The Use of Small Bowel Ultrasound to Predict Response to Remicade Induction

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NCT02488005

Document Date: 7-27-2017

Mount Sinai	Protocol Title:	The Use of Small Bowel Ultrasound to Predict Response to Remicade Induction
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	Date Revised:	07/27/2017
	Study Number:	GCO# 15-0878

Brief Summary of Research (250-400 words):

Small bowel ultrasound (SBUS) is emerging as a well tolerated, non-invasive, radiation free, low cost measure to assess inflammatory bowel disease (IBD), and is being used as first-line imaging in Europe. SBUS findings have been shown to correlate with endoscopic findings, and a small number of recent studies have looked at change in bowel wall thickness (BWT) in response to anti-TNF therapy. However, the use of SBUS to detect response to anti-TNF therapy has not been tested in pediatric patients. The purpose of this study is to apply the use of SBUS to pediatric patients with Crohn's disease and to assess response to treatment with infliximab. We will also measure C-reactive protein and fecal calprotectin at baseline, as well as measure IFX levels and anti-infliximab antibodies (ATI) at week 14 to assess change in biochemical response to infliximab treatment. Additionally, correlations between these markers with changes in patient reported outcomes via a weighted pediatric Crohn's disease activity questionnaire (wPCDAI) and changes in BWT will be assessed. This study is novel in that it will be the first study in pediatric patients to use SBUS to assess response to IFX therapy, and will also be the first study to correlate SBUS findings with therapeutic drug monitoring (TDM). This study has the potential to propagate the use of SBUS in the pediatric population, as the use of TDM in concert with small bowel imaging post-induction will allow us to tailor therapy early in the treatment course.

1) Objectives:

Research Questions:

The goals of this study are to measure Bowel Wall Thickness (BWT) prior to initiating infliximab (IFX 0) and at week 14 and to look at the correlation between:

1) **change in BWT (delta BWT) with change in clinical disease activity (delta wPCDAI)**

2) change in BWT (delta BWT) with change in biomarker levels and antibody-to-infliximab (delta IFX, delta calprotectin, delta CRP)

2) Background

Pediatric inflammatory bowel disease (IBD) patients are at increased risk for high ionizing radiation exposure in the assessment of their condition (1,2). Small bowel ultrasound (SBUS) is emerging as a well tolerated, non-invasive, radiation free, low cost measure to assess inflammatory bowel disease, and is being used as first-line imaging in Europe (3,4). SBUS findings have been shown to correlate with endoscopic findings (5). A small number of recent studies in Europe and the U.S. have looked at change in bowel wall thickness (BWT), in response to anti-TNF therapy in adult patients (6-9), in comparison to other types of imaging (), and as a potential diagnostic tool () .

The use of SBUS to detect response to anti-TNF therapy has not been tested in pediatric patients. In addition, these studies frequently use Crohn's Disease Activity Index (CDAI) as a measure of clinical activity, yet it is known from multiple studies including the SONIC trial that CDAI is not a reliable or accurate measure to predict mucosal healing. A weighted PCDAI will be used instead, which has been shown to perform better than the original PCDAI and is more feasible, especially considering the study spans 14 weeks and scoring items such as height velocity from the full PCDAI will be irrelevant (10).

The goal of this study is to use the ultrasound results to measure bowel wall thickness (BWT) prior to initiating infliximab (IFX 0) and at week 14 and to look at the correlation between change in BWT (delta BWT) with change in clinical disease activity (delta wPCDAI) between these two time points. We will measure fecal calprotectin at baseline and at week 14 with stool collected the day prior to the visit using a specimen collection kit given to subjects. We will also collect results from routine laboratories (including C-Reactive Protein, Erythrocyte Sedimentation Rate, Complete Blood Count, and Albumin) done before each infusion, and IFX levels and anti-infliximab antibodies (ATI) at week 14 to assess change in biochemical response to infliximab treatment, as well as correlation between these markers with changes in patient reported outcomes (via a wPCDAI questionnaire) and changes in BWT.

References:

(1) Desmond AN, O'Regan K, Curran C, et al. Crohn's disease: factors associated with exposure to high levels of diagnostic radiation. Gut 2008; 57:1524-1529.

(2) Sauer CG, Kugathasan S, Martin DR, et al. Medical radiation exposure in children with inflammatory bowel disease estimates high cumulative doses. Inflammatory Bowel Diseases 2011; 11:2326-2332.

(3) Panes J, Bouhnik Y, Reinisch W, et al. Imaging techniques for assessment of inflammatory bowel disease: Joint ECCO and ESGAR evidence-based consensus guidelines. Journal of Crohn's and Colitis 2013; 7:556-585.

(4) Calabrese Em, Zorzi F, Zuzzi S, et al. Development of a numerical index quantitating small bowel damage as detected by ultrasonography in Crohn's disease. Journal of Crohn's and Colitis 2012; 6:852-860.

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(6) Zorzi F, Stasi E, Bevivino G, et al. A sonographic lesion index for Crohn's disease helps monitor changes in transmural bowel damage during therapy. Clinical Gastroenterology and Hepatology 2014; 12:2071-2077.

(7) Castiglione F, Testa A, Rea M, et al. Transmural healing evaluated by bowel sonography in patients with Crohn's disease on maintenance therapy with biologics. Inflammatory Bowel Diseases 2013; (19)9:1928-1934.

(8) Moreno N, Ripolles T, Paredes JM, et al. Usefulness of abdominal ultrasonography in the analysis of endoscopic activity in patients with Crohn's disease: changes following treatment with immunomodulators and/or anti-TNF antibodies. Journal of Crohn's and Colitis 2014; 8:1079-1087.

(9) Paredes JM, Ripolles T, Cortes X, et al. Abdominal sonographic changes after antibody to tumor necrosis factor (anti-TNF) alpha therapy in Crohn's disease. Digestive Diseases and Sciences 2010; 55:404-410.

(10) Turner D, Griffths AM, Walters TD, Seah T, Markowtitz J, Pfefferkorn M, Keljo D, Waxman J, Otley A, LeLeiko NS, Mack D, Hyams J, Levine A. Mathematical weighting of the pediatric Crohn's disease activity index (PCDAI) and comparison with its other short versions. *Inflamm Bowel Dis*. 2012 Jan; 18(1):55-62

3) Setting of the Human Research

Mount Sinai Medical Center
Susan and Leonard Feinstein IBD Clinical Center
17 East 102nd Street, 5th Floor
New York, NY 10029

Pediatric Radiology Suite - Kravis Children's Hospital
1184 Fifth Avenue, MC Level
New York, NY 10029

Therapeutic Infusion Center
1470 Madison Avenue, 4th Floor
New York, NY 10029-6574

4) Resources Available to Conduct the Human Research

Mount Sinai's Susan and Leonard Feinstein Inflammatory Bowel Disease Clinical center is a comprehensive care center for patients of all ages, with one of the largest Children's IBD programs in the nation. The center offers a multidisciplinary team of pediatric gastroenterologists, nurse practitioners, social workers, nutritionists, and child life specialists that work to provide exceptional care to our patients.

The center receives over 1,000 IBD patient visits every year, with about 30% of our patients on biological drug therapy and undergoing therapeutic drug monitoring, making our center a prime facility for reaching out to eligible participants.

Mount Sinai's Department of Radiology has nationally renowned interventional radiologists and offers multimodality pediatric radiology services, including ultrasound imaging services.

Dr. Dubinsky (Principal Investigator) is a leading expert in the field of pediatric IBD, and is the Co-Director of the IBD center. Dr. Henrietta Rosenberg (Co-investigator) is the Radiologist-in-Chief at Kravis Children's Hospital at Mount Sinai and is recognized internationally for her unique ability to use ultrasound as a reliable, accurate, non-invasive practical tool.

All research investigators and personnel are CITI certified and have been trained/involved in other IRB approved research studies at MSSM. All study staff are Mount Sinai employees and are informed of the study protocol and their responsibilities regarding research-related tasks. In addition, the research team will meet regularly to discuss all aspects of the study.

5) Study Design

a) Recruitment Methods

Treating physicians will refer potential subjects to the research team when he/she knows the patient will be starting infliximab as part of their standard of care. The treating physician will first approach the subject to ensure that subject is interested in learning more about the study before the study team approaches them. Researchers will then approach the patient to inform them of the study, the consent process will then be completed, and patient will be screened. We anticipate approximately 40 subjects will be pre-screened, and 30 subjects enrolled.

b) Inclusion and Exclusion Criteria

Inclusion:

- Patients with confirmed diagnosis of small bowel Crohn's Disease patients aged ≥ 6 years and ≤ 21 years using stable doses of concomitant medications (including steroids) for at least 14 days prior to baseline SBUS
- No infliximab therapy previously initiated
- Infliximab indicated for treatment of IBD
- Patient consent/assent and/or parent/guardian consent
- Ability to remain in follow-up for 14 weeks from start of study

Exclusion:

- Lack of small bowel disease
- Inability to give consent or adhere to study protocol
- Infliximab-experienced
- Presence of active infections
- Presence of abscess or strictures
- Current or planned Pregnancy for the 14 week study duration

c) Number of Subjects

A total of 20 subjects will be enrolled in this pilot study.

Results from this study of 20 patients may inform future studies.

d) Study Timelines

Duration of individual subject's participation: 14 weeks/patient

Estimated date for enrollment completion: September 2017

Study Endpoints

Definitions:

Delta BWT = BWT at week 0 IFX infusion – BWT at week 14 IFX infusion

Delta wPCDAI: = wPCDAI activity score at week 0 IFX infusion – wPCDAI activity at week 14 IFX infusion

Delta CRP represents a change in levels of a biomarker from week 0 to week 14
Delta Calprotectin represents a change in levels of a biomarker from week 0 to week 14

Primary endpoint: **Correlation of delta BWT with delta wPCDAI**
Secondary endpoints: Frequency of BWT < 3mm at week 14
Correlation between delta BWT and delta CRP levels
Correlation of BWT and IFX levels at week 14
Correlation of delta calprotectin with delta wPCDAI
Correlation of delta BWT with delta calprotectin
Association of absolute bowel wall thickness with wPCDAI at week 14

Safety Endpoints:

Adverse event to small bowel ultrasound
Presence of stricture or abscess at week 14

Statistical Analysis Plan:

Spearman's rank correlation coefficient will be used to assess how well the variables can be described as a monotonic function

Chi-squared tests will be used to look at the association of the variables and to determine the significance of any differences between expected results and observed results

Procedures Involved in the Human Research

Procedure	Screening	Week 0 IFX Inf# 1	Week 2 IFX Inf# 2	Week 6 IFX Inf# 3	Week 14 IFX Inf#4
Screening Process (Inclusion/Exclusion Criteria Met)	X*				
Informed Consent Process	X*				
Demographic Info (Age, Height/Weight, Medication History, Disease History, etc.)	X				
Adverse Event Review		X	X	X	X
Concomitant Medication Review		X	X	X	X
Pre-infusion Routine Labs/Blood Draw (Includes CRP, CBC, ESR, and Alb results)		X	X	X	X
Small Bowel Ultrasound		X*			X*
wPCDAI		X*	X*	X*	X*
Calprotectin from Stool		X* (Stool Collected Day Prior)			X* (Stool Collected Day Prior)
IFX Trough/ATI Levels					X* 2.0 mL of additional blood will be drawn during the routine lab

*Procedures done for research purposes only
(See *Data Management and Confidentiality* for definitions of abbreviated terms)

Results of ultrasound of the small bowel will be used to determine the bowel wall thickness. Change in bowel wall thickness will be compared to clinical outcomes.

e) Specimen Banking

N/A

f) Data Management and Confidentiality

Data to be collected include:
- Patient age, height/weight
- Demographic Data
- Date of Diagnosis, Disease History/Hospitalizations, Disease Location
- Small Bowel Ultrasound
- Calprotectin from Stool Collected day prior to Visit
- C-Reactive Protein (CRP), Complete Blood Count (CBC), Erythrocyte Sedimentation Rate (ESR), and Albumin (Alb) from Routine Laboratories
- weighted Pediatric Crohn's Disease Activity Index (wPCDAI)
- Infliximab (IFX) Trough levels and Antibodies-to-Infliximab (ATI) Levels

No personal identifiers will be used on specimen collection tubes or on data collection forms. Each participant will be given a unique identifier in this study. Study data and information linking each patient with their unique identifier will be secured via password-protected files that only investigators and study staff will have access to. Files containing patient identifiers will also be encrypted.

As noted in the consent form, investigators and institutions will also provide direct access to source data/documents for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection.

g) Provisions to Monitor the Data to Ensure the Safety of subjects

The subject's original informed consent will be kept in a study binder, and subjects will be provided with a copy of the consent document. All case report forms filled out will only contain de-identified information and will be stored in a locked cabinet in IBD Clinical Center (17 E. 102nd St, 5th Floor). All subject information will also be de-identified, then entered and stored in a password-protected file saved on a network location protected by institutional firewalls, and only accessible to research personnel working on this study. Serious adverse events will be reported as detailed in Appendix A.

h) Withdrawal of Subjects

Subjects have the right to withdraw permission at any time, as described in the informed consent document. It will not be possible to destroy information that has already been given to our researchers. In the event that a subject elects to withdraw from the present study, as per the consent form, subjects will be asked to do so in writing.

6) Risks to Subjects

This study involves minimal risk to subjects.
Small bowel ultrasound carries minimal risk, as it is a well-tolerated, non-invasive, radiation-free imaging evaluation.

Risk of a blood draw includes pain, bruising, and the slight possibility of infection at the place where the needle enters the vein. Some people feel dizzy or may faint during or after a blood draw. In this study, 2.0 mL of additional blood will be collected for antibodies/drug level assays at the same time as the routine labs so no additional needle-stick will occur.
To reduce risk of loss of private information and to ensure confidentiality, data will be de-identified and no personal information will be released regarding results. Subject identity will not be revealed in any publications or release of study results. No physical, social or economic risks are anticipated.

7) Provisions for Research Related Injury

If subjects are injured as a direct result of participating in this study, immediate, short-term medical treatment related to this injury is available at Mount Sinai Medical Center, but such treatment will not be free of charge. The subject's medical insurance may pay for such treatment, but the subject will ultimately be responsible for payment.

Any additional, non-emergency treatment related to this injury is available at Mount Sinai Medical Center but such treatment will not be free of charge.

8) Potential Benefits to Subjects

There are no direct benefits to subjects through their enrollment in this study. Their participation allows for the enhancement of knowledge of inflammatory bowel disease assessment methods, which may allow for the future potential to introduce small bowel ultrasound as a viable means of disease assessment in conjunction with therapeutic drug monitoring to identify treatment failures earlier on and aid in the stratification response to infliximab.

9) Provisions to Protect the Privacy Interests of Subjects

The pediatric gastroenterologists at Mount Sinai discuss treatment options for their patients. Subjects who will be receiving Infliximab infusions as standard of care may be eligible for the study. Eligible subjects will be informed about the study in a private setting, with ample time to review the consent document and ask questions. Subjects can refuse to participate in the study. Participation is voluntary, and data obtained will be de-identified.

10) Economic Impact on Subjects

Study procedures and laboratory tests that are directly due to subjects taking part in this study will not be charged to the subject or to their insurance company. Routine clinical visits, blood work, and any services that would normally be provided as standard of care will be billed to the subject's insurance company.

11) Payment to Subjects

Patients will not receive any payment for participating in this study.

12) Consent Process

HRP-090 - SOP - Informed Consent Process for Research will be followed.

The consent process will take place during an office visit if MD and patient/parent agree to begin infliximab as a treatment for the patient's Crohn's Disease symptoms.

Consent must be obtained prior to patient's start of anti-TNF (i.e. infliximab) therapy in order to schedule for SBUS and to arrange for stool sample for calprotectin level at Week 0 infusion. To be eligible for this study, the patient must already be approved to start infliximab to treat their small bowel Crohn's disease. This study and its PI/researchers will have no role in the dosing or administration of infliximab to the patient.

All adults will sign consent forms, while all children sign assent forms along with consent of one legal guardian.

The study will be described verbally and in writing (consent form written at an sixth grade level) to patients and the parents of the children who will act on their behalf. Parents of the children will be asked to sign the consent form as an indication that they understand the procedures and risks involved. Consent will be obtained from one parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child. Assent will be obtained from all children capable of providing assent. Children 6-18 years old will have an assent document and will have the study explained to them on a level that they can understand. They will be given the opportunity to ask questions in front of a witness not related to the subject or the study. Children between the ages of 6-11 will be fully informed about the research using language to their age of maturity and assent will be obtained and documented from those children deemed capable of making a meaningful decision by the child's parents and pediatric gastroenterologist. It will be made clear that participation is voluntary and that decisions not to participate will not have any bearing upon the family's ability to receive care from the physicians involved in the study. There will be no inducements offered for enrollment. The risks will be outlined as described in the consent form. In the event that a potential participant speaks a language other than English and is eligible for participation in the study, the investigator will translate the consent document and submit the document to the PHHS office for approval. Subjects who turn 18 years of age during the course of the study will be re-consented as adults.

13) Process to Document Consent in Writing

Standard PPHS consent forms will be used.
Study team will adhere to SOP HRP-091 Written Documentation of Informed Consent.
Informed consent/assent is obtained by the subject and/or the subject's legal representative.
Original documents will be kept in the study binder, a copy will be given to the subject/subject's parent/guardian and the original will be scanned into EPIC along with a note documenting the consent/assent process.

14) Vulnerable Populations

Children; Study team will adhere to "CHECKLIST HRP-421".

15) Multi-Site Human Research (Coordinating Center)

N/A

16) Community-Based Participatory Research

N/A

17) Sharing of Results with Subjects

Research data collected will not be shared with patients at this time.

18) IRB Review History

N/A

19) Control of Drugs, Biologics, or Devices

Administration of biologic to patient, sample collections, and labs are being used/done as standard of care by treating physician and infusion staff, separate from this study. Infliximab is not protocolized, but initiating infliximab therapy is an inclusion criteria. Patients are recruited after they are cleared to start infliximab therapy, which includes being a review of vaccination records and completing a TB test. Researchers will have no role in the dosing or administration of infliximab.

APPENDIX A: Interventional IIS COMPANY Requirements for Safety Data Collection and Reporting

1. Overview

As the sponsor of the Study, Icahn School of Medicine at Mount Sinai (hereinafter referred to as the INSTITUTION) and Dr. Marla Dubinsky (hereinafter referred to as PRINCIPAL INVESTIGATOR) shall be solely responsible for complying, within the required timelines, any safety reporting obligation to competent Health Authorities, IRB/ECs and any participating (co or sub) investigators, as defined in applicable laws and regulations. For the purposes of this EXHIBIT, safety data includes adverse events, product quality complaints (PQCs), and special situations including pregnancies.

The INSTITUTION and PRINCIPAL INVESTIGATOR will provide safety information to Janssen Pharmaceuticals (hereinafter referred to as the COMPANY) on adverse events, special situations including pregnancies and product quality complaints as defined within this EXHIBIT.

2. Management of Safety Data

This Study has been designated as an interventional study. As such, all adverse events regardless of causality and special situations excluding those from subjects not exposed to a Janssen Medicinal Product and product quality complaints with or without an adverse event as described in this Exhibit will be reported from the time a subject has signed and dated an Informed Consent Form (ICF) until completion of the subject's last study-related procedure (which may include contact for follow-up safety). Serious adverse events will be reported for 30 days after the last dose of study drug.

For the purposes of this study, the Janssen medicinal product Remicade (infliximab).

3. Definitions

3.1. Adverse Event (AE)

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

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

3.2. Adverse Events of Special Interest

Any newly identified malignancy or case of active TB occurring after first administration of infliximab in subjects participating in this clinical study must be reported. Investigators are also advised that active TB is considered a reportable disease in most countries. These events are to be considered serious only if they meet the definition of an SAE.

3.3. Individual Case Safety Report (ICSR)

A valid ICSR must contain the four minimum criteria required to meet regulatory reporting requirements.

- an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)

- an identifiable reporter (investigational site)
- a Janssen medicinal product
- an adverse event, outcome, or certain special situations

The minimum information required is:

- suspected Janssen medicinal product (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- gender
- age at AE onset
- reporter ID
- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- Janssen protocol ID

3.4. Product Quality Complaint (PQC)

A product quality compliant is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g., autoinjector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

3.5. Serious Adverse Event (SAE)

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

- Results in death
- Is life-threatening

  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

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

NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT.

3.5.1. Hospitalization

For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be provided.

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]

3.5.2. Life-Threatening Conditions

The cause of death of a subject in a study within 30 days of the last dose of the study drug, whether or not the event is expected or associated with the study drug, is considered a serious adverse event.

4. Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For a medicinal product(s) with a marketing authorization, the expectedness of an adverse event will be determined by whether or not it is listed in the applicable product information.

Remicade: http://www.remicade.com/shared/product/remicade/prescribing-information.pdf

5. Special Reporting Situations

Safety events of interest for a Janssen medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a Janssen medicinal product
- Exposure to a Janssen medicinal product from breastfeeding
- Suspected abuse/misuse of a Janssen medicinal product

- Inadvertent or accidental exposure to a Janssen medicinal product
- Any failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of a medicinal product
- Unexpected therapeutic or clinical benefit from use of a Janssen medicinal product

These safety events may not meet the definition of an adverse event; however, from a COMPANY perspective, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the CRF.

Any special situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to the COMPANY **within 24 hours of becoming aware of the event.**

6. **Pregnancy**

All initial reports of pregnancy must be reported to the COMPANY by the PRINCIPAL INVESTIGATOR **within 24 hours of their knowledge of the event** using the Serious Adverse Event Form. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form.

Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the effect of the Janssen medicinal product on sperm is unknown, pregnancies in partners of male subjects exposed to a Janssen medicinal product will be reported by the PRINCIPAL INVESTIGATOR **within 24 hours of their knowledge of the event** using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant should be reported to the COMPANY

7. Maintenance of Safety Information

All safety data should be maintained in a clinical database in a retrievable format. The INSTITUTION and PRINCIPAL INVESTIGATOR shall provide all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent provision of safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at the COMPANY's request.

8. Procedures for Reporting Safety Data and Product Quality Complaints (PQCs) for Janssen Medicinal Products to the COMPANY

All adverse events and special situations, whether serious or non-serious, related or not related, following exposure to a Janssen medicinal product are to be documented by the investigator and recorded in the CRF and in the subject's source records. Investigators must record in the CRF their opinion concerning the relationship of the adverse event to a Janssen medicinal product.

All (serious and non-serious) adverse events reported for a Janssen medicinal product should be followed-up until resolution of the event or its return to baseline value/status.

8.1. SAEs and Special Reporting Situations

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

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

The INSTITUTION and the PRINCIPAL INVESTIGATOR) will transmit all SAEs, pregnancies and special situations following exposure to a Janssen product under study in a form provided by the COMPANY in accordance with Section 9,Transmission Methods, in English **within 24-hours of becoming aware of the event(s).**

In the event the study is blinded, the PRINCIPAL INVESTIGATOR will submit an unblinded SAE or pregnancy exposure report to COMPANY.

All follow-up information for serious adverse events that are not resolved at the end of the study or by the time of patient withdrawal must be reported directly by the PRINCIPAL INVESTIGATOR, **within 24 hours becoming aware**, to the COMPANY using the COMPANY's Serious Adverse Event Report

All available clinical information relevant to the evaluation of a related SAE, serious ADR or special situation is required.

- The INSTITUTION and/or PRINCIPAL INVESTIGATOR is responsible for ensuring that these cases are complete and if not are promptly followed-up. A safety report is not considered complete until all clinical details needed to interpret the case are received. Reporting of follow-up information should follow the same timeline as initial reports.

- Copies of any and all relevant correspondences with regulatory authorities and ethics committees regarding any and all serious adverse events, irrespective of association with the Janssen Product under study, are to be provided to the COMPANY using a transmission method in Section 9 within **24 hours of such report or correspondence being sent to applicable health authorities.**

8.2. Non-Serious AEs

All non-serious adverse events should be reported to COMPANY according to the timeframe outlined in the Research Funding Agreement section entitled Reporting of Data.

8.3. PQC Reporting

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and the COMPANY, and are mandated by regulatory agencies worldwide. The COMPANY has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch

#s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving a Janssen medicinal product under study must be reported to the COMPANY by the PRINCIPAL INVESTIGATOR **within 24 hours after being made aware of the event.** The Janssen contact will provide additional information/form to be completed.

If the defect for a Janssen medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the PRINCIPAL INVESTIGATOR must report the PQC to the COMPANY according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by the COMPANY.

9. Transmission Methods

The following methods are acceptable for transmission of safety information to the COMPANY:

- Electronically via Janssen SECURE Email service (preferred)
- For business continuity purposes, if SECURE Email is non-functional:
    - Facsimile (fax), receipt of which is evidenced in a successful fax transmission report
- Telephone (if fax is non-functional).

Please use the contact information and process information provided by the COMPANY

Weighted PCDAI (wPCDAI)

History (Recall, 1 week)			
Abdominal Pain			Score
0 = None	10 = Mild: Brief, does not interfere with activities	20 = Moderate/Severe: Daily, longer lasting, affects activities, nocturnal	_____
Patient Functioning, General Well-Being			Score
0 = No limitation of activities, well	10 = Occasional difficulty in maintaining age appropriate activities, below par	20 = Frequent limitation of activity, very poor	_____
Stools (per day)			Score
0 = 0-1 liquid stools, no blood	7.5 = Up to 2 semi-formed with small blood, or 2-5 liquid	15 = Gross bleeding, or ≥ 6 liquid, or nocturnal diarrhea	_____
Laboratory			
Erythrocyte Sedimentation Rate			Score
0 = < 20 mm/hr	7.5 = 20-50 mm/hr	15 = > 50 mm/hr	_____
Albumin			Score
0 = ≥ 3.5 g/dL	10= 3.1-3.4 g/dL	20 = ≤ 3.0 g/dL	_____
Examination			
Weight			Score
0 = Weight gain or voluntary weight stable/loss	5 = Involuntary weight stable, weight loss 1-9%	10 = Weight loss ≥ 10%	_____
Perirectal Disease			Score
0 = None, asymptomatic tags	7.5 = 1-2 indolent fistula, scant drainage, no tenderness	15 = Active fistula, drainage, tenderness, or abscess	_____
Extra-intestinal Manifestations (fever ≥ 38.5 °C for 3 days over past week, definite arthritis, uveitis, E. nodosum, P. gangrenosum)			Score
0 = None		10 = One or more	_____
		Total Score (0-125):	

Score Guide:

Remission: <12.5
Mild: 12.5 - 40
Moderate 41 - 57.5
Severe: >57