastfeeding Reporting (24h/7d)** | | |
|---|---|---|
| Primary | Internet | *www. secure-cimziadata.com* |
| | **Fax**: | +1 (888) 772 6919 (to be used if site is unable to access the electronic data capture [EDC] system) |
| | **Phone:** | **+1 (800) 772 3125 Study code 707501 (PRA number for EDC questions)** |
| | **Phone:** | +1 (678) 799 4007 (for questions related to adverse event reporting) |
| | **Email:** | **chosafety@praintl.com** |

Change #3 – Section 8.2 Selection of study population, paragraph 2

Old – text –

Recruitment into both cohorts will be monitored and controlled as needed in order to ensure balanced enrollment over time. In order to ensure reasonable balance between both cohorts, recruitment will be frequency matched for disease severity (mild/moderate/severe), age categories and gender.

Has been changed to –

Recruitment into both cohorts will be monitored and controlled as needed in order to ensure balanced enrollment over time. In order to ensure reasonable balance between both cohorts, **retrospective frequency matching will be applied** for disease severity (mild/moderate/severe), age categories and gender.

Change #4 Section 8.3 Subject Inclusion/Exclusion Criteria

Old text –

Cimzia cohort

Patient must be about to receive treatment with Cimzia as part of a pre-existing management plan for Crohn's disease or has already been receiving treatment with Cimzia for <6 months.

Has been changed to –

Cimzia cohort

Patient must be about to receive treatment with Cimzia as part of a pre-existing management plan for Crohn's disease or has already been receiving treatment with Cimzia for ≤6 months.

Change # 5 Section 8.5 Schedule of assessments

Old text –

Physicians will complete the baseline data for each patient after enrollment into the study. Although patient care will follow the Investigator's clinical judgment, it is recommended to the enrolling physician to report follow-up data on the patients approximately every 6 months after enrollment (months 6, 12, 18,…). In an effort to avoid missing data and unreported events over the 10 year follow-up period, patients will directly report data in parallel to the enrolling physician reported data. Direct patient follow-up will occur every 3 months after enrollment (months 3, 6, 9, 12,...) via a web-based system, by mail or phone as requested by the patient. If a patient does not provide the information via the web, mail or phone within approximately 1 week after the 3 month due date, the study patient interview service will call the patient to obtain the required information over the phone. Safety information collected directly from the patient will be available for the study investigative site to review.

| | Study Entry (Baseline) | Investigator-Reported Follow-up Year 1-10 | Direct Patient Follow-up Year 1-10 |
|---|---|---|---|
| | **ENROLLMENT** | **EVERY 6 MONTHS** | **EVERY 3 MONTHS** |
| Written informed consent/assent | X | | |
| Assessment of inclusion/exclusion criteria | X | | |
| Demography | X | | |
| Crohn's disease history | X | | |
| Medical and surgical history | X | | |
| Family history | X | | |
| Reason for initiating Cimzia or other medication | X | | |
| Planned Cimzia or other medication treatment period | X | X | |
| CD treatment medication changes and reason | | X | X |
| Concomitant medications | X | X | X |
| All SAEs and nonserious AEs of interest since time of last completed follow-up* | | X | |
| Major changes in health status since last completed follow-up | | | X |
| Investigator's assessment of disease | X | X | |
| HBI (see APPENDIX A) | X | X | |
| Patient's disease assessment | X | | X |
| Reasons for discontinuation from registry (early termination or end of Year 10) | | X | |
| *All serious adverse events; and nonserious adverse events of interest from both study arms are to be reported through the registry. | | | |



Has been changed to –

Physicians will complete the baseline data for each patient after enrollment into the study. Although patient care will follow the Investigator's clinical judgment, it is recommended to the enrolling physician to report follow-up data on the patients approximately every 6 months after enrollment (months 6, 12, 18**,…). Telephone contacts are permitted every other 6-month period, with the understanding that patients are typically seen by the Investigator every 12 months at a minimum per usual practice. All planned assessments described in Section 8.8.2 are to be completed during the telephone contacts.**

In an effort to avoid missing data and unreported events over the 10 year follow-up period, patients will directly report data in parallel to the enrolling physician reported data. Direct patient follow-up will occur every 3 months after enrollment (months 3, 6, 9, 12,...) via a web-based system, by mail or phone as requested by the patient. If a patient does not provide the information via the web, mail or phone within approximately 1 week after the 3 month due date, the study patient interview service will call the patient to obtain the required information over the phone. Safety information collected directly from the patient will be available for the study investigative site to review. **If 4 consecutive quarterly patient surveys have not been at least partially completed, the patient will be considered lost to follow-up and further attempts at contact are not required.**

| | **Study Entry (Baseline)** | **Investigator-Reported Follow-up Year 1-10[b]** | **Direct Patient Follow-up Year 1-10** |
|---|---|---|---|
| | **ENROLLMENT** | **EVERY 6 MONTHS** | **EVERY 3 MONTHS** |
| Written informed consent/assent | X | | |
| Assessment of inclusion/exclusion criteria | X | | |
| Demography | X | | |
| Crohn's disease history | X | | |
| Medical and surgical history | X | | |
| Family history | X | | |
| Reason for initiating Cimzia or other medication | X | | |
| Planned Cimzia or other medication treatment period | X | X | |
| CD treatment medication changes and reason | | X | X |

| | Study Entry (Baseline) | Investigator-Reported Follow-up Year 1-10[b] | Direct Patient Follow-up Year 1-10 |
|---|---|---|---|
| | **ENROLLMENT** | **EVERY 6 MONTHS** | **EVERY 3 MONTHS** |
| Concomitant medications | X | X | X |
| All SAEs and nonserious AEs of interest since time of last completed follow-up[a] | | X | |
| Major changes in health status since last completed follow-up | | | X |
| Investigator's assessment of disease **severity** | X | X | |
| **Investigator's** HBI[c] (see APPENDIX A) | X | X[e] | |
| **Patient's** Modified HBI[d] | X | | X |
| **Patient's assessment of disease severity** | X | | X |
| Reasons for discontinuation from registry (early termination or end of Year 10) | | X | |

**AE=adverse event; CD=Crohn's disease; HBI=Harvey-Bradshaw Index; SAE=serious adverse event**

[a]All serious adverse events; and nonserious adverse events of interest from both study arms are to be reported through the registry.

**[b] Telephone contacts are permitted every other 6-month period, with the understanding that patients are typically seen by the Investigator every 12 months at a minimum per usual practice.**

**[c.] This may also be completed by qualified site personnel as designated by the Investigator.**

**[d] The Modified HBI does not include the abdominal mass question.**

**[e] The Modified HBI is completed during the Investigator telephone contact instead of the full HBI.**

Change #6 Section 8.7 Participation and Retention Strategies

Old text –

Individual patient follow-up is approximately 10 years after enrollment, regardless of discontinuation of Cimzia or other medications.

As a means to retain patient participation, patients are followed up directly via a web-based system or if requested, by mail (including a prepaid self-addressed return envelope) or by phone every 3 months throughout the study (unless the patient withdraws consent or is deemed lost to follow-up) to complete a patient survey. "Lost to follow-up" is defined as a patient who goes one year with no data being collected/reported (1 year without Investigator visit and 4 consecutive quarterly patient surveys not completed. After informed consent/assent is obtained, the patient will complete a "Patient Contact Form", which will request contact information (phone number, email address, and physical address). This form will be submitted to an independent patient interview service by the physician. The patients will receive emails or mail reminding them to complete the survey. If they have not completed the survey one week after the due date, they will be called by the independent patient interview service to complete the survey via phone. For each survey the patient completes, they will receive a nominal appreciation gift.

In addition, patients will receive via postal mail an annual calendar with stickers placed on the months that they will be requested to complete their quarterly patient survey. They will receive a new calendar each year of their participation. Patients will also receive a registry newsletter once a year in an attempt to keep them engaged in the registry.

In the event an Investigator retires, or discontinues participation from the registry, the following transition plan is in place to enable continuing participation of their patients. The Informed Consent/Assent Forms include wording explaining that if the patient's Investigator discontinues participation in the registry, or retires, the independent patient interview service will be notified and contact them with the name and contact information of another study Investigator that they can contact during the remainder of their participation in the registry. The wording also states that the registry can continue to collect the direct patient-reported data without the need for re-consent.

In the event a patient moves to a new location or chooses to leave their current Investigator, patients are provided with information upon enrollment as to how to locate a participating Investigator in their area or how to provide the registry information to a new Investigator that may not yet be participating. Participating patients will have access to all of this information on the study specific web portal as well as being reminded of this process in the annual patient newsletters they will receive throughout their participation in the study.

The goal of these strategies is to enhance patient retention activity, potentially resulting in a lower drop-out rate and improved quality of data.

Over the course of a long-term study, patient death may occur. Additionally, patients may develop serious co-morbidities that cause them to become "lost to follow-up" in the Registry. Periodically throughout the study, and in case of "lost to follow-up", search in the National Death Index (NDI) and cancer registries will be performed for any matches.

Has been changed to –

Individual patient follow-up is approximately 10 years after enrollment, regardless of discontinuation of Cimzia or other medications.

As a means to retain patient participation, patients are followed up directly via a web-based system or if requested, by mail (including a prepaid self-addressed return envelope) or by phone every 3 months throughout the study (unless the patient withdraws consent or is deemed lost to follow-up) to complete a patient survey. "Lost to follow-up" is defined as a patient who goes one year with no data being collected/reported (1 year without Investigator visit/**telephone contact** and **failure to at least partially complete 4 consecutive quarterly patient surveys; further attempts at patient contact are not required)**. After informed consent/assent is obtained, the patient will complete a "Patient Contact Form", which will request contact information (phone number, email address, and physical address). This form will be submitted to an independent patient interview service by the physician. The patients will receive emails or mail reminding them to complete the survey. If they have not completed the survey one week after the due date, they will be called by the independent patient interview service to complete the survey via phone. For each survey the patient completes, they will receive a nominal appreciation gift.

In addition, patients will receive via postal mail an annual calendar with stickers placed on the months that they will be requested to complete their quarterly patient survey. They will receive a new calendar each year of their participation. Patients will also receive a registry newsletter once a year in an attempt to keep them engaged in the registry.

In the event an Investigator retires, or discontinues participation from the registry, the following transition plan is in place to enable continuing participation of their patients. The Informed Consent/Assent Forms include wording explaining that if the patient's Investigator discontinues participation in the registry, or retires, the independent patient interview service will be notified and contact them with the name and contact information of another study Investigator that they can contact during the remainder of their participation in the registry. The wording also states that the registry can continue to collect the direct patient-reported data without the need for re-consent. **If the patient is unable or unwilling to be followed by a new Investigator, the patient must be discontinued from the study.**

In the event a patient moves to a new location or chooses to leave their current Investigator, patients are provided with information upon enrollment as to how to locate a participating Investigator in their area or how to provide the registry information to a new Investigator that may not yet be participating. Participating patients will have access to all of this information

on the study specific web portal as well as being reminded of this process in the annual patient newsletters they will receive throughout their participation in the study.

The goal of these strategies is to enhance patient retention activity, potentially resulting in a lower drop-out rate and improved quality of data.

Over the course of a long-term study, patient death may occur. Additionally, patients may develop serious co-morbidities that cause them to become "lost to follow-up" in the Registry. Periodically throughout the study, and in case of "lost to follow-up", **searches of death or cancer registries, as appropriate,** will be performed for any matches.

Change #7 Section 8.8.1 Enrollment Visit

Old text –

For each patient enrolled in this registry, the enrolling physician will document the following information into the corresponding eCRFs within the registry study EDC system:

- Demographic information such as gender, age, race, ethnicity, socioeconomic status, occupation and smoking status
- Crohn's disease history, including length of time since initial presentation of symptoms, date of diagnosis, all past treatment and surgeries for Crohn's disease (with special focus on anti-TNFα and other biologics), and reason for switch to Cimzia or other medications since diagnosis and within the past 3 months
- Crohn's disease severity as assessed by the Investigator
- Harvey-Bradshaw Index (HBI) – See Section 16.1 APPENDIX A
- Patient's disease assessment
- Other medical history including current medical status, concomitant medications, and planned treatment period (if known) with special focus on previous occurrence of each AE of interest and related risk factors (e.g., history of serious infections, conditions that might place a patient at higher risk of serious infection)

Has been changed to –

For each patient enrolled in this registry, the enrolling physician will document the following information into the corresponding eCRFs within the registry study EDC system:

- Demographic information such as gender, age, race, ethnicity, socioeconomic status, occupation and smoking status
- Crohn's disease history, including length of time since initial presentation of symptoms, date of diagnosis, all past treatment and surgeries for Crohn's disease (with special focus

on anti-TNFα and other biologics), and reason for switch to Cimzia or other medications since diagnosis and within the past 3 months

- **Investigator's assessment of Crohn's disease severity**
- **Investigator's completion of the** Harvey-Bradshaw Index (HBI) – See Section 16.1 APPENDIX A. **This may also be completed by qualified site personnel as designated by the Investigator.**
- Patient's **assessment of Crohn's disease severity**
- **Patient's completion of the modified HBI. The modified HBI does not include the abdominal mass question contained in the full HBI.**
- Other medical history including current medical status, concomitant medications, and planned treatment period (if known) with special focus on previous occurrence of each AE of interest and related risk factors (e.g., history of serious infections, conditions that might place a patient at higher risk of serious infection)

Change #8 Section 8.8.2 Follow-up Period

Old text –

Each study enrolling physician or patient will be contacted at regular intervals throughout the study to ensure they are entering required data at the following frequencies:

- every six months for Investigator-reported information
- every three months for patient-reported information (web, mail survey or phone)

The following data will be collected by the physician in EDC at each follow-up interval:

- All SAEs and nonserious AEs of interest that have been reported since last follow-up
- HBI
- Investigator's disease severity assessment (including HBI)
- Full details on exposure (e.g., dose, frequency) to Cimzia or other medication
- Any changes in medication
- Reasons for discontinuation of Cimzia and/or other medication for Crohn's disease

The following data will be collected from the patient at each quarterly interval:

- Any major changes in health status that may have occurred since last follow-up
- Patient's disease assessment
- Full details on exposure to Cimzia or other medications

- Any changes in medication
- Any administrative changes such as change in contact information

Has been changed to –

Each study enrolling physician or patient will be contacted at regular intervals throughout the study to ensure they are entering required data at the following frequencies:

- Every six months for Investigator-reported information. Telephone contacts are permitted every other 6-month period, with the understanding that patients are typically seen by the Investigator every 12 months at a minimum per usual practice.
- Every three months for patient-reported information (web, mail survey or phone)

The following data will be collected by the physician in EDC at each follow-up interval:

- All SAEs and nonserious AEs of interest that have been reported since last follow-up
- **Investigator's HBI completed at clinic visits or modified HBI completed during telephone contacts. This may also be completed by qualified site personnel as designated by the Investigator.**
- **Investigator's assessment of disease severity**
- Full details on exposure (e.g., dose, frequency) to Cimzia or other medication
- Any changes in medication
- Reasons for discontinuation of Cimzia and/or other medication for Crohn's disease

The following data will be collected from the patient at each quarterly interval:

- Any major changes in health status that may have occurred since last follow-up
- Patient's disease assessment
- Full details on exposure to Cimzia or other medications
- Any changes in medication
- Any administrative changes such as change in contact information

Change #9 Section 9 Adverse events of interest, serious adverse events, case and exposure definitions

New text added –

Although serious adverse events and nonserious adverse events of interest are the focus of this registry, Investigators are expected to enter all AEs in the eCRF.

Change #10 Section 9.2 Adverse events of interest

New text (final bullet) –

- Other events:
  - Congestive heart failure
  - Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia and leucopenia
  - Serious bleeding events
  - Serious skin reactions (eg, Stevens Johnson Syndrome, toxic epidermal necrosis, and erythema multiforme)

Change #11 Section 9.3 Anticipated serious adverse events (new section)

New text -

The following list of Anticipated SAEs has been identified as these events are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure. This original list will remain in effect for the duration of the protocol.

This list does not change the Investigator's obligation to report all serious AEs (including Anticipated SAEs) as detailed in Section 9.7.

**Crohn's disease**
**perianal abscess**
**abdominal pain**

Change #12 Section 9.5 Exposure definition

Old text -

Cimzia Exposure:

Cimzia exposure will be calculated by two methods. The first method will assume exposure from day one of the first dose of Cimzia medication regardless of medication discontinuation through the date of the last follow-up evaluation. The second method will be a series of

sensitivity analyses and stratifications to evaluate the different clinically driven definitions of exposure to drug. Specifics to these definitions will be outlined in the SAP.

Control Exposure:

Non-Cimzia® medication exposure will be calculated by two methods. The first method will assume exposure from day one of the first dose of the non-Cimzia® medication regardless of medication discontinuation through the date of the last follow-up evaluation. The second method will be a series of sensitivity analyses and stratifications to evaluate the different clinically driven definitions of exposure to drug. Specifics to these definitions will be outlined in the SAP.

Has been changed to –

Cimzia Exposure:

Cimzia exposure will be calculated by two methods. The first method will assume exposure from day one of the first dose of Cimzia medication after enrollment regardless of medication discontinuation through the date of the last follow-up evaluation. The second method will be a series of sensitivity analyses and stratifications to evaluate the different clinically driven definitions of exposure to drug. Specifics to these definitions will be outlined in the SAP.

Control Exposure:

Non-Cimzia medication exposure will be calculated by two methods. The first method will assume exposure from day one of the first dose of the non-Cimzia medication after enrollment regardless of medication discontinuation through the date of the last follow-up evaluation. The second method will be a series of sensitivity analyses and stratifications to evaluate the different clinically driven definitions of exposure to drug. Specifics to these definitions will be outlined in the SAP.

Change #13 Section 9.7 Adverse event reporting and Figure 9.1

Old text –

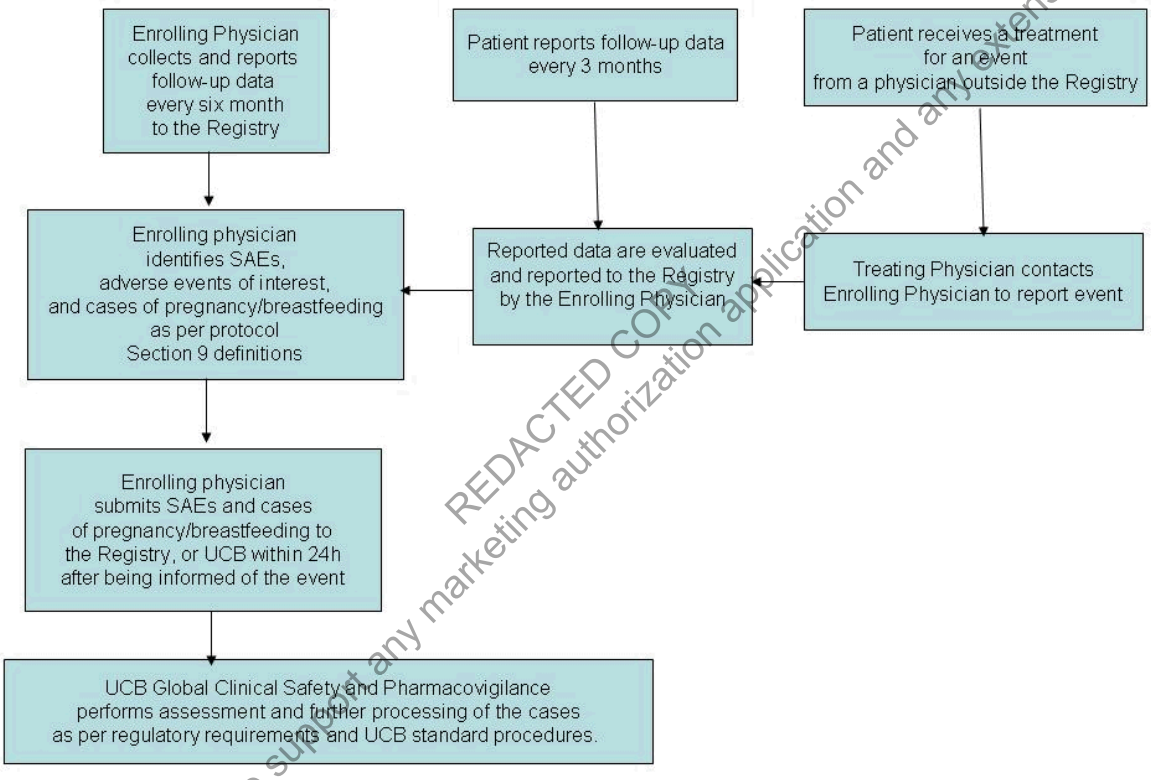
Serious adverse events and nonserious adverse events of interest from both study arms are to be reported through the registry.

All adverse events reported through registry will be forwarded to UCB Global Clinical Safety and Pharmacovigilance for assessment and further processing as per regulatory requirements and UCB procedures (see Figure 9:1 – Event Reporting Process for flow of activity).

Any major changes in health status reported by the patient during the every 3 month patient follow-up will be sent to the physician for medical confirmation. Once medical confirmation is obtained, the physician will report the event through the study EDC system.

Information and instructions informing patients about the follow-up period and how to report adverse events is included in the Informed Consent Form.

Figure 9:1 Event Reporting Process




Has been changed to –

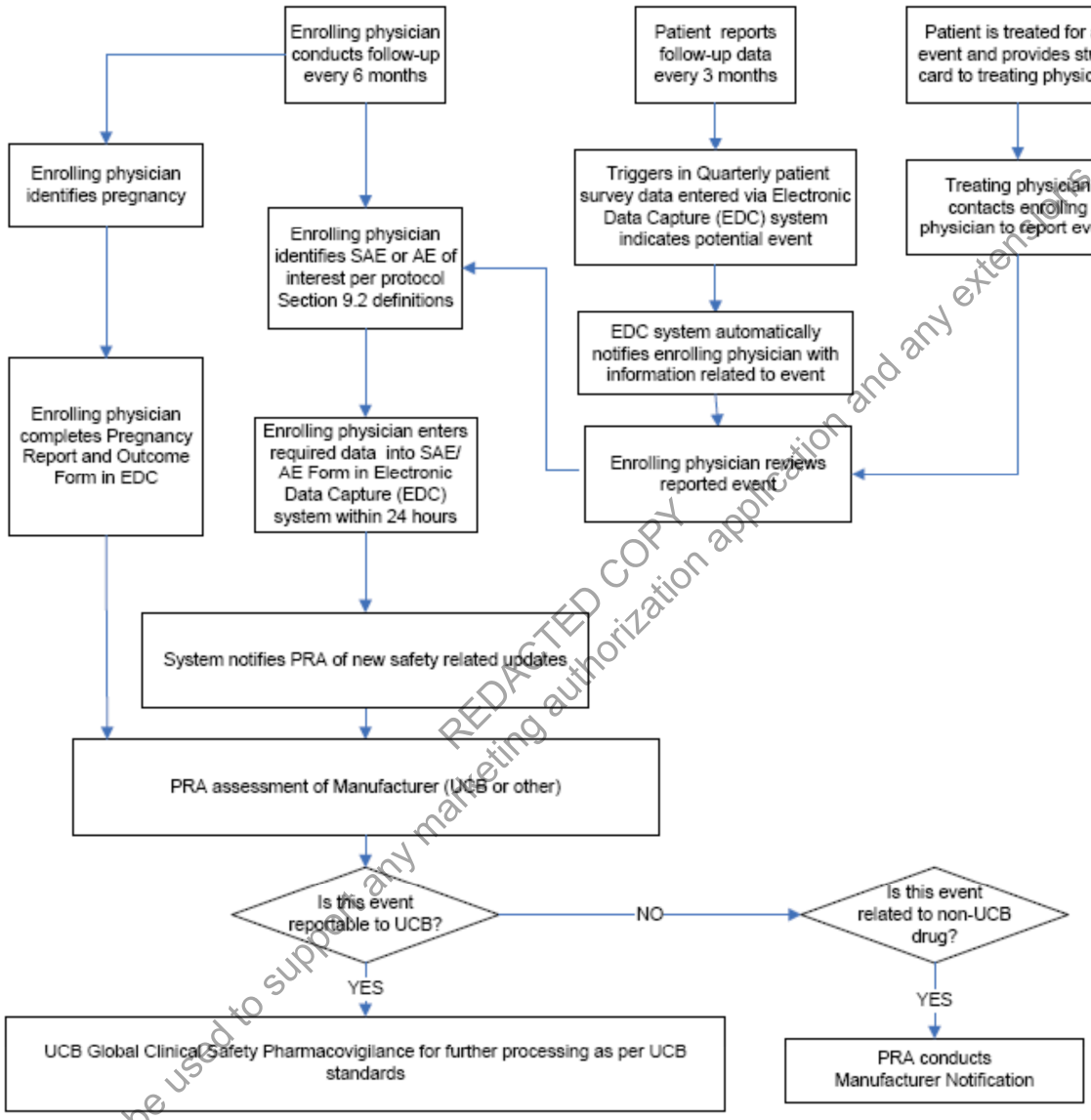
**All AE are expected to be entered in the eCRF.** Serious adverse events and nonserious adverse events of interest from both study arms are to be reported through the registry.

**All SAEs and all AEs of interest will be entered in the EDC system within 24 hours of site notification and will be automatically forwarded to PRA, International** for assessment and further processing as per regulatory requirements and UCB procedures (see Figure 9:1 – Event Reporting Process for flow of activity).

Any major changes in health status reported by the patient during the every 3 month patient follow-up will be sent to the physician for medical confirmation. Once medical confirmation is obtained, the physician will report the event through the study EDC system.

Information and instructions informing patients about the follow-up period and how to report adverse events is included in the Informed Consent Form. **More detailed instructions to sites regarding reporting of SAEs are provided in the UCB safety Guidance booklet.**

Figure 9:1 Event Reporting Process




AE=adverse event; EDC=electronic data capture; SAE=serious adverse event

Change #14 Section 9.8 Pregnancy and breastfeeding

Old text –

Investigators will be instructed to report pregnancy and breastfeeding of study participants; and pregnancy of study participant partners. An informed consent form will be provided to a

study participant's partner who becomes pregnant during the study; and who will be willing to provide information on pregnancy course and outcome.

Has been changed to –

Investigators **are required** to report pregnancy and breastfeeding of study participants; and pregnancy of study participant partners. An informed consent form will be provided to a study participant's partner who becomes pregnant during the study; and who will be willing to provide information on pregnancy course and outcome. **More detailed instructions to sites regarding reporting of pregnancy and breastfeeding are provided in the UCB safety Guidance booklet.**

Change #15 Section 10.2 Endpoints

Old text –

**Primary Endpoints**

The objective of this registry study is to track safety outcomes of patients who have taken Cimzia for treatment of Crohn's disease compared to a non-Cimzia control population. All SAEs and nonserious AEs of interest will be collected and summarized.

The AEs of primary interest are:

- Autoimmune disorders
- Demyelinating disorders
- Serious infections including opportunistic infections
- Lymphoma and other malignancies
- Hypersensitivity reactions

Has been changed to –

**Primary Endpoints**

The objective of this registry study is to track safety outcomes of patients who have taken Cimzia for treatment of Crohn's disease compared to a non-Cimzia control population. All SAEs and nonserious AEs of interest will be collected and summarized.

The AEs of primary interest are:

- Autoimmune disorders
- Demyelinating disorders

- Serious infections **or** opportunistic infections
- Lymphoma and other malignancies
- Hypersensitivity reactions

Change #16 Section 18, Protocol signature page

UCB Clinical Program Director updated and additional UCB signatories added –

**Authorized signature on behalf of UCB:**

**UCB Clinical Program Director**

_____ _____

**Signature** **Date**

**Name:** [redacted]**, DVM**

**UCB Clinical Project Manager**

_____ _____

**Signature** **Date**

**Name:** [redacted]

**UCB Clinical Trial Biostatistician**

_____ _____

**Signature** **Date**

**Name:** [redacted]

**UCB Study Investigator**

_____ _____

**Signature** **Date**

**Name:** [redacted]**, MD**

## 14.3 Protocol amendment 3

Rationale for the amendment:

The protocol has been amended to revise analytic strategy methods and analysis providing more flexibility in treatment over the duration of the registry. The safety outcomes, exposure to Cimzia and other medications will continue to be collected and evaluated.

## Specific changes

**Change #1**

The following was added to the title page:

IND Number: 011197

**Change #2**

The following was added to the title page:

| Protocol/Amendment Number | Date |
|---|---|
| Protocol | 06-Jan-2009 |
| Protocol Amendment 1 | 24-Jun-2009 |
| Protocol Amendment 2 | 05-Dec-2011 |
| Protocol Amendment 3 | 04-Dec-2013 |

**Change #3**

Contact Information

OLD TEXT

**UCB Contributors:**

**Clinical Program Director (Study related questions)**

Name: [redacted], DVM Phone: [redacted]

Fax: [redacted]

**Clinical Project Manager**

Name: [redacted]
Phone: [redacted]
Fax: [redacted]

**Clinical Trial Biostatistician**

Name: [redacted]
Phone: [redacted]
Fax: [redacted]

**Study Investigator**

Name: [redacted], MD
Phone: [redacted]
Fax: [redacted]



| **SAEs, Pregnancy, and Breastfeeding Reporting (24h/7d)** | | |
|---|---|---|
| **Primary** | **Internet** | *www. secure-cimziadata.com* |
| | **Fax**: | +1 (888) 772 6919 (PRA number to be used if site is unable to access the electronic data capture [EDC] system) |
| | **Phone:** | +1 (800) 772 3125 Study code 707501 (PRA number for EDC questions) |
| | **Phone:** | +1 (678) 799 4007 (UCB number for questions related to adverse event reporting) |
| | **Email:** | chosafety@praintl.com (PRA contact) |
| **Site Support** | | |
| | **Phone**: | +1 (800) 772 3125 (reference number: 707501) |
| **Patient Interview Service** | | |
| | **Phone**: | +1 (877) 580 7246 |

NEW TEXT:

**UCB Contributors:**

**Clinical Program Director (Study related questions)**

Name: [redacted], MD
Phone: [redacted]
Fax: [redacted]

**Clinical Project Manager**

Name: [redacted], MPH
Phone: [redacted]
Fax: [redacted]

**Clinical Trial Biostatistician**

Name: [redacted], PhD
Phone: [redacted]
Fax: [redacted]

**Study Investigator**

Name: [redacted], MD
Phone: [redacted]
Fax: [redacted]

**Study Epidemiologist**

Name [redacted], PhD
Phone: [redacted]
Fax: [redacted]

| **SAEs, Pregnancy, and Breastfeeding Reporting (24h/7d)** | | |
|---|---|---|
| **Primary** | **Internet** | *www. secure-cimziadata.com* |
| | **Fax**: | +1 (888) 772 6919 (PRA number to be used if site is unable to access the electronic data capture [EDC] system) |
| | **Phone:** | +1 (800) 772 3125 Study code 707501 (PRA number for EDC |

| | | |
|---|---|---|
| | | questions) |
| | **Phone:** | +1 (866) 822 0068 (UCB number for questions related to adverse event reporting) |
| | **Email:** | chosafety@praintl.com (PRA contact) |
| **Site Support** | | |
| | **Phone**: | +1 (800) 772 3125 (reference number: 707501) |
| **Patient Interview Service** | | |
| | **Phone**: | +1 (877) 580 7246 |

**Change #4**

The following was added to the Table of Contents:

## LIST OF FIGURES



## LIST OF TABLES



**Change #5**

List of Abbreviations

OLD TEXT:

| | |
|---|---|
| AE | Adverse event |
| CD | Crohn's disease |
| CPD | Clinical Program Director |
| CPM | Clinical Project Manager |
| eCRF | Electronic case report form |
| CRO | Contract research organization |
| EDC | Electronic data capture |
| FDA | Food and Drug Administration |

| | |
|---|---|
| HBI | Harvey-Bradshaw index |
| IRB | Institutional Review Board |
| MedDRA® | Medical Dictionary for Regulatory Activities |
| p-y | Patient years |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| Anti-TNFα | Anti-tumor necrosis factor alpha |
| USA | United States of America |
| WHO Drug | World Health Organization Drug |

NEW TEXT:

| | |
|---|---|
| AE | adverse event |
| anti-TNFα | anti-tumor necrosis factor alpha |
| CD | Crohn's disease |
| CI | confidence interval |
| CPM | Clinical Project Manager |
| CRO | Contract Research Organization |
| CSE | cross-section echocardiography |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| EEG | Electroencephalogram |
| EMG | Electromyogram |
| FDA | Food and Drug Administration |
| HBI | Harvey-Bradshaw Index |
| IRB | Institutional Review Board |
| MedDRA® | Medical Dictionary for Regulatory Activities |
| p-y | patient years |

| | |
|---|---|
| RR | Rate ratio |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| TNF | tumor necrosis factor |
| USA | United States of America |
| WHO Drug | World Health Organization Drug |

**Change #6**

Section 5, Introduction

OLD TEXT:

Following the Food and Drug Administration (FDA) approval of certolizumab pegol (Cimzia) for Crohn's disease (CD), UCB has committed to collect additional long-term, post-marketing safety data on patients exposed to the product in a real-life setting. To achieve this goal, a pharmacoepidemiologic registry study was designed. Prospective data collected on 2000 patients prescribed Cimzia will be compared to a 2000 patient prospective control group prescribed other treatments (including biologics) for Crohn's disease. Both the safety outcomes, exposure to Cimzia and other medications will be collected and calculated. This will be a significant addition to post-marketing safety assessments based on spontaneous reports. The study is anticipated to start 1st Quarter 2009 and continue monitoring all patients for approximately 10 years after enrollment.

NEW TEXT:

Following the Food and Drug Administration (FDA) approval of certolizumab pegol (Cimzia) for Crohn's disease (CD), UCB has committed to collect additional long-term, post-marketing safety data on patients exposed to the product in a real-life setting. To achieve this goal, a pharmacoepidemiologic study entitled SECURE was designed. The study began in January 2009 with the goal of collecting prospective data on 2000 patients prescribed Cimzia and a 2000 patient comparator group prescribed other treatments (including biologics) for CD.

The protocol has been amended (Amendment 3) to revise analytic strategy methods and analysis providing more flexibility in treatment over the duration of the registry. The safety outcomes, exposure to Cimzia and other medications will continue to be collected and evaluated.

The SECURE registry represents a significant addition to post-marketing safety assessments based on spontaneous reports. The study is anticipated to continue monitoring all enrolled patients for approximately 10 years after enrollment.

**Change #7**

Section 6, Registry Rationale

OLD TEXT:

This study is a post approval commitment study designed to monitor the long-term safety of Cimzia when used in customary clinical practice in patients with Crohn's disease and compared to a non-Cimzia control population. Patients will be included in the Cimzia arm of the registry when they are elected to be treated with Cimzia by their Investigator. The control group will also be included in the registry when elected by the Investigator. Patient enrollment into each of the cohorts will be tracked on an ongoing basis. When one of the cohorts reaches 2000, it will be assessed to discontinue enrollment in the applicable arm and continue enrollment in the other arm until it reaches 2000 patients.

Patients will be followed for approximately 10 years during normal Investigator visits and through direct patient follow-up in the form of web, mail surveys and/or phone follow-up calls, during which the counts and frequency of all serious adverse events (SAEs) and nonserious adverse events (AEs) of interest will be collected. All patients will receive and use their medications according to their normal course of medical treatment per Investigator clinical judgment.

NEW TEXT:

This study is a post-approval commitment study designed to monitor the long-term safety of Cimzia compared to other CD treatments when used in customary clinical practice in patients with CD. Enrolled patients will be followed for approximately 10 years during normal Investigator visits and through direct patient follow-up in the form of web, mail surveys and/or phone follow-up calls. All patients will receive and use their medications according to their normal course of medical treatment per Investigator clinical judgment.

The treating Investigator is requested to report all serious adverse events (SAEs) and nonserious adverse events (AEs) of interest to the registry. These events will be collected and summarized.

**Change #8**

Section 7, Registry Objective

OLD TEXT:

The objective of this registry study (entitled SECURE) is to track safety outcomes of patients who have taken Cimzia for the treatment of Crohn's disease compared to a non-Cimzia control population.

All SAEs and nonserious AEs of interest will be collected and summarized (see Section 5). The AEs of primary interest are: autoimmune disorders, demyelinating disorders, serious infections including opportunistic infections, hypersensitivity reactions, lymphoma and other malignancies. These events of interest are consistent with the FDA Approval Letter. In addition, UCB plans to evaluate aplastic anemia and serious cardiac events. All these events represent serious risks known to the class of TNF blocking agents. During the development program for Crohn's disease and rheumatoid arthritis consisting of over 5,000 subjects, reported events were consistent with the class.

NEW TEXT:

The objective of this registry is to measure the safety outcomes among Cimzia patients compared to those that occur while on a different CD treatment regimen.

All SAEs and AEs of interest will be collected and summarized (see Section 5). The AEs of interest are: autoimmune disorders, demyelinating disorders, serious infections including opportunistic infections, hypersensitivity reactions, lymphoma and other malignancies. In addition, UCB plans to evaluate aplastic anemia and serious cardiac events. All these events represent serious risks known to the class of tumor necrosis factor (TNF) blocking agents. During the development program for CD and rheumatoid arthritis consisting of over 5,000 subjects, reported events were consistent with the class.

**Change #9**

Section 8.2, Selection of Study Population, paragraphs 1 and 2

OLD TEXT:

This is a long-term observational study in the USA that will include 2000 Cimzia-treated Crohn's disease patients and 2000 patients treated with other Crohn's disease medications. The study will be conducted in all regions in the USA at approximately 300 enrolling investigative sites.

Recruitment into both cohorts will be monitored and controlled as needed in order to ensure balanced enrollment over time. In order to ensure reasonable balance between both cohorts,

retrospective frequency matching will be applied for disease severity (mild/moderate/severe), age categories and gender.

NEW TEXT:

This is a long-term observational study in the USA that will include approximately 4000 CD patients. To ensure a sufficient number of Cimzia-treated patients in the registry, approximately half of enrolled patients will be receiving Cimzia for ≤12 months or about to receive Cimzia at the time of enrollment. The study will be conducted in all regions in the USA at approximately 300 enrolling investigative sites.

Recruitment of Cimzia-treated and comparator patients will be monitored and controlled as needed in order to ensure balanced enrollment over time.

**Change #10**

Section 8.3, Subject Inclusion/Exclusion Criteria

OLD TEXT:

Patients who meet all of the following criteria will be eligible for inclusion into the SECURE Registry:

- Patient (or his/her legally acceptable representative) is able to provide written informed consent (patients under the age of consent must provide assent) to permit collection of data. Patients who join the registry prior to legal age of consent will provide written informed consent as an adult upon reaching the legal age of consent.
- Patient must have medically documented Crohn's disease.
- The decision to prescribe Cimzia or other medications has been made by the Investigator independently of the decision to include the patient in the study.

**Cimzia® cohort**

- Patient must be about to receive treatment with Cimzia as part of a pre-existing management plan for Crohn's disease or has already been receiving treatment with Cimzia for ≤6 months.

**Comparison cohort**

- Patient must be about to receive treatment with any other medication as part of a pre-existing management plan for Crohn's disease or has already been receiving treatment. Previous Cimzia treatment is prohibited for the control arm.
- Patients are eligible for the comparison cohort if one of the following criteria is fulfilled:
  - currently receiving or history of anti-TNF treatment
  - currently receiving or history of immunosuppressant therapy within 6 months

- currently receiving or history of systemic steroid therapy within 6 months

NEW TEXT:

Patients who meet all of the following criteria will be eligible for inclusion into the SECURE Registry:

- Patient (or his/her legally acceptable representative) is able to provide written informed consent to permit collection of data.
- Patient must be 18 years of age or older.
- Patient must have medically documented CD.
- The decision to prescribe Cimzia or other medications has been made by the Investigator independently of the decision to include the patient in the study.
- Patients participating in randomized, blinded clinical trials for CD or other conditions are not eligible for inclusion into the SECURE registry. Involvement in other registries, where patients follow routine clinical practice, is permitted, however.

**Cimzia-treated patients**

For a patient to qualify as being treated with Cimzia, they must meet one of the following criteria:

- Patient is receiving treatment with Cimzia for the first time. Patient must receive Cimzia treatment within 2 months of enrollment into the registry.
- Patient is currently receiving treatment with Cimzia for ≤12 months. Patients must also receive a Cimzia dose within 2 months following enrollment into the registry.

**Comparator patients**

Patients enrolled in the comparator group are eligible to participate in the registry if one of the following criteria is fulfilled:

- Patient is switching CD treatments or beginning CD treatment for the first time. Previous Cimzia treatment is prohibited in the comparator group. Patient must receive new CD treatment within 2 months of enrollment into the registry.
- Patient is currently receiving anti-TNF treatment for ≤12 months. Patient must receive anti-TNF treatment within 2 months following enrollment into the registry.
- Patient is currently receiving immunosuppressant therapy for ≤12 months. Patient must receive immunosuppressant therapy within 2 months following enrollment into the registry.
- Patient is currently receiving systemic steroid therapy for ≤12 months. Patient must receive systemic steroid therapy within 2 months following enrollment into the registry.

**Change #11**

Section 8.5, Schedule of Assessment

OLD TEXT:

Enrolling physicians will complete the baseline data for each patient after enrollment into the study. Although patient care will follow the Investigator's clinical judgment, it is recommended to the enrolling physician to report follow-up data on the patients approximately every 6 months after enrollment (months 6, 12, 18,…). Telephone contacts are permitted every other 6-month period, with the understanding that patients are typically seen by the Investigator every 12 months at a minimum per usual practice. All planned assessments described in Section 4.8.2 are to be completed during the telephone contacts.

In an effort to avoid missing data and unreported events over the 10 year follow-up period, patients will directly report data in parallel to the enrolling physician reported data. Direct patient follow-up will occur every 3 months after enrollment (months 3, 6, 9, 12,...) via a web-based system, by mail or phone as requested by the patient. If a patient does not provide the information via the web, mail or phone within approximately 1 week after the 3 month due date, the study patient interview service will call the patient to obtain the required information over the phone. Safety information collected directly from the patient will be available for the study investigative site to review. If 4 consecutive quarterly patient surveys have not been at least partially completed, the patient will be considered lost to follow-up and further attempts at contact are not required.

| | **Study Entry (Baseline)** | **Investigator-Reported Follow-up Year 1-10[b]** | **Direct Patient Follow-up Year 1-10** |
|---|---|---|---|
| | **ENROLLMENT** | **EVERY 6 MONTHS** | **EVERY 3 MONTHS** |
| Written informed consent/assent | X | | |
| Assessment of inclusion/exclusion criteria | X | | |
| Demography | X | | |
| Crohn's disease history | X | | |
| Medical and surgical history | X | | |
| Family history | X | | |
| Reason for initiating Cimzia or other medication | X | | |
| Planned Cimzia or other medication treatment period | X | X | |
| CD treatment medication changes and reason | | X | X |
| Concomitant medications | X | X | X |
| All SAEs and nonserious AEs of interest since time of last completed | | X | |

| | Study Entry (Baseline) | Investigator-Reported Follow-up Year 1-10[b] | Direct Patient Follow-up Year 1-10 |
|---|---|---|---|
| | **ENROLLMENT** | **EVERY 6 MONTHS** | **EVERY 3 MONTHS** |
| follow-up[a] | | | |
| Major changes in health status since last completed follow-up | | | X |
| Investigator's assessment of disease severity | X | X | |
| Investigator's HBI[c] (see APPENDIX A) | X | X[e] | |
| Patient's Modified HBI[d] | X | | X |
| Patient's assessment of disease severity | X | | X |
| Reasons for discontinuation from registry (early termination or end of Year 10) | | X | |

AE=adverse event; CD=Crohn's disease; HBI=Harvey Bradshaw Index; SAE=serious adverse event
[a]All serious adverse events; and nonserious adverse events of interest from both study arms are to be reported through the registry.
[b] Telephone contacts are permitted every other 6-month period, with the understanding that patients are typically seen by the Investigator every 12 months at a minimum per usual practice.
[c.] This may also be completed by qualified site personnel as designated by the Investigator.
[d] The Modified HBI does not include the abdominal mass question.
[e] The Modified HBI is completed during the Investigator telephone contact instead of the full HBI.

NEW TEXT:

No visits are required as part of this protocol. All visits will be scheduled and conducted per standard of care. It is anticipated that visits will occur based on routine clinical practice.

Enrolling physicians will complete the baseline data for each patient after enrollment into the study. Although patient care will follow the Investigator's clinical judgment, it is anticipated that the enrolling physician will see and, therefore, report follow-up data on the patients approximately every 6 months after enrollment (months 6, 12, 18,…). Telephone contacts are permitted every other 6-month period, with the understanding that patients are typically seen by the Investigator every 12 months at a minimum per usual practice. All data, as described in Section 4.8.2, are to be collected as available during the telephone contacts.

In an effort to minimize missing data and unreported events over the 10-year Follow-Up Period, patients will directly report data in parallel to the enrolling physician reported data. Direct patient follow-up will occur every 3 months after enrollment (months 3, 6, 9, 12,...) via a web-based system, by mail or phone as requested by the patient. If a patient does not provide the information via the web, mail or phone within approximately 1 week after the 3 month due date, the study patient interview service will call the patient to obtain the required information over the phone. Safety information collected directly from the patient will be available for the study investigative site to review. If 4 consecutive quarterly patient

surveys have not been at least partially completed, the patient will be considered lost to follow-up and further attempts at contact are not required.

| | Study Entry (Baseline) | Investigator-Reported Follow-up Year 1-10[b] | Direct Patient Follow-up Year 1-10 |
|---|---|---|---|
| | **ENROLLMENT** | **EVERY 6 MONTHS** | **EVERY 3 MONTHS** |
| Written informed consent | X | | |
| Assessment of inclusion/exclusion criteria | X | | |
| Demography | X | | |
| Crohn's disease history | X | | |
| Medical and surgical history | X | | |
| Family history | X | | |
| Reason for initiating Cimzia or other medication | X | | |
| Planned Cimzia or other medication treatment period | X | X | |
| CD treatment medication changes and reason | | X | X |
| Concomitant medications | X | X | X |
| All SAEs and AEs of interest since time of last completed follow-up[a] | | X | |
| Major changes in health status since last completed follow-up | | | X |
| Investigator's assessment of disease severity | X | X | |
| Investigator's HBI[c] (see APPENDIX A) | X | X[e] | |
| Patient's Modified HBI[d] | X | | X |
| Patient's assessment of disease severity | X | | X |
| Reasons for discontinuation from registry (early termination or end of Year 10) | | X | |

AE=adverse event; CD=Crohn's disease; HBI=Harvey-Bradshaw Index; SAE=serious adverse event

[a]All SAEs and AEs of interest are to be reported through the registry.

[b] Telephone contacts are permitted every other 6-month period, with the understanding that patients are typically seen by the Investigator every 12 months at a minimum per usual practice. No study visits are required as part of this protocol; treating Investigators are to manage patients based on clinical

| | Study Entry (Baseline) | Investigator-Reported Follow-up Year 1-10[b] | Direct Patient Follow-up Year 1-10 |
|---|---|---|---|
| | **ENROLLMENT** | **EVERY 6 MONTHS** | **EVERY 3 MONTHS** |

judgment and standard of care.

[c.] This may also be completed by qualified site personnel as designated by the Investigator.

[d] The Modified HBI does not include the abdominal mass question.

[e] The Modified HBI is completed during the Investigator telephone contact instead of the full HBI.

**Change #12**

Section 8.6, Informed Consent

OLD TEXT:

Patient (or his/her legally acceptable representative) is able to provide written informed consent or assent for participation in this registry and release of their blinded data to UCB, Inc. (sponsor) and the Contract Research Organization (CRO) for analysis. Prior to obtaining informed consent/assent, the enrolling physician or designee will explain to the patient the nature and purpose of the study. For patients who join the registry prior to legal age of consent, their legal representative will complete the informed consent form. Patients under the legal age of consent who are of established age of assent (approximately 7 years of age) will complete the informed assent form. These patients will be re-consented upon reaching legal age of consent. After informed consent/assent is obtained, the original document will be placed in the patient's medical record and a signed copy given to the patient.

For patients having been prescribed Cimzia, a Cimzia Medication Guide will be provided, and serious risks of Cimzia explained.

Upon enrollment, patients will receive an enrollment kit that includes general registry information, including a patient card that identifies them as a participant in the SECURE Registry. The card informs the treating Investigator that the patient is participating in a registry study, and provides instructions for the treating Investigator on how to report adverse event or other treatment information to the enrolling physician.

NEW TEXT:

The patient (or his/her legally acceptable representative) must be able to provide written informed consent for participation in this registry and release of their data to UCB (sponsor) and the Contract Research Organization (CRO) for analysis. Prior to obtaining informed consent, the enrolling physician or designee will explain to the patient the nature and purpose of the study. After informed consent is obtained, the original document will be placed in the patient's medical record and a signed copy given to the patient.

Medication guides will be provided per standard of care.

Upon enrollment, patients will receive an enrollment kit that includes general registry information, including a patient card that identifies them as a participant in the SECURE Registry. The card informs the treating Investigator that the patient is participating in a registry study, and provides instructions for the treating Investigator on how to report AE or other treatment information to the enrolling physician.

**Change #13**

Section 8.7, Participation and Retention Strategies, paragraph 2 and 4

OLD TEXT:

As a means to retain patient participation, patients are followed up directly via a web-based system or if requested, by mail (including a prepaid self-addressed return envelope) or by phone every 3 months throughout the study (unless the patient withdraws consent or is deemed lost to follow-up) to complete a patient survey. "Lost to follow-up" is defined as a patient who goes one year with no data being collected/reported (1 year without Investigator visit/telephone contact and failure to at least partially complete 4 consecutive quarterly patient surveys; further attempts at patient contact are not required). After informed consent/assent is obtained, the patient will complete a "Patient Contact Form", which will request contact information (phone number, email address, and physical address). This form will be submitted to an independent patient interview service by the enrolling physician. The patients will receive emails or mail reminding them to complete the survey. If they have not completed the survey one week after the due date, they will be called by the independent patient interview service to complete the survey via phone. For each survey the patient completes, they will receive a nominal appreciation gift.

In the event a Investigator retires, or discontinues participation from the registry, the following transition plan is in place to enable continuing participation of their patients. The Informed Consent/Assent Forms include wording explaining that if the patient's Investigator discontinues participation in the registry, or retires, the independent patient interview service will be notified and contact them with the name and contact information of another study Investigator that they can contact during the remainder of their participation in the registry. The wording also states that the registry can continue to collect the direct patient-reported data without the need for re-consent. If the patient is unable or unwilling to be followed by a new Investigator, the patient must be discontinued from the study.

NEW TEXT:

As a means to retain patient participation, patients are followed up directly via a web-based system or if requested, by mail (including a prepaid self-addressed return envelope) or by phone every 3 months throughout the study (unless the patient withdraws consent or is deemed lost to follow-up) to complete a patient survey. "Lost to follow-up" is defined as a patient who goes one year with no data being collected/reported (1 year without Investigator visit/telephone contact and failure to at least partially complete 4 consecutive quarterly

patient surveys; further attempts at patient contact are not required). After informed consent is obtained, the patient will complete a "Patient Contact Form", which will request contact information (phone number, email address, and physical address). This form will be submitted to an independent patient interview service by the enrolling physician. The patients will receive emails or postal mail reminding them to complete the survey. If they have not completed the survey one week after the due date, they will be called by the independent patient interview service to complete the survey via phone. For each survey the patient completes, they will receive a nominal appreciation gift.

In the event a Investigator retires, or discontinues participation from the registry, the following transition plan is in place to enable continuing participation of their patients. The Informed Consent Form include wording explaining that if the patient's Investigator discontinues participation in the registry, or retires, the independent patient interview service will be notified and contact them with the name and contact information of the closest participating study Investigator that they can contact during the remainder of their participation in the registry. The wording also states that the registry can continue to collect the direct patient-reported data without the need for re-consent. If the patient is unable or unwilling to be followed by a new Investigator, the patient must be discontinued from the study.

**Change #14**

Section 8.8, Data Collection Strategies, paragraph 3

OLD TEXT:

As this is an approximately 10-year follow up registry study, the technologies used for this registry such as EDC will be 21 CFR Part 11 compliant and evaluated on an on-going basis throughout the registry study to ensure upgrades are made when necessary.

NEW TEXT:

As this is a 10-year follow up registry study, the technologies used for this registry such as EDC will be 21 CFR Part 11 compliant and evaluated on an on-going basis throughout the registry study to ensure upgrades are made when necessary.

**Change #15**

Section 8.8.1, Enrollment Visit

The reference to "Crohn's Disease" was replaced by the abbreviation "CD"

**Change #16**

Section 8.8.2, Follow-Up Period

OLD TEXT:

The following data will be collected by the enrolling physician in EDC at each follow-up interval:

- All SAEs and nonserious AEs of interest that have been reported since last follow-up
- Investigator's HBI completed at clinic visits or modified HBI completed during telephone contacts. This may also be completed by qualified site personnel as designated by the Investigator.
- Investigator's assessment of disease severity
- Full details on exposure (e.g., dose, frequency) to Cimzia or other medication
- Any changes in medication
- Reasons for discontinuation of Cimzia and/or other medication for Crohn's disease

NEW TEXT:

The following data will be collected as available by the enrolling physician in EDC at each follow-up interval:

- All SAEs and AEs of interest that have been reported since last follow-up
- Investigator's HBI completed at clinic visits or modified HBI completed during telephone contacts. This may also be completed by qualified site personnel as designated by the Investigator
- Investigator's assessment of disease severity
- Full details on exposure (eg, dose, frequency) to Cimzia or other medication
- Any changes in medication
- Reasons for discontinuation of Cimzia and/or other medication for CD

**Change #17**

Section 9, Adverse Events of Interest, Serious Adverse Events, Case and Exposure Definitions

OLD TEXT:

Although serious adverse events and nonserious adverse events of interest are the focus of this registry, Investigators are expected to enter all AEs in the eCRF.

NEW TEXT:

Serious adverse events and AEs of interest are the focus of this registry; Investigators are not expected to enter nonserious AEs in the eCRF.

**Change #18**

Section 9.1, Definitions; last paragraph

OLD TEXT:

All Serious Adverse Events (of interest or other) must be reported within 24 hours of being acknowledged by the Investigator.

NEW TEXT:

All SAEs must be reported within 24 hours of being acknowledged by the Investigator.

**Change #19**

Section 9.2, Adverse Events of Interest

OLD TEXT:

- Other events:
  - Congestive heart failure
  - Aplastic anemia, pancytopenia, thrombocytopenia, neutropenia and leucopenia
  - Serious bleeding events
  - Serious skin reactions (eg, Stevens Johnson Syndrome, toxic epidermal necrosis, and erythema multiforme)

NEW TEXT:

- Other events:
  - congestive heart failure

- aplastic anemia, pancytopenia, thrombocytopenia, neutropenia and leucopenia
- serious bleeding events
- serious skin reactions (eg, Stevens Johnson Syndrome, toxic epidermal necrosis, and erythema multiforme)

When available, narrow scope SMQs (Standardized MedDRA Queries) from the Medical Dictionary for Regulatory Activities (MedDRA®) version 16.0 will be used to define the AEs of interest (Table 9-1). Adverse events of interest that are the clinical endpoints for the SECURE registry will be confirmed by review of the results of diagnostic tests and diagnostic criteria used by the Investigator which are further explained within each section below.

**Table 9-1 Standardized MedDRA Queries for select adverse events of interest**

| Event | SMQ Title | SMQ Code | SMQ Scope |
|---|---|---|---|
| Malignancy | Malignant tumours | 20000194 | Narrow PTs |
| Congestive Heart Failure | Cardiac failure | 20000004 | Narrow PTs |
| Serious skin reactions | Severe cutaneous adverse reactions | 20000020 | Selected Narrow PTs |
| Hypersensitivity reactions | Anaphylactic reaction | 20000021 | Narrow/Broad PTs |
| Serious bleeding events | Haemorrhage | 20000038 | Narrow PTs |
| Aplastic anemia | Haematopoietic cytopenias affecting more than one type of blood cell | 20000028 | Narrow PTs |
| Aplastic anemia | Haematopoietic erythropenia | 20000029 | Narrow PTs |
| Aplastic anemia | Haematopoietic leukopenia | 20000030 | Narrow PTs |
| Aplastic anemia | Haematopoietic thrombocytopenia | 20000031 | Narrow PTs |

For events in which SMQs are not available, MedDRA v 16.0 Preferred Terms (PT) for the System Organ Class (SOC) and High-Level Group Term (HLGT) categories will be used as appropriate. These PTs are listed in the Statistical Analysis Plan (SAP). Additional detail on the clinical validation of the primary endpoints is presented below although all safety events that meet the definition of AEs of interest will be collected and summarized as part of the study.

### 9.2.1 Autoimmune disorders

For this category, the primary events are Systemic Lupus Erythematosus and Rheumatoid Arthritis.

The diagnosis has to be supported with medical history and physical findings, serologic evidence and other evidence from biopsy, laboratory results, imaging results, or other specialized testing, where appropriate, and the exclusion of other disorders which might cause a similar pattern of findings.

### 9.2.2 Demyelinating disorders

For this category, the primary event is Multiple Sclerosis. Guillain-Barre syndrome and chronic inflammatory demyelinating polyneuropathy will be analyzed as autoimmune disorders.

Medical history and physical findings, laboratory results, imaging results (eg, MRI) and any other specialized test (EEG, EMG, CSF analysis) results have to be considered in determining the final diagnosis.

### 9.2.3 Serious and Opportunistic Infections

Serious infections are defined as all infections meeting the definition of an SAE, and/or an infection requiring parenteral administration of antibiotics.

For the opportunistic infection category, the primary events are tuberculosis and pneumonia. The definitive diagnosis of pneumonia and tuberculosis may be confirmed by obtaining sputum smears or relevant biopsies and verifying by cultures. Infections not usually seen in immunocompetent patients or infections that have an accelerated pathogenesis or a more severe outcome in a given setting will also be considered opportunistic infections.

### 9.2.4 Lymphoma and Other Malignancies

For this category, the primary events are lymphoma, including hepatosplenic T cell lymphoma and non-Hodgkin lymphoma, and solid malignant tumors.

Diagnosis has to be confirmed by tissue biopsy for histopathology (sources of tissue samples for review may include those obtained from an excisional biopsy -a tissue sample from the affected nodes or organ, a needle aspiration, or a bone marrow biopsy. Pathohistological results have to correlate clinically with imaging results and/or any other pertinent information prior to determining the final diagnosis.

### 9.2.5 Hypersensitivity Reaction

Primary endpoints for hypersensitivity reaction are events meeting the criteria of an anaphylactic reaction and acute hypersensitivity reaction occurring within 2 hours of drug administration. As described in the case definition below, anaphylactic events include all terms listed in Category A, which consists of the narrow terms Type I hypersensitivity, anaphylactic shock and anaphylactoid reaction. In addition, combinations of the AE terms listed in Categories B, C and D will also be defined as anaphylactic events.

Category A: anaphylactic reaction, Type I hypersensitivity, anaphylactic shock, anaphylactoid reaction

Category B: dyspnoea, chest discomfort, cough, swollen tongue, oedema mouth, throat tightness, wheezing, laryngeal oedema, respiratory distress, sensation of foreign body, asthma, sneezing

Category C: swelling face, urticaria, pruritus, rash, eye swelling, pruritus generalized, rash, generalized, flushing, erythema, swelling, eye pruritus, lip swelling, rash pruritic, rash, erythematous, eyelid oedema, ocular hyperaemia, injection site urticaria, angioedema

Category D: hypotension, blood pressure decreased

To meet the definition of an anaphylactic event, a case has to meet one of the following criteria:

4. A narrow term or a term from Category A;
5. A term from Category B (Upper Airway/Respiratory) AND a term from Category C (Angioedema/Urticaria/Pruritus/Flush);
6. A term from Category D (Cardiovascular/Hypotension) AND either a term from Category B (Upper Airway/Respiratory) or a term from Category C (Angioedema/Urticaria/Pruritus/Flush)

### 9.2.6 Congestive heart failure

Congestive heart failure (CHF) is the primary endpoint for cardiac events of interest. CHF will be defined by Framingham criteria. The diagnostic criteria include physical findings of low cardiac output or increased cardiac workload and radiographic evidence (chest X-ray, ECG, Echocardiogram, CT, MRI, angiogram) and laboratory findings, ECG and imaging results and any other specialized test results have to be considered for final diagnosis. CHF present at baseline and worsening during the study (worsening of New York Heart Association (NYHA) functional classification) will be captured, as well as new onset CHF.

### 9.2.7 Aplastic anemia

Aplastic anemia is a primary endpoint. Diagnosis must be confirmed by complete blood count (CBC) with peripheral smear, and bone marrow biopsy. Findings of pancytopenia (neutropenia, thrombocytopenia, and anemia), a reduction in the absolute number of reticulocytes, and a hypocellular bone marrow could be used to confirm the diagnosis.

### 9.2.8 Serious bleeding events

For this category, bleeding events meeting the criteria of an SAE are primary endpoints.

### 9.2.9 Serious skin reactions

For this category, primary endpoints are Erythema multiforme, Stevens Johnson's syndrome, and Toxic epidermal necrolysis.

**Change #20**

Deletion of former Section 9.4 through Section 9.6

## 9.4 Case Definition:

**Cimzia Case:**
Cases will be attributable to Cimzia identified by two methods. The first method will assume a case will be attributable to Cimzia after the first dose of the medication regardless of medication discontinuation and time to onset of the event. The second method will be a series of sensitivity analyses and stratifications to evaluate different clinically driven definition of cases attributable to drug. Specifics on data handling guidelines for managing missing or partial data will be documented in the Statistical Analysis Plan (SAP).

**Control Case:**
Cases will be attributable to non-Cimzia medications identified by two methods. The first method will assume a case will be attributable to the non-Cimzia medication after the first dose of the medication regardless of medication discontinuation and time to onset of the event. The second method will be a series of sensitivity analyses and stratifications to evaluate different clinically driven definition of cases attributable to drug. Specifics on data handling guidelines for managing missing or partial data will be documented in the SAP.

## 9.5 Exposure Definition:

**Cimzia Exposure:**
Cimzia exposure will be calculated by two methods. The first method will assume exposure from day one of the first dose of Cimzia medication after enrollment regardless of medication discontinuation through the date of the last follow-up evaluation. The second method will be a series of sensitivity analyses and stratifications to evaluate the different clinically driven definitions of exposure to drug. Specifics to these definitions will be outlined in the SAP.

**Control Exposure:**
Non-Cimzia medication exposure will be calculated by two methods. The first method will assume exposure from day one of the first dose of the non-Cimzia medication after enrollment regardless of medication discontinuation through the date of the last follow-up evaluation. The second method will be a series of sensitivity analyses and stratifications to evaluate the different clinically driven definitions of exposure to drug. Specifics to these definitions will be outlined in the SAP.

## 9.6 Adverse Event Collection Period

All AEs collected from the registry will be reported to the FDA as per regulatory reporting guidelines. Any reports received prior to start of the registry and after completion of the

study will be evaluated and reported as per standard UCB pharmacovigilance plans for spontaneous reporting.

To ensure the capture of any events that might occur between patient or Investigator data entry intervals, each patient will be provided a safety reporting process patient card that they can present to a Investigator if they have an event. The card will contain instructions for the Investigator on how to report event information.

**Change #21**

Renumbering of former Section 9.7 to Section 9.4 and all subsequent sections within Section 9

OLD TEXT

### 9.7 Adverse Event Reporting

All AE are expected to be entered in the eCRF. Serious adverse events and nonserious adverse events of interest from both study arms are to be reported through the registry.

All SAEs and all AEs of interest will be entered in the EDC system within 24 hours of site notification and will be automatically forwarded to PRA, International for assessment and further processing as per regulatory requirements and UCB procedures (see Figure 5–1 -Event Reporting Process for flow of activity).

Any major changes in health status reported by the patient during the every 3 month patient follow-up will be sent to the enrolling physician for medical confirmation. Once medical confirmation is obtained, the enrolling physician will report the event through the EDC system.

Information and instructions informing patients about the follow-up period and how to report adverse events is included in the Informed Consent Form. More detailed instructions to sites regarding reporting of SAEs are provided in the UCB safety Guidance booklet.

NEW TEXT

### 9.4 Adverse Event Reporting to the Registry

Serious adverse events and AEs of interest are the focus of this registry; Investigators are expected to enter all SAEs and AEs of interest in the eCRF.

All SAEs and all AEs of interest will be entered in the EDC system within 24 hours of site notification and will be automatically forwarded to PRA, International for assessment and further processing as per regulatory requirements and UCB procedures (see Event reporting process)

-Event Reporting Process for flow of activity

Any major changes in health status reported by the patient during the every 3 month patient follow-up will be sent to the enrolling physician for medical confirmation. Once medical confirmation is obtained, the enrolling physician will report the event through the EDC system.

To ensure the capture of any events that might occur between patient or Investigator data entry intervals, each patient will be provided a safety reporting process patient card that they can present to a Investigator if they have an event. The card will contain instructions for the Investigator on how to report event information.

Information and instructions informing patients about the Follow-Up Period and how to report AEs is included in the Informed Consent Form. More detailed instructions to sites regarding reporting of SAEs and AEs of interest are provided in the UCB safety Guidance booklet.

**Change #22**

Addition of Section 9.6, UCB Pharmacovigilance Reporting

NEW TEXT

Adverse events collected from the registry that occur within 70 days of last Cimzia dose will be included in UCB's safety database and reported to the FDA as per regulatory reporting guidelines. Registry cases of malignancy, death, and pregnancy will be included in UCB's safety database and reviewed and evaluated for FDA reporting even if the event occurs after 70 days of last Cimzia dose. Any reports received prior to start of the registry and after completion of the study will be evaluated and reported as per standard UCB pharmacovigilance plans for spontaneous reporting.

**Change #23**

Replacement of Section 10 and its sub-Sections

**Change #24**

Section 15, References

OLD TEXT

1. Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Chen DM, et al. Serious infections and mortality in associate with therapies for Crohn's disease: TREAT registry. Clin Gastroenterol Hepatol 2006;4:621-30.

2. Lichtenstein GR, Cohen RD, Feagan BGG, Sandborn WJ, Salzberg BA, Chen DM, et al. Safety of infliximab and other Crohn's disease therapies – TREAT Registry data with nearly 15,000 patient-years of follow-up. Gastroenterology 2006;130 (4 Suppl 2): A71.

NEW TEXT

Ecsedy J, Hunter D. Textbook of Cancer Epidemiology. Eds, Hans-Olov Adami, David Hunger, and Dimitrios Trichopoulos. New York, NY: Oxford University Press, Inc; 2002.

Lash TL, Fox MP, Fink AK. Applying Quantitative Bias Analysis to Epidemiologic Data. Springer. 2009.

Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Chen DM, et al. Serious infections and mortality in associate with therapies for Crohn's disease: TREAT registry. Clin Gastroenterol Hepatol 2006;4:621-30.

Lichtenstein GR, Cohen RD, Feagan BGG, Sandborn WJ, Salzberg BA, Chen DM, et al. Safety of infliximab and other Crohn's disease therapies – TREAT Registry data with nearly 15,000 patient-years of follow-up. Gastroenterology 2006;130 (4 Suppl 2):A71.

Massey, FJ. The Kolmogorov-Smirnov Test for Goodness of Fit. Journal of the American Statistical Association. Vol. 46, No. 253, 1951, pp. 68–78.

Shrier I, Platt RW. Reducing bias through directed acyclic graphs. BMC Med Res Methodol. 2008 Oct 30;8:70

## 14.4 Protocol amendment 4

Rationale for the amendment

The protocol has been amended to address clarification language in regards to patient visit requirements or lost-to-follow-up language. In addition, language was added to allow the sponsor to utilize patient-centric data warehouse organization(s), to extract de-identified data from healthcare channels in the US, including hospitals, providers and pharmacies. The statistical section was updated per FDA comments to account for treatment switch patterns.

**Specific changes**

**Change #1**

- Throughout the document, the term "physician" has been replaced with the term "Investigator".
- Throughout the document, the term "enrolling physician" has been replaced with the term "Investigator".

**Change #2**

Removal and replacement of second paragraph in Section 1, Introduction - second paragraph

NEW TEXT:

The protocol has been amended (Amendment 4) to address clarification language in regards to patient visit requirements or lost-to-follow-up language. In addition, language was added to allow the sponsor to utilize patient-centric data warehouse organization(s), to extract de-identified data from healthcare channels in the US, including hospitals, providers and pharmacies. The statistical section was updated per FDA comments to account for treatment switch patterns.

**Change #3**

Section 4.3, Subject Inclusion/Exclusion Criteria

Clarification for subject inclusion/exclusion criteria specific to comparator patients and biologics.

NEW TEXT:

- Patient is currently receiving for CD anti-TNF treatment (or other approved biologics) for ≤12 months. Patient must receive anti-TNF treatment (or other biologics) within 2 months following enrollment into the registry.

**Change #4**

Section 4.5, – Schedule of Assessments

OLD TEXT:

No visits are required as part of this protocol. All visits will be scheduled and conducted per standard of care.

Enrolling physicians will complete the baseline data for each patient after enrollment into the study. Although patient care will follow the physician's clinical judgment, it is anticipated that the enrolling physician will see and, therefore, report follow-up data on the patients approximately every 6 months after enrollment (months 6, 12, 18,…). Telephone contacts are permitted every other 6-month period, with the understanding that patients are typically seen by the physician every 12 months at a minimum per usual practice. All data, as described in Section 4.8.2, are to be collected as available during the telephone contacts.

In an effort to minimize missing data and unreported events over the 10-year Follow-Up Period, patients will directly report data in parallel to the enrolling physician reported data. Direct patient follow-up will occur every 3 months after enrollment (months 3, 6, 9, 12,...) via a web-based system, by mail or phone as requested by the patient. If a patient does not provide the information via the web, mail or phone within approximately 1 week after the 3 month due date, the study patient interview service will call the patient to obtain the required information over the phone. Safety information collected directly from the patient will be available for the study investigative site to review. If 4 consecutive quarterly patient surveys have not been at least partially completed, further attempts at patient contact are not required.

| | **Study Entry (Baseline)** | **Physician-Reported Follow-up Year 1-10[b]** | **Direct Patient Follow-up Year 1-10** |
|---|---|---|---|
| | **ENROLLMENT** | **EVERY 6 MONTHS** | **EVERY 3 MONTHS** |
| Written informed consent | X | | |
| Assessment of inclusion/exclusion criteria | X | | |
| Demography | X | | |
| Crohn's disease history | X | | |
| Medical and surgical history | X | | |
| Family history | X | | |
| Reason for initiating Cimzia or other medication | X | | |
| Planned Cimzia or other medication treatment period | X | X | |
| CD treatment medication changes and reason | | X | X |
| Concomitant medications | X | X | X |

| | Study Entry (Baseline) | Physician-Reported Follow-up Year 1-10[b] | Direct Patient Follow-up Year 1-10 |
|---|---|---|---|
| | **ENROLLMENT** | **EVERY 6 MONTHS** | **EVERY 3 MONTHS** |
| All SAEs and AEs of interest since time of last completed follow-up[a] | | X | |
| Major changes in health status since last completed follow-up | | | X |
| Physician's assessment of disease severity | X | X | |
| Physician's HBI[c] (see APPENDIX A) | X | X[e] | |
| Patient's Modified HBI[d] | X | | X |
| Patient's assessment of disease severity | X | | X |
| Reasons for discontinuation from registry (early termination or end of Year 10) | | X | |

AE=adverse event; CD=Crohn's disease; HBI=Harvey-Bradshaw Index; SAE=serious adverse event

[a]All SAEs and AEs of interest are to be reported through the registry.

[b] Telephone contacts are permitted every other 6-month period, with the understanding that patients are typically seen by the physician every 12 months at a minimum per usual practice. No study visits are required as part of this protocol; treating physicians are to manage patients based on clinical judgment and standard of care.

[c.] This may also be completed by qualified site personnel as designated by the physician.

[d] The Modified HBI does not include the abdominal mass question.

[e] The Modified HBI is completed during the physician telephone contact instead of the full HBI.

NEW TEXT:

No mandatory visits are required as part of this protocol. All visits will be scheduled and conducted per sites standard of care. Standard of care is defined as: A diagnostic and customary clinical treatment/practice process that a clinician should follow for a Crohn's disease patient, a certain type of illness, or clinical circumstance.

Investigators will complete the baseline data for each patient after enrollment into the study and includes the signing of the Informed Consent Form (ICF). Follow-up data for patient visits will be reported in accordance to sites standard of care or clinical judgment appointments. Telephone contacts are permitted. All data, as described in Section 4.8.2, are to be collected as available during the telephone contacts.

In an effort to minimize missing data and unreported events over the 10-year Follow-Up Period, patients will directly report data in parallel to the Investigator reported data. Direct

patient follow-up will occur every 3 months after enrollment (months 3, 6, 9, 12, etc) via a web-based system, by mail or by phone - as preferred by the patient. If a patient does not provide the information via the web, mail or by phone within approximately 1 week after the 3 month due date, the study patient interview service will call the patient to obtain the required information over the phone. Safety information collected directly from the patient will be available for the study investigative site to review. If 8 consecutive quarterly patient surveys have not been at least partially completed, further attempts at patient contact are not required. Investigator will be requested to confirm whether the patient status should be changed to 'Lost to Follow-up'.

| | **Study Entry (Baseline)** | **Investigator-Reported Follow-up[b]** | **Direct Patient Follow-up Year 1-10** |
|---|---|---|---|
| | **ENROLLMENT** | **PER STANDARD OF CARE** | **EVERY 3 MONTHS** |
| Written informed consent | X | | |
| Assessment of inclusion/exclusion criteria | X | | |
| Demography | X | | |
| Crohn's disease history | X | | |
| Medical and surgical history | X | | |
| Family history | X | | |
| Reason for initiating Cimzia or other medication | X | | |
| Planned Cimzia or other medication treatment period | X | X | |
| CD treatment medication changes and reason | | X | X |
| Concomitant medications | X | X | X |
| All SAEs and AEs of interest since time of last completed follow-up[a] | | X | |
| Major changes in health status since last completed follow-up | | | X |
| Investigator's assessment of disease severity | X | X | |
| Investigator's HBI[c] (see APPENDIX A) | X | X[e] | |
| Patient's Modified HBI[d] | X | | X |
| Patient's assessment of disease severity | X | | X |

| | Study Entry (Baseline) | Investigator-Reported Follow-up[b] | Direct Patient Follow-up Year 1-10 |
|---|---|---|---|
| | **ENROLLMENT** | **PER STANDARD OF CARE** | **EVERY 3 MONTHS** |
| Reasons for discontinuation from registry (early termination or end of Year 10) | | X | |

AE=adverse event; CD=Crohn's disease; HBI=Harvey-Bradshaw Index; SAE=serious adverse event

[a]All SAEs and AEs of interest are to be reported through the registry.

[b] Telephone contacts are permitted.

[c] This may also be completed by qualified site personnel as designated by the Investigator.

[d] The Modified HBI does not include the abdominal mass question.

[e] The Modified HBI is completed during the Investigator telephone contact instead of the full HBI.

**Change #5**

Moving of Informed Consent sentences from Section 4.7 -Participation and Retention Strategies to more appropriately Section 4.6 – Informed Consent.

"After informed consent is obtained, the patient will complete a "Patient Contact Form", which will request contact information (phone number, email address, and physical address). This form will be submitted to an independent patient interview service by the Investigators.

**Change #6**

Section 4.7, Participation and Retention Strategies

OLD TEXT:

Individual patient follow-up is approximately 10 years after enrollment, regardless of discontinuation of Cimzia or other medications.

As a means to retain patient participation, patients are followed up directly via a web-based system or if requested, by mail (including a prepaid self-addressed return envelope) or by phone every 3 months throughout the study (unless the patient withdraws consent or is deemed lost to follow-up) to complete a patient survey. "Lost to follow-up" is defined as a patient who goes one year with no data being collected/reported (1 year without physician visit/telephone contact and failure to at least partially complete 4 consecutive quarterly patient surveys; further attempts at patient contact are not required). After informed consent is obtained, the patient will complete a "Patient Contact Form", which will request contact information (phone number, email address, and physical address). This form will be submitted to an independent patient interview service by the enrolling physician. The patients will receive emails or postal mail reminding them to complete the survey. If they have not completed the survey one week after the due date, they will be called by the independent patient interview service to complete the survey via phone. For each survey the patient completes, they will receive a nominal appreciation gift.

In addition, patients will receive via postal mail an annual calendar with stickers placed on the months that they will be requested to complete their quarterly patient survey. They will receive a new calendar each year of their participation. Patients will also receive a registry newsletter once a year in an attempt to keep them engaged in the registry.

In the event a physician retires, or discontinues participation from the registry, the following transition plan is in place to enable continuing participation of their patients. The Informed Consent Form include wording explaining that if the patient's physician discontinues participation in the registry, or retires, the independent patient interview service will be notified and contact them with the name and contact information of the closest participating study physician that they can contact during the remainder of their participation in the registry. The wording also states that the registry can continue to collect the direct patient-reported data without the need for re-consent. If the patient is unable or unwilling to be followed by a new physician, the patient must be discontinued from the study.

In the event a patient moves to a new location or chooses to leave their current physician, patients are provided with information upon enrollment as to how to locate a participating physician in their area or how to provide the registry information to a new physician that may not yet be participating. Participating patients will have access to all of this information on the study specific web portal as well as being reminded of this process in the annual patient newsletters they will receive throughout their participation in the study.

The goal of these strategies is to enhance patient retention activity, potentially resulting in a lower drop-out rate and improved quality of data.

Over the course of a long-term study, patient death may occur. Additionally, patients may develop serious co-morbidities that cause them to become "lost to follow-up" in the Registry. Periodically throughout the study, and in case of "lost to follow-up", searches of appropriate databases, such as the national death index and state cancer registries, death or cancer registries will be performed for any matches.

NEW TEXT:

Individual patient follow-up is approximately 10 years after enrollment, regardless of discontinuation of Cimzia or other medications.

As a means to retain patient participation, patients are followed up directly via a web-based system or if preferred, by mail (including a prepaid self-addressed return envelope) or by the phone every 3 months throughout the study (unless the patient withdraws consent or is deemed lost to follow-up) to complete a patient survey. "Lost to follow-up" is defined as a patient who goes 2 years with no data being collected/reported (2 years without Investigator visit/telephone contact or failure to at least partially complete 8 consecutive quarterly patient surveys; further attempts at patient contact are not required). The patients will receive emails or postal mail reminding them to complete the survey. If they have not completed the survey one week after the due date, they will be called by the independent patient interview service to complete the survey via phone. Patients completing the quarterly surveys will receive a nominal appreciation gift (if approved by the site's IRB).

In addition, patients will receive via postal mail an annual calendar with stickers placed on the months that they will be requested to complete their quarterly patient survey. They will also receive a new calendar and a registry newsletter once a year in an attempt to keep them engaged in the registry.

In the event an Investigator retires, or discontinues participation from the registry, the following transition plan is in place to enable continuing participation of their patients. The Informed Consent Form include wording explaining that if the patient's Investigator discontinues participation in the registry, or retires, the independent patient interview service will be notified and the name and contact information of the closest participating study Investigator that they can contact during the remainder of their participation in the registry. The new Investigator and the patient should document re-consent of the transition. The registry can continue to collect the direct patient-reported data without the need for re-consent. If the patient is unable or unwilling to be followed by a new Investigator, the patient must be discontinued from the study.

In the event a patient moves to a new location or chooses to leave their current Investigator, patients are provided with information upon enrollment as to how to locate a participating Investigator in their area or how to provide the registry information to a new Investigator that may not yet be participating. Participating patients will have access to all of this information on the study specific web portal as well as being reminded of this process in the annual patient newsletters they will receive throughout their participation in the study.

The goal of these strategies is to enhance patient retention activity, potentially resulting in a lower drop-out rate and improved quality of data.

Over the course of a long-term study, patient death may occur. Additionally, patients may develop serious co-morbidities that cause them to become "lost to follow-up" in the Registry. Periodically throughout the study, and in case of "lost to follow-up", searches of appropriate databases, such as the national death index and state cancer registries, death or cancer registries will be performed for any matches. In addition, the sponsor may utilize patient-centric data warehouse organization(s), to extract de-identified data from healthcare channels in the US. Data sources include, but are not limited to, medical claims, pharmacy claims, hospital charge master records, behavioral and demographic information, oncology electronic medical records (EMR), long-term care pharmacy, and laboratory data. The output from this activity will not be used to solicit additional events from Investigators.

**Change #7**

Section 5.2, Adverse Events of Interest

Correction of last paragraph

OLD TEXT:

For events in which SMQs are not available, MedDRA v 16.0 Preferred Terms (PT) for the System Organ Class (SOC) and High-Level Group Term (HLGT) categories will be used as appropriate. These PTs are listed in the Statistical Analysis Plan (SAP). Additional detail on

the clinical validation of the primary endpoints is presented below although all safety events that meet the definition of AEs of interest will be collected and summarized as part of the study.

NEW TEXT:

For events in which SMQs are not available, MedDRA v 16.0 Preferred Terms (PT) for the System Organ Class (SOC) and High-Level Group Term (HLGT) categories will be used as appropriate. For AEs of interest, where no SMQ is available, medical review will occur to select AEs (eg demyelinating disorders, autoimmune disorders and serious infections). Additional detail on the clinical validation of the primary endpoints is presented below although all safety events that meet the definition of AEs of interest will be collected and summarized as part of the study.

**Change #8**

Figure 5-1, Event reporting process

Replaced process flow chart in its entirety to reflect change of terms "Enrolling physician" with "Investigator"

**Change #9**

Section 6.1.1, Primary Endpoints

OLD TEXT:

The primary events interested in this registry are incidence and recurrence rates as well as the time-to-event for the following safety events:

- Autoimmune disorders
- Demyelinating disorders
- Serious infections or opportunistic infections
- Lymphoma and other malignancies
- Hypersensitivity reactions
- Other events:
  - congestive heart failure
  - aplastic anemia
  - serious bleeding events
  - serious skin reactions

NEW TEXT:

The primary outcome of this observational study is malignancy. Additionally, the following safety events will be investigated:

- Autoimmune disorders
- Demyelinating disorders
- Serious infections or opportunistic infections
- Hypersensitivity reactions
- Other events:
  - congestive heart failure
  - aplastic anemia
  - serious bleeding events
  - serious skin reactions

**Change #10**

Removal of sections formerly entitled:

- 11.4.1.1, Determination of Event Rate Numerator
- 11.4.1.2, Person time at Risk Calculations
- 11.4.1.2.1, Person time at risk calculation for malignancy events
- 11.4.1.2.2, Person time at risk calculations for acute events
- 11.4.1.5, Time to Event Analyses

**Change #11**

Section 6.4.1, Primary Analysis

Safety events will be categorized based on event types (eg, malignancies, infections, demyelinating disorders, hypersensitivity reactions, and autoimmune disorders) with analyses conducted for each category. Analysis of specific outcomes may be conducted if appropriate.

Event rates will be calculated by dividing the number of reported safety events by the person-years at risk. Cimzia-specific rates will be calculated and compared to all other CD treatment rates. Incidence rates will be calculated by dividing the number of subjects who had reported safety events by the appropriate person-years at risk.

For incidence rate and event rate calculations, the number of events will be determined for Cimzia and for all other CD treatments based on the date of the last dose received before event onset and treatment class-specific half-life exposure of the medication. The exposure half-lives used for rate calculations for each treatment class are as follows:

- Corticosteroids: 7 days
- Immunosuppressants: 28 days
- Biologic agents (including Cimzia): 70 days

Propensity scores will be used to assess the comparability of patients who are receiving Cimzia at baseline and those who are receiving another CD medication and will be incorporated into the primary analysis. Two-sided 95% confidence intervals (CIs) will be calculated for all rates.

Appropriate analytical methodologies will be used to investigate the effect of time varying confounders.

Cancer progresses in several stages before reaching a detectable, malignant state. While this latency period may differ by cancer type, it is generally believed to occur over a long time period (Ecsedy and Hunter, 2002). Thus, a treatment-related event may not be seen until years after the initial exposure. In contrast, acute events typically have very short latency periods; therefore, it is unlikely that a treatment-related event will occur after exposure to the product has ended. For this reason, 2 different methods of person-time at risk calculations will be used, one for malignancy events (Section 6.4.1.1) and one for acute events (Section 6.4.1.2).

**Change #12**

Added Section 6.4.1.1, Malignancy Events

NEW TEXT:

The following analyses will be conducted to better elucidate treatment patterns and treatment attribution in malignancy events:

- The number of malignancy events and number of patients experiencing malignancy events will be tabulated by the number of CD treatments received during the study. Also, the mean number of treatments received per patient in the Cimzia and comparator groups (based on baseline assignment) will be calculated, as well as for both groups combined.
- The number of malignancy events and number of patients experiencing malignancy events will be tabulated by treatment patterns for biologics observed in the study. The name and order of the biologic treatment will be specified in the summary table (eg, "A-B" implies that patients received two different biologics, "A" followed by "B"; "C" implies that patients received one biologic "C" throughout the study; "A-C-D" implies that patients received three different biologics, in the order of "A", "C", then "D", etc.).
- The number of malignancy events and the number of patients experiencing malignancy events will be tabulated by the type of CD therapy received (monotherapy versus combination therapy). If a patient received combination therapy (TNF-α antagonist plus immunosuppressant) at least once during the study, then this patient will be included in the combination therapy category.

**Change #13**

Added Section 6.4.1.2, Acute Events

NEW TEXT:

The primary analysis for acute events will be time-to-event analyses using Cox proportional hazard modeling. A Kaplan-Meier analysis will be performed censoring patients at the time of their first treatment switch during the study period, including patients who switch from one non-Cimzia treatment to another non-Cimzia treatment, as a secondary analysis.

## 14.5 Protocol amendment 5

Rationale for the amendment

The protocol has been amended to close the enrollment period and to revise the patient follow up period to 8 years. Interim analysis data was provided to support the enrollment time and patient follow up period.

In addition, minor grammatical and typographical errors were corrected.

**Global Changes**

**Change #1**

The follow up period for patients enrolled was changed from 10 years to 8 years throughout the document. The following sections were affected:

- Section 1: Introduction, third paragraph, second sentence
- Section 2: Registry Rationale, first paragraph, second sentence
- Section 4.5: Schedule of Assessments, third paragraph, first sentence
- Section 4.5: Schedule of Assessments table, "Direct Patient Follow-up Year" column title
- Section 4.5: Schedule of Assessments table, first column, last row
- Section 4.7: Participation and Retention Strategies, first sentence
- Section 4.8: Data Collection Strategies, third paragraph, first sentence
- Section 6.2: Comparator Group, first sentence
- Section 6.3: Determination of Sample Size, first paragraph, first and second to last sentences

**Specific Changes**

**Change #1**

**Study Contact Information**

Name: [redacted], MD

Phone: [redacted]

Fax: [redacted]

**Has been changed to:**

Name: [redacted]

Phone: [redacted]

Fax: **Not Applicable**

**Change #2**

**Study Contact Information**

Clinical Project Manager

Name: [redacted], MPH

Phone: [redacted]

Fax: [redacted]

**Has been changed to:**

**Senior** Clinical Project Manager

Name: [redacted]

Phone: [redacted]

Fax: **Not Applicable**

**Change #3**

**Study Contact Information**

Clinical Trial Biostatistician

Name: [redacted], PhD

Phone: [redacted]

Fax: [redacted]

**Has been changed to:**

**Senior** Biostatistician

Name: [redacted]

Phone: [redacted]

Fax: **Not Applicable**

**Change #4**

**Study Contact Information**

Name: [redacted], MD

Phone: [redacted]

Fax: [redacted]

**Has been changed to:**

Name: [redacted]**,** MD

Phone: [redacted]

Fax: [redacted]

**Change #5**

**Study Contact Information**

Name: [redacted], PhD

Phone: [redacted]

Fax: [redacted]

**Has been changed to:**

Name: [redacted], PhD

Phone: [redacted]

Fax: **Not Applicable**

**Change #6**

**Section 1: Introduction**

Second paragraph

The protocol has been amended (Amendment 4) to address clarification language in regards to patient visit requirements or lost-to-follow-up language. In addition, language was added to allow the sponsor to utilize patient-centric data warehouse organization(s), to extract de-identified data from healthcare channels in the US, including hospitals, providers and pharmacies. The statistical section was updated per FDA comments to account for treatment switch patterns.

**Has been changed to:**

The protocol has been amended (Amendment **5**) **to cease enrolling patients into the SECURE registry (protocol C87075). The decision was based on the results of a current interim analysis that indicated that no new safety issues had emerged from the currently known safety profile of Cimzia. Patients who already enrolled in C87075 at the time of discontinuation will continue to be followed.**

**Change #7**

**Section 4.2: Selection of Study Population**

First paragraph

This is a long-term observational study in the USA that will include approximately 4000 CD patients. To ensure a sufficient number of Cimzia-treated patients in the registry, approximately half of enrolled patients will be receiving Cimzia for ≤12 months or about to receive Cimzia at the time of enrollment. The study will be conducted in all regions in the USA at approximately 300 enrolling investigative sites.

**Has been changed to:**

This is a long-term observational study in the USA that includes a total of **3045** CD patients **(1371 in the Cimzia Cohort and 1674 in the Comparison Cohort) as of Mar 2017.** To ensure a sufficient number of Cimzia-treated patients in the registry, approximately half of enrolled patients will be receiving Cimzia for ≤12 months or about to receive Cimzia at the time of enrollment. The study will be conducted in all regions in the USA at approximately 280 enrolling investigative sites.

**Change #8**

**Section 4.7: Participation and Retention Strategies**

The third paragraph was deleted:
~~In addition, patients will receive via postal mail an annual calendar with stickers placed on the months that they will be requested to complete their quarterly patient survey. They will also receive a new calendar and a registry newsletter once a year in an attempt to keep them engaged in the registry~~

**Change #9**

**Section 4.7: Participation and Retention Strategies**

The fourth paragraph, end of the last sentence
~~as well as being reminded of this process in the annual patient newsletters.~~

**Change #10**

**Section 5.2: Adverse Events of Interest**

First paragraph, first sentence
When available, narrow scope SMQs (Standardized MedDRA Queries) from the Medical Dictionary for Regulatory Activities (MedDRA®) version 16.0 will be used to define the AEs of interest (Section 5.2).

**Has been changed to:**

When available, narrow scope SMQs (Standardized MedDRA Queries) from the Medical Dictionary for Regulatory Activities (MedDRA®) version **17.0** will be used to define the AEs of interest (Section 5.2).

**Change #11**

**Section 5.2: Adverse Events of Interest**

Last paragraph, first sentence

For events in which SMQs are not available, MedDRA v 16.0 Preferred Terms (PT) for the System Organ Class (SOC) and High-Level Group Term (HLGT) categories will be used as appropriate. For AEs of interest, where no SMQ is available, medical review will occur to select AEs (eg demyelinating disorders, autoimmune disorders and serious infections).

**Has been changed to:**

For events in which SMQs are not available, MedDRA v **17.0** Preferred Terms (PT) for the System Organ Class (SOC) and High-Level Group Term (HLGT) categories will be used as appropriate. For AEs of interest, where no SMQ is available, medical review will occur to select AEs (eg demyelinating disorders, autoimmune disorders and serious infections).

**Change #12**

**Section 6.1.1: Primary Endpoints**

MedDRA coding version 16.0 will be used to identify and define AEs of interest. The specific MedDRA codes used to determine AEs of interest will be provided in the SAP. Narrow scope SMQs and clinical validation of primary endpoints are provided in Section 5.2 of the protocol.

**Has been changed to:**

MedDRA coding version **17.0** will be used to identify and define AEs of interest. The specific MedDRA codes used to determine AEs of interest will be provided in the SAP. Narrow scope SMQs and clinical validation of primary endpoints are provided in Section 5.2 of the protocol.

**Change #13**

**Section 6.3: Determination of Sample Size**

First paragraph

A total of 4000 patients (2000 patients per arm) are planned to be enrolled in the first 5 years of the study, with a total duration of participation (treatment and follow-up) of 10 years for each patient. Assuming an 8% annual drop-out rate (1) (withdrawal, lost-to-follow-up or death), approximately 25,000 (12,500 per arm) total patient years (p-y) post-enrollment is expected in this registry. With a two-sided significance level of 0.05, the study is designed to have at least 80% power to detect incidence rate ratios (calculated based on observed rates in the control group) of 1.5 for serious infections, 3.3 for lymphoma, and 1.56 for solid malignancies after 10 years. Event rate estimates for this study were calculated using corresponding event rates observed in a CD anti-TNFα registry study control group (1, 2).

**Has been changed to:**

**Prior to Amendment 5, the study planned for a total of 4000 patients (2000 patients per arm.** A total of **3045** patients **(1371 in the Cimzia Cohort and 1674 in the Comparison Cohort) were enrolled as of Mar 2017**. The total duration of participation (treatment and follow-up) of 8 years is planned for each patient. Assuming an 8% annual drop-out rate (1) (withdrawal, lost-to-follow-up or death), approximately 25,000 (12,500 per arm) total patient years (p-y) post-enrollment is expected in this registry. With a two-sided significance level of 0.05, the study is designed to have at least 80% power to detect incidence rate ratios (calculated based on observed rates in the control group) of 1.5 for serious infections, 3.3 for

lymphoma, and 1.56 for solid malignancies after 8 years. Event rate estimates for this study were calculated using corresponding event rates observed in a CD anti-TNFα registry study control group (1, 2).

# C87075 Protocol Amendment 5 SECURE

## ELECTRONIC SIGNATURES

| Signed by | Meaning of Signature | Server Approval Date (dd-mon-yyyy (HH:mm)) |
|---|---|---|
| [redacted] | Clinical Approval | 13-Sep-2017 17:13 GMT+02 |
| [redacted] | Clinical Approval | 13-Sep-2017 18:38 GMT+02 |